

# **Fanconi Anemia: Guidelines for Diagnosis and Management**

Fourth Edition • 2014



**Fanconi Anemia**  
RESEARCH FUND, INC.

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to the following generous donors,  
who made this publication possible:*

Pat and Stephanie Kilkenny

Phil and Penny Knight

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# Fanconi Anemia: Guidelines for Diagnosis and Management

Fourth Edition • 2014

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These guidelines for the clinical care of Fanconi anemia (FA) were developed at a conference held April 5-6, 2013 in Herndon, VA. We owe a tremendous debt of gratitude to Eva Guinan, MD, for serving as moderator of the conference, as she did for the consensus conferences for the first three editions, and for her skill in helping the participants arrive at consensus.

We would like to thank all the participants for donating their time and expertise to develop these guidelines. The names and contact information of all participants appear in the Appendix.

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# Fanconi Anemia

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The **Fanconi Anemia Research Fund, Inc.**, was founded in 1989 to provide support to FA families and to raise money for scientific research. The Fund publishes a newsletter twice a year, sponsors an annual family meeting and a meeting for adults with FA every 18 months, and provides resource identification and counseling support to families. To aid research into FA, the Fund gives grants to scientists and sponsors scientific conferences, including an annual scientific symposium.

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# Introduction

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*Fanconi Anemia: Guidelines for Diagnosis and Management*, Fourth Edition, is the result of a Consensus Conference held by the Fanconi Anemia Research Fund in Herndon, Va., April 5-6, 2013. It replaces earlier editions published in 1999, 2003, and 2008. These guidelines are published for physicians who provide care for FA patients, and for patients and families who wish to secure optimal treatment by improving their understanding of all facets of Fanconi anemia, medical consultation, and appropriate referral.

These guidelines begin with detailed information on diagnosis and evaluation of FA. Subsequent chapters examine more specific health issues faced by persons with FA, followed by two chapters on psychosocial considerations that bear upon the well-being of the person with FA and his or her extended family. The guidelines conclude with a comprehensive checklist and diagnostic criteria for physicians and medical specialists.

Where possible, the guidelines rely on evidence-based medicine. Where adequate data are lacking because of limitations of numbers, time frame, or present knowledge, the consensus of expert opinion underlies the recommendations. Every effort has been made to give fair voice to discordant medical opinions when evidence is lacking and controversy exists. All chapters have been peer-reviewed and describe best practices as of the date of publication. To avoid being excessively prescriptive, the title of this book was changed in our last edition from “Standards” to “Guidelines.” From the discussions at this and earlier Consensus Conferences, the authors realize that a more robust clinical database must be developed to gather additional evidence upon which to base recommendations.

FA-related science has significantly advanced since the last publication in 2008:

- At least 16 FA genes now have been identified. The understanding of interactions among molecular pathways has become increasingly complex and sophisticated. Genotype determination and mutation analysis for each

patient bear directly on the appropriateness of some treatment choices and it is anticipated that this information will become increasingly relevant to patient care.

- Phenotypic and genotypic predictors of the natural history and outcome of the disease are beginning to emerge. As the costs of full genomic analyses continue to fall, we may expect the development of even more specific and powerful methods of diagnosis and, hopefully, therapy.
- The identification of *BRCA2* and other FA genes linked to breast cancer susceptibility has brought an influx of new scientific talent and interest to the field of FA research. The relevance of these findings to heterozygotes (carriers) is being evaluated.
- A growing cohort of post-transplant adult FA survivors presents new medical surveillance and treatment issues that include the unknown issues of aging with underlying FA, the pitfalls of pharmaceuticals commonly used in adult medicine in persons with FA, and the common presentation of anticipated post-transplant complications with the unknowns of alternative presentations and treatment tolerance in individuals with FA.
- With increased longevity for patients with FA the management of transfusion-acquired iron overload requires serious consideration.
- A series of major scientific publications on the role of aldehydes in FA has markedly changed the focus of research inquiry and therapeutic strategy in very recent years. These discoveries bear not only on the on-going debate as to whether DNA damage is the primary biological mechanism underlying FA disease pathology, but suggest that attention be turned to understanding the relevance of limiting exposure of persons with FA to exogenous and endogenous aldehydes, including alcohol. Finally, this rapidly developing research has inspired development of new small molecule therapies and other forms of intervention that might lessen damage to FA stem cells, suppress malignant transformation, or both.
- The availability of pre-implantation genetic diagnosis (PGD) for FA and for HLA determination provides a potential parental choice for securing a HLA-matched umbilical cord stem cell transplantation.
- Evaluation of adult FA patients reveals a striking and ominous incidence of squamous cell carcinomas (SCC), especially of the head and neck and gynecological tract. This underscores the need for continuous monitoring and more effective treatment options throughout the patient's lifetime.

## General Considerations

As was true of earlier occasions, the Consensus Conference was guided by the following general considerations that form the underlying basis for more specific recommendations.

### **FA is a very rare genetic disorder.**

- Accuracy in diagnosis is crucial and requires sophisticated expertise.
- The mode of inheritance is important for further genetic testing of siblings; finding matched donors; identification of genotype for purpose of predicting onset of symptoms and consequences; family planning (including PGD); selection of appropriate persons for FA gene therapy trials; and genetic counseling to the family.
- Expertise in FA treatment is highly specialized and to date is heavily concentrated in a few, critically important centers. Many persons with FA do not have access to such expertise locally, but the use of referral networks and provider cooperation should help provide adequate care.

### **FA is a complex and chronic disorder.**

- Well-orchestrated multi-disciplinary care across several medical and surgical specialties is typically required for adequate monitoring and treatment.
- Clinical trials or at least the collection of longitudinal data are required to inform treatment choices for patients with FA in the future.
- The transition from pediatric to adult care, and from parent monitoring to self-care, presents particularly important challenges which require thoughtful management.

### **FA must be considered a multi-system disease.**

- The name of the disorder, Fanconi anemia, may dissuade both doctors and patients because the hematologic manifestations of FA are not the sole (or often even the most important) problem for persons with FA.
- The FA phenotype is quite variable and leads to misdiagnosis and failure of diagnosis. Monitoring must be multi-disciplinary and include hearing evaluation, assessment of endocrine system and GI tract issues, and long-term cancer surveillance.
- For the majority of persons with FA, hematopoietic stem cell transplantation is the ultimate therapy for marrow dysfunction.

Consequently, early involvement with a major transplant center experienced in FA transplants and with a multi-disciplinary consultation team is optimal.

**FA is a cancer-prone disorder.**

- Close monitoring, especially for the high incidence of SCC, is a special consideration throughout the FA person's lifetime, even post-transplant.
- The intrinsic genetic instability of FA cells means that exposure to ionizing radiation, environmental carcinogens, and chemotherapeutic agents likely poses special risks to persons with FA. Consequently, diagnostic x-ray exposure and some otherwise routine medical tests or agents may need to be limited, or used with great caution. Thus, lifestyle choices such as tobacco and alcohol use may well have serious adverse consequences, even beyond those encountered in the general population.

**FA is a psychosocially demanding disorder.**

- The pressures on patients, parents, and siblings over an extended time can be overwhelming, particularly where there are multiple affected family members.
- Persons with FA, their families, and providers must be sensitive to issues of expense, the sophistication and availability of medical and family counseling, and the significant and continuing emotional trauma resulting from this diagnosis.
- FA adults experience quite distinct issues, and their psychosocial concerns are emerging as a distinct field of inquiry.

**The underlying diagnosis and the many drugs often necessary for treatment may put FA patients at particular risk for hazardous pharmaceutical cross-reactions.**

- The family and primary physician must continuously coordinate and monitor both prescribed and over-the-counter medications taken by a patient.

**The authors recognize that a significant proportion of affected families seek out and utilize “alternative” medicine.**

- We accept this approach, but at the same time ask families to be open with their providers in discussing what alternative practices they are using. Effective therapies may emerge and need to be shared. However, we also caution that unforeseen toxicities and drug interactions need to be identified.

We commend these guidelines in the profound hope that they will better serve the lives of patients who have this serious and life-threatening disorder. We welcome comments that may inform future improvements in care and treatment.

On behalf of the Fanconi Anemia Research Fund, we extend profound thanks to the many authors and editors who contributed to this work. Our special gratitude goes to those persons with FA, and their families. The toll of this affliction inspires our efforts, and their fervent hope for a cure motivates the urgency of our collective work. Finally, the remarkable progress in understanding FA biology buoys our optimism for ever-improving clinical outcomes.

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# Chapter 1: Diagnosis and Evaluation

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## Note

This chapter is divided into two sections. The **Scientific Background** section uses technical language to effectively describe the genetics and biochemistry of FA to scientists and clinicians. The **Diagnosis** section is geared towards clinicians and families.

## Introduction

Fanconi anemia (FA) is primarily inherited as an autosomal recessive disorder, though about 2% of all cases (1 of 16 known genotypes) are inherited as an X-linked recessive condition.

This chapter will explore the underlying molecular and genetic processes by which FA contributes to conditions such as bone marrow failure, leukemia, squamous cell carcinoma, endocrine abnormalities, and mild-to-severe birth defects<sup>(1-3)</sup>. In general, these conditions arise from genetic mutations that cause chromosome instability and reduce the cell's ability to repair damage to DNA. At publication, FA-associated mutations have been identified in 16 genes. A few patients with FA do not have mutations in the known genes; thus, more genes likely await discovery.

The oft-cited estimate of an FA carrier frequency of 1 in 300 was recently revised to be 1 in 181 for North America and 1 in 93 for Israel. Specific populations have founder mutations with increased carrier frequencies (less than 1 per 100), including Ashkenazi Jews (*FANCC*, *BRCA2/FANCD1*), northern Europeans (*FANCC*), Afrikaners (*FANCA*), sub-Saharan Blacks (*FANCG*), and Spanish Gypsies (*FANCA*) and others as detailed in *Chapter 17*<sup>(4)</sup>.

## Scientific Background

### FA genes and the DNA damage response pathway

The products of at least 16 FA-associated genes interact in a unified response that unfolds in the cell after exposure to DNA damage, i.e., a “DNA damage

response pathway” (Figure 1 and Table 1) <sup>(5-7)</sup>. As this pathway includes the two main breast cancer-associated genes, *BRCAl* and *BRCA2/FANCD1*, it will be referred to here as the FA/BRCA pathway.

## Helpful Words and Phrases

**Genotype** refers to a specific set of variations in genes or the genetic makeup. It can also be used to describe a particular cancer.

An **autosomal recessive** disorder shows up clinically when a person inherits two copies of an abnormal gene: one copy from the mother and another from the father. It’s **recessive** because the person must inherit both copies to develop the condition. The affected gene is located on one of the chromosomes numbered 1-22, which are known as **autosomes**.

An **X-linked recessive** condition means that females must inherit two copies of an abnormal gene for the disease to develop, whereas males need only inherit one copy. That is because males have one X chromosome; females have two.

The **carrier frequency** is the proportion of individuals who carry in their DNA a single copy of an abnormal gene for an autosomal recessive disorder. Carriers usually do not develop the disorder, but can pass a copy of the abnormal gene onto their children.

A **founder mutation** is a genetic change that is present in a population over several generations.

**Biallelic mutations** are genetic changes found in both copies (alleles) of the same gene.

**Hypomorphic mutations** are changes that cause the gene product to only lose partial function.

Because each patient generally has just one FA gene containing biallelic mutations <sup>(1)</sup>, patients can be assigned to complementation groups FA-A to FA-Q. These groups are defined by the absence of a normal gene product in the cells, even if the specific mutation(s) in that gene is/are not known. In 2013, the first patient (female) was reported with biallelic mutations in the *BRCAl* gene, which plays an important role in DNA repair and has been heavily associated with breast and ovarian cancer susceptibility. This patient had one hypomorphic missense mutation (known as p.Val1736Ala), and exhibited short

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1 With one notable exception: There has been a single published report of a *FANCM* patient who also has two germ-line mutations in *FANCA* <sup>(8)</sup>.

stature, microcephaly (an abnormally small head), developmental delay, early-onset ovarian cancer, and significant toxicity from chemotherapy. Nonetheless, though *BRCA1* is an essential part of the FA/BRCA pathway, it is currently not considered to be a true FA gene <sup>(9)</sup>.

A simplified model for the roles of the FA proteins in the DNA damage response to interstrand cross-links at stalled replication forks is shown in Figure 1 (for reviews, see <sup>5, 10-12</sup>). After FANCM and the FA-associated protein FAAP24 detect the DNA damage, the proteins produced from eight FA genes (*FANCA/B/C/E/F/G/L/M*) form the FA core complex, which facilitates activation of the pathway by monoubiquitination of the FANCD2 and FANCI proteins. These two activated proteins bind to form a dimer (ID2), which stabilizes the stalled replication fork and then in turn interacts in nuclear repair foci with the downstream FA gene products in the FA/BRCA DNA damage repair pathway. Damage repair is then achieved by the late FA proteins in cooperation with proteins from other DNA repair pathways (not shown in Figure 1). The FA/BRCA pathway has been elucidated almost in its entirety through the study of FA genetics and by biochemical studies in FA cells. In addition, germ-line (heritable) mutations in at least six of the downstream FA genes, *FANCD1/BRCA2*, *FANCI/BRIP1*, *FANCN/PALB2*, *FANCO/RAD51C*, *FANCP/SLX4*, and *FANCF/XPF*, have been associated with breast/ovarian, pancreatic, and other cancers in heterozygote individuals. In these individuals, loss of the second, wild-type allele occurs during their lifetime in a somatic (nonreproductive) cell and subsequently leads to malignant (cancerous) transformation <sup>(13-15)</sup>.

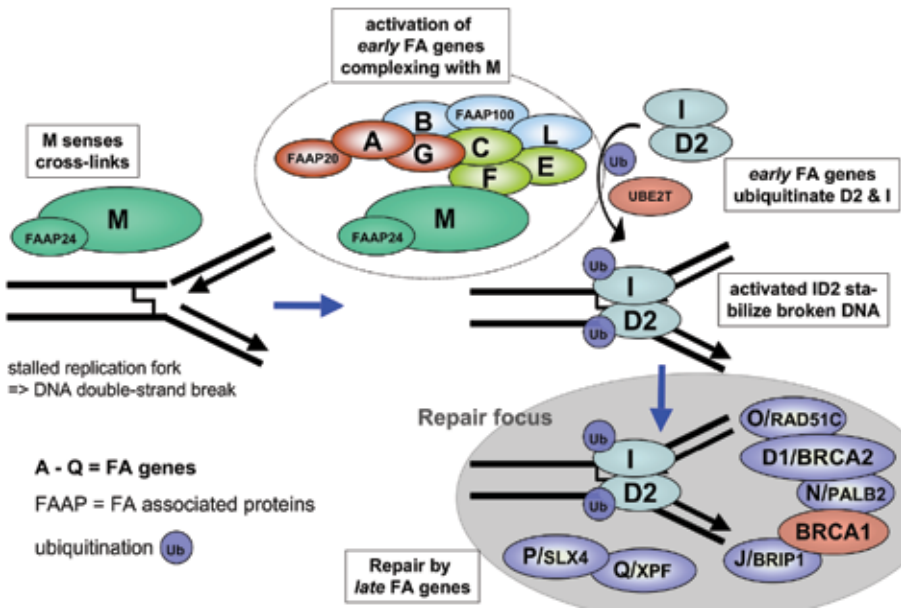
## Good to Know

DNA forms a double-helix structure that looks like a twisted rope ladder. When this ladder is unwound so that it can be copied to make additional ladders, it forms a Y-shaped area called a **replication fork**.

The replication process can be interrupted by cross-links, which occur when another molecule binds to two positions on the same side of the ladder (**intrastrand cross-links**) or on opposite sides of the ladder (**interstrand cross-links**).

Two cross-linking chemicals used in screening tests for FA are mitomycin C (MMC) and diepoxybutane (DEB).



**Figure 1.** DNA damage response pathway, linking the FA and BRCA pathways.

## Complementation Groups

Historically, a **complementation group** is defined by a “reference cell line” (i.e., a lineage of laboratory-grown cells with a well-studied genotype) that is not functionally corrected by fusion with other cells of the same complementation group, because both cells have defects in the same recessive gene(s) and therefore cannot “complement” (i.e., correct) each other.

Cells from patients with FA can be classified into sub-categories known as **complementation groups** without knowing which defective genes or DNA mutations the patient carries. This can be done by fusing the patient’s cells with the reference cells for a particular complementation group, or by expressing a normal (“wild-type”) cDNA for the specific gene that defines the complementation group. This is usually performed in a laboratory using viral or plasmid vectors.

Each complementation group is defined by the defect(s) in both alleles, or copies, of a particular FA gene. That is, individuals who belong to FA complementation group A (known as FA-A) have at least one loss-of-function mutation in each allele of the *FANCA* gene, whereas individuals who belong to complementation group B (FA-B) have a mutation in the X-chromosomal *FANCB* gene. With the exception of *FANCB*, patients belonging to the same complementation group are therefore said to have “biallelic recessive mutations” in the same FA gene.

**Table 1.** Fanconi anemia genes and gene products.

Gene	Locus	Genomic DNA kB	cDNA kB	No. of Exons	Protein kD	Amino Acids	Approximate % of Patients	Genetics
<i>FANCA</i>	16q24.3	80	5.5	43	163	1455	60	AR
<i>FANCB</i>	Xp22.31	30	2.8	10	95	859	2	XLR
<i>FANCC</i>	9q22.3	219	4.6	14	63	558	14	AR
<i>FANCD1 (BRCA2)</i>	13q12.3	70	11.4	27	380	3418	3	AR
<i>FANCD2</i>	3p25.3	75	5	44	162	1451	3	AR
<i>FANCE</i>	6p21.3	15	2.5	10	60	536	1	AR
<i>FANCF</i>	11p15	3	1.3	1	42	374	2	AR
<i>FANCG (XRCC9)</i>	9p13	6	2.5	14	70	622	9	AR
<i>FANCI (KIAA1794)</i>	15q25-26	73	4.5	38	150	1328	1	AR
<i>FANCL (BRIP1)</i>	17q22.3	180	4.5	20	150	1249	3	AR
<i>FANCL (PHF9/POG)</i>	2p16.1	82	1.7	14	43	375	<1	AR
<i>FANCM (Hef)</i>	14q21.3	250	6.5	22	250	2014	<1	AR
<i>FANCN (PALB2)</i>	16p12.1	38	3.5	13	130	1186	<1	AR
<i>FANCO (RAD51C)</i>	17q25.1	42	1.3	9	42	376	<1	AR
<i>FANCP (SLX4)</i>	16p13.3	26.6	5.5	15	200	1834	<1	AR
<i>FANCQ (XPF/ERCC4)</i>	16p13.12	39.2	6.8	11	104	916	<1	AR

## Good to Know

A **heterozygote** individual is a person who carries two different copies of a gene: one normal copy and one mutated copy. **Wild-type** refers to the natural, non-mutated copy of a gene.

**Complementation analysis by somatic cell methods** refers to the study of a patient's nonreproductive cells to determine to which complementation group (defined by a single FA gene) the patient might belong.

**Flow cytometry** is a laboratory technique in which single cells in solution are used to diagnose blood cancers and other conditions. This technique can separate, count, and evaluate cells with distinct characteristics.

A **Western blot** is a laboratory technique that allows identification of proteins in cell extracts based on their size and movement in an electric field.

### Scientific techniques used for diagnostics

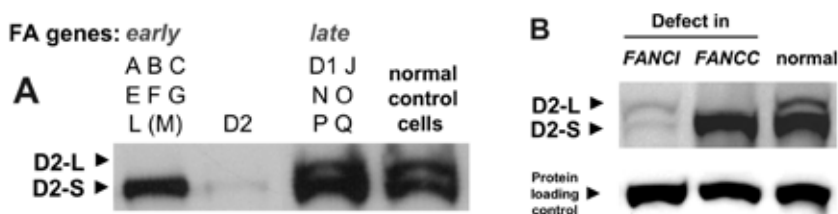
Although next-generation sequencing is currently available as a standard routine diagnostic procedure for patients in most developed countries (discussed in detail in *Chapter 2*), complementation analysis by somatic cell methods has been the mainstay for distinguishing specific genetic lesions/complementation groups and is still used in a number of countries. In this technique, cells from an FA patient are tested by various methods in culture to identify the gene that corrects the FA cell's hypersensitivity to DNA damaging agents. Initially, this was done by fusing FA cells possessing unknown defects with reference cells from patients possessing a known FA gene defect or defined complementation groups, resulting in hybrid cells in which the unknown FA cells grew normally if they were corrected (or "complemented") with the known FA genes <sup>(5)</sup>.

A more modern method—the only one clinically-certified in the U.S. (albeit used both clinically and in research worldwide)—is the transduction/infection of the unknown FA cells with retroviral vectors expressing normal wild-type FA proteins <sup>(16)</sup>. The patient cells can be either Epstein-Barr virus-transformed lymphoblast cell lines, primary or transformed skin or bone marrow fibroblasts, or primary T-cells from peripheral blood or bone marrow. Read-out of the retroviral complementation analysis can be any type of cellular or biochemical assay. The clinically-certified approach uses flow cytometry to determine correction of G2/M arrest in cells treated with DNA-damaging agents <sup>(17)</sup>. Each retrovirus contains only one of the FA genes. While the early FA genes

(*FANCA*, -*B*, -*C*, -*E*, -*F*, -*G*, and -*L*, though not -*M*) are easier to express, vectors also exist for the other genes and have been used for research purposes.

Alternatively, or if correction does not occur with these vectors, a Western blot can be performed to identify FANCD2 or mono-ubiquitinated FANCD2 protein and thus to determine whether the mutated FA gene is 1) upstream, which would involve the core complex needed for the ubiquitination of FANCI and FANCD2, or which would occur if *FANCD2* itself is mutated and absent; or 2) downstream, which would involve *FANCD1/BRCA2*, *FANCI/BRIP1*, *FANCN/PALB2*, *FANCO/RAD51C*, *FANCP/SLX4*, or *FANCD2/XPF* <sup>(18)</sup>. As shown in Figure 2A, mutations in the FA core complex early genes lead to a single band of FANCD2 protein (D2-S = short), while mutations in the late FA genes are associated with normal monoubiquitination of FANCD2 and therefore have both the D2-L (= long) and the D2-S bands. Here, the classification of a patient as having defects in a late FA gene can be based on the hypersensitivity of cells in the chromosomal breakage test after crosslinker exposure and the normal FANCD2 Western blot. At least one of the mutations in *FANCD2* patients is hypomorphic and associated with residual protein function <sup>(19)</sup>. Therefore, residual FANCD2 protein can be detected in Western blots of all *FANCD2* patient cells using longer exposures. Defects in FANCI are associated with reduced FANCD2 protein levels <sup>(20)</sup>, albeit monoubiquitination of the residual FANCD2 protein can be detected (Figure 2B).

**Figure 2.** FANCD2 Western blots for identifying the defect in the FA/BRCA pathway.



Any of these complementation group analyses should be confirmed for clinical purposes and for genotype-phenotype correlations by finding the mutation(s) in the FA gene identified in these studies and confirming the complementation group.

# Diagnosis

## Diagnostic screening

### Good to Know

**Hematopoietic stem cells** are unique blood cells found in the bone marrow and umbilical cord. These cells are immortal based on their ability for self-renewal and can develop into any of the various types of blood cells found in the body.

In a person with **somatic hematopoietic mosaicism**, some cells in the blood system are genetically different from others. In FA, mosaicism is mainly used to describe cells where a spontaneous mutation reverts the defective FA gene back to the normal DNA sequence, either in stem cells or in T-lymphocytes.

The experience of hematologists familiar with FA suggests that while most individuals with the condition present early in life, a significant number of patients present beyond childhood. They may have been undiagnosed or misdiagnosed, and may not have been diagnosed until they presented with leukemia or a solid tumor or even as a “normal” stem cell transplant donor. For some patients, somatic hematopoietic mosaicism may have resulted in a less severe hematologic phenotype masking the diagnosis. The imperative is to have an index of suspicion that will lead to an early diagnosis of FA in all patients. It is essential that prospective parents be given the opportunity and benefit of reproductive choices through genetic counseling to avoid the significant consequences of the failure to diagnosis FA in a timely fashion. Indeed, genetic counseling is crucial because of the 25% risk of FA in each subsequent pregnancy (50% for the X-linked *FANCB*). Without being judgmental or proscriptive, early diagnosis provides the opportunity for family planning, prenatal diagnosis, and preimplantation genetic diagnosis, if desired by the couple/family (for more information, see *Chapter 17*).

Currently there is no established preventative treatment option to delay or avoid the clinical manifestations of FA, especially the bone marrow failure or the development of malignancies. Nevertheless, there are several benefits to consider by an early/timely diagnosis, including:

- *Avoiding medical complications from unrecognized subtle congenital abnormalities*
- *Ending the diagnostic odyssey that significant numbers of patients experience*

- *Enabling appropriate monitoring and management of hematologic disease [aplastic anemia (AA), myelodysplastic syndrome (MDS), acute myeloid leukemia (AML)]*
- *Modifying radiation and chemotherapy protocols as needed to ameliorate the risk of severe side effects in patients where malignancies are the first clinical sign of FA*
- *Providing an opportunity to make life-style modifications to reduce risks (e.g., avoiding smoking, sunlight, alcohol exposure, or unhealthy workplace environments)*
- *Time to make family planning decisions in light of premature menopause and limited window of fertility*

For example, planned surgeries might be expedited so that they are completed before the development of significant cytopenias (i.e., abnormally low blood cell counts). Physicians can also offer targeted and intensified cancer surveillance, and early extensive surgery for solid tumors and thus avoid unnecessary and incrementally toxic chemo- and radiation therapy. In addition, experts can discuss a realistic prognosis prior to the onset of predictable adverse events. Early diagnosis also allows the patient time to consider the appropriate use of therapeutic options, including hematopoietic stem cell transplantation, androgens, hematopoietic growth factors, or supportive care while minimizing iron overload from red blood cell transfusions. Finally, the mutations can be identified prior to the next pregnancy in the family, thus giving parents time to consider their options.

## Good to Know

**The chromosome breakage (fragility) test** is often the first test to diagnose a patient with FA. This test measures the types and rates of breakages and rearrangements found in the chromosomes of cells after challenge with DNA cross-linking agents. It also reveals how well the chromosomes can repair themselves after injury.

The tests noted here (e.g., chromosome breakage testing, mutation analysis) are described in more detail in Chapter 2, which also includes an algorithm for the laboratory diagnosis of FA. Generally speaking, the chromosome breakage test using peripheral blood T-lymphocytes is the accepted screening assay for FA. Primary skin fibroblasts have also been used as a readily available screening alternative, particularly if the T-cell analyses are ambiguous or

do not give a clear result that the patient has FA, especially when there is a question of mosaicism. The cross-linking agents mitomycin C (MMC) and/or diepoxybutane (DEB; due to its toxicity as a carcinogen, DEB is not available everywhere) are used to induce chromosome breakage, and FA cells are more sensitive than normal cells to these agents. Either or both agents are acceptable, as described in *Chapter 2*.

However, it is important to note that although a “diagnosis” of FA can be made by using a chromosome breakage assay as a screening method, this alone may lead to some confusion, as other genetic conditions can be associated with hypersensitivity, albeit less severe, to these agents. These genetic conditions, including Nijmegen breakage syndrome, are listed in *Chapter 2*, Table 1. Several important reasons for patients and families to identify the mutations in the affected FA gene are described in Table 2. A more detailed description of genetic counseling for FA is provided in *Chapter 17*.

**Table 2.** The benefits of genetic counseling and/or mutation identification.

Genetic Counseling and/or Mutation Identification
<p>For the current patient</p> <ul style="list-style-type: none"> <li>• Understand appearance and consequences (genotype/phenotype)</li> <li>• Suggest complications and provide nuanced discussion of therapeutic alternatives (genotype/outcome)</li> <li>• Commence regular clinical review and surveillance</li> <li>• Confirm a sibling stem cell transplantation (SCT) donor does not have FA</li> </ul>
<p>For current family members</p> <ul style="list-style-type: none"> <li>• Identify undiagnosed affected siblings, who could be considered as SCT donors, and who need genetic counseling and surveillance for complications of FA</li> <li>• Identify carriers at risk for healthcare consequences, including cancer (e.g., Ashkenazi Jewish <i>FANCC</i> IVS5+4 A&gt;T, <i>FANCD1/BRCA2</i>, <i>FANCI/BRIP1</i>, <i>FANCN/PALB2</i>, <i>FANCO/RAD51C</i>, <i>FANCP/SLX4</i>, and <i>FANCG/XPF</i> mutations)</li> </ul>
<p>For future children in the family</p> <ul style="list-style-type: none"> <li>• Prenatal diagnosis of an established pregnancy</li> <li>• In vitro fertilization (IVF) and preimplantation genetic diagnosis (PGD) to create an unaffected child or identify an HLA-matched, unaffected sibling hematopoietic stem cell donor</li> </ul>

Advances in molecular diagnostics coupled with reliable clinical information now permit genotype/phenotype correlations that can prove valuable in assisting the clinician with risk-appropriate care. New insights into the pathophysiology of FA and individual polymorphisms in detoxifying genes (e.g., aldehyde detoxification) <sup>(21)</sup> might be associated with better prognostic information and therapeutic options in the future.

### **Genotype/phenotype/outcome correlations**

Correlations between genotype and other features can include birth defects (physical phenotype), hematologic outcomes (hematopoietic phenotype), and development of cancer (malignant outcomes), as shown in Table 3. In general, null mutations lead to a more severe phenotype (e.g., congenital anomalies, early-onset bone marrow failure, and MDS/AML) compared with the phenotypes associated with hypomorphic mutations. In particular, lower rates of anomalies are associated with mutations in *FANCA* and *FANCC* c.67delG (=322delG) <sup>(22-25)</sup>. Early bone marrow failure occurs more frequently in patients with *FANCA* null, *B*, *C* IVS5+4A>T, *F*, *G*, and *D219,22-25* mutations, while AML is clearly associated with *FANCD1/BRCA2*, *FANCN/PALB2*, *FANCA* null, and maybe *FANCG* mutations <sup>(23, 25-28)</sup>. Comparing the phenotypic consequences of homozygous IVS5+4A>T *FANCC* mutations in the clinically severely affected Ashkenazi Jewish patients and in the mildly affected Japanese patients revealed that unknown ethnic factors also play an important role in the clinical manifestations of FA <sup>(22,24,25,29)</sup>. The most common solid tumors in FA are head and neck squamous cell carcinomas (HNSCC) and vulvar/vaginal SCC <sup>(25,30,31)</sup>. These tumors **appear** to be more frequent in patients with FA genotypes who do not succumb to early death from bone marrow failure or AML, however, this may be due to a survival bias, rather than a genetic predisposition to these cancers. Specific additional solid tumors, most often medulloblastoma and Wilms tumor, are associated with mutations in *FANCD1/BRCA2* and *FANCN/PALB2* <sup>(27,28,32,33)</sup>. Table 3 will be expanded as more clinical data from large cohorts is linked to detailed genotypic information.



**Table 3.** Genotype/phenotype/outcome.\*

Gene	Congenital Anomalies	BMF	AML	Brain/ Wilms Tumors	References
<i>A null</i>	+	+	+		23,25
<i>A hypomorph</i>	Fewer	Later	Later		23
<i>B</i>	+	+			34-36
<i>C IVS5+4A&gt;T (former IVS4)</i>	+	+	+		22,24,29
<i>C c67delG</i>	Fewer	Later	Later		22,24,25,29
<i>E</i>	+				23,37
<i>F</i>	+	+			23,38
<i>G</i>		+	+		23,25
<i>L</i>	+	+			39,40
<i>D2</i>	+	+			19
<i>D1/BRCA2</i>	+++		+++	+++	25,26,32,33,41
<i>N/PALB2</i>	+++		+++	+	27,28

\*Includes genes with reasonably well-documented associations.

Abbreviations: BMF, bone marrow failure; AML, acute myeloid leukemia; +, those with a relatively increased frequency compared with other genotypes; +++, those with a very high frequency compared to other genotypes.

## Index of suspicion

The most frequent birth defects noted in patients with FA, in descending frequency from approximately 50 to 20%, include skin hyperpigmentation; hypopigmentation and café au lait spots; short stature; abnormal thumbs and radii; and abnormal head, eyes, kidneys, and ears. Although there is an inherent bias in anomalies featured in published case reports, the list of anomalies compiled in Table 4 is a helpful guide for evaluating a patient whose appearance suggests a diagnosis of FA. However, at least 25% of known FA patients have few or none of these features <sup>(25,42)</sup>.

Patients with FA may present with AA, MDS, single cytopenias, or macrocytic red cells without another explanation. A diagnosis of FA should be considered in all children and young adults with androgen-responsive or ATG/cyclosporine A-non-responsive “acquired” aplastic anemia. It is absolutely imperative to test for FA if a stem cell transplant is planned, as standard stem cell transplant

conditioning will result in significant morbidity and high mortality rates for patients with FA.

In addition, patients with FA are at a particularly high risk of developing specific solid tumors (e.g., head, neck, esophageal, and gynecological squamous cell carcinomas) as well as liver tumors, particularly in young patients without the usual viral or alcohol-related risk factors. Here, the role of human papillomavirus (HPV) infections as an additional risk factor in FA has not been unequivocally determined. However, numerous experiences with the two currently available HPV vaccines seem to indicate that vaccination is well tolerated in FA patients. This topic is discussed in detail in *Chapter 6*.

A diagnosis of FA must be considered and excluded in patients with MDS/AML, solid tumors, and other malignancies who experience excessive sensitivity to chemotherapy and/or radiotherapy. The presentation of specific cancers at an unusually young age and in patients who lack the usual risk factors for a specific type of cancer suggest the presence of genetic factors, such as FA, but also Li Fraumeni syndrome or other conditions, some of which are depicted in *Chapter 2*, Table 1. Somatic mosaicism in T-lymphocytes and even hematopoietic stem cells due to the reversion of an inherited mutation in an FA gene occurs in a minority of patients and should be considered in all young patients with the features described above. To reveal somatic mosaicism, DEB or MMC testing should then be performed using primary skin fibroblasts. The risk of head and neck squamous cell carcinoma is even higher in patients with FA who have received a bone marrow transplant, predominantly in those patients who experienced chronic graft-versus-host disease (GvHD) <sup>(43)</sup>. A significant number of patients with FA-associated cancers—approximately 25% of reported FA patients—were not aware that they had FA until they developed cancer (and/or significant complications from a standard cancer treatment) <sup>(30)</sup>. This finding substantiates the concern that older patients with FA may be significantly underdiagnosed. Table 4 provides a guide to determining which individuals should be screened for FA.

Often neglected, testing for FA should also be performed if spontaneous chromosome breaks are found during prenatal tests (e.g., chorionic villus sampling or amniocentesis), during the postnatal evaluation of genetic conditions, and possibly in males and females with unexplained infertility.

**Table 4.** Which patients should be evaluated for FA? <sup>1,2</sup>

Who?	Feature	Details
<b>ANY PATIENT</b>	Height	Short stature Microsomia
	Skin	Café au lait spots Skin pigmentation (hyper, hypo)
	Upper Limbs	<b>Radius:</b> absent, hypoplastic, absent or weak pulse <b>Thumb:</b> absent, hypoplastic, bifid, duplicated, rudimentary, attached by thread, triphalangeal, long, low set, digitized <b>Thenar-eminence:</b> flat, absent <b>Hand:</b> absent first metacarpal, clinodactyly, polydactyly <b>Ulna:</b> short, dysplastic
	Skeletal	<b>Head:</b> microcephaly, hydrocephaly <b>Face:</b> triangular, birdlike, dysmorphic, mid-face hypoplasia <b>Neck:</b> Sprengel, Klippel-Feil, short, low hairline, web <b>Spine:</b> spina bifida, scoliosis, hemivertebrae, coccygeal aplasia small, strabismus, epicanthal folds, hypotelorism, hypertelorism
	Eyes	Strabismus, cataracts, ptosis
	Renal	Horseshoe, ectopic, pelvic, hypoplastic, dysplastic, absent, hydronephrosis, hydroureter
	Gonads, male, urology	Hypogonitalia, undescended testis, hypospadias, micropenis, absent testis, infertility
	Gonads, female, gynecology	Hypogonitalia, bicornuate uterus, malposition, small ovaries, late menarche, early menopause, infertility
	Development	Mental retardation, developmental delay
	Ears	<b>Deafness:</b> conductive, sensorineural, mixed <b>Shape:</b> abnormal pinna, dysplastic, atretic, narrow canal, abnormal middle ear bones <b>Speech:</b> delayed, unclear
	Cardiopulmonary	<b>Congenital heart disease:</b> patent ductus arteriosus, atrial septal defect, ventricular septal defect, coarctation, situs inversus, truncus arteriosus
	Low birth weight	

Table 4 continued on next page.

*Fanconi Anemia: Guidelines for Diagnosis and Management*

Who?	Feature	Details
	Lower limbs	<b>Hips:</b> congenital hip dislocation <b>Feet:</b> toe syndactyly, abnormal toes, club feet
	Gastrointestinal	<b>Tracheoesophageal fistula</b> <b>atresia:</b> esophagus, duodenum, jejunum, imperforate anus, annular pancreas Malrotation Poor feeding
	Central nervous system	<b>Pituitary:</b> small, stalk interruption <b>Structure:</b> absent corpus callosum, cerebellar hypoplasia, hydrocephalus, dilated ventricles
<b>FAMILY HISTORY</b>	Any suspicion or patient	
<b>VACTERL-H</b>	Any patient	Especially if both radial ray and renal anomalies are present
<b>HEMATOLOGY</b>	Aplastic anemia	Any patient
	Acute myeloid leukemia	
	Myelodysplastic syndrome	
<b>TUMORS</b>	Head and neck SCC	"Young" - less than 50 years old
	Vulvar/vaginal SCC	
	Cervical SCC	
	Esophageal SCC	
	Brain Tumor	Midline, medulloblastoma
	Wilms tumor	
	Neuroblastoma	
	Retinoblastoma	
<b>SIBLING OR CHILD OF FA PATIENT</b>		
<b>CYTOGENETICS</b>	Abnormal chromosome tests (e.g., breaks) without DNA crosslinker in study done for non-FA purpose	

**IMPORTANT NOTE:** Any combination of the above should raise the level of suspicion and lead to peripheral blood testing for FA.

## Acknowledgments

We would like to thank the patients with FA, families, and family support groups worldwide for supporting our work in FA. We apologize to all our colleagues that we could not include or cite in this chapter. The guidelines presented here are the result of our combined experiences in these highly diverse patients and the lessons that our patients have taught us. Based on the complexity and diversity of the disease, we have tried to give a general overview; however, we are aware that there is really no standard patient with FA and the clinical care is really a team effort of many, including the patients and their families, the doctors, nurses and other personnel, and the colleagues in the different medical departments for diagnostic and therapeutic processes.

## Chapter Committee

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# Chapter 2: Laboratory Diagnostics

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## Introduction

### Good to Know

**United States:** The Clinical Laboratory Improvement Amendments (CLIA) and the College of American Pathologists (CAP) provide laboratory certification and accreditation. The American College of Medical Genetics (ACMG) provides detailed guidelines for genetic testing.

**Canada:** The Ontario Laboratory Accreditation and the Canadian College of Medical Genetics (CCMG) provide laboratory oversight and guidelines, respectively.

**Europe:** Recognized accreditation bodies include the Belgian Accreditation Council (BELAC), the French Accreditation Committee (COFRAC), the German Accreditation Council (DAkkS), the Swiss Accreditation Service (SAS), and the United Kingdom Accreditation Service (UKAS).

Any physician who suspects that a patient may have Fanconi anemia (FA) should refer the patient to a hematologist and/or geneticist, who can arrange for diagnostic testing. The laboratory should be accredited and certified to perform FA testing for clinical care, and should have evaluated many patients with and without FA. Evaluating a large number of patients enables a laboratory to validate its FA testing procedures, and to establish ranges for normal and abnormal test results. The recommended testing procedures are outlined in the flow chart in Figure 1.

This chapter will describe three types of analyses that are commonly used in the diagnosis of FA:

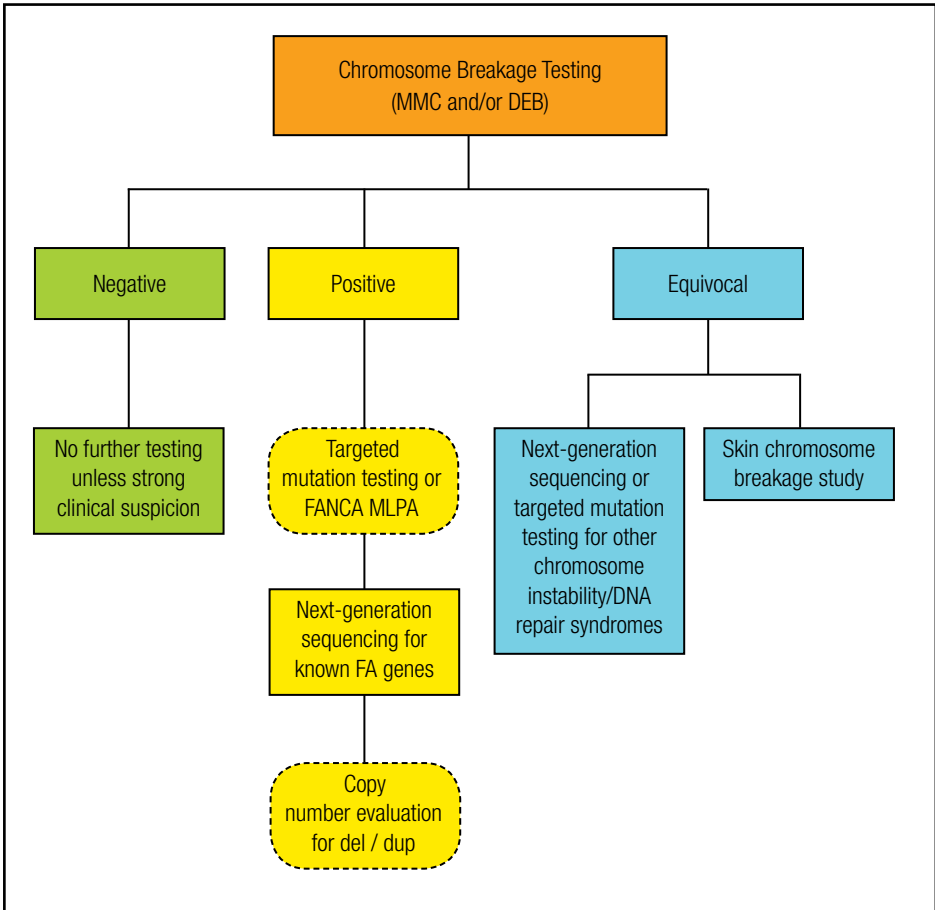
- *Chromosome breakage tests*
- *Mutation analyses*
- *Bone marrow chromosome analyses*

# Test 1: Chromosome Breakage in Peripheral Blood Lymphocytes

## Chromosome breakage test

The first test that should be used to diagnose FA is the chromosome breakage test, which is performed on a sample of the patient’s blood in a clinical cytogenetics laboratory. The initial step involves culturing a sample of the patient’s blood with a chemical substance known as a T-cell mitogen, which stimulates lymphocytes (a type of white blood cell) to divide. Next, the culture is treated with chemicals known as DNA cross-linking agents, such as mitomycin C (MMC) and/or diepoxybutane (DEB). Finally, the types and rates of breakages and rearrangements found in the chromosomes of cells are

Figure 1. Flow chart for FA-related laboratory tests.



evaluated<sup>(1, 2)</sup>. Normal cells can correct most of the chromosomal damage caused by the DNA cross-linking agents, whereas cells from patients with FA typically show multiple chromosomal breaks and rearrangements per cell, including complex rearrangements such as radial figures. As detailed by the American College of Medical Genetics guidelines for cytogenetic laboratories, the test results report should include the breakage and rearrangement rates, as well as the distribution of chromosomal breakage among cells or the average number of aberrations per cell with and without radial figures. Further, all tests should include at least two independent cultures (e.g., samples treated with different concentrations of MMC, or one sample treated with MMC and the second with DEB, or another relevant combination) to show that the results are reliable. Because some patients' specimens will have very low white blood cell counts, it may not be possible to set up two cultures for a given test. In such cases, a second specimen should be obtained from the patient, if possible, to confirm the findings obtained from the first culture.

The laboratory should also obtain measures of baseline chromosome breakage by evaluating cells that have not been treated with MMC and/or DEB. These findings may help to guide the follow-up molecular testing, because the measurements of baseline breakage can vary markedly among the various complementation groups. For example, patients with mutations in the *FANCD1* gene have very high levels of baseline breakage and unusual constellations of abnormalities compared with other groups of patients with FA<sup>(3)</sup>. The baseline breakage may also aid the differential diagnosis of other chromosome instability disorders that display specific types of chromosomal abnormalities, such as rearrangements of chromosomes 7 and/or 14, which commonly occur in ataxia-telangiectasia and Nijmegen breakage syndrome; telomeric rearrangements, which often occur in dyskeratosis congenita; and railroad figures and premature centromere separation, both of which are characteristic of Roberts syndrome<sup>(4, 5)</sup>.

### **Cell cycle analysis in peripheral blood lymphocytes**

MMC- and/or DEB-induced chromosome breakage analysis is the most common first-line test for the diagnosis of FA. However, a few laboratories diagnose FA by measuring cell cycle kinetics, rather than chromosome breakage, in peripheral blood lymphocytes treated with mitogen and DNA cross-linking agents<sup>(6, 7)</sup>. Normal lymphocytes that do not have any DNA damage will progress through all the normal phases of the cell cycle [the phases are Gap1 (G1)-> DNA Synthesis (S)-> Gap 2 (G2)-> Mitosis (M)]

without significant delay. However, cells that have DNA damage will stop at the G2 phase of the cycle to repair the damage before they progress to M. Because FA cells have more unrepaired damage after treatment with DNA crosslinking agents, a higher percentage of cells (generally 40% or more) from FA patients will be arrested during the G2 phase when compared to cells from individuals without FA. A flow cytometer instrument is used to measure the progression of the cells through the cell cycle and provide the percentage of cells arrested at G2. Some laboratories may use cell cycle analysis in conjunction with a chromosome breakage test. The principles and flow chart delineated for the chromosome breakage test should be applied to cell cycle analysis. Positive, negative, and equivocal results should be followed up as described for the chromosome breakage test results delineated in Figure 1.

### **Interpreting chromosome breakage test results**

**Positive:** A patient is considered to have a positive test for FA if the lymphocytes display markedly increased chromosomal breakage and rearrangement after treatment with MMC and/or DEB. Typically, more than 90% of the lymphocytes in the culture of blood derived from a patient with FA will show increased breakage, and the rates and types of breakage observed will fall within the abnormal range. In the event of a positive test result, the patient and his or her family should be referred to a genetic counselor, who can help coordinate the necessary follow-up testing and explain the test results to the family after the testing is completed (see *Chapter 17*). Importantly, follow-up testing should be performed to identify the patient's disease-causing genetic mutation(s) using the molecular methods described under "*Test 2: Mutation Analysis*." All of the patient's siblings should be tested for FA either by chromosome breakage analysis or, if his or her sibling's disease-causing gene mutation(s) have been identified, by mutation analysis<sup>(2)</sup>.

**Negative:** A test result is considered to be negative if the patient's lymphocytes do not show increased chromosomal breakage or rearrangement in response to MMC and/or DEB, and the types and rates of breakage are within the normal range. If the chromosome breakage test is negative and the clinical evidence that the patient may have FA is weak, no further studies are needed. By contrast, if the chromosome breakage test is negative but there is *strong* clinical evidence that the patient may have FA, then skin fibroblast testing should be performed to rule out the possibility of mosaicism as described below in the discussion of equivocal results. In addition, many disorders have some clinical features in common with FA and are associated with some form

of chromosome instability (Table 1). Therefore, patients who have a negative chromosome breakage test but have some of the clinical features of FA should undergo DNA sequencing that includes the genes implicated in FA as well as genes relevant to the conditions described in Table 1.

**Table 1.** Disorders that may share clinical features with FA and manifest with chromosome instability.

Disorder	Putative Genes Involved
Ataxia-telangiectasia	<i>ATM</i>
Ataxia-telangiectasia-like disorder	<i>MRE11</i>
Bloom syndrome	<i>BLM</i>
DNA ligase 4 syndrome	<i>LIG4</i>
Dubowitz syndrome	
Dyskeratosis congenita	<i>DKC1, TERT, TERC, WRAP53, NOP10, NHP2, TINF2, RTEL1, CTC1</i>
Nijmegen breakage syndrome	<i>NBN</i>
Nijmegen breakage syndrome-like disorder	<i>RAD50</i>
Roberts syndrome	<i>ESCO2</i>
Rothmund-Thomson syndrome	<i>RECQL4</i>
Seckel syndrome 1	<i>ATR</i>
Severe combined immunodeficiency	<i>NHEJ1</i>
Warsaw breakage syndrome	<i>DDX11</i>

**Equivocal:** Test results are considered equivocal, or inconclusive, if the percentage of cells that display chromosomal breakage patterns characteristic of FA is much lower than the laboratory typically sees for FA or if there is increased breakage but the pattern is not characteristic of FA. In general, there are two underlying causes of inconclusive test results:

- **Possibility #1:** *There is mosaicism in the patient's peripheral blood.*

Mosaicism is characterized by two distinct populations of lymphocytes in the blood. One population has normal sensitivity to DNA cross-linking agents due to a spontaneous correction of an FA mutation, while the other population is hypersensitive to DNA cross-linking agents due to the presence of FA mutations. Mosaicism can be diagnosed by sending a sample of the patient's skin, obtained via a skin biopsy, to a certified clinical cytogenetics laboratory, which can perform the chromosome

breakage test on fibroblast cells present in the skin sample. The diagnosis of FA can be confirmed by a chromosome breakage test that reveals increased breakage in the fibroblasts, with the types of breaks and rearrangements characteristic of FA. Mosaicism testing should be performed if the clinical evidence that the patient may have FA is strong, but the blood chromosome breakage test results were reported as negative or equivocal.

Approximately 10-20% of patients with FA have a form of mosaicism in which the fibroblast cultures show increased breakage, while the lymphocytes do not. The percentage of normal cells in the blood of these patients may range from less than 50% to 100%. Over time, a patient with a low percentage of normal cells may develop a high percentage of normal cells, and this process may be associated with spontaneous improvement in the patient's blood cell counts. However, the mosaicism measured in peripheral blood lymphocytes may not reflect mosaicism in the bone marrow cells. This means that a patient with a high percentage of normal cells in the tested lymphocytes may have no (or a very low percentage of) normal cells in his or her bone marrow. As the bone marrow cells are involved in the development of leukemia, their status should not be generalized from the lymphocyte results. It is not possible to directly test the bone marrow cells using the same chromosome breakage tests used for lymphocytes. Thus, it remains unclear whether the clinical course of the disease will be altered in patients who have normal cells in the peripheral blood. Importantly, the presence of mosaicism—either in the blood or bone marrow—does not protect the individual from the development of clonal chromosome abnormalities within the population of cells that retain their FA mutations. This, in turn, can lead to the development of hematologic malignancies and solid tumors.

- **Possibility #2:** *The patient has a condition other than FA that manifests with increased chromosomal breakage.*

Depending on the pattern of breakage and the clinical findings, the patient may have a condition other than FA that is associated with chromosome instability, such as Nijmegen breakage syndrome, ataxia-telangiectasia, ataxia-telangiectasia-like disorder, DNA ligase 4 syndrome, Seckel syndrome 1, Bloom syndrome, dyskeratosis congenita, Roberts syndrome, Warsaw breakage syndrome, Cornelia de Lange syndrome, or FAN1 deficiency.



Because most of the gene mutations that cause these conditions have been identified, molecular testing can be performed to establish the diagnosis.

## Test 2: Mutation Analysis

If the results from the chromosome breakage test are positive, then mutation analysis should be performed to identify the specific genetic mutation that has caused the patient to develop FA. Identifying the mutation is valuable for the following reasons:

- It enables mutation-specific testing of family members, and permits the accurate diagnosis of individuals who have only one mutated copy of a FA gene (e.g., the parents of FA patients) and who do not have the clinical findings of FA, as well as the diagnosis of individuals who have two mutated copies of a FA gene (e.g., the patients) and manifest, or will be expected to manifest, the clinical findings of FA. This information allows for appropriate medical management and focused genetic counseling.
- It can be used for premarital screening, prenatal diagnosis, and preimplantation genetic diagnosis.
- It aids the accurate genotyping of potential bone marrow donors, such as siblings who do not appear to have FA, so that any individuals who have undiagnosed FA will not be used as donors.
- It enables patients who are clinically well to be monitored closely for the potential development of aplastic anemia, myelodysplastic syndrome, leukemia, or solid tumors.
- It provides information that determines a patient's future prospects for pharmacologic or gene therapies.

### Genetic mutations in patients with FA

Researchers are just beginning to identify the associations between certain FA gene mutations and the physical abnormalities and bone marrow disease that they cause (see *Chapter 1*, Table 3). The most severe physical defects, which sometimes include features of VACTERL-H syndrome, are most frequently reported in patients with mutations in the following genes: *FANCC* (specifically, the IVS4+4 A > T mutation), *FANCD1/BRCA2*, *FANCD2*, *FANCG*, *FANCI*, and *FANCN/PALB2*. An early onset of aplastic anemia has been reported for *FANCC* (specifically the IVS4 mutation in Ashkenazi Jewish patients) and *FANCG* has been associated with more severe aplastic anemia and increased incidence of leukemia. Patients with mutations in *FANCD1/BRCA2*

and *FANCN/PALB2* tend to develop leukemia, or solid tumors (particularly medulloblastoma and Wilms' tumors) by age 5<sup>(21)</sup>. In general, null mutations, which result in the complete loss of a gene's normal function, are thought to be more severe than hypomorphic mutations, which result in a partial loss of a gene's function<sup>(8,9)</sup>. However, it was recently shown that this is not the case for *FANCA* mutations<sup>(22)</sup>. Researchers have concluded that other genetic and environmental factors influence the genotype-phenotype relationship. Two examples that illustrate this point are the observed variability in disease severity between siblings with the same *FANCA* mutations, and the much more severe disease that occurs in patients of Ashkenazi heritage who harbor the IVS4 mutation, compared with patients of Japanese heritage with the same mutation<sup>(23)</sup>.

Worldwide, the majority of patients with FA have mutations in the *FANCA* gene; several hundred different *FANCA* mutations have been documented. However, a limited number of specific mutations tend to be common in certain populations of people that have descended from a small group of founders (see Table 1 in *Chapter 17*). For patients and their families that belong to such populations, and for individuals with clinical findings and/or a family history of cancer associated with a particular mutation, analysis may begin with targeted tests for the specific suspected mutations. However, for most new diagnoses of FA, there will likely be no specific mutation that is suspected. Several strategies have been adapted by different laboratories to ensure that the testing maximizes the possibility of identifying the patient's mutations while at the same time minimizing costs and decreasing the amount of time it takes to get the test results. Gene sequencing is a critical component of these strategies.

### **Gene sequencing approaches**

Until recently, a genetic test known as complementation analysis, which involves somatic cell-based methods such as retroviral gene transfer, was the primary method available for determining which *FANCA* genes were mutated in a given patient. However, such complementation analysis is labor-intensive, expensive, and time-consuming. In the last few years, the development of next generation sequencing (NGS) methodology, also referred to as massively parallel sequencing, has transformed the field of genetic testing because it enables detailed analysis of thousands of genes simultaneously (i.e., in parallel). Such analyses would be too time-consuming and costly to attempt using classic DNA sequencing methodologies, such as Sanger sequencing, that analyze a single gene at a time. Many laboratories have developed targeted

panels of genes to be assessed by NGS to search for mutations among a group of genes that have been previously documented or have been suggested to be important in a particular disease. Such panels may include anywhere from a few genes to greater than 500. The number of genes examined varies from laboratory to laboratory depending on the testing platform and algorithm being used. An NGS approach that is more comprehensive than the sequencing of targeted panels of genes is known as whole-exome sequencing, which involves sequencing of all of the exons (segments of DNA that contain information needed to make proteins) of all known genes, representing approximately 2-3% of the human genome. An even more comprehensive NGS application is whole-genome sequencing, which involves analyzing the entire human genome. At the time of this writing, whole-genome sequencing is primarily limited to research studies. The high cost of such testing prohibits this from being used as a frontline testing tool at this time. However, sequencing technologies are rapidly evolving, and it is likely that by the time of publication of this chapter, there will be new methods and instrumentation being evaluated that not only improve sensitivity for detection of different types of mutations, but also increase efficiency and decrease cost. Multiple laboratories are now offering, or developing, NGS-based applications for FA testing and have targeted panels that include all 16 of the known FA genes<sup>(10)</sup>. Some panels also include genes that are known to be associated with other bone marrow failure or chromosome instability disorders. Targeted panels can identify novel mutations within known FA genes, but only tests such as whole exome sequencing, which screen regions of the genome that do not contain one of the targeted genes, can identify novel FA genes<sup>(11)</sup>. Further, other whole genome screening methods, such as genomic microarray testing, are being successfully implemented to detect FA gene mutations (specifically large deletions) that cannot be identified by NGS<sup>(24)</sup>. Complementation testing and functional studies can be used to validate and confirm the clinical significance of novel mutations identified using these methods.

## Limitations of next generation sequencing and complementary molecular tests

Fanconi anemia gene function can be affected by numerous types of deleterious mutations, such as base pair substitutions, small deletions of only one or a couple of base pairs, large deletions involving hundreds of thousands of base pairs of DNA, and insertions. These various types of mutations have implications for FA testing. NGS is very effective for certain types of

mutations, such as single base pair substitutions and small deletions, but is problematic for other mutation types such as large deletions and duplications<sup>(12)</sup>. Large deletions represent the most common type of mutation encountered in the *FANCA* gene<sup>(13, 14)</sup>. Ameziane et al. (2012) developed a statistical method for detecting large deletions by NGS. Other laboratories currently use techniques other than sequencing to detect these larger abnormalities. One such technique is known as multiplex ligation-dependent probe amplification (MLPA), a very efficient and sensitive method for identifying large deletions as part of an FA testing algorithm. MLPA is used as a first-line test to rule out large deletions in *FANCA*, followed by either conventional Sanger sequencing for a small number of FA genes<sup>(15)</sup> or NGS for a targeted FA gene panel.

Genomic microarray is another technique that can be used as a first-line strategy to search for deletions and duplications among FA and related genes. Several different types of microarrays are available, two of which are commonly referred to as array comparative genomic hybridization (aCGH) and SNP arrays. Similar to NGS, these microarrays can be targeted for detection of deletions and duplications (collectively referred to as copy number variants (CNV) or copy number aberrations (CNA)) within a set of known genes, or can be designed to detect these CNA anywhere in the genome. Most laboratories use a hybrid model, where the microarray is enriched (i.e., has extra coverage) for certain genes of interest, while also having some coverage of the remaining genome. As with all of the testing methods described in this chapter, the laboratory performing the microarray analysis should be certified and have well-established guidelines to distinguish a clinically significant result from a technical artifact or normal benign variation. The choice of testing methods, and the order in which they are performed to identify a given patient's mutation, depends in part on the patient's clinical features and ancestry and the expertise and experience of the laboratory. As there is no single test method that is equally able to detect all types of mutations, and there is more than one technique that can detect a particular type of mutation, the combination and priority of testing applied varies between laboratories.

The ability of a DNA sequencing assay to detect and characterize a mutation can be influenced by a number of variables, including the statistical methods used to analyze the findings. Both the technical and statistical methods for NGS are rapidly evolving. It is critical that a clinically certified laboratory perform the test to ensure adherence to rigorous standards for quality control and quality assurance. Moreover, it is strongly recommended that a genetic counselor or other genetics professional help guide the testing. Close communication

between the laboratory director and the genetics professional is critical. Prior to the initiation of testing, the genetic counselor should confer with the laboratory director about the limitations of the testing methodology and analysis being used. Specifically, the genetic counselor and laboratory director should discuss the types of mutations that can and cannot be detected, and the number of FA genes and other relevant genes that will be included in the testing. This information should be summarized by the genetic counselor and communicated to the patient and the patient's family. The laboratory should also share its methods for validating positive test results.

## Test 3: Bone Marrow Chromosome Analysis

### G-banding analysis

Following the diagnosis of FA, the chromosomes of the patient's bone marrow cells should be analyzed using Giemsa banding (G-banding; a cytogenetics technique which marks the chromosomes with colored bands and is used to elicit the unique and characteristic staining pattern of each chromosome) to determine whether a clone with acquired chromosome abnormalities is present, and if so, to characterize the abnormalities observed. Specifically, G-banding analysis can detect clonal chromosome abnormalities acquired by a subset of bone marrow cells.

### Good to Know

A **clone** is a population of cells.

**Clonal abnormalities** are changes in the structure or number of chromosomes in certain cells (in FA, generally cells of the bone marrow).

**Clonal evolution** is a process by which cells acquire new abnormalities.

**Clonal expansion** is an increase in the percentage of cells with identical abnormalities.

Myelodysplastic syndrome (MDS), leukemia, and other hematologic malignancies are associated with clonal abnormalities that arise in the malignant cells; therefore, the observation of a clonal abnormality may herald the emergence of cancer or of a precancerous condition. Some clonal abnormalities in patients with FA may persist for a long time without causing adverse consequences; others have been recognized as being associated with more rapid progression or more aggressive disease. In either case, clonal evolution and clonal expansion are frequently associated with disease

progression. If no clonal abnormalities are observed in the patient's bone marrow, then the G-banding analysis should be repeated annually. If a clonal abnormality is observed, then follow-up analyses should be performed more than once per year to monitor the behavior of the clone. To fully interpret the results of the bone marrow chromosome analysis, a hematopathologist should also analyze a sample of the patient's bone marrow using additional techniques to enable correlation between the hematopathology and cytogenetics findings.

The guidelines for chromosome analysis for acquired abnormalities are specified in the 2009 (revised January 2010) edition of the *Standards and Guidelines for Clinical Genetics Laboratories* by the American College of Medical Genetics (available at: [www.acmg.net/ACMG/Publications/Laboratory\\_Standards\\_Guidelines.aspx?hkey=8d2a38c5-97f9-4c3e-9f41-38ee683bcc84](http://www.acmg.net/ACMG/Publications/Laboratory_Standards_Guidelines/ACMG/Publications/Laboratory_Standards_Guidelines.aspx?hkey=8d2a38c5-97f9-4c3e-9f41-38ee683bcc84)). Specifically, the guidelines state that:

- At least 20 different cells in the metaphase stage of the cell cycle should be analyzed using G-banding, with follow-up and screening of additional cells as necessary.
- The chromosomes from normal and abnormal cells should be documented with karyograms (digital images or photographs of the chromosomes, with each pair of the chromosomes aligned in numerical order from 1 – 22, XX or XY).
- The results should be summarized using the standard nomenclature found in the most recent version of the International Standards for Cytogenetic Nomenclature (ISCN).

Recurring clonal chromosome abnormalities may be found in patients with MDS, acute myelogenous leukemia (AML), and other cancers. Certain chromosomal abnormalities occur more frequently in patients with FA, including a gain of material from the long arm of chromosome 1 (1qG), gain of material from the long arm of chromosome 3 (3qG), and loss of chromosome 7 (7L). These abnormalities can occur alone or in combination with each other, or with other abnormalities involving other chromosomes<sup>(16-20)</sup>. One study found that 1qG, 3qG, and/or 7L accounted for 75% of the clonal abnormalities observed in patients with FA<sup>(16)</sup>.

### **FISH analysis**

The clinical laboratory performing the chromosome analysis should have expertise in cancer cytogenetics and be familiar with FA and the types of

abnormalities associated with the disorder. Because the cells of patients with FA are genetically unstable, it is likely that some cells will develop random, non-clonal abnormalities; therefore, it is important for the laboratory to distinguish *non-clonal* abnormalities, which are limited to single cells and do not represent an emerging malignant process, from *clonal* abnormalities, which can herald the development of a premalignant or malignant condition. Clonal chromosome abnormalities can involve the loss or gain of a whole chromosome, the loss or gain of parts of chromosomes, or the structural rearrangement of parts of different chromosomes. Some clones have cells with only one clonal abnormality, while other so-called complex clones have cells with multiple numerical and structural abnormalities. G-banding is sometimes insufficient to accurately characterize these abnormalities. The same is true for the reverse of G-banding, known as R-banding.

Accurate characterization is important because some abnormalities (such as 3q gain) are associated with higher risk for transformation of disease than other abnormalities. In such cases, a technique known as fluorescence in situ hybridization (FISH), which employs fluorescently labeled chromosome region-specific probes, can be a highly informative tool. For example, the gain of a 3q (3qG) abnormality can be challenging to identify by G-banding, because it often involves the translocation of only a small portion of chromosome 3 to another chromosome. To definitively determine whether the translocated material originated from 3q, it might be necessary to perform FISH analysis. Other subtle abnormalities may be completely overlooked without the use of FISH. While G-banding examines all chromosomes for abnormalities, FISH analysis typically examines cells for a small set of pre-specified abnormalities. Furthermore, G-banding is limited to the dividing cells and is rather labor intensive, which limits the overall number of cells analyzed. FISH analysis, on the other hand, can be used to quickly examine more than 100 cells. Thus, the two techniques of G-banding and FISH complement each other. Because the gain of 1q (1qG) and/or 3q (3qG), and loss of 7 (7L) comprise the majority of the clonal abnormalities seen in cells from patients with FA, it is recommended that, in addition to the G-band analysis of 20 metaphase cells, FISH analysis of 100 to 200 interphase cells be performed to detect low-level presence of a clone harboring one of these three abnormalities. Some laboratories use FISH analysis for a larger number of regions involved in MDS and AML (e.g., 5q, 20q) in both FA and non-FA patients. Such FISH panels can be applied to either unstimulated peripheral blood or to bone marrow. The concordance between FISH results on blood and bone marrow in

patients with FA has not yet been clearly established; however, some physicians and laboratories have started to perform FISH analyses on peripheral blood samples that are collected at time points in between the annual scheduled bone marrow testing. This intervening blood FISH study is being tested as a noninvasive means of monitoring, on a more frequent basis, for the emergence of an abnormal clone with 1qG, 3qG or 7L.

### **Genomic microarray testing**

Genomic microarray testing is a relatively new technique that has become a major tool for cytogenetics and/or molecular laboratories. Microarray techniques such as array comparative hybridization and/or SNP analysis can identify regions of chromosomal loss and/or gain that may be too small, too ambiguous in banding pattern, or too complex to be identified by G- (or R-) banding. Sometimes there are so many abnormalities in a single cell, that a specific abnormality is essentially hidden. Microarray techniques are highly sensitive for detecting and identifying the origin of regions of chromosome loss and gain. For example, microarray techniques can rapidly detect and characterize the presence of a 3qG abnormality and provide specific information about the boundaries of the region that is gained. However, one limitation of this technique is that the clonal abnormality must be present in a sufficiently high percentage of cells (generally higher than 10%) to be detected. Unlike FISH and conventional G-banding analyses, microarray analysis does not provide information about individual cells, but rather provides results based on the total population of cells sampled.

As noted above for the G-banding analyses, all cytogenetic findings should be interpreted within the context of the patient's complete hematological profile and other clinical features to obtain a comprehensive assessment of the patient's status. Communication between the cytogenetics laboratory director, other laboratory directors (e.g., molecular genetics and hematopathology directors), physicians, and the genetic counselor is critical for optimal patient care.

## **Chapter Committee**

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# Chapter 3: Hematologic Abnormalities in Patients with Fanconi Anemia

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## Introduction

Patients with FA generally develop some degree of bone marrow dysfunction, resulting in a deficiency in blood cells or the production of abnormal cells. Bone marrow dysfunction can cause a variety of health concerns, which can each have various signs and symptoms <sup>(1-3)</sup>.

Concerns related to the blood and marrow most commonly include:

- *Anemia: Low red blood cell count which can cause weakness and fatigue*
- *Thrombocytopenia: Low platelet count which can cause spontaneous bleeding in the skin and mucous membranes*
- *Neutropenia: Low neutrophil (also known as granulocyte or polymorphonuclear cell) – “poly” – count which can cause increased risk for serious infections*
- *Leukemia and myelodysplastic syndrome (MDS): Cancer or a pre-cancerous condition of the blood-forming cells in the bone marrow*

The hematological care team should include a **hematologist** and **hematopathologist**. This team should work in close collaboration with other FA specialists to provide comprehensive care. The involvement of multiple types of care providers in the care of patients with FA introduces the risk that diagnoses and management plans are not effectively communicated or that medications prescribed by one physician might adversely interact with those prescribed by another. Therefore, it is essential that all subspecialists communicate with the primary physician, usually the hematologist/oncologist, to coordinate care.

## Bone Marrow Dysfunction

Bone marrow dysfunction in patients with FA can range from mild, asymptomatic cytopenia to severe aplastic anemia, MDS, or acute myelogenous leukemia (AML). The absence of marrow failure, however, does

not exclude the diagnosis of FA. Most patients with FA (more than 90%) will have macrocytosis (red blood cells that are larger than normal) in infancy, childhood, or adolescence. However, macrocytosis may be mitigated by concomitant iron deficiency or an inherited blood disorder such as alpha- or beta-thalassemia minor<sup>(1-3)</sup>.

## Good to Know

The **bone marrow** produces the blood cells that our bodies need to function and fight infection.

The blood stem cells that reside in the bone marrow produce three blood cell types: **red blood cells** (erythrocytes) carry oxygen to the body's tissues; **white blood cells** (leukocytes) defend the body against infections; and **platelets** help the blood clot.

Bone marrow dysfunction can manifest in the following ways:

**Cytopenia**, a deficiency of any blood cell type

**Aplastic anemia (previously called pancytopenia)**, a deficiency of all three blood cell types

**Thrombocytopenia**, a deficiency of platelets.

**Neutropenia**, a deficiency of neutrophils.

**Myelodysplastic syndrome (MDS)**, a diverse group of bone marrow disorders characterized by abnormal production of immature and defective blood cells

**Acute myelogenous leukemia (AML)**, a rapidly progressing malignancy of myeloid blood cells predominantly expanding in the blood, spleen and bone marrow

The age of onset of bone marrow failure in patients with FA is highly variable, even among siblings. Approximately 3 out of every 4 patients develop evidence of marrow failure ranging from mild to severe within the first decade of life<sup>(4-6)</sup>. Rarely, marrow failure from FA can present in infants and small children. An analysis of 754 patients in the International Fanconi Anemia Registry (IFAR) suggested that the average age of onset is 7.6 years. However, that study analyzed patients who mainly had defects in the *FANCA*, *FANCC*, and *FANCG* genes, which are the most frequently mutated FA genes; therefore, the results may not be representative of patients with rarer gene defects<sup>(5)</sup>. In adults as compared to children, FA is less commonly diagnosed due to primary bone marrow failure; instead, the diagnosis of FA more commonly occurs as a consequence of presentation with cancer or with severe toxicity after chemotherapy treatment for a malignancy<sup>(7,8)</sup>. Severe, usually transient, bone

marrow failure can also develop in non-transplanted female patients with FA during pregnancy.

Despite its potentially misleading name, FA frequently involves the development of neutropenia (low numbers of neutrophils) and thrombocytopenia (low numbers of platelets) as well as anemia (low numbers of red blood cells). Ironically, the cytopenia that commonly leads to the diagnosis of FA is thrombocytopenia (usually with erythrocyte macrocytosis and elevated levels of fetal hemoglobin (HbF)). FA should be considered in the evaluation of any patient with hypoproliferative cytopenia.

Cytopenias in patients with FA warrant a thorough hematologic workup to rule out additional causes of cytopenias other than primary bone marrow failure. Marrow cellularity is best evaluated by bone marrow biopsy. Results must be interpreted in the context of peripheral blood counts, because marrow cellularity may be patchy and subject to sampling variation. It is helpful to follow the patient's trends in marrow cellularity and peripheral blood counts over time. Therapeutic intervention should not be based on marrow cellularity alone in the absence of clinically significant peripheral cytopenias or clear evidence (usually cytogenetic changes) of a myelodysplastic or malignant process.

Patients with FA are at high risk of developing MDS and AML, which are sometimes associated with recurring changes on chromosomes 1, 3, and 7 (see below) <sup>(9)</sup>. Acute lymphocytic leukemia (ALL) and lymphomas are rare in patients with FA and usually restricted to patients with genetic defects in the *FANCD1/BRCA2* gene <sup>(5,10-12)</sup>.

### **Clonal abnormalities and serial bone marrow findings**

The bone marrow of patients with FA can exhibit signs of dysplasia (abnormal development or growth), such as nuclear/cytoplasmic dysynchrony, hypolobulated megakaryocytes, and binucleated erythroid cells. These features must be distinguished from true forms of MDS. Baseline marrow dysplasia is commonly associated with the inherited marrow failure syndromes and is not necessarily a harbinger of AML. In patients with inherited marrow failure syndromes, it is often challenging to distinguish between a bone marrow with dysplastic but stable features versus new dysplasia and MDS associated with progression to AML. It is important to obtain regular bone marrow cytogenetic analyses (see below). Therefore, to avoid mistaken or premature referral of patients with FA and other bone marrow failure syndromes for allogeneic

stem cell transplantation, putative bone marrow dysplasia warrants careful evaluation by a hematopathologist with expertise in these rare syndromes.

Most hematologists agree that a patient with FA should have a bone marrow examination (which includes aspiration, biopsy, and cytogenetic analysis) at the time of diagnosis; many also perform this test annually. Compliance issues may arise when patients with FA reach adolescence or adulthood, or in situations where adherence to this regimen is simply not possible. The purpose of serial marrow examinations is to identify early signs of the development of MDS or AML. A minority of hematologists prefer to monitor the peripheral blood counts frequently and analyze chromosomes using a test known as fluorescence in situ hybridization (FISH, as outlined below and discussed in *Chapter 2*), and only perform a marrow examination if the peripheral blood counts change. Because AML in patients with FA is difficult to treat and currently is managed by going rapidly to stem cell transplantation, hematologists should strongly consider performing annual marrow examinations or regular analyses of the peripheral blood (including cytogenetic analyses), proceeding to bone marrow examination if any suspicion arises.

The marrow of a patient with FA often contains fewer cells than normal for the patient's age, even if the peripheral blood counts are normal or close to normal; therefore, marrow cellularity may not be the best parameter to indicate a need for intervention. Intervention criteria are defined below and are based upon declining blood counts (Table 1).

The morphology, or appearance, of the cells in the bone marrow may suggest early transformation of MDS into AML. However, the definition of MDS has changed with time. Adult MDS, which occurs in the absence of a genetic propensity, was initially classified according to the French-American-British (FAB) criteria. This classification scheme has been replaced by the World Health Organization (WHO) criteria, which has a specific category for pediatric MDS known as refractory cytopenia of childhood (RCC); MDS in patients with FA is classified as a secondary MDS. According to the WHO criteria, to be considered MDS, or RCC, the bone marrow should have dysplastic changes (proportion not specified) in two different myeloid cell lineages, or in more than 10% of cells in a single cell line<sup>(13)</sup>. One study, however, found that up to 25% of healthy bone marrow donors have more than 10% cells with dysplastic changes in two or more lineages<sup>(14)</sup>. Another problem with this classification is that it generally reflects MDS arising in individuals without an identified, inherited marrow failure syndrome and therefore may not be the best reflection

of what is seen and expected in individuals with FA. An analysis of 4 cohorts of patients with FA revealed that the cumulative incidence of AML was around 15-20% by age 40, and the incidence of MDS (not centrally reviewed) reached about 40% by age 50 <sup>(15)</sup>. Marrow morphology should be examined by a hematopathologist/hematologist who is experienced in the evaluation of MDS in patients with inherited bone marrow failure, in particular FA, and should be considered in the context of blood counts and cytogenetic results.

## Good to Know

A **cytogenetic clone**, or clonal abnormality, arises when a blood progenitor or stem cell acquires a mutation that provides a competitive advantage.

The presence of cytogenetic clones in a patient with FA may determine the patient's prognosis. The marrow is usually examined by evaluation of G-banded metaphase cells, although fluorescent in situ hybridization (FISH) is increasingly used to seek specific common mutations [e.g., monosomy 7 or del(7q)], and comparative genomic hybridization (CGH) has also been proposed for elucidating more details. The results of cytogenetics analyses of the marrow have revealed varying types and frequencies of clones in several reported cohorts of patients with FA. In some cases, these results led to patients being classified as having MDS/AML. An early analysis from the IFAR found that the risk of developing of MDS or AML within 3 years after the observation of a clone was approximately 1 in 3 (35%), whereas the risk for patients without a clone was 1 in 30 (3%); abnormalities in chromosomes 1 and 7 were most commonly involved <sup>(16)</sup>. In another cohort, clones were noted to disappear, appear, or reappear in serial marrow evaluations. These fluctuations were usually based on the analysis of a limited number of cells due to the aplastic nature of the marrow and therefore complicate the interpretation of the results of single marrow sample <sup>(17)</sup>.

The role of aberrations of chromosome 3 was first reported in a study of 53 German patients, 18 of whom had chromosomal abnormalities (partial trisomies or tetrasomies) involving the long (q) arm of chromosome 3. In this group of patients, the 3-year risk of MDS/AML was 9 in 10 (90%), compared with 1 in 10 (10%) for patients without aberrations in chromosome 3 <sup>(9)</sup>. In other studies, the prognostic implications have been more difficult to establish. Of a group of 119 patients who were referred for a bone marrow transplant in Minneapolis, Minn., 32% had clonal aberrations and 20/119 had

a clonal gain of chromosome 3q<sup>(18)</sup>. However, many of the participants were referred to Minneapolis for a diagnosis of MDS and because the gain of 3q and the diagnosis of MDS were simultaneous in most reported patients<sup>(18)</sup>, the prognostic implications of 3q could not be evaluated. Among 20 patients who had a gain of 3q, 4 had MDS, 2 were borderline, 3 did not have MDS, and 11 had additional clones and had MDS. A group from India did not find any 3q aberrations in 10 FA patients that progressed to MDS or AML. Five of these patients developed other clones<sup>(19)</sup>. In a group of patients from Cincinnati, 4 of 64 without MDS and 6 of 13 with MDS/AML had gain of 3q, but when time of follow up was taken into account, there was no significant association of aberrations in chromosome 3 with the risk of MDS/AML<sup>(20)</sup>. Finally, a French study of 57 patients with FA detected gain of 3q in 12 of 29 patients with MDS/AML and in none of 20 with aplastic anemia<sup>(21)</sup>. It is important to note that the methodology used in cytogenetic analysis differed in these reports, and the optimal methodology for detecting, confirming and following aberrations is not firmly established. Taken together, the results of these studies suggest that the gain of 3q may be associated with MDS/AML, although its prognostic significance is not entirely clear, particularly when it occurs in isolation.

As in non-FA settings, the appearance of monosomy 7 and most 7q deletions is generally held to portend a poor prognosis with high risk of developing MDS/AML whereas trisomy of 1q has not been convincingly shown to associate with prognosis. However, longitudinal prospective studies of larger numbers of patients are required to clarify the prognostic role of specific types of clones and specific combinations of aberrations. An ongoing prospective study in Berlin is using interphase FISH to compare the occurrence and detection of chromosomal aberrations on chromosome 1, 3, and 7 in both the bone marrow and peripheral blood. The results of this study are eagerly awaited and certainly will influence the standards of care for patients with FA in the future<sup>(22)</sup>.

In summary, based on our current knowledge, physicians must be cautious and assess the latest literature when treating a patient who has a clone but lacks other abnormalities of blood counts or myelodysplastic changes in the marrow. Despite the presence of a clone, the patient may have stable hematopoiesis (production of blood cells) and possibly a relatively favorable long-term prognosis; in such cases, a stem cell transplant may subject the patient to an unwarranted risk of morbidity and mortality.



**Definition of bone marrow failure**

Bone marrow failure manifests clinically by blood counts that are below age-appropriate norms due to decreased production of effective blood cells. While many patients progress to frank aplastic anemia, others may maintain mildly abnormal blood counts for years and even decades. Clinical surveillance and therapeutic management are guided by the severity of the cytopenia(s), the stability of the blood counts, the presence of morphologic and cytogenetic marrow abnormalities, the presence of potentially high-risk genotypes as described in *Chapter 1*; Table 3, the patient’s quality of life, and the wishes of the patients and their families.

Bone marrow failure can be classified into three broad categories, depending upon the degree of cytopenia(s) observed (Table 1). These definitions are more than semantic as they also define points at which different clinical management options should be considered.

**Table 1.** Severity of bone marrow failure.

	Mild	Moderate	Severe
Absolute neutrophil count (ANC)	<1,500/mm <sup>3</sup>	<1,000/mm <sup>3</sup>	<500/mm <sup>3</sup>
Platelet count	150,000-50,000/mm <sup>3</sup>	<50,000/mm <sup>3</sup>	<30,000/mm <sup>3</sup>
Hemoglobin (Hb) level	≥8 g/dL*	<8 g/dL	<8 g/dL

\*Less than normal for age but ≥ 8 g/dL.

Importantly, to meet these criteria for marrow failure, the cytopenias must be persistent and not transient or secondary to another treatable cause, such as infection, medication, peripheral blood cell destruction/loss, or nutritional deficiencies.

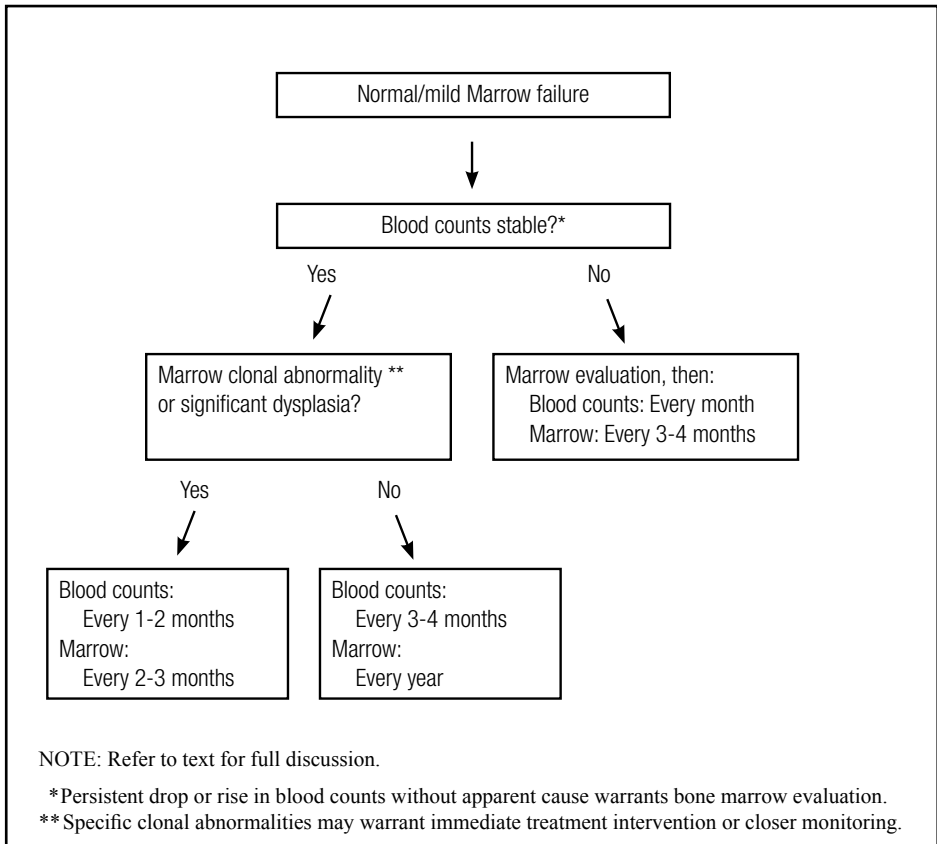
**Clinical monitoring of bone marrow failure**

Current guidelines for monitoring bone marrow failure are summarized below. These recommendations may be modified as new data become available, and patients are urged to consult with a hematologist with expertise in FA. Testing should be individualized as indicated.

At a minimum, bone marrow examination should consist of an aspirate to assess morphology and cytogenetics with G-banding and FISH (where available) to look for chromosomal abnormalities that are commonly associated with MDS and AML in patients with FA. A bone marrow trephine biopsy provides valuable information regarding marrow architecture and cellularity.

Periodic monitoring is important to assess the significance of a clonal cytogenetic abnormality and the onset of MDS or frank leukemia, and to identify the presence of cytogenetic abnormalities that may suggest immediate intervention or at least initial consideration for transplantation. Annual evaluation of the bone marrow, beginning at age 2, allows for comparison of a patient's marrow to previous specimens from the same patient. The availability of serial marrow specimens facilitates assessment of the progression of that patient's marrow and enables informed decisions about the significance of a clonal abnormality. Interphase FISH cytogenetic analysis in peripheral blood cells with specific probes for MDS/AML in FA may reduce the frequency of bone marrow examinations to longer than 1 year; however, this technique may not be widely available, and the efficacy of such an approach has not yet been published.

**Box 1.** Clinical monitoring of bone marrow failure.



Recommendations for clinical monitoring of bone marrow failure (Box 1) include the following:

- ***Peripheral blood counts stable in the normal to mild marrow failure range and NO clonal cytogenetic abnormalities***

For patients with normal counts and no cytogenetic clonal marrow abnormalities, a peripheral blood count and differential white blood cell count should be reviewed approximately every 3 to 4 months and a bone marrow aspirate and biopsy with cytogenetics considered yearly. A similar monitoring regimen is recommended for patients with mildly abnormal but stable peripheral blood counts without any associated clonal marrow abnormalities.

- ***Peripheral blood counts stable in the normal to mild marrow failure range AND clonal cytogenetic abnormalities present***

For patients with a cytogenetic clonal marrow abnormality (in the absence of morphologic MDS) together with normal or mildly low, but stable, blood counts, more frequent surveillance of counts and bone marrow examinations should be considered (as indicated by the patient's clinical status) to monitor for progression to MDS or leukemia. It would be reasonable to examine the blood counts every 1 to 2 months and the bone marrow every 1 to 6 months initially to determine if the blood counts are stable or progressively changing. Cytogenetic abnormalities and marrow morphologic changes should be similarly monitored. If the blood counts are stable, then the interval between bone marrow exams may be increased. Appropriate plans for stem cell transplantation—including HLA typing of family members, clarification of donor status and availability, contact with a HSC transplant center, and communication with the insurance company—should be in place, as adverse clonal progression or worsening marrow failure may evolve rapidly. However, in some cases clones have remained stable for more than a dozen years without transplantation.

- ***Peripheral blood counts falling or rising***

Patients with progressively changing blood counts without a clinically apparent underlying cause (e.g., transient response to an acute infection or suppression secondary to medication) require immediate evaluation with a complete blood count and bone marrow examination with cytogenetics. Rising peripheral blood counts can be due to either the development of MDS/AML (for which stem cell transplantation would be a potential urgent undertaking) or, rarely, reversion of a germ-line mutation in a

stem cell, which repopulates the marrow with normal cells (somatic stem cell mosaicism). Such patients warrant continued close monitoring with complete blood counts at least every 1 to 2 months and a marrow exam with cytogenetics every 1 to 6 months. Appropriate plans for intervention should be in place, as adverse clonal progression or worsening marrow failure may evolve rapidly.

## Treatment Options for Bone Marrow Failure

Available treatments for bone marrow failure in patients with FA are described below. The risks and benefits of each treatment are discussed. A suggested treatment algorithm is presented under “Management Guidelines for Bone Marrow Failure” in this chapter.

### **Hematopoietic stem cell transplant**

Hematopoietic stem cell transplantation (HSCT; described in detail in *Chapter 11*) is currently the only curative treatment for bone marrow failure, although it does not cure non-hematopoietic complications of FA. Patients with FA generally experience undue toxicity from the chemotherapy and radiation used in standard transplant conditioning regimens due to their underlying defect in DNA repair. Excellent results for matched sibling donor transplants have been achieved in the last 15 years using the chemotherapy drug fludarabine and modified transplant regimens<sup>(23,24)</sup>. Compared with past regimens, the currently available alternative donor regimens appear to have markedly improved results so far, representing a new opportunity for patients<sup>(25-27)</sup>. These regimens for alternative or unrelated donor transplantation will continue to evolve over the coming years and need to be discussed on an individual basis with a physician experienced in transplants for patients with FA.

Because the best transplant outcomes are associated with young patients who have not yet developed medical complications from their bone marrow failure, patients and families who opt to pursue transplantation are generally encouraged to proceed early in the course of the disease. However, issues regarding timing of transplant are complicated by the up-front risk of transplant-related morbidity and mortality and the unknown long-term side effects of transplantation in patients with FA. Most importantly, as it is currently not possible to predict for the vast majority of patients who will progress to severe marrow failure and who will not, transplantation prior to the development of significant marrow failure may unnecessarily subject a subset of patients to both early and late transplant-related morbidity and mortality.

The effect of current transplant approaches on long-term transplant-related risks such as increased risk of solid tumor development remains unknown. For example, graft-versus-host disease (GvHD) was identified as a major risk factor for oral squamous cell carcinoma in patients with FA <sup>(28,29)</sup>, but several innovations have decreased the rate of GvHD. Ongoing dialogue with an FA transplant specialist should be initiated early after the diagnosis of FA.

### **Androgens**

Synthetic androgens have been widely used for the treatment of cytopenias in patients with FA for more than 50 years. The beneficial effects of androgens are most pronounced in the red cells and platelets, but neutrophil counts may also improve <sup>(30,31)</sup>. The mechanisms by which androgens raise peripheral blood counts and bone marrow cellularity in patients with FA are unclear. The advantages of androgens include the absence of short-term, and low long-term, risks of therapy-related mortality and the long history of experience with their use. Side effects have been well documented and are related to the absolute dose of androgens given per kilogram (kg) of body weight. The major potential side effects associated with androgen therapy are listed in Table 2. More than half of patients with FA that are treated with androgens will respond at least transiently. Although a subset of patients who initially respond may become refractory over time, it appears as if as many as 10-20% of patients receiving continuous low dose androgen therapy might never need a transplant, unless MDS/AML develops. Thus, androgen treatment may delay a transplant for months and even years in responsive patients. This is particularly important for patients and families who decline immediate HSCT, patients without a suitable donor, cases in which hematopoietic stem cell transplant facilities do not exist, and patients for whom transplant would be associated with very high risk.

The use of androgens to delay transplantation may be associated with the following risks:

- *Androgens do not prevent progression to AML, which, once developed, may significantly increase the risks associated with transplant.*
- *Patients will be older when transplantation may be necessary, or may have acquired viral infections, which will be problematic at transplant.*

The decision about whether to use androgens to delay transplantation can be very difficult for patients with FA and their families, and may require time and consultations with more than one specialist and/or center.

**Table 2.** Possible side effects of androgens.

Androgen use has been associated with ...
<ul style="list-style-type: none"><li>• Virilization, including acne, facial hair growth/scalp hair loss, deepening of voice, development of pubic hair, enlargement of penis or clitoris, and priapism (painful erection) in young boys</li><li>• Growth spurt followed by premature closure of epiphyses (the regions of bones involved in skeletal growth) and exacerbation of short adult stature</li><li>• Hyperactivity and behavioral changes such as puberty and aggressiveness</li><li>• Cholestatic jaundice or transaminitis</li><li>• Hepatic adenoma (benign) or hepatocellular carcinoma (malignant)</li><li>• Peliosis hepatis (the development of blood-filled cavities in the liver)</li><li>• Hypertension</li></ul>

The major outcome of androgen therapy is increased/stabilized hemoglobin levels, although it may also improve/stabilize the platelet count. Androgen therapy should be considered when the patient's hemoglobin drops below 8 g/dL or the platelet count falls below 30,000/mm<sup>3</sup> (classified as severe AA in Table 1). Because there is no evidence (i.e., no trial has been performed/ reported) that androgens can forestall bone marrow failure, treatment should begin when blood counts drop to clinically significant levels, but before the marrow becomes completely devoid of hematopoietic stem cells for androgens to stimulate (this may be the point at which patients/parents wish to start some active treatment).

The most commonly used androgen since 1961 is oxymetholone<sup>(30,31)</sup>. The starting dose of oxymetholone should be ~2 mg/kg/day (but doses as high as 5 mg/kg may be required) rounded to the nearest ¼ tablet (50 mg tablets are usually available but can be broken). Most patients respond within 3 months to the initial dose with a stabilization or an increase in the hemoglobin or platelet levels. If a response occurs, then the general strategy is to slowly taper the daily dose of oxymetholone in 10-20% decrements every 3 to 4 months until an effective dose with minimal side effects is obtained. Over time, the side effects of accelerated linear growth (ultimately with premature closure of the growth plates) and weight gain effectively reduce the individual's dose per kilogram body weight; therefore, the patient's dose per kg should be recalculated prior to making dose adjustments.

The patient and family should be counseled about the possible side effects of oxymetholone and the child, especially teenagers, should be forewarned about

them. Every effort should be made to minimize the side effects by tapering the dose to the minimum effective dose whenever possible. Aggressive acne treatment with topical benzoyl peroxide and topical antibiotics (clindamycin or erythromycin) may make the treatment more tolerable. Long-term androgen usage may lead to shrinkage/impaired development of the testis in males due to suppression of the hypothalamic-pituitary-gonadal axis (a complex hormone-based system that regulates many bodily functions, including the function/sex hormone production of gonads). An appropriate discussion of the masculinizing side effects of androgen therapy is very important. However, critical marrow failure is life-threatening and all parties must weigh the side effects for both male and female patients versus the potential benefits.

If no response is seen after 3 to 4 months, then—in the absence of other causes of cytopenias such as viral or bacterial infection—oxymetholone should be discontinued, although there are anecdotal reports of patients responding after 6 or more months. Improvements in hemoglobin levels may be seen earlier than improvements in platelet counts, and white cell responses may occur later or be nonexistent.

Oxymetholone was the first androgen approved by the Food and Drug Administration (FDA) for the treatment of aplastic anemia. It is noteworthy, however, that bodybuilders consider oxymetholone to be the strongest and most effective oral steroid with extremely high androgenic and anabolic effects. It has been utilized widely in bodybuilders, athletes, and also racehorses. Other synthetic androgens are also used in patients with FA worldwide. For example, stanozolol has been used in Asia, and oxandrolone has been used recently in Cincinnati, Ohio<sup>(32,33)</sup>; however, these two androgens have strong anabolic and androgenic effects and, like oxymetholone, are banned from usage in athletes.

A few reports<sup>(34-36)</sup> in the literature show that both male and female FA patients may benefit from treatment with danazol, an attenuated synthetic androgen that produces fewer virilizing effects than oxymetholone. A recent retrospective study demonstrated the effectiveness of danazol in 7 of 8 patients with FA (starting dose 3.5-7.7 mg/kg/day): Three patients (2 females and 1 male) were treated successfully for more than 3 years and 1 female for more than 10 years without exhibiting progressive marrow failure requiring stem cell transplantation<sup>(36)</sup>. The comparative efficacy of danazol versus oxymetholone to treat marrow failure in patients with FA is unknown. Danazol has been used at doses of 200-800 mg/day (3.3-13.3 mg/kg for a 60 kg woman) for months

in women to treat endometriosis and is still used as long-term prophylaxis for hereditary angioedema at a dose of approximately 5 mg/kg/day<sup>(37)</sup>.

There are no data to support the provocative notion of using low doses of prednisone to prevent androgen toxicity. Furthermore, prednisone therapy carries a risk of additional bone toxicities, such as avascular necrosis or osteoporosis. Therefore, its use is no longer recommended in patients with FA. Among potential toxicities, hepatic toxicities are one for which routine surveillance should be initiated. Patients taking androgens should be monitored for liver tumors and undergo regular liver function tests (LFT) for abnormalities. Blood tests for LFTs should be performed every 3 to 6 months, and a liver ultrasound should be performed every 6 to 12 months. Liver-derived  $\alpha$ -fetoprotein has been used as an early marker for hepatocellular carcinomas<sup>(32)</sup>. Unfortunately, the levels of transaminases in the blood do not always correlate with the degree of liver inflammation determined by liver biopsy. If the levels of liver transaminases increase to 3 to 5 times above normal, the androgen dose should be tapered until the blood tests improve. Androgen-associated liver adenomas may develop with long-term androgen treatment and are predominantly due to the cellular liver toxicities of the  $17\alpha$ -alkylated androgens (which include oxymetholone, oxandrolone, stanazolol, and others, but not danazol). Liver adenomas may resolve after androgens are discontinued, but some may persist for years after androgen therapy has ended. Liver adenomas are not a contraindication for transplantation. If screening tests raise a concern for hepatocellular carcinoma, a liver biopsy using a technique appropriate to the patient's bleeding risk should be considered. Even without additional risk factors, malignant transformations may occur after years of androgen treatment<sup>(32)</sup>.

### **Cytokines**

Several cytokines have been evaluated for their capacity to stimulate the failing bone marrow in patients with FA, but none have proven entirely successful. The cytokines granulocyte colony-stimulating factor (G-CSF)<sup>(38)</sup> and granulocyte-macrophage colony-stimulating factor (GM-CSF)<sup>(39)</sup> can indeed improve the neutrophil count in patients with FA. GM-CSF is no longer available for clinical use. Importantly, low absolute neutrophil counts that occur in isolation and are not associated with bacterial infections are not an indication for cytokine treatment. Treatment with other cytokines has not shown any benefit in patients with FA. However, newer agents such as thrombopoietin-mimetic drugs have not been tested in patients with FA.



Treatment with G-CSF may be considered if the neutropenia is associated with recurrent or serious infections, particularly if the neutrophil count is persistently below  $500/\text{mm}^3$  or as a short-term bridge to transplant. Historically, a few patients have also shown improvements in hemoglobin levels or platelet counts while on G-CSF; these effects are most likely due to the treatment of or reduction in infections. Long-term follow-up has not been published. G-CSF is typically started at a low dose of  $5 \mu\text{g}/\text{kg}/\text{day}$ ; one published study on G-CSF<sup>(38)</sup> reported that no patients with FA required a higher dose to maintain an absolute neutrophil count (ANC) of greater than  $1,000/\text{mm}^3$ . Patients have been maintained on lower doses given less frequently (e.g., every other day or 2 to 3 times per week), and the dose should be tapered to the lowest effective dose. Treatment should generally be discontinued if the neutrophil count fails to improve after 8 weeks of G-CSF therapy. Recently, long-acting preparations of G-CSF have become available and offer the advantage of decreased injection frequency (a particularly appealing prospect for thrombocytopenic patients); however, there are no reports of their use in patients with FA.

A bone marrow aspirate/biopsy with cytogenetics is recommended prior to the initiation of cytokine treatment, given the theoretical risk of stimulating the growth of a leukemic clone. It is reasonable to monitor the bone marrow morphology and cytogenetics every 6 months while patients are treated with cytokines. In the setting of a compelling clinical indication for cytokine therapy, there is no literature to mandate withholding cytokines from patients with clonal abnormalities. In such cases, the use of hematopoietic cytokines should be pursued in consultation with experts in the care of patients with FA.

### **Transfusion of blood products**

Transfusions of red cells or platelets may be needed prior to surgery or in the following clinical situations:

- *To manage the symptoms of anemia*
- *For patients with significant bleeding (thrombocytopenia)*
- *For patients with progressive marrow failure who fail to respond to androgen or G-CSF therapy*
- *For patients with marrow failure who have no prospect of early transplant (due to the lack of an acceptable transplant, comorbidities, socio-economic situations that preclude transplant and or lack of interest in pursuing transplantation as a therapy)*

Long-term transfusions with red cells and platelets may become a lifeline for patients for whom no other treatment options are available. Transfusions may be required as frequently as once per week. Complications of long-term transfusions include iron overload (see below) and allosensitization, both of which may complicate HSCT, as well as allergic reactions. However, physicians at most FA transplant centers believe that receiving fewer than 10-20 transfusions does not increase the risk for transplantation.

### **Investigational protocols**

Investigational protocols for new therapies should be considered in all patients with FA and their families who want to participate. It might be especially important for patients who fail to respond to androgens or cytokines, who have no acceptable transplant donor, or who have an unacceptably high transplant risk (see *Chapter 11*).

## **Management Guidelines for Bone Marrow Failure**

Because FA is a rare disease, prospective randomized trials comparing different treatment approaches are not available to guide therapeutic decisions. For this reason, the risks and benefits of the available treatment options need to be discussed with hematologists who are experienced with FA. A suggested treatment algorithm is presented below (Box 2).

### *At the time of diagnosis with FA:*

- Patients should be referred to a hematologist with expertise in FA for medical monitoring and management.
- Patients with any degree of bone marrow failure should be referred immediately to a transplant center with expertise in FA to initiate a discussion of available treatment options and to assess potential transplant options. This will give families the opportunity to initiate transplant at a time that is optimal for the patient and also the family. If the patient has no hematologic abnormalities at the time of diagnosis, it is reasonable to defer referral to a transplant center. The physician should take a detailed family history and perform high-resolution HLA-typing of the patient, parents, and siblings to assess the availability of tissue-matched bone marrow donors for the patient (likely donors should undergo additional testing to

rule out FA). In consanguineous families or families with unusual HLA types, members of the extended family may undergo HLA typing.

- Some families may wish to conceive children without FA who can serve as a tissue-matched donor for a sibling with FA (see *Chapters 11 and 17*). Such families should be referred for appropriate medical/genetic counseling.

*Guidelines for patients with normal blood counts or mild bone marrow failure:*

- Physicians should monitor the patient's blood counts, bone marrow morphology, and cytogenetics as described previously until further therapeutic intervention is warranted. Because transplant risk is lowest in patients younger than age 10, a few physicians have proposed that transplants might be offered to young patients with FA prior to the potential development of marrow failure. However, this suggestion, known as preemptive transplantation, remains controversial, because some patients who might never progress to significant marrow failure would be unnecessarily subjected to both early and late risks of morbidity and mortality associated with transplant. Further, transplantation may minimize the risk of marrow malignancy but increase the risk of other malignancies in patients with FA. Research is ongoing to elucidate the factors that can be used to identify the patients with FA who might benefit from a transplant at a young age. Families interested in this investigational approach should have a careful discussion with a hematologist and a transplant physician.

*Guidelines for patients with moderate marrow failure:*

- Physicians should consider allogeneic stem cell transplantation for patients who have an HLA-identical sibling; otherwise, if the patient is asymptomatic, continue monitoring blood counts, bone marrow morphology, and cytogenetics.
- Some patients and families may not feel ready for transplant despite having an ideal HLA-identical sibling donor, and may prefer to delay the transplant by using androgens (sometimes at a reduced dose). In such cases, individual counseling is important; contact with other families and family support groups may also be very helpful.
- Patients who lack an HLA-identical sibling should consult with a transplant center to plan for a possible future transplant from an unrelated donor (see "Guidelines for patients with severe marrow failure" below). Management should include high-resolution HLA typing and a preliminary search through the National Marrow Donor Program (or other national and

international donor registries/organizations) for a free, preliminary screen of potential HLA-matched donors. Selection of a donor requires additional confirmatory testing as well as a determination of donor availability. This process accrues a substantial charge and should not be undertaken until active plans for transplant are underway. Information regarding the number of potential donors available is helpful in estimating the amount of time that will likely be required to complete a full donor search if the marrow failure progresses and an imminent need for transplant emerges.

- Patients who do not wish to proceed to transplant at all, or who have risk factors that strongly increase the risks associated with transplant, should receive androgens and/or transfusions if the hemoglobin levels fall below 8 g/dL, if the platelets are under 20,000-30,000/mm<sup>3</sup>, or if clinical signs of anemia or bleeding are present.

*Guidelines for patients with severe marrow failure:*

- Eligible candidates should consider a hematopoietic stem cell transplant from a related or unrelated donor.
- Patients who have risk factors that confer an unacceptable transplant risk or who do not wish to proceed to transplant should consider treatment with androgens, cytokines, and/or transfusions.

*Guidelines for patients with severe marrow failure that is unresponsive to androgens/cytokines and who have unacceptable transplant risks or lack an appropriate donor:*

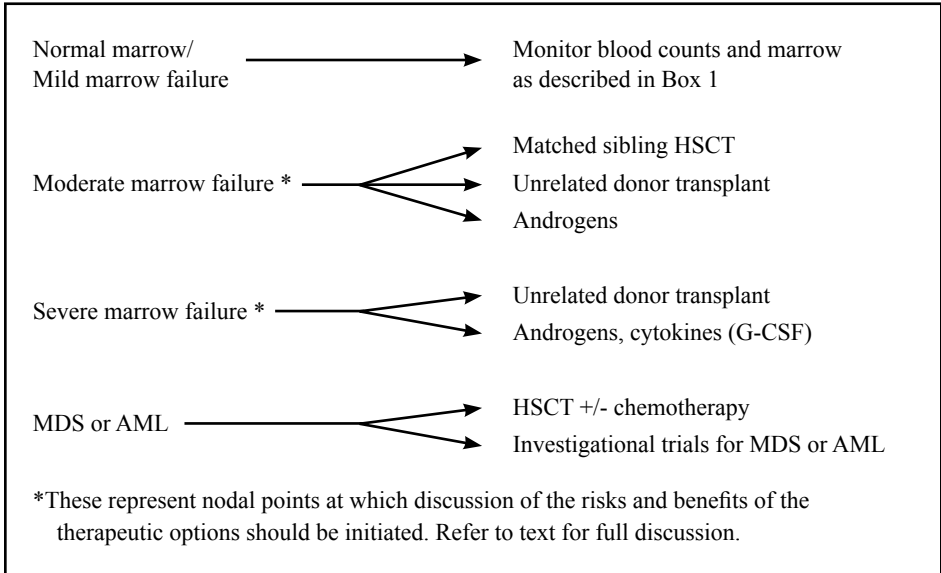
- Consider supportive management with transfusions and/or investigational protocols.

*Guidelines for patients with MDS or AML:*

- No standard therapy has been established for patients with FA who have MDS or AML. Treatment options include chemotherapy, hematopoietic stem cell transplant with or without prior induction chemotherapy, and Phase I/II trials for MDS or AML. Chemotherapy should be undertaken by centers experienced with FA. Because chemotherapy may cause severe, prolonged, or even irreversible myelosuppression in patients with FA, back-up plans for potential stem cell rescue should be considered. If patients have MDS/AML at the time of their diagnosis with FA, then low-intensity chemotherapy may be used to prepare the patients for transplantation. Published reports of chemotherapy regimens for AML in patients with FA are sparse and limited by the lack of longitudinal follow-

up. It remains unclear whether chemotherapy prior to transplant improves or worsens outcomes.

**Box 2. Marrow failure algorithm.**



## Supportive Care for Patients with Severe Marrow Failure

### Anemia

The onset of anemia in patients with FA is insidious. Hemoglobin levels should be monitored closely, as outlined above, so that treatment may be instituted before transfusion with packed red blood cells is required. Treatment of anemia should be considered when the patient's hemoglobin level consistently falls below 8 g/dL. The hemoglobin level at which treatment is started should be raised for patients who live at high altitude, which increases the normal range for hemoglobin levels. Patients with cardiorespiratory problems in addition to anemia also have elevated baseline hemoglobin levels and may require a higher threshold Hgb value for recognition of failing erythropoiesis and for treatment. When treatment is anticipated, it should be initiated under the care of a hematologist. Many patients with FA will require red blood cell transfusions. Transfusions should be scheduled regularly to help patients with bone marrow failure to maintain as normal a quality of life as possible. A patient should be transfused to maintain hemoglobin levels at a minimum of approximately 7-8

g/dL so that the patient will be asymptomatic for his or her activity level. A post-transfusion hemoglobin level of 10-12 g/dL is generally sufficient to allow for normal activity, growth, and development in children, with a 3- to 4-week interval between transfusions. Clinical adequacy of the transfusion regimen must be assessed continuously. As discussed above, other treatment options for anemia currently consist of bone marrow transplant or androgens.

All patients should receive red blood cells that have been depleted of leukocytes to reduce the risk of cytomegalovirus (CMV) infection. Some centers only use red blood cells that are CMV-negative, whereas most accept leukocyte-depletion as an equally effective alternative to CMV-negative products. Irradiated blood products should be used to avoid transfusion-associated graft-versus-host disease. A procedure known as extended antigen matching may be important for patients in certain racial groups for whom minor antigen mismatch is more commonly encountered. Directed donation for a specified recipient should be discouraged, especially from family members of the patient. Patients who receive blood transfusions from family members may develop an immune response towards substances in the donor blood (a process known as alloimmunization) that would increase the risk of graft rejection after related donor hematopoietic stem cell transplant. Blood from unrelated designated donors offers no increase in transfusion safety.

### **Secondary iron overload**

Each mL of packed red cells contains approximately 0.7 mg of iron. Because the human body lacks mechanisms to actively eliminate excess iron, patients who receive multiple red blood cell transfusions are at risk of accumulating toxic levels of iron (for reviews see<sup>40-43</sup>). The liver is a primary site of iron accumulation, and hepatic fibrosis and cirrhosis may result. Iron deposition in the myocardium (the muscular tissue of the heart) may cause irregular heartbeats and cardiac failure, which may be sudden and acute despite regular monitoring with electrocardiograms and measurements of cardiac function. Recent data from patients with thalassemia (a condition in which the body makes less hemoglobin and fewer red blood cells than normal) strongly suggest that magnetic resonance imaging (specifically, T2\* MRI) is the best technique to use to follow cardiac siderosis (the deposition of iron in the heart) and risk of cardiac disease in patients with significant iron overload<sup>(41,44)</sup>. Iron also targets endocrine organs such as the pituitary, pancreas, thyroid, and parathyroid.

The clinical complications of iron overload include the following:

- *Liver disease with fibrosis and cirrhosis*
- *Cardiac failure and arrhythmias*
- *Hypopituitarism, including central hypogonadism, growth hormone deficiency, and central hypothyroidism*
- *Poor growth*
- *Diabetes mellitus*
- *Primary hypothyroidism*
- *Primary hypogonadism*
- *Hypoparathyroidism*

While ferritin levels are often followed as a convenient marker for total body iron load, their interpretation is complicated by additional factors such as acute or chronic inflammation, infection, hepatitis, and androgen treatment. In addition, ferritin levels fail to correlate with iron stores in many patients. Ferritin levels may be useful to monitor trends in total body iron over time but quantitative measurement of hepatic and cardiac iron burden are essential. The measurement of total body iron by liver biopsy has been largely replaced, where available, by MRI techniques. However, a liver biopsy is the only technique that can determine the degree of hepatic fibrosis/cirrhosis. Liver iron concentrations of 3-7 mg/g dry weight indicates mild iron overload. Liver iron concentrations between 7-15 mg/g dry weight are associated with an elevated risk of iron toxicity. A liver iron concentration of greater than 15 mg/g dry weight is associated with a high risk of cardiac toxicity<sup>(45)</sup>. The possible complications of surgical, blind or image-directed biopsy procedures include bleeding or infection, which are of heightened concern in patients who are thrombocytopenic or neutropenic. Non-invasive MRI R2 and T2\* imaging techniques to measure hepatic and cardiac iron burden do not pose the risks associated with biopsy<sup>(44)</sup>. The use of MRI-based techniques is now widely accepted and they are the preferred way to measure hepatic and cardiac iron burden.

Little data on iron overload in FA is available. Guidelines for the institution of iron chelation therapy in patients with bone marrow failure as a general class are based on the guidelines established for patients with thalassemia, with the caveat that thalassemia patients, who have accelerated (albeit ineffective) production of red blood cells, often have concomitant increases

in iron absorption and are transfused to the point of suppressing endogenous hematopoiesis. The total volumes of red blood cells that are transfused into patients with FA must be carefully monitored, particularly in infants and small children. Total body iron status, as reflected in liver iron, cardiac iron, and ferritin levels, should also be monitored. Iron overload may be treated or—better yet—prevented with chelation therapy. As a general guide, chelation therapy should begin when the total volume of red cells transfused reaches 200 mL/kg (which roughly corresponds to a total of 12-18 red cell transfusions) or the liver iron concentration reaches 3-7 mg/g dry weight. Chronically transfused patients heading to a hematopoietic stem cell transplant may also benefit from total body iron measurements and chelation therapy to reduce the iron burden to safe levels. A serum ferritin level that is persistently greater than 1,000 µg/L without other apparent causes has been used as a surrogate, albeit imperfect, marker of elevated iron burden in situations where liver iron measurements are not clinically available.

Chelation must be adjusted over time to reduce or prevent iron accumulation while avoiding excessive amounts of chelator relative to total body iron levels. The risk of side effects increases as the dose of chelator exceeds body iron stores. The notion of a “safe” hepatic iron load is controversial. The target liver iron concentration level is typically between 3-7 mg iron/g dry weight but many experts prefer levels less than 3 mg iron/g dry weight. Two chelators are currently clinically available in the US: deferoxamine (Desferal) and deferasirox (Exjade). In the US, deferiprone (L1) is indicated only for iron chelation in patients with thalassemia, and may be associated with significant neutropenia. The features of each chelator are summarized in Table 3.

Deferoxamine therapy for transfusional iron overload has been used extensively and its efficacy in treating iron overload is well established. Although generally effective, its use is complicated by the need for subcutaneous or intravenous injection. Furthermore, deferoxamine must be administered over prolonged periods of time (8 to 24 hours) because only a small proportion of total body iron is available for chelation at any given moment and deferoxamine is eliminated from the body quickly. Subcutaneous infusions pose a risk of bleeding or infection in patients with thrombocytopenia or neutropenia. Side effects of deferoxamine include loss of hearing or peripheral vision, particularly when deferoxamine doses are high relative to iron burden, and risk of infection with iron-chelating organisms (known as siderophores) such as the bacterium *Yersinia enterocolitica*. Patients who develop a fever should immediately cease deferoxamine therapy and undergo medical evaluation. Continuous intravenous



infusion of deferoxamine over a period of weeks to months is a very effective way to rescue patients with severe iron overload.

**Table 3.** Iron chelation therapies.

Drug	Route	Toxicities	Advantages	Disadvantages	Monitoring
<i>Deferasirox (Exjade)</i>	PO	GI symptoms Rash Renal Transaminitis Neutropenia	Convenience (PO) Low toxicity No risk of cutaneous bleeding or infection	Relatively new Limited long-term experience	Creatinine monthly Creatinine clearance ALT monthly (and 2 weeks after initiation of the drug) Neutrophil count monthly Ferritin every 3 months Liver iron annually Cardiac iron and cardiac function annually (after age 10)
<i>Deferoxamine (Desferal)</i>	SQ, IV	Skin irritation Hearing impairment Decreased visual acuity, night blindness, color vision abnormality, retinobulbar optic neuropathy, and retinal pigment degeneration Skeletal abnormalities Infection risk ( <i>Yersinia</i> )	Well-defined efficacy and toxicity profile Efficacious Treatment of cardiac iron overload	In-convenience Poor compliance Infection and bleeding risks with SQ infusion if neutropenic or thrombocytopenic	Annual auditory and visual testing Ferritin every 3 months Liver iron annually Cardiac iron and cardiac function annually (after age 10)
<i>Deferiprone (Ferriprox)</i>	PO	Neutropenia Arthritis Hepatic fibrosis	Convenience (PO) May enhance cardiac iron chelation	Possible lower efficacy Risk of cytopenias Frequent laboratory monitoring Not approved in US for patients with FA	Regular CBC with differential ALT monthly Ferritin every 3 months Liver iron annually Cardiac iron and cardiac function annually (after age 10)

Abbreviations: *By mouth*, PO; *subcutaneous*, SQ; *intravenous*, IV; *gastrointestinal*, GI; *alanine aminotransferase*, ALT; *complete blood count*, CBC

Given the disadvantages of a parenterally administered drug, deferasirox offers an attractive alternative for iron chelation. Deferasirox is conveniently administered orally once a day as a slurry with a variety of palatable beverages, however more palatable preparations are forthcoming. Short- and long-term side effects of deferasirox include renal toxicity, gastrointestinal symptoms, skin rash, and elevated levels of the liver enzyme alanine aminotransferase (ALT), and are generally well tolerated. The optimal dose of deferasirox is between 20-40 mg/kg, which can maintain iron balance in most patients, but unlike deferoxamine, may not be sufficient to reduce iron overload. Therefore, patients who continue to have unacceptable iron levels on deferasirox despite maximal dose escalation should be switched back to deferoxamine (perhaps as a 24 hour/day intravenous infusion) until target iron levels have been achieved. A recent study from Turkey reported that average ferritin levels of 3377 ng/mL were decreased by one third in FA patients taking oral deferasirox therapy for 13 months, and 6 out of 39 patients demonstrated renal or hepatic toxicities <sup>(46)</sup>.

Deferiprone is currently not licensed for clinical use in the US for patients with FA. Studies in populations of patients without FA suggest that deferiprone may be more efficient than deferoxamine at removing cardiac iron. However, the utility of deferiprone is limited by its side effects, which include neutropenia and fatal agranulocytosis, a particular concern in individuals with bone marrow failure, and arthralgias and arthritis. There is only one published case report of deferiprone use in a patient with FA <sup>(47)</sup>.

Continuous high dose (e.g. 50 mg/kg/day) intravenous infusion of deferoxamine has been shown to reduce dysrhythmias and to improve left ventricular function in patients with severe iron overload or with cardiac functional compromise (arrhythmias or failing left ventricular function) <sup>(48)</sup>. A small pilot study found that deferoxamine in combination with deferasirox was efficacious in individuals with severe iron overload. Cases of iron overload that are significant enough to warrant such aggressive treatments should be discussed with an expert who is familiar with combination therapy.

There is no demonstrated role for the use of erythropoietin (a hormone produced by the kidneys that stimulates red blood cell production) to treat anemia in patients with FA in the absence of erythropoietin deficiency (e.g., in association with renal failure).

### **Thrombocytopenia**

Bone marrow transplant should be discussed/considered when the platelet counts fall below 50,000/mm<sup>3</sup>. If transplant is not pursued, then thrombocytopenia should be treated with androgens as the platelet count declines toward 30,000/mm<sup>3</sup>. As noted above, a long trial of oxymetholone or danazol (up to 6 months) is required before treatment is considered unsuccessful due to the lack of a platelet response or unacceptable side effects.

Platelet transfusion is indicated in patients with severe bruising or bleeding, or who are undergoing invasive procedures. The strict use of a numeric trigger for transfusion is probably not necessary. However, platelets under 10,000/mm<sup>3</sup> are more often treated with transfusion of platelets. Platelets from a single donor should be provided in an effort to decrease the risk that the patient will develop an immune response to the transfusion. Transfused platelets should be depleted of leukocytes and irradiated.

The drugs epsilon aminocaproic acid (Amicar) or tranexamic acid may be used as an adjunct to platelet transfusion in a patient with mucosal bleeding. The drug Amicar is given at a dose of 50-100 mg/kg every six hours, with a maximum dose of around 12 g/day. A loading dose of 200 mg/kg may be considered. Amicar is usually administered for several days until the clot is stabilized. Amicar is generally contraindicated in patients with hematuria.

Additional factors that increase bleeding risk should be minimized. Drugs that inhibit platelet function, such as aspirin, non-steroidal anti-inflammatory drugs (e.g., ibuprofen), and some antihistamines, should be avoided. Supplements and foods such as omega 3s, flax seed and green tea are associated with increased bleeding and should be avoided in thrombocytopenic individuals and in anyone anticipating surgery. A soft toothbrush should be used. Stool softeners should be administered if constipation poses a risk of GI mucosal trauma. Activities carrying a high risk of significant trauma (particularly to the head or trunk) should be avoided. To date there are no data supporting the use of thrombopoietin-mimetic drugs.

### **Neutropenia**

Patients with mild neutropenia are often asymptomatic. Treatment with G-CSF as described above may be considered if the patient is having neutropenia-related infectious complications with neutrophil counts <500/mm<sup>3</sup>. G-CSF may also be considered for patients with a history of recurrent or severe infections. Patients with fever and neutropenia should have a thorough examination,

have samples of their blood cultured in a lab, and should receive broad-spectrum antibiotics until the blood cultures test negative for infection and the fevers resolve. There is no demonstrated role or/special need for the use of prophylactic antibiotics or antifungals in patients with FA, except as indicated for any patient (for prophylaxis of certain dental procedures for example). Such practices may lead to increased risks of fungal infections and antibiotic resistance. Recently, non-systemic antibiotics or ethanol lock therapy in concert with scrupulous line hygiene have been employed successfully to reduce infections associated with vascular access devices.

### **Sedation and analgesia for invasive procedures**

Given the need for frequent evaluation of the bone marrow, adequate sedation and analgesia should be offered to every patient undergoing bone marrow examination. The use of local anesthetic alone may be insufficient to alleviate the anxiety and pain that is associated with frequent, repeated bone marrow procedures. The use of propofol, an intravenous anesthetic, or a locally preferred regimen used in accordance with the guidelines established by the American Academy of Pediatrics is strongly recommended. Such regimens may make it easier for families and patients to accept a yearly bone marrow examination as a routine part of the care for FA.

## **Chapter Committee**

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# Chapter 4: Gastrointestinal, Hepatic, and Nutritional Problems

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## Introduction

### Good to Know

The **gastrointestinal system** digests food and absorbs the nutrients our bodies need to function properly.

This system is a complex group of cells organized as a long, hollow tube that begins at the mouth, continues through the esophagus, stomach, and intestines, and ends at the anus. The liver aids digestion by producing bile, which helps the body break down fats. The liver also clears some toxins from the body and synthesizes certain nutrients.

Both Fanconi anemia (FA) and medications used to treat the disease can cause gastrointestinal disorders, liver disease, and nutrition-related challenges. Many patients experience symptoms such as reduced appetite, nausea, abdominal pain, and diarrhea. Without proper treatment, these symptoms can interfere with daily living and create hurdles to healthy growth and development.

Concerns related to the gastrointestinal tract most commonly include:

- *Abnormalities of the gastrointestinal tract*
- *Gastrointestinal symptoms, including poor food intake, nausea, abdominal pain, and/or diarrhea*
- *Poor weight gain or malnutrition, often resulting from reduced food intake or difficulty absorbing nutrients from food*
- *Overweight or obesity*
- *Cancers of the gastrointestinal tract*
- *Liver disease*
- *Gastrointestinal-related complications of hematopoietic stem cell transplant (HSCT)*

The gastrointestinal clinical care team should include a **gastroenterologist** or **pediatric gastroenterologist** and, when needed, a **dietician**. This team should work in close collaboration with other FA specialists to provide comprehensive care. The involvement of multiple types of providers in the care of patients with FA introduces the risk that medications prescribed by one physician might adversely interact with those prescribed by another. Therefore, it is essential that all subspecialists communicate with the primary physician, usually the hematologist/oncologist, to coordinate care.

## Gastrointestinal Tract Anatomic Abnormalities

Approximately 7% of patients with FA are born with anatomic (structural) abnormalities in the gastrointestinal tract<sup>(1)</sup>. The most common abnormalities include:

- **Esophageal atresia (EA)**, in which the lower end of the esophagus—the tube that connects the mouth to the stomach—is incomplete or blocked and does not allow food to pass from the esophagus into the stomach.
- **Esophageal atresia** (see above) with **tracheoesophageal fistula (TEF)**, an abnormal passage between the esophagus and the trachea, or windpipe, that may result in food from the esophagus crossing into the airways or air entering the esophagus.
- **Duodenal atresia**, in which the entrance to the small intestine, or duodenum, is incomplete or blocked and does not allow the contents of the stomach to enter the intestines.
- **Anorectal malformations**, a spectrum of disorders involving the rectum and anus. These malformations may include a blockage of the anus, a failure of the rectum to connect to the anus, or an abnormal passage between the rectum and another part of the body, such as the urinary tract or reproductive system.

Most anomalies are diagnosed and treated in early infancy, often before the diagnosis of FA. Although the gastrointestinal tract abnormalities may occur in isolation, they may also appear together with other birth defects, including the VACTERL spectrum of disorders—a group of abnormalities that are not necessarily related to each other, but tend to occur together. The term “VACTERL” is an acronym that stands for the following:

- ***Vertebral defects***
- ***Anorectal malformations***
- ***Cardiac abnormalities***
- ***Tracheo-Esophageal abnormalities***
- ***Renal defects***
- ***Limb defects***, such as extra fingers or toes, or abnormally formed forearms

Most patients with these anomalies do not have FA. However, because an early diagnosis of FA may help to prevent complications, all children exhibiting kidney and/or radial (referring to a bone in the forearm) abnormalities in addition to other disorders belonging to the VACTERL spectrum should be tested for FA <sup>(2)</sup> as described in *Chapter 2*.

Patients with FA may experience complications of these anatomic abnormalities and their surgical treatment throughout their lives. The long-term complications of these anomalies, described below, are similar in patients with and without FA.

### **Esophageal atresia and tracheoesophageal fistula**

Esophageal atresia, with or without tracheoesophageal fistula (EA/TEF), is rarely diagnosed during pregnancy. Symptoms of EA/TEF in newborns may include excessive drooling, feeding intolerance or respiratory difficulties. Survival of EA/TEF is very good—more than 98% of EA/TEF infants who weigh more than 3 pounds 5 ounces (1500g) and lack major heart defects survive to childhood and beyond <sup>(3)</sup>.

The severity of the EA/TEF defect and the quality of the repair determine the long-term complications the patient may experience. One form of EA/TEF, known as long gap atresia—characterized by a gap in the esophagus that spans a distance greater than 3 vertebrae of the spine—is difficult to repair and increases the risk that the esophagus will narrow, resulting in additional complications. A second, more severe form of EA/TEF is called ultra-long gap atresia, defined as a gap in the esophagus that spans 5 or more vertebrae. In this form of atresia, the esophageal segments are very short and it is likely that significant complications will occur. Therefore, these patients may require advanced surgical techniques, including reconstruction of the esophagus using tissue from the colon or stomach, or operations that induce esophageal growth. These procedures are associated with many complications, including leakage from the repaired esophagus connections, swallowing problems such as pain

with solid foods, frequent reflux, and vomiting. There may also be a long-term risk of colonic cancer in colon tissue used to reconstruct the esophagus. Experts continue to debate the preferred method for the treatment of ultra-long gap EA/TEF <sup>(3)</sup>.

EA/TEF repair in infancy frequently leads to gastroesophageal reflux disease (GERD), difficulty swallowing, and breathing problems in adulthood <sup>(4)</sup>. Diagnosis and management of GERD, a condition in which the contents of the stomach leak backwards into the esophagus, is essential to reduce pain, bleeding, and narrowing of the esophagus; anti-reflux surgery is often necessary. Respiratory problems, including cough, pneumonia, and wheezing may suggest the need for bronchoscopy, a procedure that enables clinicians to look inside the airways. Recurrent TEF should be considered if pneumonia or pain develops after a period of relatively good health.

### **Duodenal atresia**

Duodenal atresia occurs less frequently than EA/TEF. More than 50% of patients with duodenal atresia have other birth defects. Approximately 90% of infants survive the surgical repair of the intestines, and will grow normally and develop few symptoms. However, 12-15% of patients develop complications in the months and years after the surgery, including abdominal pain, delayed gastric emptying (slowed movement of food from the stomach to the intestines), peptic ulcer, megaduodenum (enlargement of the duodenum), reflux of fluids from the intestines into the stomach and esophagus, and blind loop syndrome—a condition in which food slows or stops moving through the intestine. Patients with duodenal atresia frequently experience slow movement of food through the digestive tract above the intestinal passage formed by surgery. Enlargement of the duodenum can occur up to 18 years after surgery and is associated with poor weight gain, vomiting, abdominal pain, and blind-loop syndrome, and usually requires additional surgery <sup>(5)</sup>.

### **Anorectal malformations**

Anorectal malformations are a spectrum of birth defects in which the gastrointestinal tract is closed off and not connected to the anus, or instead opens at an improper location, such as the skin, urinary tract, or reproductive system. The long-term outlook for patients with anorectal malformations varies and depends on the type of malformation, surgical technique used to repair the malformation, presence of additional disorders, ongoing medical care, and follow up. Management of these complications requires a multidisciplinary

approach. Long-term problems may include fecal incontinence, occasional soiling, and constipation with or without encopresis (involuntary leakage of stool) <sup>(6)</sup>. In most cases, bowel control can be restored with medication, although some patients may require a surgical procedure known as antegrade continence enema (ACE).

## Gastrointestinal Symptoms

Many patients with FA experience gastrointestinal symptoms, including poor food intake, nausea, abdominal pain, and/or diarrhea. These symptoms cause significant discomfort and may contribute to poor weight gain in FA patients. During routine clinic visits, clinicians should encourage patients and their families to report gastrointestinal symptoms, as patients often do not spontaneously disclose these concerns.

- **Poor food intake** can result from many factors, including complications of anatomic gastrointestinal abnormalities (narrowing of the digestive tract or complications of repair), chronic inflammation and/or infection, medication side effects, or neurologic/behavioral problems.
- **Nausea** in patients with FA often results from infections (particularly urinary tract or sinus infections), delayed gastric emptying caused by infection, or medications. Nausea is usually temporary, resolving once the infection has been cured or the medication stopped. Psychological stress, anxiety, and depression can also lead to nausea and abdominal pain, and may worsen existing gastrointestinal complaints.

### Good to Know

**Opportunistic infections** are caused by microorganisms that are normally controlled by a healthy immune system but can become harmful when the body's immune system is impaired and incapable of fighting off the infection.

**Short bowel syndrome** occurs when nutrients from food are not properly absorbed because a large segment of the small intestine is non-functional or has been surgically removed.

- **Abdominal pain** may also result from partial blockage of the digestive tract, which can be caused by complications of structural defects in the gastrointestinal system. Abdominal pain can also result from abnormal gastrointestinal motility, overgrowth of bacteria in the small intestine, or gallbladder disease.

- **Diarrhea** can occur for a variety of reasons, including opportunistic infection of the gastrointestinal tract, overgrowth of bacteria in the small intestine, medications, and short bowel syndrome. Constipation with accidental leakage of stool may be mistaken by some families for diarrhea.

### **Initial evaluation of gastrointestinal symptoms**

In all cases, the initial evaluation of gastrointestinal symptoms in patients with FA begins with a history and physical exam. Most problems can be diagnosed at this level, without need for further study. If the patient has non-specific poor food intake, with or without nausea and abdominal pain, evaluation for evidence of an unobvious infection may be useful. Infection or systemic inflammation may be identified through laboratory studies, including urine culture, measurement of serum C-reactive protein, and red blood cell sedimentation rate. Patients with diarrhea should have stool examination for ova and parasites, giardia and cryptosporidia antigen, and other opportunistic agents. To diagnose suspected overgrowth of bacteria in the small intestine, hydrogen breath test or an experimental trial of the antibiotic metronidazole are recommended. Duodenal intubation to collect small intestinal juice for culture is impractical and not recommended for FA patients, who have both increased radiation sensitivity and increased risk for bleeding.

### **Limiting Radiation Exposure**

Patients with FA are more sensitive to radiation than the general population. Therefore, physicians caring for a patient with FA should be judicious in the use of diagnostic tests that involve radiation, and should be in close contact with the pediatric radiologist when tests involving radiation exposure are warranted. The radiologist may help reduce exposure to diagnostic radiation by substituting imaging techniques that don't involve radiation exposure, such as ultrasound or magnetic resonance imaging (MRI).

If CT scans, a radiation-based imaging technique, are necessary, they should be limited to the area considered most important. Because pediatric and adult CT scan protocols differ in the amount of radiation used in each scan, care should be taken to use a pediatric-specific CT scanner managed by qualified pediatric radiologists who can minimize radiation exposure when radiographs are essential for pediatric patients. In some cases, digital radiographs may deliver less radiation than conventional techniques and are thus preferred.

As a general rule, studies involving radiation exposure should be avoided when possible, because patients with FA are more sensitive to radiation than the

general population. Radiographic imaging of the gastrointestinal tract should be reserved for patients with FA with compelling clinical evidence of bowel obstruction, whenever possible. Children with gastroesophageal reflux disease can be treated if they are old enough to reliably explain their symptoms. Alternatively, reflux can be diagnosed with a manometric-placed pH/impedance probe. Gastritis and other peptic diseases should be diagnosed by a procedure called endoscopy with biopsies without radiographic imaging. Peptic disorders should be treated with drugs known as proton pump inhibitors (e.g., omeprazole or lansoprazole at a dose of 1 mg/kg/day); H<sub>2</sub>-antagonists should be avoided because these drugs increase the risk of bone marrow suppression.

### **Evaluation of gastric emptying delay**

Gastric emptying delay should be suspected in patients who experience nausea, feel full sooner than usual, and vomit food eaten several hours earlier. Some patients, however, may experience no symptoms. Delayed gastric emptying in the general population is commonly diagnosed using the nuclear medicine gastric emptying study, which involves radiation. To avoid radiation exposure in patients with FA, a gastric emptying study can be omitted and a trial of medication can be initiated, provided that the patient has classic symptoms, normal physical exam, and no evidence of obstruction in the digestive tract. Ultrasound-based diagnosis of delayed gastric emptying may be available at some clinics.

If the diagnosis of delayed gastric emptying is entertained, the patient should undergo dietary counseling with a dietitian to adjust meal content and frequency; small and frequent meals that restrict fats and nondigestible fibers while maintaining adequate caloric intake should be favored. A trial of medication that enhances gastrointestinal motility may be given, including erythromycin (5 mg/kg/dose, 3 times per day), or—in Canada and Europe—domperidone (0.25 – 0.5 mg/kg/dose 3 to 4 times per day; maximum daily dose of 2.4mg/kg or 80mg/day). Prior to prescribing, the physician must determine if the patient is on any medication that may interact adversely with the gastric emptying medication. For example, the azole group of medications (i.e., fluconazole, itraconazole, or ketoconazole), used to treat fungal infections are known to interact adversely with erythromycin. The use of metoclopramide is not recommended because of potentially dangerous side effects including irreversible tardive dyskinesia, a movement disorder characterized by repetitive and involuntary movements. Amoxicillin/clavulanic acid has been shown to improve small intestine motility and may be prescribed when the above



medications have failed or if a patient is not tolerating jejunal feeds (feeding directly into the small intestine) (20 mg/kg amoxicillin and 1 mg/kg clavulanate twice a day, with a maximum of 250 mg of amoxicillin 3 times a day) <sup>(8,9)</sup>.

Cases of delayed gastric emptying that do not improve with medication may require surgical procedures, such as endoscopic therapy with pyloric dilatation and botulinum toxin injection, jejunostomy, or gastro-jejunostomy. Before performing surgery, which could introduce further gastrointestinal complications, physicians should note that most cases of delayed gastric emptying in children that occur without an identifiable cause will resolve over time. Patients who report symptoms such as nausea or abdominal pain within 30 minutes of starting a meal might have impaired gastric accommodation, a condition in which the stomach fails to relax and accept food. These patients may benefit from treatment with the medication cyproheptadine, given 30 minutes before meals. In cases of severe, uncontrollable nausea without a detectable cause, a trial of the medication ondansetron may be warranted if there is no improvement with cyproheptadine or domperidone.

## Poor Weight Gain

### Good to Know

**Growth curves** allow physicians to monitor a child's growth over time in comparison with other children of the same age and gender.

These tools can track a child's progress using various measurements, including height, weight, and body mass index (BMI).

If a child's growth curve deviates from those of his healthy peers, physicians may search for an underlying health problem.

Parents of children with FA are often concerned about their child's poor weight gain and "picky eating." These two issues should be addressed separately. Approximately 60% of children with FA have short stature as part of the genetic disease. These children will also have proportionately lower weights. Parents should have a chance to discuss the pattern of their child's growth curves, particularly the changes in weight relative to height from birth to 2 years of age, and body mass index (BMI), a measure of body shape based on weight and height, after age 2. Parents should be encouraged to accept as normal a child whose weight is appropriate for their somewhat short height. Aggressively trying to increase the child's food intake will not increase their

height or overall health, and may create disordered eating or family problems with meals.

Children who are “picky eaters” and their families may benefit from behavioral therapies to increase the variety of foods eaten. These therapies have not been studied in patients with FA, but have been effective in other patient populations with poor food intake. For example, in patients with cystic fibrosis, behavioral modification has demonstrated long-term improvements in food intake <sup>(7)</sup>.

### **Evaluating poor growth**

Many children with FA experience poor growth. Weight and height should be measured at each clinical visit using methods appropriate for the age of the child and plotted on a graph called a growth curve (measurements of weight relative to height should be plotted for children less than 2 years of age, and measurements of body mass index (BMI) relative to age should be plotted for children more than 2 years of age).

Children with FA may be shorter than expected based on the genetic condition itself, the (non-FA related) genetics contributing to growth pattern in their families, the multiple hormonal abnormalities documented in these patients <sup>(10)</sup>, or growth suppression due to inflammation associated with infection. Nevertheless, children with FA should have a normal weight-for-height or BMI for age. Evaluation by a pediatric endocrinologist may be needed for children with FA who exhibit poor growth.

Malnutrition, whether the result of poor food intake, high energy utilization, or excessive stool losses, initially results in a growth curve demonstrating low weight relative to height or low BMI relative to age. Attention must also be paid to children exhibiting weight loss or reduced growth rate. One study found that 22% of patients with FA were underweight, indicative of malnutrition <sup>(10)</sup>. The overall nutritional status of patients with FA can be determined during each routine physical exam by assessing muscle mass, skin and mucus membrane health, and energy and activity levels.

### **Poor food intake versus malabsorption**

In patients with documented poor weight gain or weight loss, both poor food intake and/or diarrhea with malabsorption (poor absorption) of nutrients must be considered. Analysis of the patient’s 3-day dietary record may indicate inadequate protein and calorie intake. Dietary counseling, with or without evaluation by a feeding specialist, may be enough to improve oral intake in

some patients; however, if food intake does not increase, counseling should be aimed at maximizing calories by addition of high calorie foods and liquid or powder supplements. Patients with FA may also have deficiencies in or increased need for specific vitamins and minerals, including folate and zinc. Even children with adequate weight-for-height may benefit from a daily vitamin-mineral supplement (generally, an iron-free supplement should be selected, and excessive doses of vitamins should be avoided, as discussed below). All patients should be screened for vitamin D deficiency at least once a year, preferably during the winter, by checking blood levels of the active form of vitamin D, known as 25-hydroxyvitamin D. If the level of 25-hydroxyvitamin D is less than 30, then supplementation with oral vitamin D once a week is indicated. Patients under 44 pounds (20 kg) should receive 8,000 IU once a week; those over 44 pounds (20 kg) should receive 50,000 IU once a week. Vitamin D levels should be rechecked after 8 weeks, and supplementation should continue until the 25-hydroxyvitamin D level is above 30.

### **Supplemental feeding**

Supplemental feeding may be needed to achieve a healthy nutritional status in children who are persistently less than 85% of the expected weight for their height, who have a BMI that is persistently less than the 3rd percentile for their age, or who have failed to gain weight over a 3- to 6-month period. This strategy involves delivering a liquid food mixture directly into the bloodstream, stomach, or small intestine, thereby bypassing appetite and food interest. In this way, supplemental feeding allows the child to achieve normal growth to meet his/her genetic potential, have the energy to meet the demands of daily living, and store adequate nutritional reserves to face short-term malnourishment during acute illness.

Supplemental feeding via feeding tube, known as enteral supplementation, is preferable to supplementation by intravenous infusion, known as parenteral nutrition. Supplemental parenteral feeds require placement of a central catheter, which increases the risk of infection, metabolic disorders, and liver injury. Parenteral feedings should be limited to those patients unable to meet their needs with enteral nutrition.

Enteral supplementation may be delivered by feeding tubes inserted into the nose, such as a nasogastric tube or nasojejunal tube, or by a tube surgically inserted into the abdomen, known as a gastrostomy tube. In general, it is recommended that patients have a nasogastric or nasojejunal feeding trial

before proceeding to gastrostomy, thereby avoiding surgery unless absolutely necessary. Most patients tolerate nasal tubes well; the major objection, particularly among older children, is the unattractive nature of a visible tube in the nose. Nonetheless, for patients who need supplemental feedings for less than 3 months, the nasal route is the best. Many children can be taught to place the tube at bedtime and remove it on awakening before going to school. It should be noted, however, that nasal tubes increase the risk of sinus infection. Furthermore, infants and neurologically impaired children may be at risk for dislodging the tube at night and inhaling the formula into the lungs. Nasojeunal tubes carry less risk of dislodgment than nasogastric tubes and, perhaps, less risk of gastroesophageal reflux of formula feedings. Dislodged tubes must be replaced by a radiologist using an X-ray-based imaging technique known as fluoroscopy.

Gastrostomy tubes provide more permanent access to the gastrointestinal tract for administration of enteral feedings. Placement requires a brief surgical procedure, generally performed by endoscopy, in which a small camera on the end of a thin, flexible tube is inserted into the gastrointestinal tract. In general, complications are limited to local irritation and/or infection, which can be treated with antibiotic ointments applied directly at the site of infection, rather than oral antibiotics that act on the whole body. Rarely, the gastrostomy tube can become dislodged, increasing the risk of infection. If the patient's platelet level is very low at the time of surgery, excessive bleeding is a risk. Unfortunately, many patients with FA have an abnormally low count of neutrophils, a type of white blood cell that helps defend the body against infections, resulting in a significantly elevated risk of infection at the gastrostomy tube site that may prevent placement of the tube.

To improve daytime appetite, supplemental feedings can be given over a period of 8-10 hours at night, using a high-calorie formula, if possible; patients may still refuse breakfast, but are generally hungry by lunch. Once an appropriate weight-for-height has been attained, it may be possible to reduce the number of days of the week supplementation is given. For example, older children appreciate not having to use supplemental feeds during sleepovers or group activities. In addition, parents usually do not need to transport feeding equipment on short vacations if the child can eat during the day.

Some patients experience heartburn after starting enteral feeding supplementation, particularly with nighttime feeds. Vomiting may also occur, particularly in the morning, and diarrhea can be a problem at night. Usually, a

dietitian or physician can make simple modifications to the therapy that will alleviate these symptoms. It is also advisable that patients monitor blood sugar levels regularly when on a high-calorie diet.

The preferred choice of enteral feeding methods may vary from patient to patient. Therefore, patients and their families must be educated about all of the available options. Importantly, the choice must not limit the child's social life—for example, even if supplemental feeds are likely to end after several months, a gastrostomy may be better accepted than a nasogastric tube by an image-conscious teenager.

### **Appetite stimulants**

Several medications have alleged appetite-stimulating side effects (e.g., cyproheptadine, megestrol acetate, and the atypical antipsychotic agents olanzapine and mirtazapine). Although these drugs were not originally formulated or prescribed as appetite stimulants, they have been used to try to prevent unwanted weight loss in patients with cancer, HIV/AIDS, and cystic fibrosis<sup>(11, 12)</sup>; however, none of these drugs has been tested in patients with FA. *The inclusion of this material in this chapter should not be construed as a recommendation.*

Before prescribing appetite stimulants, physicians must first investigate and appropriately manage diagnosable causes of poor appetite and inadequate growth. Appetite stimulants will not treat delayed gastric emptying, depression, chronic infection, or other treatable causes of inadequate weight gain and growth. It remains unclear whether any weight gained while taking appetite stimulants will be maintained after the medication has been stopped.

Cyproheptadine, an antihistamine used to treat allergic reactions, is a popular appetite stimulant because it has few side effects besides temporary sleepiness. In randomized, double-blind, placebo-controlled trials, the drug was well tolerated by patients with cancer or cystic fibrosis, but resulted in little or no weight gain<sup>(12, 13)</sup>. However, some physicians elect to try this medication before resorting to nasogastric or gastrostomy feedings. Patients may benefit from cyproheptadine, as it improves gastric accommodation to reduce retching<sup>(14)</sup>.

## **Overweight and Obesity in FA**

As in the general population, some patients with FA are overweight or obese. In one study, 27% of patients with FA were overweight or obese; furthermore,

these overweight or obese patients tended to also have diabetes <sup>(15)</sup>. Children who have a BMI greater than the 85th percentile and less than the 95th percentile for age are considered overweight, and those who have a BMI greater than the 95th percentile for age are considered obese. Both diagnoses must be confirmed by physical exam. Significant complications may result from overweight and obesity, including elevated levels of fat and cholesterol in the blood, diabetes, obstructive sleep disorder, and other aspects of metabolic syndrome—a combination of disorders that increase the risk of developing cardiovascular disease and diabetes. Some families may be surprised to find that a patient with FA may become overweight or obese after previous concerns with being underweight, but modification of lifestyle is essential.

While a full discussion of the management of overweight and obesity is beyond the scope of this chapter (see references <sup>16-18</sup> for a review), some useful starting points can be offered. Physicians should ask patients to keep a 6-day diary of diet and daily activity, both of which provide the foundation for counseling regarding dietary and exercise changes. Most families will require monthly counseling sessions for a time to insure achievement of appropriate weight. Psychological counseling may also help, especially if an eating disorder is suspected.

The obese patient should be assessed for the primary health consequences of obesity. At a minimum, measurements should include blood pressure using an appropriately sized cuff, fasting lipid profile, oral glucose tolerance with insulin levels, and blood levels of the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Obese patients with sleep disturbance or snoring will require a sleep study and may need an echocardiogram (a non-invasive imaging procedure that is used to assess heart function).

Management of overweight and obesity is a long-term process, requiring the commitment of the entire family for success. Patients should be urged to avoid fad diets and over-the-counter weight loss preparations and to focus on healthy lifestyle modifications.

## **Cancer Screening**

Cancers of the gastrointestinal system are potential complications of FA. Only one case of colon cancer in a person with FA has been documented. Thus, the expert group preparing this review cannot recommend early colon cancer screening for patients with FA. Screening for esophageal carcinoma can be

done using an endoscope, a thin, flexible tube-like device used to look inside the body. Because esophageal cancers in patients with FA tend to be located in the upper part of the esophagus, an endoscope with a small diameter can be used with minimal sedation. Some experts recommend yearly ultrasound imaging of the liver to screen for liver tumors, even for the youngest patients.

## Good to Know

**Androgens** are hormones produced in the body that stimulate the development of male sex characteristics, such as testes formation and sperm production.

Androgens can be used therapeutically to increase the production of blood cells.

## Liver Disease

Liver disease in patients with FA is generally a complication of treatment. As a general rule, patients with liver disease should be referred to a gastroenterologist with expertise in liver disease. The following sections provide an overview of the most common liver-related problems that affect patients with FA.

### Liver complications of androgens

The androgenic steroids used to treat low blood cell counts in patients with FA can cause multiple liver complications, including a rare condition called peliosis hepatis, subcellular changes in liver cells called hepatocytes, and benign liver tumors known as hepatocellular adenomas<sup>(19)</sup>. One study of patients with FA found a 5-fold increase in liver enzyme levels—an indicator of liver injury—in patients with a history of androgen therapy compared with those without a history of androgen therapy; furthermore, 3 of the 20 patients treated with androgens developed liver tumors<sup>(20)</sup>. Thus, careful monitoring for hepatic complications of androgen therapy is essential. See Figure 1 for suggestions for managing liver complications in patients with FA on androgen therapy.

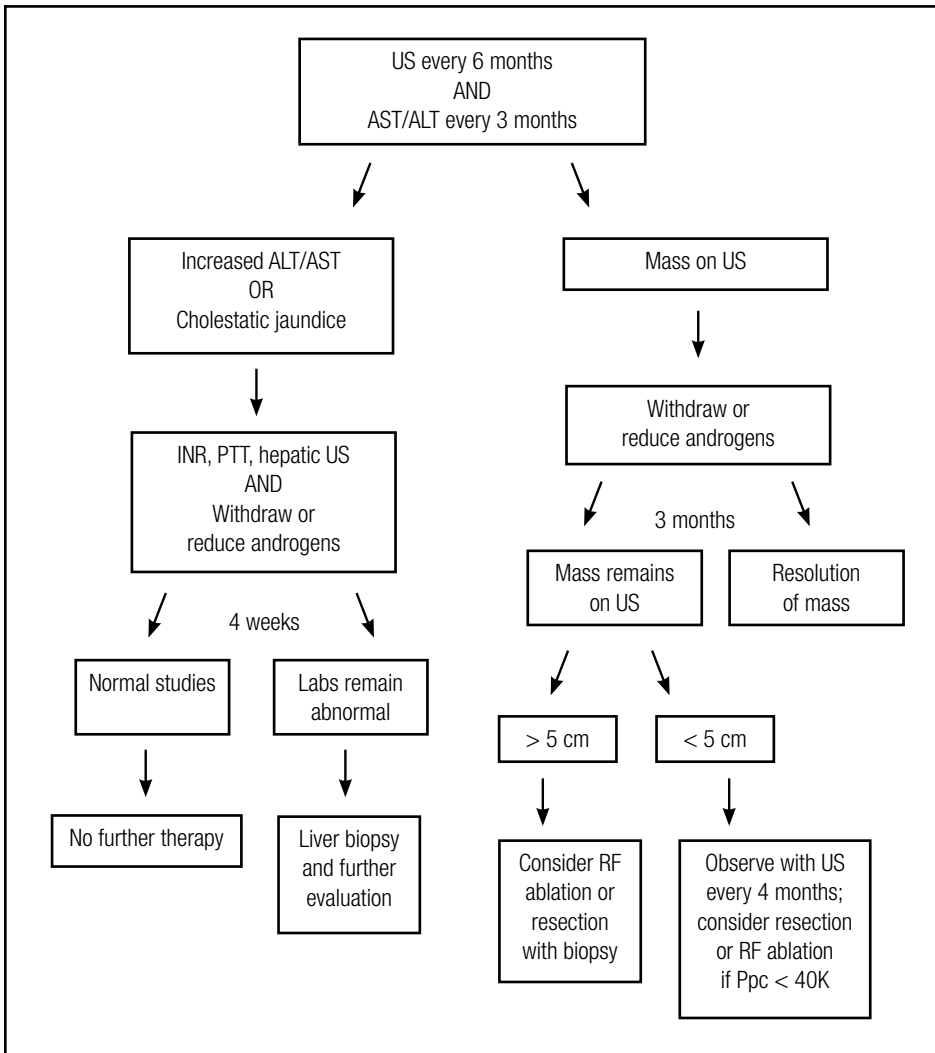
- ***Peliosis hepatis (PH)*** occurs when blood vessels in the liver called sinusoids become excessively dilated and form large blood-filled spaces, like cysts, that are scattered throughout the liver. This condition can occur with any dose of androgen therapy and at any time during treatment. Although many cases of PH are asymptomatic, symptoms may include abnormal enlargement of the liver, and pain and tenderness in the upper

right portion of the abdomen. This condition can be life-threatening if the sinusoids rupture. Patients with PH display normal levels of liver enzymes, bilirubin, and tests of liver function. This condition is best diagnosed via liver biopsy, although imaging techniques (e.g., ultrasound, angiography, and computed tomography) may reveal large lesions. Liver biopsy may be impossible in patients who have a high risk of bleeding. The lesions may regress after androgen therapy ends <sup>(19, 21)</sup>.

- ***Nonspecific damage to the cells of the liver***, a potential consequence of androgen therapy, can lead to cholestatic jaundice—yellowing of the skin and eyes due to obstructed bile flow in the liver—or hypertransaminasemia—elevated levels of the liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST). There are case reports of liver cirrhosis in patients on continued androgen therapy <sup>(19)</sup>. Cessation of androgen therapy will usually lead to complete resolution of symptoms. However, if liver enzyme levels do not return to normal after androgen withdrawal, then liver biopsy may be indicated (see more information on androgens in *Chapter 3*).
- ***Hepatocellular adenomas*** can also result from androgen therapy. An adenoma is a benign tumor that does not invade surrounding tissue; however, it can rupture, leading to life-threatening bleeding. The risk of bleeding in hepatocellular adenomas is increased in patients with thrombocytopenia, a condition in which the blood has an abnormally low number of platelets, which help blood to clot. Patients with FA may develop hepatocellular adenomas rapidly, often within 3 months of beginning androgen therapy <sup>(21-23)</sup>. Hepatocellular adenomas are generally diagnosed by ultrasound. Contrast-enhanced CT scans and MRI are more sensitive than ultrasound in detecting hepatocellular adenomas. Hepatocellular adenomas may regress after cessation of androgen therapy, but if they persist, surgical removal or radiofrequency ablation may be necessary, particularly prior to hematopoietic stem cell transplantation (HSCT).



**Figure 1.** Management of potential hepatic complications in the patient with FA on androgen therapy.



*Abbreviations:* AST, aspartate transaminase; ALT, alanine transaminase; INR, international normalized ratio; PPT, partial thromboplastin time; US, ultrasound; RF, radiofrequency; Ppc, platelet count

**IMPORTANT NOTE:** Despite the radiation exposure from CT, we strongly recommend that all patients receive both CT and MRI scans before hematopoietic stem cell transplantation (HSCT) if they have previously undergone androgen therapy <sup>(24)</sup>.

- **Hepatocellular carcinoma (HCC)**, or malignant liver cancer, is occasionally reported in association with androgen use. Some studies have suggested that patients with FA may have an increased risk for HCC resulting from androgen use. The HCC associated with androgen therapy is characterized by the absence of  $\alpha$ -fetoprotein in the blood, distinguishing it from other forms of HCC <sup>(19)</sup>. Patients who develop HCC should discontinue androgen therapy.

### **Prevention and management of liver disease**

General protective measures for patients with FA at risk of liver disease include screening, immunization, and avoidance of substances that may be toxic to the liver. Screening for liver disease includes measuring blood levels of the hepatocellular enzymes ALT and AST, and the biliary enzymes, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), and 5'-nucleotidase. To screen for bile cell injury in children, measurements of GGT and 5'-nucleotidase are preferred over alkaline phosphatase, as alkaline phosphatase can be elevated by bone injury or bone growth.

Elevated levels of conjugated bilirubin reflect obstruction of bile flow in the liver or significant liver cell injury. Liver cell function can be investigated by testing how quickly the blood clots (e.g., international normalized ratio (INR) and measurements of albumin levels). A Doppler ultrasound may reveal the accumulation of fat or scar tissue, impaired blood flow, and obstruction of bile flow in the liver.

Patients with elevated liver enzyme levels should have a full evaluation of their liver by a hepatologist or pediatric hepatologist. The evaluation should include screening for the common causes of liver disease and iron overload disorder, a genetic condition in which the liver absorbs excessive amounts of iron from the diet (which might exacerbate iron overload from transfusions in patients with FA), and an assessment of the severity of liver disease. In some cases, liver biopsy may be required.

Patients should be immunized against varicella zoster virus (unless live virus vaccines are contraindicated), hepatitis A virus, and hepatitis B virus. The levels of antibodies against these viruses should be measured to insure that the patient has acquired immunity. Drugs that are toxic to the liver, including alcohol, should be avoided when possible. Levels of fat-soluble vitamins should be monitored on a yearly basis in patients with most forms of liver disease, particularly in cases where bile flow is reduced, known as cholestatic disease.

### **Gastrointestinal and liver complications of hematopoietic stem cell transplant (HSCT)**

To treat the blood abnormalities associated with FA, many patients undergo hematopoietic stem cell transplantation, a procedure in which abnormal stem cells are replaced with healthy stem cells. Prior to HSCT, patients must undergo a complete gastrointestinal, liver, and nutritional evaluation. If undiagnosed chronic abdominal pain exists, endoscopy for detection of potential sources of bleeding or infection may be required. Patients who require supplemental feeding via a gastrostomy tube would ideally have it inserted at least 3 months prior to HSCT to insure complete healing of the insertion site. Infections or irritation at the insertion site should be treated prior to HSCT. In addition, diarrhea should be evaluated to detect opportunistic organisms, optimal nutritional status should be achieved, and the liver cell injury and/or function should be evaluated (see above) prior to the transplant. Patients who previously received androgens must be evaluated for adenomas with ultrasound, CT scan, and an MRI.

A review of the full spectrum of liver- and gastrointestinal-related complications of HSCT is beyond the scope of this work (for a recent review, see reference <sup>25</sup>). This section focuses on the complications that may occur during the first 100 days after HSCT.

While it is not clear that this remains the case with current regimens, historically patients with FA who undergo HSCT had an increased risk of graft-versus-host disease (GvHD), in which the transplanted cells regard the recipient's body as foreign and attack the body, damaging the intestines, skin, and liver <sup>(26)</sup>. FA patients who develop chronic GvHD after undergoing HSCT may experience diarrhea with poor absorption of nutrients from the diet, resulting in difficulty maintaining weight. Occasionally, the intestinal tract narrows, causing pain. Pancreatic insufficiency—a lack of digestive enzymes made by the pancreas that results in impaired food digestion—is uncommon, but should be considered in patients with poor absorption of fat.

Patients with chronic liver GvHD usually experience cholestasis (reduced bile flow) in the liver, with elevated levels of the liver enzymes ALT and AST. ALT and AST may increase rapidly if the patient has GvHD and as the doses of immune system-suppressing medications (given to patients to prevent immune rejection of the transplanted cells) are reduced. It is uncommon for patients to acquire chronic viral hepatitis from HSCT, but this should be considered if liver enzymes are increasing. If the diagnosis of chronic liver GvHD is

uncertain, liver biopsy is indicated. Chronic GvHD of the liver is treated with immune system-suppressing medications and ursodeoxycholic acid (20 mg/kg/day). Cholestasis may lead to poor absorption of the fat-soluble vitamins A, E, D, and K; therefore, levels of these vitamins should be monitored to determine whether vitamin supplementation is needed. Vitamin A, E, and D levels can be measured via blood tests, and vitamin K levels can be inferred by measuring the clotting tendency of blood using the PIVKA test or the INR test <sup>(27)</sup>.

Perhaps most importantly, it should be noted that chronic GvHD increases the risk of squamous cell carcinoma in patients with FA <sup>(28)</sup>. Physicians participating in the long-term management of these patients must be aware of this risk.

## Good to Know

**Transferrin** is a protein in the body that binds and transports iron in the blood. **Transferrin saturation** refers to the amount of iron carried by the transferrin protein in the blood. Saturation increases as the amount of iron in the body increases.

**Ferritin** is a protein that binds and stores iron. The levels of ferritin in the blood increase as the amount of iron in the body increases.

The **unsaturated iron binding capacity** test reveals the amount of transferrin that is not being used to transport iron. Binding capacity decreases as the amount of iron in the body increases.

## Secondary iron overload

Many patients with FA require repeated red blood cell transfusions, which can lead to excessive iron accumulation in the body, a condition known as iron overload (discussed in detail in *Chapter 3*). A single transfusion unit of packed red blood cells contains 200-250 mg of elemental iron. The body is unable to excrete excess iron; thus, all iron obtained via transfusions must be deposited somewhere in the body. When tissue iron levels become too high, organ dysfunction ensues. The organs most commonly affected by iron overload include the liver, pancreas, and heart.

Patients with iron overload are generally asymptomatic; fatigue is the only commonly reported symptom. Patients often have an enlarged liver, which may be discovered by physical exam, and elevated blood levels of the liver enzyme aminotransferase. Cirrhosis is a rare but irreversible complication of iron overload; therefore, it is important to prevent liver fibrosis, the scarring process

that occurs in response to liver injury that can lead to cirrhosis. Fibrosis may occur earlier than usual in patients with viral hepatitis (particularly hepatitis C), non-alcoholic fatty liver disease, and/or alcohol abuse.

Diabetes, joint pain, and heart disease are common in patients with severe iron overload and liver disease. Heart disease may include cardiomyopathy (weakening and enlargement of the heart muscle), irregular heartbeats, or heart failure.

Patients receiving blood transfusions should be screened yearly for iron overload. Iron overload and its therapies are also discussed in *Chapter 3*. Screening is performed using blood tests to measure transferrin saturation, ferritin, and unsaturated iron binding capacity. A transferrin saturation measurement of greater than 45% or a transferrin saturation measurement of less than 45% with elevated levels of ferritin should prompt further testing and investigation into the patient's medical history.

The method of choice for estimating the levels of iron in the liver is a form of magnetic resonance imaging (MRI) called MRI T2\*. MRI is non-invasive and may also detect cirrhosis or hepatocellular carcinoma. Patients with highly elevated blood levels of amino acids, obesity, or those suspected of chronic alcohol consumption may need a liver biopsy to detect liver disease or to determine the extent of liver injury due to other causes. A liver biopsy may assist in choice of therapy. Patients who develop iron overload at an early stage in their blood transfusion history or who have a family history of primary iron overload should undergo genetic testing for hemochromatosis, an inherited disorder that causes the body to absorb too much iron. Patients who test positive for inherited hemochromatosis may need to undergo HSCT earlier than other patients with FA.

## Good to Know

**Oxidative stress** refers to the harmful effects of compounds called free radicals, which can damage cellular structures such as proteins and DNA.

**Free radicals** are naturally produced in the body as our cells use energy, and may be produced in response to environmental factors such as pollution.

**Antioxidants** are substances that neutralize free radicals.

Patients with iron overload should avoid vitamins or medications containing iron and vitamin C, but do not need to restrict their consumption of foods

containing iron and vitamin C. Phlebotomy (removal of blood), the mainstay of classic treatment of iron overload, is not an option for patients with FA who have not yet undergone HCST, but may be used after transplantation and recovery. Another treatment option for patients with FA who have undergone HCST is chelation therapy with drugs that bind iron and remove it from the body<sup>(29)</sup>. This is also discussed in detail in *Chapter 3*. The chelating agent deferasirox has been used in one study of children with FA and iron overload due to blood transfusions, leading to a significant reduction in ferritin levels; of the 39 children who received the drug, 3 developed renal toxicity and 3 developed liver toxicity<sup>(30)</sup>. Oral chelation should be chosen and monitored in consultation with a physician with some experience with these agents.

## Nutrition as Therapy

Complementary and alternative therapies include any treatments and practices that have not been shown to be effective by evidence-based clinical studies. Complimentary therapies are used *in conjunction* with standard medical care, and alternative therapies are used *in place* of standard medical care. Many families view food, and by extension, dietary supplements, vitamins, and micronutrients, as “natural” and thus safe. The multi-billion dollar industry that produces complementary/alternative nutritional regimes lacks federal regulation and has a clear incentive to promote its products regardless of the degree of evidence of the effectiveness of these products. Many complementary/alternative nutritional regimes and supplements are directly harmful or, by displacing standard medical therapy, indirectly harmful.

Some patients with FA might consider taking large doses of vitamins, antioxidants, or trace elements. Although studies suggest that it may be important to counteract oxidative stress in patients with FA<sup>(31)</sup>, this research does not conclusively prove that supplementation with oral antioxidants changes the course of the disease. It remains unclear whether oral antioxidants even reach the intracellular site of oxidant stress in patients with FA. Some of these supplements may be toxic and some may promote tumor development. In particular, vitamins A, D, C, and niacin may be toxic in excess. Micronutrient supplementation to prevent cancer in patients without FA has shown supplementation may reduce cancer risk in populations with nutrient deficiency, but populations with healthy nutrient levels see no effect or, sometimes, increased cancer risk<sup>(32)</sup>. No therapy involving large doses of vitamins, antioxidants, or micronutrients has been shown to be effective in the treatment of FA using evidence-based criteria. Controlled clinical trials of

supplements are necessary to demonstrate effectiveness and limit the risk of toxicity.

Products containing supplemental iron, vitamins A (including b-carotene), C, and E, and omega-3 fatty acids may lead to health risks in patients with FA<sup>(33)</sup>. Products containing iron must be avoided to reduce the risk of exacerbating iron accumulation in the liver and other tissues. Vitamin C increases iron absorption; therefore, products containing vitamin C, such as multivitamins or fortified fruit juices/drinks should be avoided. In large studies, both vitamin A and vitamin E supplements have been associated with an *increased* risk of some cancers; therefore, they should be avoided until further study indicates otherwise. Large doses of omega-3 fatty acids, commonly found in fish oil supplements, can increase the risk of bleeding due to inactivation of platelets, blood cells that mediate blood clotting. Because patients with FA have reduced levels of platelets, products that impair platelet function should be avoided.

It is essential for physicians who manage patients with FA to become knowledgeable about complementary and alternative therapies, and question patients and families about their use of these therapies. Patients and their families often have the desire to control some aspect of the patient's care; in this respect, diet seems a harmless choice. Because patients with FA have significant nutritional problems that are often ignored, there is little to dissuade parents and patients from trying complementary and alternative therapies unless their physician becomes involved in these decisions. Establishing a non-judgmental, but candidly informative discussion of complementary and alternative therapies offers the physician a chance to educate parents about their choices. Physicians and families can access information about complementary/alternative nutritional therapies at the website of the Office of Complementary and Alternative Medicine of the National Institutes of Health, available at: <http://www.cancer.gov/occam>, where there are several links to reliable information.

## Chapter Committee

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# Chapter 5: Hand and Arm Abnormalities

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*Note: Color versions of all figures can be found in Supplemental Information on the FARF website ([www.fanconi.org](http://www.fanconi.org)).*

## Introduction

### Good to Know

Common terms in this chapter:

**Hypoplasia.** Underdevelopment or incomplete development of an organ or tissue in the body.

**Pollicization.** A surgical procedure that creates a functional thumb by moving the index finger and its nerves, arteries, tendons, and muscles to the thumb position.

**Pouce flottant.** A so-called “floating” thumb that lacks bones and is composed of skin and soft tissue.

**Radius.** The shorter and thicker of the two long bones in the forearm.

**Radialization.** A surgical procedure that realigns the patient’s wrist.

**VACTERL Association.** A group of birth anomalies that tend to occur together. See Table 1 for more information about these anomalies.

Approximately half of all children with Fanconi anemia (FA) have skeletal anomalies, most (~70%) of which affect the upper extremities. The most common abnormalities of the upper limbs involve the thumb and radius. Children with these anomalies might have a shortened or absent thumb, radius, or both, due to incomplete growth. Therapy or surgery may be required to maximize the function and appearance of the patient’s hands and arms.

This chapter will describe five common concerns related to the hand and arm in patients with FA:

- *An underdeveloped, missing, or duplicated thumb*
- *A shortened or missing radius*
- *A shortened, curved forearm*
- *A hand that develops perpendicularly to the forearm*
- *Impaired movement in the wrist, fingers, and elbow*

The hand and arm clinical care team should include a **hand and upper extremity surgeon** and, when needed, a **physical therapist** or occupational therapist. This team should work in close collaboration with other FA specialists to provide comprehensive care. The involvement of multiple types of care providers in the care of patients with FA introduces the risk that medications prescribed by one physician might adversely interact with those prescribed by another. Therefore, it is essential that all subspecialists communicate with the primary physician, usually the hematologist/oncologist, to coordinate care.

There are no standardized treatment procedures for congenital hand and arm abnormalities; treatments must be tailored to each child and family. The decision process is multi-factorial and requires participation from the family, physician team, and a physical or occupational therapist.

## Initial Evaluation

Children born with limb abnormalities should be referred to an upper extremity specialist within the first few months of life. This physician should be comfortable with and proficient in the diagnosis and management of congenital limb anomalies. Ideally, a patient with FA should be referred to a hand and upper limb surgeon who specializes in pediatrics, because many physicians who care for limb problems in adults are not comfortable treating children.

The initial exam will lay the foundation for the relationship between the doctor, patient, and the patient's family. It will also provide parents with an opportunity to ask questions about the potential causes, treatments, and outcomes of their child's limb abnormalities. It is important for physicians to encourage this type of conversation; otherwise, parents often seek health information via the Internet, which can be a source of misinformation.

Many children with upper limb abnormalities require physical or occupational therapy, which may begin after the initial assessment. A physical therapist can help to stretch and strengthen the affected limb, and provide adaptive devices that maximize the patient's independence. As children get older and begin to perform increasingly complex physical activities, many parents will worry that their child's impairment is worsening, but in reality their child's activities may simply require additional strength and dexterity. A physical or occupational therapist can offer adaptive devices or techniques to help the child accomplish these tasks.

Limb evaluation often occurs before a patient is diagnosed with FA. Because the radius develops at the same time as many organ systems, the physician must evaluate the patient's entire body. Furthermore, radial deficiency—incomplete formation of the radius—is associated with numerous syndromes, further emphasizing the need for a thorough investigation (Table 1). Many children with VACTERL association have symptoms that are similar to those of children with FA, a diagnostic dilemma that can be solved with the chromosomal breakage test—the definitive clinical test for diagnosing FA. Some patients with VATER (or VACTERL-H) actually have FA, and a combination of radial and renal anomalies in VATER is an important clue in this diagnosis<sup>(1)</sup>. The precise clinical indication for FA testing in children with limb anomalies is still evolving. Every child with isolated thumb or hand abnormalities should be tested for FA, and we recommend testing all children with deficiencies of the thumb and radius. Additional findings, such as skin discoloration (e.g., flat, light brown birthmarks known as café au lait spots), kidney abnormalities, growth retardation, and microcephaly (a small head), add to the suspicion of FA.

**Table 1.** Syndromes and other health conditions associated with radial deficiency.

Syndrome or Health Condition	Characteristics
Holt-Oram Syndrome	Heart defects, particularly defects of the cardiac septa (the tissues that separate the chambers of the heart)
Thrombocytopenia Absent Radius (TAR) Syndrome	Thrombocytopenia (platelet deficiency) present at birth May require blood transfusions, but improves over time Thumbs are present in TAR, but may be abnormal in shape
VACTERL Association (also discussed in Chapter 4)	<b>V</b> ertebral (spine) abnormalities <b>A</b> nal atresia (obstructed or improperly located anus) <b>C</b> ardiac (heart) abnormalities <b>T</b> racheoesophageal fistula (defects of the trachea (windpipe) and esophagus) <b>E</b> sophageal atresia (defects of the esophagus) <b>R</b> enal (kidney) defects <b>R</b> adial dysplasia (abnormal development of the radius on the thumb side of the forearm) <b>L</b> ower limb abnormalities
Fanconi anemia	Aplastic anemia that is not present at birth, but develops after about 6 years of life. (Aplastic anemia occurs when the body no longer produces enough blood cells.) If radii are absent in a patient with FA, thumbs are often absent as well.
CHARGE Syndrome	<b>C</b> oloboma of the eye <b>H</b> ear defects <b>A</b> tresia of the nasal choanae (blockage of one or both nostrils) <b>R</b> etardation of growth and/or development <b>G</b> enital and/or urinary abnormalities <b>E</b> ar abnormalities and deafness

## Thumb Anomalies

In patients with FA, the thumbs may be underdeveloped or completely absent. The most common types of thumb anomalies that occur in children have been classified into five types depending on the degree of underdevelopment <sup>(2)</sup>:

- **Type I deficiency.** In this type of deficiency, the child’s thumb is slightly smaller than normal but all of the thumb’s structures (including the bones, muscles, ligaments, tendons, and joints) are intact. This mild deficiency may go unrecognized, and many individuals with this type of deficiency are not diagnosed until later in life when everyday activities such as buttoning a shirt or tying shoes have become more difficult.
- **Type II deficiency.** This deficiency is more involved and is characterized by a narrowing of the web space between the thumb and index finger,

absence of the thenar (thumb) muscle at the base of the thumb, and instability of the metacarpophalangeal joint in the middle of the thumb (Figures 1A and B).



Figure 1A



Figure 1B

**Figure 1.** A 2-year-old child with type II thumb hypoplasia. *A)* Absent thenar muscles; *B)* Narrowed thumb-index web space with instability of the metacarpophalangeal joint. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

- **Type III deficiency.** A child with this hypoplasia possesses the same characteristics as a Type II deficiency, as well as additional skeletal, muscular, and tendinous abnormalities. These abnormalities usually involve tendons that arise within the forearm and travel into the thumb. Type III anomalies are subdivided into types III-A and III-B depending upon the presence or absence of a stable carpometacarpal joint at the base of the thumb.
- **Type IV deficiency.** This type of deficiency, known as a pouce flottant (floating thumb) or residual digit, lacks bones and muscles and is mainly comprised of skin and soft tissue (Figure 2).



Figure 2 (see Figure legend on next page)

**Figure 2.** A 1-year-old child with severe type IV thumb hypoplasia (also known as a ‘pouce flottant’ or floating thumb). *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

- **Type V deficiency.** This type of hypoplasia is noted by the complete absence of a thumb (Figure 3).



Figure 3

**Figure 3.** An 18-month-old child with type V hypoplasia and complete absence of the thumb. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

The thumb classifications listed above can guide treatment recommendations, as shown in Table 2<sup>(3,4,5)</sup>. The degree of hypoplasia and deficiency varies among children with FA. As a result, treatment recommendations depend on the severity of the abnormality.

**Table 2.** Thumb deficiency classification and treatment paradigm.

Type	Findings	Treatment
I	Minor generalized hypoplasia	No treatment
II	Absence of intrinsic thenar muscles First web space narrowing Ulnar collateral ligament (UCL) insufficiency	Opponensplasty First web release UCL reconstruction
III	Similar findings as type II plus: Extrinsic muscle and tendon abnormalities Skeletal deficiency Stable carpometacarpal (CMC) joint (sub-Type III-A) Unstable CMC joint (sub-Type III-B)	Reconstruction (for sub-Type III-A) Pollicization (for sub-Type III-B)
IV	“Pouce flottant” or floating thumb	Pollicization
V	Absent thumb	Pollicization



### Treatments for hypoplastic, floating, and absent thumbs

A thumb that is slightly smaller than normal (Types I, II, and III-A) can be reconstructed or stabilized by transferring tendon from another part of the hand to improve the thumb's motion and function. Type I deficiencies usually do not require surgical treatment, whereas multiple elements may need to be addressed in thumb reconstruction for Types II and III-A (Figure 4A thru C):

- **Tightness in the web space** can be released using skin flaps to increase the space between the thumb and index finger (Figure 4A).
- **Thenar muscle deficiency** can be treated by transferring tendon and/or muscle from the ring or long finger to the thumb. Tendon transfer improves the active motion and function of the thumb and has a negligible effect on the donor finger (Figure 4B).



Figure 4A



Figure 4B



Figure 4C

**Figure 4.** Thumb reconstruction in Types II and III-A requires the surgeon to address all deficient elements. *A)* Z-plasty of the narrowed thumb-index web space; *B)* tendon transfer to overcome the deficient thenar muscles; *C)* ligament reconstruction to stabilize the metacarpophalangeal joint instability. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

- **Metacarpophalangeal joint instability** can be improved through the use of grafts to the ulnar and/or radial collateral ligaments at the base of the thumb (Figure 4C). In cases with severe instability, fusion of the joint may be the best option to provide a stable thumb for firm grasps.

The main distinction between a thumb that can be surgically reconstructed and a thumb that requires amputation is the presence or absence of a stable base (e.g., a carpometacarpal joint). A thumb without a stable carpometacarpal joint (Types III-B, IV, and V) cannot be reconstructed and should be removed. Clinical examination and X-ray will show marked deficiencies (Figure 5 & 6). Furthermore, Type III-B and IV thumbs will not be functional and the child will not incorporate his/her thumb into pinch or grasp. The decision to remove a hypoplastic thumb without a stable base is often a difficult process for parents and caregivers. Discussions with the surgeon and conversations with families who have made similar decisions are often helpful to parents tasked with making this decision for their child (Video 1 in online supplementary information).



Figure 5



Figure 6

**Figure 5.** An X-ray of a 2-year-old child reveals a thumb metacarpal that tapers to a point, indicative of an unstable carpometacarpal joint. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

**Figure 6.** A 5-year-old child with bilateral thumb hypoplasia. The right index-long web space has widened and the index has rotated out of the palm. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

Because an opposable thumb is critical for manipulating many objects, a functional replacement can be constructed by surgically moving the index

finger and its nerves, arteries, tendons, and muscles to the thumb position. This procedure, known as pollicization, is generally performed when the child is between 6 months and 2 years of age, depending on the health status of the child, the degree of forearm deficiency, and the surgeon's preference<sup>(2,3)</sup>. This age range remains controversial, however, and there has been a trend toward surgery between 6 months to 1 year of age, which is prior to the normal development of oppositional or fine pinch at about 15 months of age. An intervention at an early age takes advantage of the growing brain's ability to adjust to the new thumb, and prevents the child from developing a compensatory side-to-side pinch pattern between adjacent fingers. The general medical health of a child with FA should also be taken into consideration prior to surgery, especially if the child's blood counts are decreasing over time. Surgery can be safely performed in patients who have platelet counts greater than 80,000. In reality, parents should not feel pressured to make an immediate decision about surgery for their child; some children undergo successful surgery during adolescence. Pollicization requires meticulous surgical technique because the index finger must be shortened, rotated, and reconstructed with the index muscles to give the appearance and function of a thumb (Figure 7). The surgeon should be experienced with this procedure.



Figure 7

**Figure 7.** Pollicization of the index finger requires careful surgical technique to give the appearance and function of a thumb. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

## Distinguishing Between Type III-A and Type III-B Thumb Deficiencies

The clinical differentiation between Types III-A and III-B can be difficult. The child's pattern of thumb usage often helps discriminate between these types. An unstable thumb (Type III-B) will not be incorporated into pinching and grasping motions; rather, the child will learn to pinch and grasp using the index finger and the long digits, and the index finger will tend to rotate out of the palm toward a thumb position (Figure 5).

The differentiation is further complicated by the delayed maturation of the bones at the base of the thumb; these bones (the trapezium and trapezoid) do not finish developing until 4 to 6 years of age. Advanced imaging techniques such as magnetic resonance imaging (MRI) can reveal the extent of bone and cartilage development; however, young children require general anesthesia during MRI. Ultrasound imaging shows promise as a tool for defining the anatomy without the need for anesthesia.

A thumb metacarpal (the bone that connects the thumb to the wrist) that tapers to a point at the base of the metacarpal is also indicative of an unstable carpometacarpal joint (Figure 6).

The outcome of pollicization is directly related to the status of the index finger prior to surgery: A mobile index finger can provide stability for grasp and mobility for fine pinch, whereas a stiff index finger will provide a stable thumb for coarse grasping, but fine pinching will be unlikely (Figure 8; Video 2 in online supplementary material). Good results shortly after pollicization have been shown to persist into adulthood <sup>(6,7)</sup>.



Figure 8A  
(see Figure legend on next page)



Figure 8B

**Figure 8.** A 2-year-old status post-pollicization of a mobile left index finger. *A)* Thumb used for grasping large objects; *B)* mobile thumb incorporated into fine pinch. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

### Other thumb anomalies

Although hypoplasia is the most common thumb anomaly in children with FA, other abnormalities have been reported. For example, the thumb can possess an extra bone (an anomaly referred to as a triphalangeal thumb) or can be duplicated (a condition called pre-axial polydactyly). The exact prevalence of these rare anomalies is unknown.

- ***A triphalangeal thumb*** has an extra bone (called a phalanx) that can vary in size and shape (Figure 9). The alignment and length of this type of thumb must be monitored until the bones have finished growing. An extra phalanx that is small and normally shaped can be treated without surgery; however, a small wedge-shaped phalanx may cause the thumb to curve away from its midline as it grows and treatment is recommended. A small wedge-shaped bone can be surgically removed and the ligaments of the remaining bones can be reconstructed to form a functional joint. A large wedge-shaped phalanx will cause the thumb to curve and become excessively long, but removal is not recommended because joint instability is common after surgery. A better option involves removing only the wedge-shaped portion of the abnormal phalanx and fusing the remainder to an adjacent thumb bone. This procedure eliminates the extra joint and shortens and realigns the thumb.



Figure 9A



Figure 9B

**Figure 9.** An 8-year-old child with triphalangeal thumbs. *A)* Clinical appearance with mild angulation; *B)* X-rays show an extra phalanx that is triangular in shape causing the angulation. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

- **Pre-axial polydactyly**, or duplication of the thumb, results in a hand that has more than one thumb. The thumbs may be partial and appear fused together, or they may be complete and separate from each other. Thumb duplications have been classified into various types depending on the degree of skeletal replication (Table 3)<sup>(8,9)</sup>. Treatment requires salvaging portions of each duplicated structure, including bones, nails, tendons, ligaments, joints, nerves, and blood vessels, to construct a properly aligned and functional thumb (Figure 10)<sup>(10)</sup>. This procedure is not always straightforward and requires careful examination. The soft tissues from the amputated thumb, including the skin, nail, ligaments, and muscle, should be used to augment the retained thumb. The articular surface of the joint may require realignment via osteotomy (cutting the bone) or modification through recontouring (cartilage shaving) to optimize thumb function. Irrespective of treatment, the reconstructed thumb may be smaller compared to a normal thumb and usually will lack some movement.

**Table 3.** Classification of duplicated thumbs<sup>(9)</sup>.

Type	Duplicated Elements
I	Bifid distal phalanx (a partial duplication of the bone at the tip of the thumb)
II	Duplicated distal phalanx (a complete duplication of the bone at the tip of the thumb)
III	Bifid proximal phalanx (a partial duplication of the bone in the middle of the thumb)
IV	Duplicated proximal phalanx* (a complete duplication of the bone in the middle of the thumb)
V	Bifid metacarpal phalanx (a partial duplication of the bone that connects the thumb to the wrist)
VI	Duplicated metacarpal phalanx (a complete duplication of the bone that connects the thumb to the wrist)
VII	Triphalangeal component (a thumb duplication with one or both of the thumbs having an extra phalanx or bone)

*\*Most common type of duplicated thumb.*

*Modified from:* Wassel HD. The results of surgery for polydactyly of the thumb: A review. In: 1969;125:175-193.



Figure 10A



Figure 10B



Figure 10C

**Figure 10.** A 1-year-old child with a duplicated left thumb. *A)* Clinical presentation; *B)* skin incision designed to incorporate parts of the deleted component; *C)* surgical reconstruction using the soft tissues from the deleted thumb to augment the size and girth of the retained thumb. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

## Radial Deficiency

Radial deficiency is a condition in which the radius—the bone that runs along the thumb side of the forearm—develops abnormally. The radius can be slightly smaller than average, considerably smaller, or altogether absent. The severity of radial deficiency is variable and can be determined through X-rays and clinical examination. Radial deficiency is classified as follows<sup>(11,12)</sup>:

- **Type 0 and 1 deficiencies.** These are the mildest forms and are characterized by little or no shortening of the radius and negligible curvature in the ulna. The hand may be tilted slightly inward toward the thumb side of the arm, a condition known as a radial deviation of the wrist, and substantial thumb hypoplasia may be present that requires treatment.
- **Type 2 deficiency.** This deficiency is characterized by a miniature radius that has abnormalities in the growth plate (the region of the bone responsible for lengthening the bone) and a moderate radial deviation of the wrist.
- **Type 3 deficiency.** This involves a partial absence of the radius—most commonly affecting the end of the bone that is closest to the wrist—and a severe radial deviation of the wrist.

- **Type 4 deficiency.** In the most common type of radial deficiency, characterized by a complete absence of the radius, the hand tends to develop perpendicularly to the forearm (Figure 11A and B). In children with FA, a complete absence of the radius typically occurs in conjunction with an absent thumb.



Figure 11A



Figure 11B

**Figure 11.** A 2-year-old child with complete absence of the radius (Type 4). *A)* X-ray reveals complete absence of the radius; *B)* hand with a perpendicular relationship with the forearm. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

The maturation of the radius takes more time than usual in patients with radial deficiency; therefore, the differentiation between total and partial absence (Types 3 and 4) cannot be determined until the child is approximately 3 years of age. The different types of radial deficiencies have been combined into a classification scheme that includes the other upper limb abnormalities that are associated with radial deficiency, including thumb, carpal (wrist), and forearm abnormalities (Table 4).



**Table 4.** Classification of radial longitudinal deficiency<sup>(11, 12)</sup>.

Type	Thumb	Carpus (wrist)	Distal radius (the end of the radius that is closest to the wrist)	Proximal radius (the end of the radius that is closest to the elbow)
N	Hypoplastic or absent	Normal	Normal	Normal
0	Hypoplastic or absent	Absence, hypoplasia, or coalition (fusion of two or more wrist bones)	Normal	Normal, radioulnar synostosis (an abnormal connection between the radius and ulna), or congenital dislocation of the radial head (a dislocated elbow)
1	Hypoplastic or absent	Absence, hypoplasia, or coalition	> 2 mm shorter than ulna	Normal, radioulnar synostosis, or congenital dislocation of the radial head
2	Hypoplastic or absent	Absence, hypoplasia, or coalition	Hypoplasia	Hypoplasia
3	Hypoplastic or absent	Absence, hypoplasia, or coalition	Physis (the bone region responsible for elongation of the bone) absent	Variable hypoplasia
4	Hypoplastic or absent	Absence, hypoplasia, or coalition	Absent	Absent

*Modified from:* Bayne LG, Klug MS. Long-term review of the surgical treatment of radial deficiencies. *J Hand Surg (Am)* 12:169-179, 1987; and Jame MA, McCarroll HR Jr, Manske PR. The spectrum of radial longitudinal deficiency: A modified classification. *J Hand Surg (Am)* 24:1145-1155, 1999.

### Functional consequences of radial deficiency

The outcome of radial deficiency depends on the severity of the abnormality. In a patient with a Type 4 deficiency, the humerus (the bone between the elbow and shoulder) may be shorter than expected and the elbow may not be able to bend properly. Furthermore, the forearm will always be shortened because these children are born with an ulna that is approximately 60% of the normal length at birth and remains short even after the skeleton has completely matured<sup>(13)</sup>. The ulna will also be thickened and often curved toward the absent radius. In cases of partial or complete absence of the radius, the forearm will not be able to rotate, although some rotation may occur through the wrist or carpal bones. The wrist may be shifted a variable amount towards the deficient radius, a condition known as a radial deviation. The carpal bones

will be delayed in their growth, and the scaphoid and trapezium (two of the wrist bones) are often absent or reduced in size, or hypoplastic. The index and middle fingers can be stiff and slender and may have limited motion, whereas the ring and little fingers are less affected and often have better motion.

The radial artery and nerve are also often absent, although the ulnar nerve and artery are normal<sup>(13)</sup>. An enlarged median nerve substitutes for the absent radial nerve and communicates with its dorsal nerve branch, which is positioned in the fold between the wrist and forearm, to provide sensation to the thumb side of the hand. It is critical that surgeons are aware of the location of the dorsal branch when operating along the thumb side of the wrist.

### **Goals for treatment**

The fundamental goals of treatment are to:

- *Correct the radial deviation of the wrist*
- *Balance the wrist on the forearm*
- *Maintain wrist and finger motion*
- *Promote growth of the forearm*
- *Possibly lengthen the forearm*
- *Improve the function of the arm*

### **Treatment considerations**

A slightly shortened radius (Type 0 and 1 deficiency) requires repeated stretching and may need a tendon transfer to balance the wrist. These treatments are relatively straightforward. Partial or complete absence of the radius is more common (Types 2, 3, and 4) and is entirely more difficult to treat because the wrist has shifted toward the thumb side of the arm, shortening an already undersized forearm, placing the forearm flexor and extensor tendons at an awkward angle, and producing functional deficits. Children who have radial deficiency on only one arm (known as a unilateral deficiency) may be able to compensate for any functional deficits using their unaffected limb and thus have a lower overall degree of functional impairment than children who have radial deficiency on both arms (known as a bilateral deficiency). Finger and thumb abnormalities, if present, also require consideration during the formulation of a treatment plan, as stiff fingers and a deficient thumb will further hamper pinch and grasp.

### Nonsurgical treatments

The treatment for radial deviation of the wrist begins shortly after birth and involves a combination of surgical and nonsurgical treatments. The initial treatment for an absent radius consists of stretching the soft tissues, including the tendons, ligaments, skin, and muscles. This treatment is typically performed both by a physical or occupational therapist and the caregiver. The therapist should be experienced in pediatric clinical interventions for the hand. Stretching should be performed at every diaper change and is an important part of the overall treatment plan. A splint can help to keep the hand in a straight alignment and prevent the hand from developing perpendicularly to the forearm; however, fabrication of a splint is difficult in a newborn with a shortened forearm because the splints tend to fall off the arm. Therefore, this treatment is usually postponed until the forearm is long enough to accommodate a splint. On occasion, the hand will develop in a perpendicular position despite treatment.



Figure 12

**Figure 12.** Surgical centralization requires placing the wrist on top of the ulna to realign the carpus onto the distal ulna. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

### Surgical treatment

Surgical treatment for Types 2, 3, and 4 deficiencies involves moving and centering the wrist over the end of the ulna, which is the only substantial bone remaining within the forearm. This procedure is known as “centralization” or “radialization” depending on the exact position in which the wrist is placed, and remains the standard treatment for realigning the wrist<sup>(14,15)</sup>. Centralization involves releasing and reorganizing the tight muscles and tendons of the wrist, and positioning the hand over the end of the ulna (Figure 12). One end

of a functioning tendon is then shifted from its original attachment site to the wrist to rebalance the forces acting on the wrist, a procedure known as tendon transfer. If the ulna has curved to an angle of 30 degrees or more, then it must be straightened via a procedure called concomitant wedge osteotomy at the time of surgery. Once the surgery is complete, the wrist is held in position by a stout wire (Figure 13), which can be removed 8 to 12 weeks after surgery, although some surgeons prefer to leave the wire in place for as long as possible. Once the wire has been removed, a splint should be used for 4 to 6 weeks. The splint can be removed for physical therapy exercises, but should be worn during sleep until the bones have completely matured.



Figure 13

**Figure 13.** Centralization is maintained by placement of a stout wire across the wrist. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

Centralization is typically performed when the child reaches approximately 1 year of age. The initial correction is often impressive; however, the results are unpredictable and, unfortunately, recurrence and complications are common. Furthermore, not all children are candidates for centralization. The caregiver and surgeon must remember that function trumps form, and many children function quite well despite having a deviated wrist. Such children typically have a mobile and dexterous little finger along with a stiff index finger, and are able to pinch and grasp using their palm and the fingers on the outside edge of the hand, known as an ulnar grasp pattern; straightening the child's wrist would move the outside edge and fingers downward and prevent the child from approaching objects with this side of the hand. Therefore, straightening may be detrimental to the child's overall function and independence.

### **Contraindications for surgery**

Mild deformities with adequate support for the hand (Type 0 or 1) do not require surgery. Surgery is also not advised for children with impaired bending at the elbow. In these children, the radial deviation of the wrist enables the hand

to reach the mouth and straightening the wrist would impair important tasks such as eating and reaching the face.

### Alternative treatments for recurrent radial deviation

In severe cases, the radial deviation cannot be straightened and alternative measures are necessary. Surgical options include removing a portion of the wrist bones via a procedure called carpectomy, shaving some of the bone off of the wrist end of the ulna, or applying a device called an external fixator prior to centralization. An external fixator stretches the soft tissues (including the tendons, ligaments, skin, and muscles) prior to centralization and facilitates correction of the radial deviation<sup>(16, 17, 18)</sup>. The fixator may be unilateral with pins or ringed multiplanar with wires (Figure 14).



Figure 14A



Figure 14B

**Figure 14.** Radial deficiency with rigid deformity is often treated with preliminary soft tissue distraction. *A)* Uniplanar device along the radial side of the forearm; *B)* multiplanar device for additional control of hand and forearm.

*Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

Numerous other technical modifications have been proposed to maintain alignment of the wrist position. These include:

- **Overcorrection of the radial deviation.** In this procedure, the patient's hand is positioned slightly off-center into ulnar deviation to help prevent recurrence of the radial deviation.
- **Tendon transfers** to correct the alignment.
- **Prolonged wire fixation** following centralization (leaving the wire in place longer than the typical 8-12 weeks).

- **Microvascular free toe transfer**, which involves transplanting one of the second toes (without its skin but with its arteries and veins intact) to the thumb side of the wrist to provide additional support (Figure 15). A study of the outcomes of this procedure during an 8-year period revealed that patients tended to have improved wrist motion and limited recurrence<sup>(19)</sup>. This is a technically demanding operation, however, and complications are common.

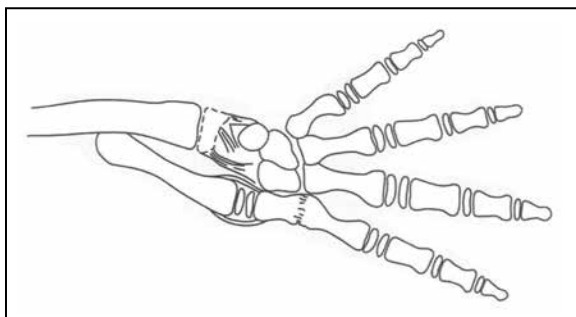


Figure 15

**Figure 15.** Diagram of free toe transfer to support the radial side of the wrist. The toe proximal phalanx is fused to the base of the second metacarpal and the proximal metatarsal affixed to the side of the distal ulna. Reprinted with permission from Kozin SH. Congenital Anomalies. Hand Surgery Update. Trumble TE, Budoff JE (eds), *American Society for Surgery of the Hand*, 2007, pp. 455-468.

Unfortunately, no treatment method consistently and permanently corrects the radial deviation, balances the wrist, and allows continued growth of the forearm<sup>(14, 15)</sup>. Recurrence can prove frustrating to the child, parent, and surgeon (Figure 16). Maintaining the wrist on the end of the ulna without sacrificing wrist mobility or stunting forearm growth remains a daunting task. Many factors contribute to recurrence, including the inability to obtain complete correction at surgery, inadequate release of the tightness in the soft tissues, and failure to balance the forces acting on the wrist. Prolonged wire fixation and use of a splint may help to prevent recurrence. In some children, there is a natural tendency for the shortened forearm and hand to deviate in a radial direction for hand-to-mouth use. Fortunately, recurrence is not always associated with a loss of function (Video 3 in online supplementary material). In fact, although patients with severe radial deviation may have limitations in their range of motion and strength, long-term studies have found that they have the same levels of activity and participation as children with less severe deformities<sup>(20, 21, 22, 23)</sup>.



Figure 16



Figure 17

**Figure 16.** An 11-year-old child with recurrent radial deviation following centralization as an infant. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

**Figure 17.** Bilateral forearm lengthening using an external fixator. *Courtesy of Shriners Hospital for Children, Philadelphia Unit.*

The management of recurrent deformity must be individualized to each patient and his/her specific deformity. The indications for an additional procedure have yet to be clearly defined. Similarly, the indication for forearm lengthening to overcome the inherent problem of shortening has yet to be delineated. Lengthening surgery is offered to patients and families interested in correcting the deformity and willing to comply with a long and arduous recovery. The procedure, called distraction osteogenesis, involves inducing new bone growth, typically by pulling on the bone in a controlled manner using an external fixator (Figure 17). Lengthening is a sophisticated form of treatment that introduces additional complications such as infection at the insertion sites of the external fixator, fracture of the regenerated bone, and finger stiffness. These complications must be discussed prior to surgery. Forearm lengthening is laborious and may require the device to remain in place for extended periods of time, sometimes up to a year. In general, children with unilateral forearm shortening tend to be bothered by the asymmetry between the forearms and request lengthening more often than children with bilaterally shortened forearms, who have symmetry between the arms.

Ultimately, fusion of the joint between the wrist and ulna may be contemplated in certain instances to keep the wrist straight<sup>(24)</sup>. Wrist fusion results in a permanently stiff, straight wrist. Careful assessment of hand usage and compensatory motion is mandatory prior to this procedure. A functional

evaluation by a therapist is a valuable preoperative tool. Painstaking measures should be taken to ensure that wrist fusion does not lead to loss of function.

## **Emotional Issues**

Parents of children born with limb abnormalities are extremely concerned about the possibility that their child might experience peer pressure and taunting<sup>(25)</sup>. The physician should acknowledge these concerns and encourage parental support. Literature is available to help children and families understand their child's limb anomalies, although discussions between clinicians and parents are the mainstay for improving understanding<sup>(25)</sup>. School-age playmates are keenly aware of congenital limb differences and will be a source of questions and possible teasing. As congenitally different children grow, they develop inward and outward coping mechanisms to handle their anomalies. Support groups are invaluable, whether they are online or in person. The Internet, particularly social media, can be a valuable source of support for children and their families.

The physician should play an active role in the child's support system by encouraging open discussions about the limb differences and asking questions about the child's interactions with his or her peers. These conversations are often insightful and revealing to both the physician and family. Difficulties with peer pressure may require counseling to promote emotional development. Clinics that treat congenital hand abnormalities often have staff members with expertise in supporting the functional, emotional, and psychological needs of children and parents. Ideally, these staff members will include an occupational therapist, psychologist, and social worker. Children also benefit from peer-contact activities, such as summer camps for kids with upper extremity differences.

## **Transition from Childhood to Adulthood**

By the time they reach adulthood, most children with FA have completed all necessary hand surgeries and will not require regular follow-up with their surgeon; however, occasional evaluation is recommended to check for any developing problems. Unfortunately, many pediatric facilities do not treat adults. Thus, patients should ask their pediatric hand surgeon to recommend a physician who cares for hand and upper extremity abnormalities in adults.

## **Chapter Committee**

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# Chapter 6: Issues Facing Women with Fanconi Anemia: Improved Survival and New Dilemmas

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## Introduction

Although the diagnosis and treatment of FA remains challenging, recent advances in the management of FA have enabled patients to survive longer than previously possible, resulting in gender-specific health concerns as they reach reproductive age. The issues that females with FA face during their reproductive lifetime most commonly include:

- *Late onset of puberty and early onset of menopause*
- *Cancer, including gynecologic cancer, breast cancer, or secondary cancers following hematopoietic stem cell transplant (HSCT)*
- *Reduced fertility and reproductive lifespan*
- *Excessive menstrual bleeding*

The clinical care team for females with FA should include a gynecologist and, when needed, an **adolescent gynecologist, reproductive endocrinologist, maternal-fetal medicine specialist, or gynecologic oncologist**. This team should work in close collaboration with other FA care specialists to provide comprehensive care. The involvement of multiple types of care providers in the care of patients with FA introduces the risk that medications prescribed by one physician might adversely interact with those prescribed by another. Therefore, it is essential that all subspecialists communicate with the primary physician, usually the hematologist/oncologist, to coordinate care.

## Menarche

Approximately 9 out of every 10 healthy women experience their first menstrual period, known as menarche, about 3 years after breast buds develop, as early as age 11 and before age 16. Most females with FA undergo puberty within this age range, but may not experience menarche until their mid-teens and, once menstruation begins, they may have irregular menstrual periods. In addition, many females with FA reach menopause prematurely<sup>(1)</sup>. As a result, females with FA often have a shorter reproductive lifespan compared with women in

the general population. This reduction in fertility may stem from the genetic changes underlying FA, which are associated with hypogonadism<sup>(2)</sup>, or they may result from chronic disease, low body weight, or treatments for bone marrow failure such as stem cell transplantation. Androgen therapy, which is often used to boost the formation of new blood cells in patients with FA, may suppress menstruation, delay menarche, or contribute to irregular menstrual periods.

## Good to Know

**Hypothyroidism** is a condition caused by low levels of the thyroid hormone. This condition can contribute to reproductive issues, including irregular periods and difficulty becoming pregnant.

As discussed in *Chapter 7*, many females with FA experience other endocrine disorders, including hypothyroidism and hypothalamic dysfunction. Hypothyroidism, if unrecognized and untreated, may contribute to irregular periods and infertility. Hypothalamic hypogonadism is associated with delayed puberty, amenorrhea (absence of menstrual periods), and infertility<sup>(3)</sup>.

Pubertal delay is defined as occurring in any female who has not developed breast buds by age 13, or by age 14 in patients who have low body weight<sup>(4,5)</sup>. Although pubertal delay in patients with FA may result from low body mass index, chronic disease, or after stem cell transplantation during childhood, patients who start their periods later in life than their healthy peers (3 years after breast buds develop or age 16) should be evaluated for hypothalamic dysfunction<sup>(3-5)</sup>. Such patients may need hormonal supplementation to optimize growth and to help develop secondary sexual characteristics.

## Sexuality and Contraception

It is important to remember that there is more to a patient with FA than just the disease. Along these lines, contraceptive counseling should be considered a central part of gynecologic care for sexually active patients who do not desire pregnancy. Women of reproductive age should also be counseled about safe sex practices and screening for sexually transmitted infections (STIs)<sup>(6)</sup>. All patients with FA should be encouraged to undergo vaccination against human papillomavirus (HPV), a STI that can cause genital warts as well as cervical cancer and other types of malignancies.

### HPV vaccination

Two HPV vaccines, Gardasil® and Cervarix®, are available and approved for use in females between the ages of 9-26. The vaccines were also recently approved for use in males in the same age range <sup>(7)</sup>. Gardasil®, approved in 2006, is effective against HPV types 6 and 11, which are associated with 90% of cases of genital warts, and types 16 and 18, which are implicated in about 70% of cases of cervical cancer. Gardasil® has been shown to be effective in preventing cervical cancer <sup>(8)</sup>. Cervarix® is effective against the two most common types of HPV that cause cancer—types 16 and 18—but does not protect against genital warts <sup>(9)</sup>. Because women with FA have an increased risk of squamous cell cancers of the lower genital tract, it is reasonable to consider HPV vaccination after age 9, although it remains unclear whether vaccination at such a young age protects against squamous cell cancers that may develop during young adulthood. Three doses of the vaccine are recommended: The second dose is administered 2 months after the first, and the third dose is given 6 months after the first. The long-term effectiveness of HPV vaccination is unknown, but studies have shown that Gardasil® remains effective for at least 5 years and Cervarix® for at least 6.4 years <sup>(9)</sup>. It is currently unknown whether patients, including those with FA, who receive the vaccination will require subsequent booster vaccinations. Although the HPV vaccines will not cure existing HPV-related disease, they may prevent the acquisition of additional HPV types. Because the HPV vaccines do not prevent all lower genital tract cancers, vaccinated women should still undergo regular gynecologic screening.

### Good to Know

**Human papillomavirus (HPV)** is the most common sexually transmitted infection.

There are more than 100 different types of HPV. These viruses can cause genital warts, cervical cancer, and several other types of malignancies.

Vaccines against HPV can prevent some of the cancers caused by these viruses.

## Cancer Screening and Treatment

### Gynecologic cancers

High rates of lower genital tract squamous cell cancers, including cervical, vaginal, vulvar, and anal cancers, have been reported in women with FA. Patients who have undergone hematopoietic stem cell transplantation—

especially those who developed graft-versus-host disease—have a higher risk of squamous cell cancer compared with patients who have not undergone transplantation <sup>(10)</sup>. On average, women with FA tend to develop cervical and vulvar cancer at ages 25 and 27, respectively, whereas women in the general population tend to develop cervical cancer at age 47 and vulvar cancer at age 72 <sup>(11-13)</sup>. In other words, although the absolute risk of such a cancer is very low in all younger women, young women with FA have a several thousand-fold higher risk for vulvar cancer and at least a 100-fold higher risk for cervical cancer compared with young women in the general population <sup>(11-13)</sup>. In fact, FA testing should be considered in any patient who is diagnosed with cervical cancer prior to age 30 or vulvar cancer prior to age 40.

It remains unclear whether the elevated rates of squamous cell cancers of the genital tract in women with FA are HPV-related. One recent study found that 84% of patients with FA who had head and neck squamous cell cancers were infected with HPV <sup>(14)</sup>. By contrast, another study revealed that HPV was present in only 10% of patients with FA who developed anogenital cancers, and in none of the patients with FA who had head and neck cancers <sup>(15)</sup>. Similarly, a study published in 2013 reported low rates of HPV infection in patients with FA who had genital or head and neck cancers <sup>(16)</sup>. These discrepancies in the prevalence of HPV in squamous cell cancers from patients with FA may be due to many factors, including differences in the way that the laboratory testing was performed, the amount of virus in the patients studied, geographic differences in the prevalence of HPV infection, or differences in the mode of squamous cell cancer development among patients with FA.

Early detection of precancerous lesions in patients with FA is imperative to maximize survival. There is ongoing debate regarding the gynecologic cancer-screening schedule for females with FA. While it is important to be vigilant, it is equally important not to overburden patients by subjecting them to extra testing, anxiety while awaiting results, and potentially unnecessary procedures. With that understanding, yet recognizing the high risk for early vulvar cancer and pubertal delay, women with FA should begin receiving gynecologic care at a younger age than is typically recommended for women in the general population. Females with FA should begin having visual examinations of the external genitalia at age 13. Sexually active women with FA should undergo regular, comprehensive gynecologic exams, including a Pap test and a careful inspection of the cervix, vagina, and vulva. Sexually inactive patients should begin having comprehensive gynecologic examinations at age 18, 3 years earlier than recommended for healthy women <sup>(17)</sup>.

Colposcopy should be done when any abnormal areas are seen on visual inspection or if a cervical cytology test is abnormal. Lesions that are identified during colposcopy or routine examination should be biopsied. Any woman with FA who is diagnosed with dysplasia—a precancerous condition that increases the risk of developing cancer—should receive gynecologic exams with biopsy of any identified lesions every 4 to 6 months. HPV testing can be performed at the same time as the Pap test, although it is important to note that the absence of high-risk HPV types in patients with FA does not mean that this screening interval should be extended. Patients with genital tract dysplasia may also need to undergo anal cytology and/or anoscopy to identify anal cancers, which to date have only been reported in women who also have genital tract disease. In addition, women with FA should be encouraged to receive HPV vaccination, and may benefit from counseling about risks related to STIs.

### Good to Know

A **Pap test** (cervical cytology testing) is used to detect cervical cancer and precancerous lesions. During the test, cells are scraped from the cervix and examined under a microscope to identify abnormalities.

During **colposcopy**, the doctor uses an illuminated magnifying device called a colposcope to examine the vulva, vagina, and cervix. The procedure allows the doctor to find abnormal tissues that may be missed by the naked eye.

During a **biopsy**, the doctor removes a small piece of tissue, which is then examined under a microscope to determine whether dysplasia (pre-cancer) or cancer is present.

**Anal cytology** (sometimes called an anal Pap test) is a screening test used to detect anal cancers and precancerous lesions. During the test, cells are collected from the anus and examined under a microscope to identify abnormalities.

During **anoscopy**, the doctor uses a tube-shaped instrument called an anoscope to search inside the anus and rectum for abnormalities.

The optimal treatment for genital warts or dysplasia is surgical excision or ablation. Vulvar lesions may be treated with immune modulating drugs, such as Aldara, 5-fluorouracil (5-FU), or alpha interferon<sup>(18, 19)</sup>. The patient's genital area should be inspected periodically during immune modulator treatment to determine whether the treatment is working and to identify any adverse side effects. Patients with FA who have extensive vulvar dysplasia may benefit from a combination of surgical and medical treatment as reported in other patient

populations<sup>(20)</sup>. Patients with other immune deficiencies typically respond to immune modulators within a few weeks. It is possible that women with FA may benefit from long-term immune modulator treatment due to the likelihood of recurrent or refractory dysplasia. Patients diagnosed with genital tract cancer should be referred to a gynecologic oncologist immediately.

Surgery remains the mainstay of treatment for gynecological cancers in patients with FA. These patients tolerate chemotherapy and radiation poorly due to the genetic changes underlying FA, which impair cells' ability to repair the DNA that is damaged by these therapies<sup>(21)</sup>. Therefore, the patient's hematologist should be consulted prior to administering radiation or chemotherapy.

### **Breast cancer**

One of the genes implicated in FA, *FANCD1*, is the well-known breast cancer susceptibility gene, *BRCA2*; thus, patients with FA may be at increased risk of breast cancer, although few such cases have been reported<sup>(22)</sup>. Mutations in *BRCA2* also increase the risk of ovarian cancer, but there is no evidence that this risk is enhanced in patients with FA, perhaps because of these patients' shortened lifespan.

Screening for breast cancer in patients carrying *BRCA2* mutations generally begins by age 25-30. Screening is typically performed twice a year, and often includes clinical breast examinations and mammography alternating with MRI<sup>(23)</sup>. In some instances, both mammography and MRI are performed at the same time, either annually or semi-annually. Ultrasound is often used in conjunction with mammography. These screening guidelines can be extrapolated to patients with FA, regardless of their specific FA gene mutation, because mutations in *BRCA2* or the genes underlying FA disrupt the same DNA repair pathway in cells.

Women with an elevated risk of breast cancer should begin regular breast cancer surveillance, including a clinical breast exam and education about breast self-examination, by the time they reach their early 20s. Mammography may be considered beginning at age 25. Palpable breast lumps should be evaluated immediately. It is unclear whether the mammography screening recommendations apply to patients with FA, as these patients have an elevated sensitivity to radiation exposure due to their underlying genetic defects in DNA repair. The long-term risks of radiation exposure must be weighed against the benefits of early detection<sup>(24)</sup>.



Magnetic resonance imaging (MRI) is very sensitive for detecting breast tumors that may be missed by other screening techniques. However, MRI cannot definitively classify tumors as benign or malignant and has a high false-positive rate; therefore, this technique is usually used in conjunction with mammography<sup>(23)</sup>. A study that evaluated the use of MRI for breast cancer screening found that scans of premenopausal women had high background enhancement regardless of timing within the menstrual cycle, resulting in a high rate of false-positive cancer diagnoses; however, the diagnostic criteria for suspicious lesions remained the same regardless of the increased false-positive rate<sup>(25)</sup>. MRI appears to be more sensitive for detecting tumors in patients who have undergone menopause, which causes the breast tissue to become less dense<sup>(26)</sup>. In the future, MRI may be preferred over mammography in post-menopausal patients with FA as a way to minimize radiation exposure from mammograms<sup>(27)</sup>; however, this concept has not been studied in this population.

## Reproductive Lifespan, Fertility, and Pregnancy

Women with FA may be able to have children, but they often experience reduced fertility and a shortened reproductive lifespan due to delayed menarche and/or early menopause. Very few patients with FA become pregnant after age 30; most reach their maximum childbearing potential by their mid-20s.

Some factors that affect fertility and reproductive health in women with FA include:

- *Early menopause*
- *Irregular menstrual periods (oligomenorrhea)*
- *Absence of menstrual periods (amenorrhea)*
- *Excessive menstrual bleeding (menorrhagia) arising in women with low platelets (thrombocytopenia) and anovulation (failure to ovulate)*
- *Radiation and chemotherapy prior to stem cell transplant*

Most information about fertility in women with FA is compiled from case reports, which suggest that these women have a low pregnancy rate, ranging from 15% among women on androgen therapy to 29% for women not taking androgens<sup>(28)</sup>. Women who conceive while taking androgens should discontinue androgen therapy immediately to minimize the risk of masculinizing a female fetus.

A study of 285 women with FA who underwent HSCT during a 30-year period found that only 10 of the women subsequently conceived and delivered infants and all were under age 26 <sup>(29)</sup>. Of those 10 women, 4 had 2 infants each, and 5 showed signs of gonadal failure prior to pregnancy, although 2 of those women recovered spontaneously. All of the pregnancies included in the study occurred 4-17 years after HSCT <sup>(29)</sup>.

### **Risk factors during pregnancy and childbirth**

When a woman with FA does conceive, the pregnancy is not life-threatening but it is important to have a multi-disciplinary approach to the pregnancy. Therefore, a specialist in maternal-fetal medicine should work closely with the patient's hematologist.

### **Good to Know**

**Pre-eclampsia** occurs when a woman develops high blood pressure and protein in her urine during the second or third trimester of pregnancy.

If left untreated, pre-eclampsia can lead to a life-threatening condition called **eclampsia**, which includes seizures and the possibility of coma.

One study found that blood cell counts decreased during pregnancy in more than half of women with FA. This was associated with thrombocytopenia and the need for blood transfusions, but did not increase the risk of death <sup>(28)</sup>. In addition, compared with women in the general population, women with FA had a higher rate of pregnancy complications, such as pre-eclampsia, eclampsia, and spontaneous abortions <sup>(28)</sup>. This study also reported that women with FA had a higher rate of caesarean section than their healthy peers, which was attributed to the short stature and small pelvises of the women with FA, and a higher rate of failure to progress during labor.

### **Fertility and cancer treatment**

Recent improvements in cancer treatment have increased the lifespan of cancer patients. Unfortunately, cancer treatment often results in reduced fertility. In February 2013, the Ethics Committee of the American Society for Reproductive Medicine issued guidelines for fertility preservation and reproduction in cancer patients <sup>(30)</sup>. ***The most important take-home message from these guidelines is that physicians should inform patients who are undergoing therapies that are potentially toxic to the gonads about the options for fertility preservation prior to the start of treatment.***

Cryopreservation (freezing) of both embryos and eggs has an excellent success rate and can be considered whenever it is clinically available and does not compromise timely treatment of cancer or other conditions. However, the patient's medical status remains the rate-limiting issue. Some fertility preservation strategies may require a woman to postpone her cancer treatment for a month or more while she undergoes fertility treatment. Some reproductive endocrinologists are attempting to retrieve eggs while the patient is in the luteal phase of her menstrual cycle, which allows two opportunities for egg retrieval in a given month rather than just one opportunity. This approach is not performed by many clinicians and remains less successful than conventional egg retrieval methods. The effectiveness of cryopreservation of embryos and eggs from individuals with FA is unknown.

Other realistic options to achieve motherhood should be discussed with patients, including donor eggs, adoption, and surrogacy. Several experimental options hold great promise, including ovarian tissue cryopreservation and the use of leuprolide acetate, which may protect the ovaries from the gonadotoxic effects of radiation and chemotherapy. However, proven methods of fertility preservation are preferred over experimental options.

## Menopause

On average, women in the U.S. naturally undergo menopause around age 51. By contrast, most women with FA experience ovarian failure and menopause by their early 30s. As premature menopause is defined by occurrence prior to age 40, most women with FA have premature menopause. The symptoms and health risks associated with menopause, such as osteoporosis, cardiovascular disease, hot flashes, and vaginal dryness, should be managed in patients with FA to maximize their health. Hormone therapy remains the most effective treatment for the symptoms of menopause. Findings from the Women's Health Initiative, an ongoing study of health issues in postmenopausal women, suggest that while hormone therapy may protect against bone loss, it is associated with a slightly increased risk of breast cancer and increased risks of heart attack, stroke, and thromboembolic disease<sup>(31)</sup>. Nonetheless, women who experience premature menopause and do not use hormone therapy tend to have higher rates of illness and death compared with those who take hormones<sup>(32)</sup>. Thus, hormone therapy should be recommended for young women with FA who undergo premature menopause.

Hormone replacement therapy may be contraindicated for patients who have cardiovascular disease risk factors. The risk of cardiovascular disease in patients with FA is not known, but an individual patient's family history can provide some important clues. Lipid profiles, insulin resistance (see *Chapter 7*), and blood pressure should be monitored as part of a cardiovascular disease risk assessment. Special attention should be paid to the effects of androgen therapy on lipids.

Women with FA may have low bone density due to the side effects of treatments leading to premature ovarian failure. However, a recent study showed that most children and adolescents with FA have a normal bone mineral density when the results are adjusted for stature<sup>(33)</sup>. Individuals with low bone density may be at risk for bone fractures, and may develop osteoporosis with further bone loss. There are many osteoporosis treatment options discussed in detail in *Chapter 7*.

Two types of hormone therapy can be administered to women with FA until they reach age 50: oral contraceptive pills (OCPs) or postmenopausal hormone therapy (also known as hormone replacement therapy, HRT), which consists of low doses of conjugated estrogen and progesterone. Given their young age at menopause, women with FA may benefit more from oral contraceptives than from post-menopausal hormone therapy. From a psychological standpoint, young women with FA may feel more like their peers when they use oral contraceptives. Furthermore, oral contraceptives protect against ovarian cancer in the general population as well as in patients with mutations in the *BRCA1* and *BRCA2* genes, and may have the same protective effect in patients with FA who have mutations in the *BRCA2/FANCD1* gene<sup>(34)</sup>.

Menopause can be accompanied by many symptoms that can impair a woman's sexual function, including hot flashes, vaginal dryness, and pain during intercourse—a condition called dyspareunia. Many options exist for managing menopausal symptoms (Tables 1-4). It is important for clinicians to address these aspects of menopausal health because such symptoms can negatively impact the quality of life for many patients.

## Good to Know

**Thrombocytopenia** is a condition caused by low levels of platelets. Platelets help the blood clot and form a scab at the site of an injury. People with this condition are prone to excess bleeding.

## Management of Excessive Menstrual Bleeding Before and During HSCT

Women with hematological abnormalities frequently have excessive menstrual bleeding as a result of thrombocytopenia or anovulatory cycles. Excessive menstrual bleeding can cause anemia, present the need for a transfusion, and, in women who have low white blood cell counts, increase the risk of infection. Ideally, a plan for managing excessive menstrual bleeding should be defined and enacted prior to HSCT rather than during the transplant period. Suppression of menstrual bleeding can take approximately 1-2 months, independent of the bone marrow suppression induced by immunosuppressive medications prior to HSCT. Regardless of the timing, the options described below have been shown to be effective for treating excessive menstrual bleeding both before and during the transplant period, or in patients who are not planning to undergo HSCT.

### Options for treating excessive menstrual bleeding

Women with FA and excessive menstrual bleeding should undergo a complete blood count. Thyroid level testing may also be useful as hypothyroidism can also cause excessive menstrual bleeding. An ultrasound can be performed to rule out other potential causes of excessive menstrual bleeding, such as polyps or submucosal fibroids that form on the lining of the uterus. Treatments may include surgery or medication, depending on the severity of the bleeding and the patient's hematologic status.

Medications for the treatment of excessive menstrual bleeding in patients with FA include reproductive hormones such as estrogen (administered with or without the hormone progesterone) and a class of drugs known as gonadotropin releasing hormone (GnRH) agonists<sup>(35)</sup>. Leuprolide acetate, a type of GnRH agonist that is administered via intramuscular injection, has been shown to be effective in inducing menopause in women scheduled for bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT)<sup>(36-39)</sup>.

Ideally, medications that suppress menstrual bleeding should be initiated 1 to 2 months prior to HSCT to increase the likelihood that menstruation will cease by the time of transplant. However, many patients are too ill and cannot delay HSCT for such a long time. In those women, high-dose oral contraceptives (containing 50 micrograms or more of ethinyl estradiol) are an effective alternative. These contraceptives avoid the potential complications

associated with intramuscular injections in patients who are prone to excessive bleeding elsewhere in the body due to low platelet levels<sup>(36)</sup>. However, oral contraceptives may not be an option for patients who have already undergone HSCT. These individuals often cannot tolerate oral medications (due to inflammation of the gastrointestinal tract, nausea, and vomiting) and often have abnormalities in their liver function tests due to hemolysis (the destruction of red blood cells), the toxic side effects of medications, or graft-versus-host disease.

Previously, high-dose oral contraceptives have been used for managing mild to moderate excessive menstrual bleeding. However, studies have shown that low-dose oral contraceptives (containing 35 micrograms or less of ethinyl estradiol) can be as effective as high-dose oral contraceptives for the management of excessive menstrual bleeding and can minimize the risk of endometrial atrophy (thinning of the uterine lining), which is associated with continuous or long-term oral contraceptive use and can eventually lead to excessive bleeding<sup>(35, 36)</sup>. The treatment regimen has conventionally been 2 tablets per day for 5 days, followed by 1 tablet daily (with no placebo break) until the patient is deemed stable enough to resume menstrual cycles or is considered menopausal<sup>(40)</sup>. A retrospective review of 33 females who had undergone HSCT and were referred to gynecologists for excessive menstrual bleeding during the transplant period revealed that hormone therapy eliminated symptoms in 97% of the women, and that 79% of the women required only one oral contraceptive regimen<sup>(36)</sup>. The study found no differences in the response rates among women using low-dose versus high-dose oral contraceptives, monophasic versus multiphasic oral contraceptives, or ethinyl estradiol delivered in the form of pills versus transdermal patches. Patients who have severe excessive menstrual bleeding or are unresponsive to low-dose oral contraceptives may be prescribed high-dose oral contraceptives or injections of conjugated estrogens (25 micrograms every 6 hours for 24 hours). These patients should be switched to some other form of continuous hormonal treatment, such as low-dose oral contraceptives or leuprolide, once their excess bleeding has stopped.

If a patient's excessive menstrual bleeding cannot be managed using medication, additional treatment options are available for individuals who are considered suitable for surgery:

- ***Dilation and curettage***, a procedure in which the doctor dilates the cervix (the narrow passageway between the vagina and the uterus) and inserts a tool called a curette, which is used to gently scrape off some of the tissue

lining the uterus. This tissue is known as the endometrium, which is responsible for menstrual bleeding.

- **Endometrial ablation**, a procedure that permanently destroys the endometrium. This procedure results in infertility.
- **Hysterectomy**, a procedure in which the entire uterus is removed.
- Patients who are being treated with leuprolide acetate to reduce excessive menstrual bleeding can also take oral contraceptives to manage any menopausal symptoms and to prevent osteoporosis, which is associated with long-term (more than 6 months) exposure to leuprolide acetate and other GnRH agonists <sup>(1)</sup>.

## Future Research Directions

Though FA research has been transformed by a number of remarkable discoveries in recent years, much work remains. Premature ovarian insufficiency and early menopause in women with FA remains poorly understood, and women in their reproductive years need access to better methods of fertility and ovarian preservation before they undergo stem cell transplantation. Future research should also aim to define the risk of breast cancer, delineate the optimal methods for breast cancer screening, and quantify the frequency of successful pregnancies in women with FA. Finally, further studies are needed to improve the diagnosis and treatment of genital tract dysplasia before cancer arises.

## Recommendations for Women with FA

- Clinical experts recommend screening for gynecological cancer every 6-12 months. Biopsies should be performed on any visible lesions, because dysplasia can rapidly progress to cancer.
- Gynecologic assessment for pubertal delay and genital lesions in women with FA should begin at age 13. Thorough vulvovaginal examinations and Pap testing can begin when women become sexually active or by age 18, whichever is earlier. Anal pap smears and anoscopy may be considered in those women who have vulvar disease.
- As with the general population, colposcopy is appropriate in the setting of abnormal cytology or suspicious lesions noted on examination.
- Current consensus guidelines for cervical cancer screening, which are published by the American Society for Colposcopy and Cervical Pathology (ASCCP) and call for longer screening intervals than previous guidelines, do not apply to patients with FA.
- To help prevent against HPV infection, females between the ages of 9-26 should get vaccinated with either Gardasil® or Cervarix®.
- Suspicious genital tract lesions should be biopsied. If dysplasia is found, surgical resection or ablation is the preferred method of treatment. Medical therapy with immune modulators or a combination of medical and surgical therapy can also be used, but the patient must be closely monitored for treatment success and adverse effects.
- Patients diagnosed with genital tract cancer should be referred to a gynecologic oncologist immediately. Early referral may enable surgical treatment of the cancer, thereby avoiding the risks associated with chemotherapy or radiation in patients with FA.
- Patients with FA should begin breast cancer screening at a younger age than women in the general population. The screening recommendations for patients with FA are similar to the recommendations for other populations at high risk for breast cancer, such as individuals with mutations in the *BRCA1* and/or *FANCD1/BRCA2* genes, and those who have undergone mantle field radiation (a type of treatment that delivers radiation to a large portion of the upper body).
- Breast cancer screening modalities include mammography and MRI. Please see detailed discussion earlier in the chapter under the *Breast Cancer* section.
- Women who are diagnosed with cervical cancer before age 30 and vulvar cancer prior to age 40 may benefit from screening for FA.
- Women with FA who experience premature ovarian failure as a result of FA or HSCT may benefit from oral contraceptive pills or traditional hormone replacement therapy until age 50, at which time other options for managing menopausal symptoms can be discussed with symptomatic patients.



**Table 1.** Medications for the management of hot flashes.

Agent	Type of drug	Dose	Comments
Traditional hormone replacement therapy (HRT) (31)	Hormone (estrogen is a key component)	Several oral and transdermal (skin patch) options are available	Generally contraindicated for breast cancer survivors  Combination therapy recommended for patients who have a uterus  Patients may experience uterine bleeding upon cessation of therapy
Fluoxetine (41)	Selective serotonin reuptake inhibitor (SSRI)	20 mg by mouth daily	Significant improvement in the frequency and intensity of hot flashes
Paroxetine (41)	SSRI	10-20 mg by mouth daily	67% reduction in the number of hot flashes  75% reduction in the intensity of hot flashes
Megestrol acetate (42, 43)	Hormone (progestin)	20-40 mg daily	Improvement in hot flashes in up to 70% of women  Patients may experience uterine bleeding upon cessation of therapy  May cause bloating  Stimulates appetite
Clonidine hydrochloride (44)	Antihypertensive	0.1 mg by mouth twice per day, or 0.1 mg by transdermal patch weekly	10-20% reduction in hot flashes  Side effects include lethargy, irritability, hypotension, and vomiting
Venlafaxine (45, 46)	SSRI	25-75 mg daily	Improvement in hot flashes  Side effects including dry mouth, anorexia, and nausea are more common at doses of 75 mg per day
Gabapentin (47)	Anticonvulsant	300 mg by mouth 3 times per day	

**Table 2.** Medications for the management of vaginal dryness.

Agent	Type of drug	Dose	Comments
HRT (48)	Hormone (estrogen-based vaginal creams available)	½-1 applicator full, inserted into the vagina at bedtime for 10 days; twice per week thereafter for maintenance	Messy Absorbed into the general circulation Improves vaginal symptoms
Estradiol vaginal ring (49)	Hormone (estrogen)	1 ring, inserted into the vagina every 3 months	Minimally absorbed into the general circulation (7.5 mcg/24h) Improves vaginal symptoms
Estradiol tablets (48, 50, 51)	Hormone (estrogen)	10 microgram tablets 1 tablet inserted into the vagina at bedtime for 14 days; twice per week thereafter for maintenance	Minimal absorption into the general circulation Improves vaginal symptoms

**Table 3.** Behavioral therapy for the management of hot flashes.

Agent	Type of Drug	Dose	Comments
Paced respirations (52)		6-8 slow, deep breaths per minute, for 15 minutes at least twice a day May do at outset of a hot flash	40-50% reduction in hot flashes (measured objectively)

**Table 4.** Over-the-counter options for the management of vaginal dryness and painful intercourse <sup>(53-55)</sup>.

Replens®
Astroglide®
Lubrin®; K-Y Jelly®
Vitamin E (capsules/suppositories)
Hyalo GYN®
Bodyglide®

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# Chapter 7: Endocrine Disorders

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## Introduction

### Good to Know

The **endocrine system** produces hormones that allow our bodies to develop and function.

This system consists of glands in the head, neck, and abdomen that release many different types of hormones into the bloodstream.

These hormones perform a variety of functions in the body, from regulating blood sugar levels after meals to triggering physical changes during puberty.

Both Fanconi anemia (FA) and its treatment can harm the endocrine system. About 8 of every 10 children and adults with FA have at least one endocrine abnormality <sup>(1-9)</sup>.

These abnormalities can affect the body in a variety of ways, delaying puberty in one person, for example, while causing diabetes, brittle bones, or short body height in another.

A complete list of concerns related to the endocrine system is shown below:

- *Short stature*
- *Challenges related to weight and nutrition*
- *Abnormal glucose or insulin metabolism (often contributing to pre-diabetes or diabetes)*
- *Underactive thyroid gland (known as hypothyroidism)*
- *Insufficient production of growth hormone (GH) or other pituitary hormones*
- *Pubertal delay, underactive testes or ovaries (known as hypogonadism), and infertility*
- *Low bone mineral density (often contributing to osteoporosis, or brittle bones)*



Because endocrine abnormalities influence so many aspects of growth and development, the endocrine clinical care team should include an **endocrinologist** or **pediatric endocrinologist**, a **dietician**, and for females a **gynecologist** or a **reproductive endocrinologist**. The endocrine team should work in close collaboration with other FA specialists to provide comprehensive care.

## Height

Short stature is a common characteristic of patients with FA. More than half (60%) of children and adults with FA are shorter than all but 2.5% of their healthy peers. In scientific terms, this means the average person with FA is two standard deviation (SD) units, or -2 SD, shorter than the average in the general population<sup>(7)</sup> (Table 1). The average height of adult women with FA is about 150 cm (4 feet, 11 inches), while the average adult man with FA is 161 cm (5 feet, 3.5 inches). In children considered “short” by FA standards (at least shorter than 2 SD below the average in the general population, or < -2 SD), body heights ranged from 7.8 SD to 2 SD shorter than the average in their healthy peers (median, about -3.4 SD)<sup>(1, 2, 7)</sup>. However, a number of individuals with FA have normal height, and about 1 of every 10 patients is taller than the average in the general population<sup>(7)</sup>.

**Table 1.** Average height of patients with FA, by research center.

	Number of Patients	Average Height SD	Range of Height SD
NY (1)	54	-2.4	-6.3 to +0.8
NIH (2)	45	-2.1	-7.8 to +0.8
CCHMC (7)	120	-2.1	-5.4 to +1.8
<b>Overall</b>	<b>219</b>	<b>-2.2</b>	<b>-7.8 to +1.8</b>

*Abbreviations:* New York Center, NY; National Institutes of Health, NIH; Cincinnati Children’s Hospital Medical Center, CCHMC; height Z-score in standard deviation units from the mean for age and gender, HtSD

In patients with FA, short stature can be traced back to a number of factors:

- **Endocrine abnormalities**

People with FA who have hormone deficiencies tend to be shorter than the average of people with FA who have normal hormone levels, with average differences of -1 SD in children and -1.7 SD in adults<sup>(1, 7)</sup>. Adult heights may be even shorter in children with untreated GH deficiencies or

hypothyroidism. However, it is important to note that endocrine defects are not the only possible reasons for short stature. Even FA patients with healthy hormone levels tend to be shorter than average for the general population, with about half of them being within the height range considered normal. Conversely, some patients with FA are very short despite having normal hormone levels. As a result, hormonal replacement therapy does not always result in normal growth.

- ***Genetic mutations***

Certain genetic mutations are strong predictors of short stature in patients with FA, independent of hormone levels. For example, a subset of patients with the IVS4 A to T mutation of *FANCC* have an average height of -4.3 SD; these patients are significantly shorter than FA patients with other mutations <sup>(1)</sup>. In contrast, patients in the FA-A complementation group have heights similar to the other complementation groups as a whole <sup>(7)</sup>.

- ***Parental heights***

Height is an inherited trait, and parental heights may be used to predict the adult heights of their children. However, this prediction may not be helpful in patients with FA because FA children are shorter than average despite their parents' heights being similar to that of the general population <sup>(7)</sup>.

Therefore, predicted adult heights may not be accurate in patients with FA because short stature is influenced by additional factors.

- ***Birth size***

Average birth weight in infants with FA is at the lower end of the normal range, typically about 1.8 SD less than average for the general population. Approximately half of all children with FA are considered small for gestational age (SGA) at birth, with length or weight about 2 SD less than average <sup>(7)</sup>. In the general population, about 90% of children who are considered SGA at birth catch up to the normal range for height. In contrast, only about one-quarter of FA children who are considered SGA at birth catch up to the normal range <sup>(7)</sup>. In a series of FA patients studied at Cincinnati Children's Hospital Medical Center, the median height of children considered SGA at birth was -2.6 SD, while the median height of children considered appropriate for gestational age (AGA) at birth was -2.0 SD <sup>(7)</sup>.

- **Poor nutrition**

Being underweight is linked with short stature in patients with FA <sup>(7)</sup>, and suboptimal nutrition may also predispose children to stunted growth, or growth failure.

- **Transplant status and medications**

It remains unclear whether the transplant process directly affects the growth of patients with FA. However, medications such as androgens and corticosteroids, which are used to treat FA patients, may affect growth and bone maturation, and impair adult height. Some medications or irradiation used during hematopoietic stem cell transplantation (HSCT) may affect thyroid or gonadal function, which in turn may negatively impact growth and adult height. These factors are discussed in more detail later in the chapter. In addition, total body, abdominal, or thoracic irradiation used in preparation for HSCT may directly influence the growth of the spinal cord.

### **Evaluation of growth**

*Regular screening:* Growth should be closely followed in children with FA. Accurately measuring height with the use of a stadiometer (the ruler and sliding paddle mounted on the wall—not the weight scale—of most doctors’ offices) is important, and height should be plotted on a growth chart. Children with FA who consistently fall low on the growth chart (with heights  $\leq -2$  SD compared with the average in the general population) or children with FA whose height gradually falls to a lower percentage on the growth chart, indicating a decline in annual growth velocity, should be evaluated by a pediatric endocrinologist. Endocrine evaluation should include a full assessment of growth and thyroid hormones, as well as pubertal status (Table 2). Nutritional and medical causes for poor growth should be identified in children with FA as early as possible.

*Targeted testing for patients with abnormal growth:* Determining the patient’s bone age (BA) is part of a standard endocrine evaluation for short stature, and involves a radiograph of the left hand and wrist. Bone age may need to be reassessed every 1 to 2 years in short children. The results of BA assessments are sometimes used in height prediction algorithms, wherein if BA appears younger than the patient’s actual age, the height prediction algorithm may suggest that adult height will be more favorable as the child has more “room to grow”. This prediction assumes that the child will continue to experience healthy growth, optimal nutrition, normal hormone secretion, and normal timing of puberty; however, these assumptions are not necessarily correct in FA patients. Androgen therapy may accelerate BA, while hypothyroidism,

GH deficiency, hypogonadism, and corticosteroid therapy may delay BA. Therefore, estimates of adult height based on BA may lead to over-optimistic height predictions in patients with FA. Adult height predictions should be re-evaluated after a decrease in the growth velocity or following initiation of androgen therapy and after HSCT<sup>(10)</sup>.

In addition to tracking the patient's bone age, GH secretion can be indirectly evaluated by measuring insulin-like growth factor 1 (IGF-1) and IGF-binding protein 3 (IGFBP-3) levels. Levels of these proteins may be used to screen patients with short stature or growth failure. A thorough evaluation for GH deficiency by stimulation testing and MRI of the pituitary gland may be performed in consultation with a pediatric endocrinologist.

### **Recommendations for therapy**

Treatment for growth failure or short stature requires identifying the underlying cause. Healthy nutrition is important for maintaining optimal growth and dietary changes may be indicated. In that case, if the dietary changes aren't enough, hormone replacement therapy may be needed. Replacement of specific hormone deficiencies is discussed later in this chapter.

**Table 2.** Endocrine screening recommendations for patients with FA.

	Annual screenings for all patients	Detailed testing for selected patients
Growth	<ul style="list-style-type: none"> <li>Plot patient's height and weight on a growth chart</li> </ul>	<p>If patient exhibits signs of growth failure:</p> <ul style="list-style-type: none"> <li>Test levels of IGF-1, IGFBP3</li> <li>Obtain a bone age radiograph</li> <li>Test levels of FT4/TSH</li> <li>If patient has suspected GHD:</li> <li>Perform GH stimulation tests</li> <li>Obtain a pituitary MRI if evidence of pituitary hormone deficiency</li> </ul>
Thyroid Activity	<ul style="list-style-type: none"> <li>Plot patient's height and weight on a growth chart</li> <li>Perform early morning TSH and FT4 tests</li> </ul>	<p>If patient has suspected central hypothyroidism:</p> <ul style="list-style-type: none"> <li>Determine the ratio of 0800h TSH to afternoon TSH</li> </ul>
Cortisol Levels		<p>Perform low dose ACTH stimulation test if evidence of:</p> <ul style="list-style-type: none"> <li>Any other pituitary hormone deficiency</li> <li>A pituitary abnormality on MRI</li> </ul>
Glucose, Insulin, and Metabolism	<ul style="list-style-type: none"> <li>Consider fasting glucose and insulin testing; 2-hr post-prandial glucose and insulin tests</li> <li>Measure HbA1c (after HSCT)</li> <li>Consider fasting lipid profile in patients older than 10 years</li> </ul>	<p>If patient is overweight/obese/has hyperlipidemia:</p> <ul style="list-style-type: none"> <li>Perform a 2-hour OGTT test</li> <li>If patient previously had an abnormal OGTT but does not have diabetes:</li> <li>Repeat OGTT yearly</li> </ul>
Puberty and Gonadal Function	<ul style="list-style-type: none"> <li>Perform pubertal staging of pubic hair and either breasts (girls) or testes (boys) during physical examination</li> <li>Assess menstrual history and clinical evidence of hypogonadism in post-pubertal patients</li> </ul>	<p>If patient has early/delayed puberty or suspected hypogonadism:</p> <ul style="list-style-type: none"> <li>Obtain a bone age radiograph</li> <li>Test LH, FSH, estradiol, or testosterone levels</li> </ul>
Bone Mineral Density	<ul style="list-style-type: none"> <li>Assess the patient's dietary calcium and vitamin D intake</li> <li>Measure 25OH-vitamin D level</li> </ul>	<p>Consider DXA scan to evaluate BMD:</p> <ul style="list-style-type: none"> <li>Every 5 years starting at age 14</li> <li>Before HSCT and 1 year after HSCT</li> <li>Repeat in 1 year if patient has low BMD</li> <li>Repeat every 2 years if patient has hypogonadism or premature ovarian failure, or as in line above.</li> </ul>

*Abbreviations:* Thyrotropin, TSH; free thyroxine, FT4; insulin-like growth factor, IGF-I; IGF binding protein 3, IGFBP3; growth hormone, GH; magnetic resonance imaging, MRI; hematopoietic stem cell transplant, HSCT; glycosylated hemoglobin, HgBA1c; luteinizing

hormone, LH; follicle-stimulating hormone, FSH; 25-hydroxy-vitamin D level, 25OH-vitamin D; dual X-ray absorptiometry, DXA; standard deviation units (Z-score) from the mean (SD); bone mineral density, BMD; adrenocorticotrophic hormone, ACTH; two-hour oral glucose tolerance test, OGTT

## Weight and Nutrition

### Good to Know

**Body mass index (BMI)** reveals whether your body weight is healthy, given your height.

Here's what the numbers mean in adults:

Healthy weight: BMI 18.5 to 25

Overweight: BMI greater than 25

Obese: BMI greater than 30

Approximately half of FA children are born SGA<sup>(7)</sup>. In a series of patients studied at Cincinnati Children's Hospital Medical Center, infants with FA who were considered SGA were not only shorter but were also thinner than infants considered to fall within normal parameters at birth. Specifically, the average body mass index (BMI) was -1.3 SD in infants considered SGA, compared with -0.5 SD in infants considered to fall in the average range<sup>(7)</sup>.

The BMIs of children and adults with FA are generally similar to the non-FA population, with average BMIs of -0.2 SD in children and -0.95 SD in adults. However, about one-quarter to one-third of all patients with FA are thin or underweight, while a few are overweight<sup>(2, 7)</sup>. The frequency of overweight in children with FA is similar to that in the general population, with a range of 11% to 27% depending on the group of patients studied<sup>(2, 7)</sup>.

In some cases, being underweight may stem from the nutritional and gastroenterological problems common in patients with FA. Some children may have a smaller than expected appetite; others have trouble absorbing nutrients from food. In addition, illnesses like those that affect FA patients can raise caloric requirements. Glucose intolerance and insulin deficiency may also contribute to poor weight gain.

Excess weight gain, on the other hand, may reflect lifestyle factors and a genetic predisposition to obesity.

### **Evaluation of under- or overweight patients**

Body weight should be assessed at least annually; more frequently if there is concern about failure to thrive or excessive weight gain relative to standard norms. If there are concerns related to body weight, a registered dietitian should assess the patient's nutritional intake. In addition, the primary care provider should thoroughly evaluate the patient for underlying medical conditions, concurrent medications, specific hormone-related conditions, and related co-morbidities.

### **Recommendations for intervention**

Healthy dietary intake should be encouraged, including sufficient calcium and vitamin D from foods or supplements. Input from a registered dietitian may be needed. The underlying causes of under- or overweight should be addressed, including treatment of endocrine disorders. Related co-morbidities due to obesity should be prevented and treated, as discussed later in this chapter in the sections on abnormal glucose metabolism, lipid abnormalities, and metabolic syndrome.

**Table 3.** Endocrine disorders in children and adolescents with FA, by research center.\*

Research Center	Average Patient Weight	Thyroid Activity	Growth Hormone	Glucose/ Insulin Levels	Onset of Puberty	Bone Mineral Density
NY (1)	Of 54 patients studied, including a few adults, the average BMI was lower (-1.3 SD ± 0.2) than the average in the general population.	Of 53 patients, about one-third (36%) had low thyroid activity.	Of 48 patients, nearly half (44%) had low levels of GH.	Of 40 patients, 20% had impaired glucose tolerance, 5% had diabetes, and 72% had higher than normal levels of insulin.	Not studied.	Not studied.
NIH (2)	When 24 patients were compared with the general population, about 1 in 5 (21%) had BMI greater than 85th percentile.	Of 20 patients, 1 in 5 (20%) had low thyroid levels.	Of 14 patients with suspected GHD#, half (50%) had low levels of GH. Of 24 patients with GHD or suspected GHD#, MRI revealed a midline defect in almost 1 in 5 patients (17%).	Of 24 patients, 4% had diabetes, 17% had insulin resistance, and 29% had dyslipidemia (unhealthy levels of cholesterol and triglycerides).	Of 14 males, about two-thirds (64%) had small testes. Of 17 females, more than 1 in 10 (12%) had delayed menarche, starting their periods later in life than their healthy peers.	Not studied.
CCHMC (3-5, 7, 9)	One third of patients (33%) studied had BMIs lower than average in the general population (< -1.8 SD). Far fewer patients (11%) had BMIs greater than average in the general population (> +1.8 SD).	Of 70 patients, about two-thirds (61%) had low thyroid levels.	Of 32 patients, about 1 in 10 (12%) had low levels of GH. Of 11 patients, almost half (45%) had small pituitary glands on MRI.	Of 47 patients, 68% had hyperglycemia, or high blood sugar. Of 39 patients, 34% had high insulin levels. Of 24 patients, 17% had dyslipidemia (unhealthy cholesterol and triglyceride levels).	Of 22 males, most (86%) had small gonads. Of 7 females, 14% had delayed menarche, and 13% had high FSH levels.	Of 29 patients, only 3% had low bone mineral density.
U of M (6, 8)				Of 17 patients, 6% had impaired fasting blood sugar, 24% had low first-phase insulin release, 17% had increased first-phase insulin release and high fasting insulin, and 8% had impaired glucose tolerance.		Of 49 patients, about half (52%) had low bone mineral density following HSCT.



\* Different studies used different biochemical criteria.

# Suspected GHD was defined by growth failure, low levels of IGF-1, and/or low levels of IGFBP-3.

*Abbreviations:* New York Presbyterian Hospital-Cornell University Medical Center, NY; National Institutes of Health, NIH; Cincinnati Children's Hospital Medical Center, CCHMC; University of Minnesota, U of M; body mass index Z-score in standard deviation units from the mean for age and gender, BMI SD; hematopoietic stem cell transplantation, HSCT

## Abnormal Glucose or Insulin Metabolism

### Glucose elevation/delayed insulin secretion

Diabetes mellitus occurs more commonly in patients with FA than in the general population <sup>(1)</sup>; moreover, patients with FA have a relatively high incidence of high blood sugars, also known as impaired glucose tolerance. One study detected diabetes in approximately 8% of patients with FA, while an additional 27% to 68% of these patients had impaired glucose tolerance (Tables 3 and 4) <sup>(1, 2, 4, 6, 7)</sup>. In addition, as many as 72% of patients with FA had elevated insulin levels 1 to 2 hours after eating. Interestingly, insulin levels were low 10 to 45 minutes after an oral glucose test, suggesting slow initial insulin secretion, but became elevated 60 to 120 minutes after the test <sup>(4, 6)</sup>. Although the elevated levels suggest that insulin resistance may contribute to diabetes in patients with FA, these findings also support the possibility that insulin-producing cells known as beta cells ( $\beta$ -cells) do not function properly in these patients, which could impair first-phase insulin secretion <sup>(4, 6)</sup>. So the diabetes in FA is not typical for either Type 1 or Type 2 diabetes.

### Good to Know

The foods and drinks you consume are broken down into sugars—such as **glucose**—that enter your blood and fuel your body.

- Patients with **impaired glucose tolerance** have trouble breaking down the sugars found in their diets, but they do not yet have diabetes.
- Impaired glucose tolerance is sometimes a warning sign that the patient may eventually develop diabetes

The cause of impaired first phase insulin secretion in patients with FA is unknown, but could stem from possible damage inflicted by enhanced reactive oxygen species (ROS) on the  $\beta$ -cells that secrete insulin or, alternatively, from iron overload in heavily transfused patients. Several medications used in the treatment of FA, particularly androgens and corticosteroids, are known to alter

glucose metabolism. Androgen treatment can significantly elevate both blood sugar and insulin levels <sup>(1)</sup>. Chronic steroid therapy also predisposes patients to insulin resistance and high blood sugar, known as hyperglycemia <sup>(12-14)</sup>. The guidelines regarding glucocorticoid use in FA should be the same as in any other subject: use the lowest possible dose of medication.

### **Screening for abnormal glucose and insulin metabolism**

All patients should be screened for abnormalities related to glucose and insulin homeostasis upon diagnosis with FA and, if possible, every year thereafter (see Table 2). Patients can be screened for glucose tolerance by measuring blood sugar and insulin concentrations after fasting for 8 hours, and by measuring post-prandial blood sugar and insulin concentrations 2 hours after a meal. The danger of measuring only serum glucose values, or relying solely on fasting values, is that some patients may be overlooked—particularly those with impaired glucose tolerance whose blood sugar and insulin levels are normal after fasting but elevated 2 hours after a meal. Glycosylated hemoglobin (HbA1c) and fructosamine levels may be deceptively normal, presumably due to impaired glycosylation or to elevated levels of fetal hemoglobin in patients with bone marrow failure <sup>(7)</sup>, and therefore are not helpful in FA patients prior to HSCT. HbA1c scores may provide more useful information after HSCT compared to before HSCT.

In patients who have suspected endocrine abnormalities and possess risk factors such as overweight/obesity or hyperlipidemia, a more detailed evaluation is needed in consultation with an endocrinologist. This evaluation should include a 2-hour oral glucose tolerance test (OGTT, 1.75 g glucose/kg body weight, maximum dose 75 g glucose). Some clinical centers obtain serum samples to measure blood sugar and insulin levels every 30 minutes during a 2-hour OGTT. Patients with abnormal OGTTs must be followed at least annually with repeat testing. The prevalence of diabetes mellitus in patients with FA increases with age and disease progression, and the majority of FA patients may be at risk.

## Treatment of blood sugar and insulin abnormalities

### Diet

All persons diagnosed with FA—regardless of OGTT results— should be placed on a healthy diet that avoids excessive consumption of concentrated sweets such as juices, soda, and candy. A registered dietician can provide valuable guidance, particularly by helping the patient distinguish unhealthy “simple” carbohydrates (such as candy) from healthier “complex” carbohydrates (such as whole grain breads). It is important to encourage adequate caloric consumption and regular exercise.

### Diabetes medications

Patients who have FA and diabetes should be treated by an endocrinologist. Insulin or oral medications should be tailored to the cause of diabetes, just as in the general population, with the goal of improving blood sugar control without causing low blood sugar, or hypoglycemia.

- *Treatment of hyperglycemia without obvious diabetes:*  
It remains unclear whether FA patients with normal fasting blood sugar but impaired glucose tolerance should be treated with insulin. Administration of short-acting insulin with meals may be more beneficial than metformin, due to the abnormal pattern of insulin release in patients with FA. Some practitioners recommend treatment with short-acting insulin at mealtime, to help the body process carbohydrates, if post-prandial blood sugar is consistently higher than 180 mg/dL.
- *Insulin therapy during HSCT:*  
During HSCT, many children with FA require insulin therapy to treat the high blood sugar, or hyperglycemia, that is often triggered by steroid therapy. A combination of long-acting and short-acting insulin may be required for adequate blood sugar control. The duration of therapy may vary depending on the duration, dose, and type of transplant medications used—particularly for corticosteroids, tacrolimus, sirolimus, or similar medications.
- *Isolated hyperinsulinemia:*  
Some practitioners have begun using oral diabetes medications such as metformin to treat otherwise normal children and adolescents with FA who occasionally have high levels of insulin, known as isolated hyperinsulinemia, but do not have glucose impairments. In overweight patients with FA, metformin may indeed be the best first choice. Patients who are treated with metformin should be monitored closely for side effects, as there have been no long-term studies on the risks or benefits of metformin in patients with FA.

## Dyslipidemia, Obesity, and Metabolic Abnormalities

The scientific literature includes lipid test results from 29 patients with FA. Of these patients, about half (55%) had unhealthy levels of cholesterol and triglycerides, a condition known as dyslipidemia. Of these patients, 21% had elevated levels of LDL, 31% had low levels of HDL, and 10% had elevated triglycerides <sup>(2)</sup>. An abnormal lipid profile was observed in nearly half (40%) of patients with hyperglycemia or insulin resistance. Of the patients with FA and diabetes, 75% were overweight or obese. Adults with FA and diabetes tended to be overweight or obese, compared with those without these metabolic abnormalities. About 1 in 5 (21%) adults with FA were diagnosed with metabolic syndrome, a condition in which patients are overweight/obese, have dyslipidemia, and develop resistance to the effects of insulin. Half of the 24 children tested had at least one metabolic abnormality, including 4 children with insulin resistance, 1 with diabetes, and 7 with dyslipidemia <sup>(2)</sup>. FA patients are at risk for metabolic syndrome, so we recommend a healthy diet and a regular exercise regimen, and careful screening for blood pressure and lipid abnormalities.

### Good to Know

Cholesterol comes in two forms:

- **LDL** is a “bad” cholesterol that builds up on the walls of arteries;
- **HDL** is a “good” cholesterol that scours these build ups from the artery wall to prevent heart attacks and stroke.

**Triglycerides** are the building blocks of fats and oils.

A person with **dyslipidemia** has unhealthy levels of cholesterol and triglycerides.

## Hypothyroidism

Many children with FA have mildly abnormal levels of serum thyroid hormones—that is, hormones secreted from the thyroid gland into the bloodstream—including borderline low levels of thyroxine (T4) or free T4 (FT4), or borderline high levels of thyroid-stimulating hormone (TSH) (Tables 3 and 4) <sup>(1, 2, 5, 7)</sup>. This combination of test results is consistent with mild hypothyroidism, or low thyroid activity. Mild hypothyroidism can occur either

because the thyroid gland is abnormal and cannot make enough T4 hormone (known as primary hypothyroidism) or because the thyroid gland is normal but the pituitary gland does not make enough TSH to stimulate the thyroid (known as central hypothyroidism).

About 60% of individuals with FA have thyroid function tests that suggest primary hypothyroidism. The mechanism of hypothyroidism in patients with FA remains unclear, but there is no indication that the primary hypothyroidism stems from an autoimmune process, in which the body mounts an immune attack against itself. Therefore, the thyroid appears to fail for other, yet-to-be-determined reasons in patients with FA. Hypothetically, some thyroid cells may die because of unrepaired DNA damage stemming from oxidative injury. One study described reduced thyroid hormone binding in persons with FA <sup>(1)</sup>. Although reduced thyroid hormone binding is often not clinically significant, it can make total T4 levels appear low and falsely suggest hypothyroidism without causing TSH elevation. Thyroid hormone binding globulin (TBG)-bound T4 (but not other bound forms) was lowest in individuals receiving androgen therapy <sup>(1)</sup>, suggesting the need to use Free T4 and TSH as the most important tests.

### **Thyroid evaluation**

Thyroid function should be evaluated by obtaining an early morning (e.g., 8:00 am) blood sample and measuring free T4 and TSH levels. All patients with FA should undergo screening for hypothyroidism once a year or more often if clinically indicated, for example, if the patient shows signs of growth failure (Table 2). Central hypothyroidism is suggested by low levels of free T4 and by a TSH ratio of less than 1.3 at 8:00 am compared to afternoon TSH <sup>(16)</sup>. Patients who are diagnosed with central hypothyroidism should undergo evaluation for other pituitary hormone deficiencies; specifically, the physician should rule out central adrenal insufficiency and consider ordering a pituitary MRI.

### **Recommendations for treating hypothyroidism**

Hypothyroidism should be treated promptly, particularly in children younger than 3 years of age. Thyroid hormone replacement treatment should be initiated just as in non-FA patients, based on low thyroid hormone levels: specifically, a free T4 level below the laboratory reference range and/or a TSH level above the reference range. Thyroid hormone therapy should strive to reduce TSH levels to the range of 0.5 to 2 mU/L in patients with primary hypothyroidism. In central hypothyroidism, therapy should aim to raise free T4 levels to just above the middle of the normal range.

There is ongoing controversy about the use of TSH levels greater than 3 mU/L as a threshold for the treatment of mild hypothyroidism <sup>(15)</sup>. Some endocrinologists may use a TSH level of 3 mU/L, or even 4.5 to 5 mU/L, as the upper limit of a normal TSH level in healthy individuals. However, treatment, especially in adults, is often not considered necessary unless TSH levels are persistently 10 mU/L or higher, or unless free T4 levels are low <sup>(16-18)</sup>. Among pediatric endocrinologists, some use the above approach, while others prefer to treat mildly elevated TSH levels in the hopes of improving their patients' growth <sup>(15)</sup>.

In one study, 8 children with FA were treated for 7 months with thyroid hormone and for 7 months with placebo; the treatment and placebo phases occurred in random order. Children grew significantly better on thyroid hormone than on placebo, and parents felt that their children had better energy levels during the thyroid hormone phase <sup>(5)</sup>. This study suggests that children with FA who have short stature and borderline results on thyroid function tests may benefit from using thyroid hormone therapy; however, it should be noted that a small number of patients were studied and the effects were not conclusively proven.

## Growth Hormone Deficiency

Growth hormone deficiency (GHD) has been described in case reports of a few patients with FA <sup>(19-23)</sup>. In one study, more than half (54%) of patients younger than 20 years failed to produce growth hormone (GH) in response to clonidine, a medication known to stimulate GH. Similarly, most patients (72%) failed to raise GH levels in response to another GH stimulator, arginine. Using a more stringent criterion for diagnosing GHD (specifically, peak GH levels  $\leq 5$  mcg/L), but without priming the patients in advance, 12% of 32 children tested had GHD <sup>(7)</sup>. Growth hormone deficiency was more common in patients who had undergone HSCT (25%) than in patients who did not have HSCT (8%) <sup>(7)</sup>. The processes that underlie secretion of GH may be abnormal in children with FA during spontaneous overnight GH secretion studies <sup>(1)</sup>, although these results are sometimes difficult to interpret because of the significant overlap with values observed in children without GHD <sup>(7)</sup>. Taken together, these test results suggest that while few children with FA have GHD, others may have an underactive hypothalamus, leading to "partial" GH deficiency or, alternatively, to neurosecretory GH deficiency. In these individuals, GH and insulin-like growth factor I (IGF-I) values may not be as severely affected as the patient's height.

### Evaluation for GHD

Screening for GHD in a child with poor growth can be performed by drawing a blood sample and measuring IGF-I and IGFBP3 levels (Table 2). If IGF-I and IGFBP3 values are below -2 SD for the patient's age, evaluation should include standard GH stimulation testing. One caveat is that IGF-1 is known to be a poor marker of GHD in thin individuals or in those who have received total body or cranial irradiation. Sex steroid priming should be considered prior to GH stimulation testing in pre-pubertal girls age 10 and older, and in pre-pubertal boys age 11 and older or who are in stage 2 of puberty<sup>(24, 25)</sup>. Evaluation of GH secretion in a slowly growing child should be done through the use of two standard GH stimulation tests, including clonidine (150 mcg/m<sup>2</sup>, maximum dose 300 mcg), arginine (0.5 g/kg, maximum dose 20 g), or glucagon (0.3 mg/kg, maximum dose 1 mg)<sup>(25-27)</sup>. Peak GH levels are considered normal if they rise to 10 ng/mL or greater<sup>(28)</sup>. Patients diagnosed with GHD should be evaluated for central hypothyroidism, central adrenal insufficiency (as discussed below), and should also undergo an MRI scan of the pituitary gland.

### Recommendations for treatment

Patients with GHD can be treated with recombinant human GH therapy. A short child with FA is a candidate for treatment with GH if GHD has been convincingly documented by the child's short stature, slower than normal growth rate, and low GH peak on a stimulation test. Physicians should counsel FA families about the risks and benefits of therapy. To date, there is no clear consensus on the safety of GH therapy in FA patients. Though having FA is not an absolute contraindication to GH treatment, there is some controversy surrounding the use of GH in patients without GHD. It should be recognized that in some instances, treatment with GH may be instituted in the absence of GHD if deemed appropriate by the patient care team, either before or after HSCT. In the absence of safety data, GH therapy in FA patients should be titrated to achieve IGF-I concentrations in the mid-to-normal range for the patient's age (i.e., between 0 and 1 SD). Therapy should be discontinued immediately if routine hematological examination reveals clonal hematopoietic stem cell proliferation. Growth hormone therapy should be temporarily discontinued immediately prior to HSCT and for at least 6 months after HSCT, as well as during critical illness<sup>(29)</sup>.

Although no studies have examined the effectiveness of GH treatment in children with FA after HSCT, significant growth responses to GH therapy have

been observed in some patients with FA (Petryk, Polgreen, Miller, MacMillan, Wagner, unpublished data). In studies of patients without FA, the response to GH treatment after HSCT has varied <sup>(30-33)</sup>. Ongoing use of glucocorticoids after HSCT may limit the patient's growth response. In a study that included HSCT recipients, GH treatment was associated with significantly improved adult height (on average, patients treated with GH grew about 4 to 5 cm taller than untreated children) <sup>(34)</sup> and did not increase the risks of recurrent leukemia, secondary malignancies, or diabetes in post-HSCT patients treated with GH compared with those who were not treated. A beneficial effect of GH treatment on growth rate after HSCT has also been reported by others <sup>(35, 36)</sup>.

Patients with FA are inherently at an increased risk of cancer, particularly for acute leukemia prior to HSCT as well as malignancies of the head and neck and gynecological cancers <sup>(37-39)</sup>. At this time, there is no evidence that this risk is enhanced in FA patients treated with GH. Patient registries have provided useful safety and efficacy data on the use of GH in the general population and in cancer survivors, but have included few patients with FA <sup>(40-46)</sup>. A large study of 13,539 cancer survivors, including 361 patients treated with GH, did not find an increased risk of cancer recurrence in GH-treated survivors <sup>(47)</sup>. However, the risk of a second neoplasm, mostly solid tumors, was slightly increased in survivors treated with GH.

Despite these possible risks, it should be noted that severe short stature may have a negative impact on the patient's quality of life and daily functioning. Families should be counseled regarding the predicted adult heights of their children, the effects of available treatment modalities on growth rate, and the potential risks and benefits of GH treatment—with the caveat that there is no clinical information about the long-term safety of GH therapy in patients with FA.



## Cortisol Sufficiency

### Good to Know

- **Cortisol** is a steroid produced by the body that plays important roles in stress response, immunity, metabolism of nutrients, and other processes.
- Cortisol levels ebb and flow in response to the body's **circadian rhythm**. Levels are lowest when you fall asleep, highest just after you wake, and gradually decline until the following night.

Most FA patients have normal circadian cortisol levels and experience normal responses to treatment with adrenocorticotrophic hormone (ACTH). ACTH stimulation testing has been normal even in patients with reported pituitary stalk interruption syndrome (PSIS) and multiple pituitary hormone deficiencies <sup>(2)</sup>. However, cortisol sufficiency should be evaluated in young children with FA who have poor growth and who require major surgery because of possible central hypothalamic dysfunction, even in the absence of a detectible midline central nervous system defect <sup>(3,20)</sup>. Finally, ACTH stimulation testing is recommended to rule out central adrenal insufficiency if the patient has other pituitary hormone deficiencies.

## Multiple Pituitary Hormone Deficiencies

In previous studies, MRI scans of the brain and pituitary gland have suggested that the pituitary gland is smaller and has a thinner stalk in patients with FA compared with age-matched children without FA <sup>(3)</sup>, unpublished data NIH]. Four patients with FA at the National Institutes of Health (NIH) had an abnormal brain MRI with midline defects ranging from absent corpus callosum and septum pellucidum to septo-optic dysplasia. In addition, 1 patient was noted to have a thickened pituitary stalk while 2 patients had pituitary stalk interruption syndrome (PSIS) <sup>(2)</sup>, unpublished data NIH]. This syndrome has previously been reported in 8 other patients with FA <sup>(23,48-50)</sup>, and was associated with permanent GHD and severe growth failure. Specifically, the average height SD of all the children with PSIS at diagnosis was -4.6, with a range of -3.7 to -5.7. These patients were also at risk for multiple pituitary hormone deficiencies: 5 of 10 patients with FA and PSIS had hypothyroidism, 1 of 10 patients had hypogonadotropic hypogonadism, and the remaining 4 patients were too young to evaluate. Furthermore, 5 of 6 male patients had cryptorchidism, in which one or both testicles fail to descend, and 4 of 6 male

patients had microphallus (an abnormally small penis). Together, these findings suggest that in addition to GHD, the male patients had hypogonadotropic hypogonadism, a condition in which the testes produce lower than normal amounts of sex hormones due to an underlying problem with the pituitary gland or hypothalamus.

Based on the available evidence, a brain MRI with emphasis on the pituitary/hypothalamic area should be obtained in any FA patient who has one or more pituitary hormone deficiencies, including GHD, central hypothyroidism, or ACTH deficiency. Serum IGF-1 testing has been proposed as a screening test, as all patients with PSIS and GHD had a low IGF-1<sup>(48)</sup>. Serial endocrine testing is essential in patients with PSIS, because pituitary hormone deficiencies may evolve over time.

## Puberty, Hypogonadism, and Fertility

### Early onset of puberty

Children and adolescents with FA may enter puberty earlier than their healthy peers. If puberty starts too early or progresses too quickly, it may limit the number of years a child can grow and thus compromise adult height. A child with FA who experiences an early onset of puberty and has short stature may benefit from gonadotropin-releasing hormone agonist therapy. A previous study suggests this therapy can delay puberty to increase the patient's adult height by an average of 4 to 5 cm after 4 years of therapy<sup>(51)</sup>.

### Good to Know

- **Puberty** normally begins around age 10 in girls, and around age 11 in boys.
- Puberty is considered **delayed** if no physical changes have occurred by age 14 in boys, or by age 13 in girls. Additionally, puberty is considered delayed in girls if menstrual cycles have not yet begun by age 16 or 3 years after developing breast buds.

### Delayed puberty

More commonly, children with FA enter puberty later than their healthy peers. While delayed puberty is fairly common, its underlying cause is not well understood. There may be blunted and/or prolonged gonadotropin [primarily luteinizing hormone (LH)] responses to stimulation, suggesting abnormal regulation of the hypothalamic and pituitary glands. Chronic illness is also associated with delayed pubertal maturation. Total body irradiation and some chemotherapy agents used during HSCT may also affect gonadal function.

### **Evaluation for pubertal disorders**

In patients with FA, the onset, pubertal stage, and tempo of progression of puberty should be monitored during annual physical examinations. Physical exams should include Tanner staging of pubic hair, and assessments of breast development in girls and testicular size in boys (Table 2). Assessment of bone maturation can be useful in adolescent children who experience delayed or abnormal progression of puberty, while measuring the concentrations of certain hormones—particularly LH, FSH, estradiol, or testosterone—can be useful in adolescents and in adults who develop symptoms of hypogonadism, a condition in which the testes or ovaries produce insufficient amounts of hormones.

### **Recommendations for treatment of delayed puberty**

A boy who shows no signs of puberty by age 14 years should be evaluated for possible causes of delayed puberty. After evaluation, low-dose testosterone therapy can be initiated according to the child's height and growth potential. Young boys with confirmed hypogonadism can be treated using topical gel preparations or by injections of testosterone started at an appropriately low dose and gradually increased over several years to adult replacement levels. It is important to avoid rapid increases in testosterone levels in adolescents to ensure continued height gain and avoid premature fusion of the growth plates. Bone age should be monitored during therapy.

Similarly, a girl with FA who shows no signs of puberty by age 13 years should receive a full hormonal work up. After evaluation, low-dose estrogen therapy may be started and slowly titrated under the care of the pediatric endocrinologist or adolescent gynecologist, taking into account the child's height and potential for growth. It is important to avoid rapid increase in estradiol levels in adolescents to ensure continuing height gain and to avoid premature fusion of the growth plates. Bone age should be monitored during therapy. Estrogen therapy will increase bone mineralization, optimize the child's growth rate, and achieve breast development. Progesterone (i.e., medroxyprogesterone, 10 mg by mouth daily for 10 days) should be added when breakthrough bleeding occurs or after 2 years of estrogen replacement therapy.

Estrogen therapy is not needed if a girl has normal pubertal development or is having normal menstrual cycles, even if there is evidence of ovarian hormone deficiency. In patients with FA, there is no medical contraindication to the use of oral contraceptive pills.

## **Hypogonadism**

Hypogonadism is very common in adults with FA. In addition, hypogonadism with small testes and penis size affects two-thirds (64%) of men with FA, while premature ovarian failure affects most (77%) females with FA <sup>(2)</sup>. In another study, almost half (40%) of adults with FA had evidence of hypogonadism <sup>(7)</sup>. Both hypergonadotropic (either testicular or ovarian) hypogonadism <sup>(50)</sup> and hypogonadotropic (specific to the hypothalamic-pituitary glands) hypogonadism have been reported in patients with FA. Gonadal function may be affected by several factors, including FA itself, SGA status at birth, gonadotropin deficiency, cryptorchidism, and/or the conditioning regimen used for HSCT, including radiation and chemotherapy <sup>(48)</sup>.

## **Genital Tract Abnormalities**

Developmental anomalies of the genital tract are more frequent in patients with FA than in the general population. Boys may be born with undescended testicles and hypospadias, a condition where the urethra opens on the underside of the penis. Many boys with FA have small testes for their age and pubertal status, most likely reflecting reduced Sertoli cell mass and spermatogenesis. Girls with FA may be at higher risk for certain reproductive malformations, including a smaller than normal uterus, half-uterus, or uterus that does not open into the vagina <sup>(52)</sup>.

## **Fertility**

Patients with FA often experience fertility problems, with males often being infertile and females often having premature menopause in their 20s or 30s, although rare pregnancies have been documented as described in *Chapter 6* <sup>(52)</sup>. Contraception should always be used when pregnancy is not desired. Infertility may stem from a number of different factors, including a reduced sperm count in men, treatments for HSCT, and the type of genetic mutation underlying FA. Gonadotropin-releasing hormone has been shown to acutely upregulate the expression of *FANCA* mRNA and protein, suggesting that *FANCA* plays a regulatory role in gonadal function <sup>(53)</sup>. Disruption of *Fanca* in mice is associated with hypogonadism and a reduction in fertility <sup>(54)</sup>. Animal studies have also shown that the *Fance* protein is required for the proliferation of primordial germ cells <sup>(55)</sup>. In addition, radiation or chemotherapy with HSCT may contribute to decreased fertility after HSCT. Cryopreservation of embryos or sperm is being investigated as a reproductive option. Future studies are needed to more fully address the fertility issues in patients with FA.

## Bone Mineral Density

### Good to Know

- Someone with **osteopenia** has lower-than-normal bone density. Osteopenia often leads to osteoporosis.
- A person with **osteoporosis** has brittle bones that break easily. This occurs when minerals and protein are depleted from the bones.

Bone mineral density (BMD) in FA has been reported in a few studies with differing conclusions. An earlier report described osteopenia or osteoporosis in 12 of 13 adults with FA, but the BMD was not corrected for the short stature commonly observed in individuals with FA <sup>(2)</sup>. In contrast, another report showed that BMD is normal in children and adolescents with FA, if adjustments are made for height. In 34 children and 3 adults with FA (including roughly equal numbers of patients with prior HSCT and no HSCT), lumbar spine BMD Z-scores adjusted for height age were in the normal range <sup>(9)</sup>. In 9 children and adolescents with FA who were followed at the NIH (half of whom had undergone HSCT) (unpublished data), height-adjusted lumbar spine BMD Z-scores were completely normal, according to an online BMD Z-score calculator <sup>(56)</sup>. We recommend that the BMD of children with FA be adjusted for height and that Z-scores be calculated. An online calculator (<http://www.bmdcspublic.com/zscore.htm>) may be used to calculate the height-adjusted Z-score in children with FA. There is limited information as to whether BMD in adults with FA should be adjusted for height, and few studies have examined the correlation of height-adjusted BMD and fracture risk.

Bone mineral density may decrease after HSCT in many patients including those with FA, but the underlying reasons for this remain unclear. In a study of 49 children, including 12 with FA, BMD decreased during the first year after HSCT, with the most significant bone loss occurring by 6 months <sup>(57)</sup>. The effects of HSCT on BMD in children with FA were similar to those in children without FA. The average areal lumbar BMD Z-score declined 0.5 SD units during the first 6 months after HSCT, and the number of patients with a Z-score below  $-1$  increased from 34% at baseline to 52% 1 year after HSCT <sup>(8)</sup>. The reduction in lumbar BMD at 6 months correlated with the cumulative dose of glucocorticoids <sup>(57)</sup>. While BMD remained within normal limits, the average height-adjusted lumbar BMD Z-score was lower in patients who had undergone prior HSCT ( $-0.9$ ) compared with those who had not had prior HSCT ( $-0.3$ ) <sup>(9)</sup>.

Long-term prospective studies are needed to examine the mechanisms underlying decreased BMD following HSCT in FA children.

In adults, HSCT is associated with decreased bone formation and increased resorption, and similar mechanisms may apply in children<sup>(58)</sup>. Medications used during HSCT, such as glucocorticoid therapy, may also contribute to low BMD. Long-term prospective studies should explore whether BMD declines further or recovers over time after HSCT. Hypogonadism and GHD may also predispose patients with FA to low BMD.

### **Screening for bone health**

Dual energy absorptiometry (DXA) should be used to evaluate BMD in patients with FA before HSCT and 1 year after HSCT. The first DXA evaluation may be performed at about age 14 if the patient has not undergone HSCT, and follow-up scans should be dictated by the patient's risk factors. Patients with FA who have hypogonadism and growth hormone deficiency should be evaluated for low BMD and treated as necessary. Levels of serum calcium, magnesium, and 25-OH vitamin D levels should be measured in HSCT recipients and in patients with low BMD<sup>(59)</sup>. Patients exposed to prolonged or high doses of corticosteroids, or who have a history of fractures, immobility, hypogonadism, or hormone deficiencies should be referred to an endocrinologist.

### **Recommended therapies for bone health**

Among other dietary recommendations, it is important to maintain adequate dietary intake of calcium and vitamin D to provide the opportunity for normal bone growth and mineralization. Supplementation should meet RDA requirements. More aggressive intervention with calcium and vitamin D replacement may be indicated if the patient's BMD is low after adjusting for height. Vitamin D levels should be targeted to achieve sufficient concentrations (>30 ng/mL)<sup>(60)</sup>. Treatment of hormone deficiency—specifically treatment of pubertal delay, hypogonadism, and GHD—is beneficial for bone mineralization.

Bisphosphonates are effective in preventing bone loss after HSCT in adults and may be effective in improving the BMD in HSCT-recipient children as well, but more studies are needed before a routine recommendation can be made regarding their use for the treatment of low BMD<sup>(61)</sup>. Experienced endocrinologists or nephrologists may consider treatment with bisphosphonates in children with FA who, after vitamin D deficiencies have been addressed, sustain two or more low-

impact fractures and have height-adjusted BMD Z-scores lower than -2 SD. Oral bisphosphonates should be used with caution as they may worsen esophageal reflux and have other potential health concerns. The risk/benefit ratio of this treatment must be evaluated by a specialist prior to treatment.

## Adults with Fanconi Anemia

Endocrine results have been reported for only a small number of adults with FA <sup>(1, 2, 7, 9)</sup> (Table 4). Endocrinopathies clearly persist into adulthood, though the treatment of FA with HSCT can alter the course of disease. Early endocrine diagnosis and therapy may improve the patient's quality of life. Treatment of endocrine issues in adults with FA should be monitored by endocrinologists who care for adults, with attention to the patient's thyroid status, glucose tolerance, lipid abnormalities, maintenance of normal BMI, gonadal function, and bone mineral density.

Lipid abnormalities were frequently seen in nearly 40 patients with FA who were followed at the NIH (unpublished data). More than half of the adults had one or more of the following lipid abnormalities: total cholesterol > 200 mg/dL, HDL cholesterol < 40 mg/dL, LDL cholesterol > 129 mg/dL, or triglycerides > 150 mg/dL. Insulin resistance, as determined by the homeostatic model assessment (HOMA), and metabolic syndrome were also common in adults.

Thyroid abnormalities remain prevalent in FA patients older than 18 years, with 37% to 57% of patients having hypothyroidism. These patients typically present with either elevated TSH levels or low free T4 levels <sup>(2, 7)</sup> (Table 4). In one study, a low stimulated GH peak was observed in a small number (6 of 16) of adults with FA <sup>(2, 7)</sup>. Hypogonadism with small testes was present in at least half (50%) of men with FA, and hypogonadism was present in one-third (30%) of women with FA. As mentioned earlier in this chapter, many women with FA experience premature menopause.

One study reported decreased BMD in 12 of 13 adults with FA; of the 8 females with decreased BMD, 7 experienced premature ovarian failure and early menopause <sup>(2)</sup>. However, the BMD was not adjusted for height in this study, and the measured BMD may have underestimated the volumetric BMD in several individuals with short stature whose bones were likely smaller than those of other participants <sup>(62)</sup>. It is not clear whether BMD in adults with FA should be routinely adjusted for height. The correlation of fracture risk with height-adjusted

BMD in adults with FA is also unknown. Additionally, many FA adults have hypogonadism, other endocrine deficiencies, and HSCT—all of which may adversely affect bone health and trigger the early development of osteoporosis.

**Table 4.** Endocrinopathies in adults with FA\*.

Research Center	No. Patients	Adult Height	Thyroid Activity	Growth Hormone	Blood Sugar/Insulin Levels	Gonadal Function	Bone Mineral Density
NIH (2)	17	On average, adults with FA were -1.9 SD shorter than average for other adults.	Of 15 patients, more than half (57%) had abnormal thyroid activity.	Of 5 patients, 3 had suspected GHD#.	Of the patients, 18% had diabetes, 35% had insulin resistance, and 21% had metabolic syndrome.	Of 4 males, half had hypo-gonadism. Of 13 females, about two-thirds (69%) had premature ovarian failure.	Of 13 patients, most (92%) had low bone mineral density.
CCHMC (7, 9)	42§	More than half (58%) of adults with FA were -1.8 SD shorter than average for other adults.	Of 27 patients, more than one-third (37%) had abnormal thyroid activity.	Of 9 patients, about one-fifth (22%) had GHD.	Of 16 patients, 2 had diabetes, one-third (30%) had hyperglycemia and about one-fifth (19%) had dyslipidemia.	Of 25 males, nearly half (40%) had hypo-gonadism.	Of 15 patients, 13% had low bone mineral density.

\* Different studies used different biochemical criteria.

§ Adults were defined as post-pubertal. Of the 42 patients in the study, 26 were 18 years or older.

Abbreviations: National Institutes of Health, NIH; Cincinnati Children’s Hospital Medical Center, CCHMC

# Cases of suspected GHD were defined by growth failure, low IGF-1 levels, and/or low IGFBP-3 levels.



## Medications and Treatments That Affect Endocrine Function

### **Androgen therapy**

Androgen therapy is used to improve the blood counts of patients with FA, and can cause endocrine-related side effects that need to be monitored. Androgens can improve growth rates, but often hasten the maturation of growth plates, which reduces the time available for childhood growth. Children treated with androgens may appear to be growing well, but their potential adult height may decline due to rapid skeletal maturation and premature fusion of cartilage plates at the end of long bones, known as epiphyseal fusion. Androgen use may also result in virilization in both males and females. The impact of androgen therapy on height and bone maturation should be discussed with the patient's family. Prior to beginning androgen therapy, a bone age X-ray should be performed. During androgen therapy, the patient's bone age should be reassessed periodically, and may be checked every 6-12 months.

### **Multiple transfusion therapy**

Multiple red blood cell transfusion therapy can affect endocrine function by causing iron overload (see *Chapter 3*). The accumulation of iron in endocrine glands can affect testicular and ovarian function, contribute to diabetes, and may lead to primary hypothyroidism, hypoparathyroidism, or pituitary dysfunction.

### **Hematopoietic stem cell transplantation**

Transplantation is inherently associated with a state of illness. Illness is not an optimal time to assess any hormone concentrations, as thyroid levels, growth, gonadal function, nutrition, and glucose regulation are often altered during this period. The treatments and irradiation used during HSCT may exacerbate the patient's underlying intrinsic risk for endocrine disorders and lead to growth failure as a consequence of GHD, primary hypothyroidism, gonadal failure, and decreased BMD. Therefore, FA patients who undergo HSCT should be closely monitored for hormonal abnormalities. Some of the guidelines are outlined in the Children's Oncology Group website on long-term follow-up, available at: <http://www.survivorshipguidelines.org/>.

## How Specific Therapies Affect the Endocrine System: Examples

- **Busulfan** can adversely affect thyroid function<sup>(63)</sup> and sometimes growth<sup>(64, 65)</sup>. It is highly toxic to gonads and can lead to gonadal failure, particularly in females<sup>(66, 67)</sup>.
- **Cyclophosphamide (Cytoxan)** has a known dose-related effect on gonadal function in both males and females, particularly when used in combination with busulfan<sup>(68-71)</sup>.
- **Glucocorticoids** can lead to increased appetite, weight gain, insulin resistance, and hyperglycemia, sometimes creating the need for insulin therapy. Prolonged use of glucocorticoids may cause linear growth failure and delayed puberty. Glucocorticoids adversely affect bone mineralization<sup>(72)</sup>.
- **Methotrexate** increases the risk for bone loss<sup>(73, 74)</sup>.
- **Total body irradiation (TBI)** increases the risk of primary hypothyroidism<sup>(75, 76)</sup>, growth impairment<sup>(64, 77)</sup>, hypogonadism<sup>(71, 78)</sup>, and poor bone mineralization<sup>(79, 80)</sup>.
- **Metoclopramide** raises prolactin levels. This can lead to leakage of fluid from the breasts, known as galactorrhea, and alteration of thyroid function or pubertal development.
- **Anticonvulsant therapy** can alter thyroid function or thyroid dose requirements. Some anticonvulsants, such as Valproate, can lead to weight gain and altered ovarian function.

## Conclusions

Endocrine problems are common in patients with FA. These patients are often—though not always—shorter than the general population. Individuals with FA may have reduced GH secretion, hypothyroidism, and abnormal glucose homeostasis with deficient pancreatic beta cell secretion of insulin and/or insulin resistance. Puberty, gonadal function, and fertility may be affected in these patients. Children with FA tend to have normal BMD. In adults it is not clear if the BMD, which is typically low, should be adjusted for height and if these measures correlate with the risk of bone fractures. However, the high incidence of endocrine dysfunction—especially hypogonadism, corticosteroid use, and HSCT—may predispose adults with FA to osteoporosis.

The origin of endocrine disorders in patients with FA remains unclear. Hypothyroidism is generally accompanied by elevated TSH levels and thus seems to arise from problems with the thyroid gland, although hypothalamic-pituitary dysregulation leads to abnormal central TSH release in some patients. Hyperglycemia/hyperinsulinemia is generally thought to arise from pancreatic beta cell dysfunction, but insulin resistance and metabolic syndrome are also common in patients with FA. In contrast, GH insufficiency probably arises from problems with the hypothalamus or pituitary gland.

Currently, a single unifying cause for all of these endocrinopathies is not known. It is possible that endocrine secretory cells are damaged by excessive reactive oxygen species, with inadequate repair mechanisms in patients with FA. In addition, treatments used in FA such as androgens, glucocorticoids, chemotherapy, or irradiation with HSCT may contribute to endocrine dysfunction.

Individuals with FA should be followed for the most common endocrine abnormalities, including growth failure, hypothyroidism, hypogonadism, and glucose/insulin abnormalities. The multidisciplinary patient care team should include an endocrinologist to initiate the work up and management of endocrine disorders.

## Chapter Committee

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# Chapter 8: Hearing and Ear Abnormalities in Fanconi Anemia

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## Introduction

Hearing and ear anomalies are prevalent among patients with Fanconi anemia. About 3 of every 20 patients with FA have ear malformations <sup>(1)</sup>, and reported prevalence of hearing loss in patients with FA ranges from 11% up to 50% <sup>(2-3)</sup>. Although the hearing loss in patients with FA is typically mild, it can impair an individual's communication abilities and interfere with language development and learning.

This chapter will describe the normal anatomy and function of the ear, common concerns related to the ear and hearing in patients with FA, amplification tools, surgical management, routine auditory monitoring, and useful resources for the hearing impaired.

In particular, this chapter will explore the following three concerns in patients with FA:

- *Abnormal ear anatomy and function*
- *Hearing loss*
- *Impaired learning and development of speech, language, and communication skills as a result of hearing loss*

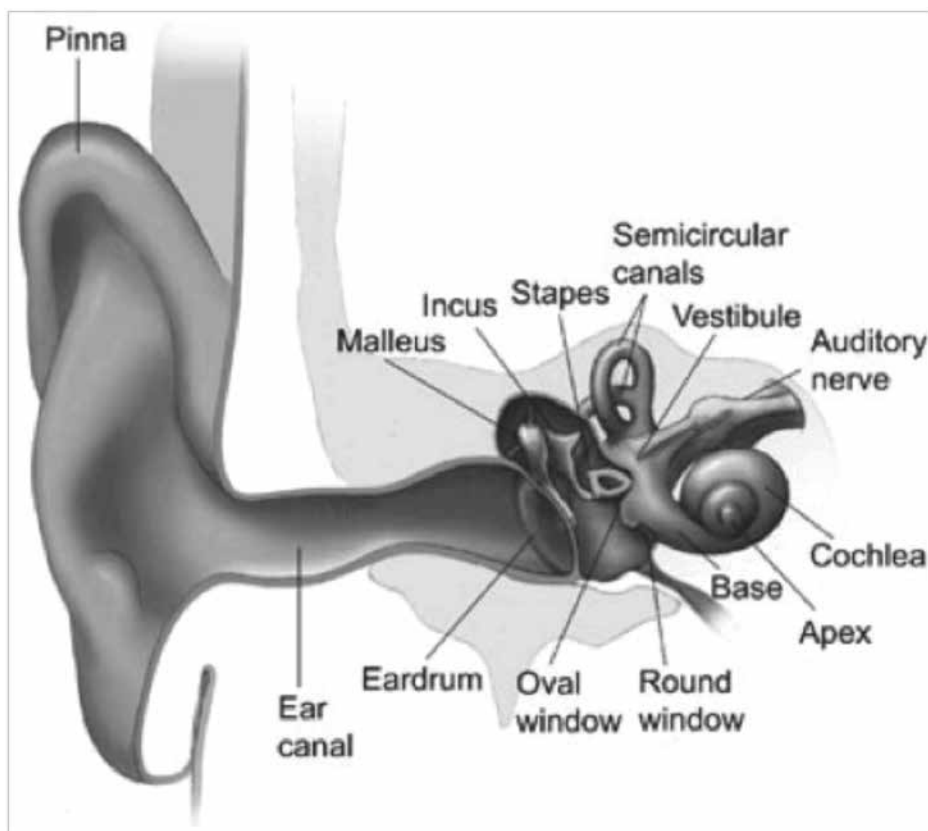
The ear and hearing clinical care team should include an **otologist** (an ear specialist) and an **audiologist** (a hearing specialist) and, when needed, a **speech-language therapist**. This team should work in close collaboration with other FA specialists and the primary physician, usually the hematologist/ oncologist, to coordinate care.

## Anatomy and Function of the Ear

The ear is made up of three main sections: the outer, middle, and inner ear (Figure 1). The two main portions of the outer ear are the pinna and the ear canal. The pinna collects sound waves and directs them down the ear canal to the eardrum.

The middle ear consists of the eardrum, which is also known as the tympanic membrane, and three tiny bones known as ossicles: the malleus, incus, and stapes (commonly called the hammer, anvil, and stirrup, respectively). The malleus is attached to the eardrum, the stapes is connected to the inner ear, and the incus lies in between the two; together, the three ossicles vibrate, converting sound energy into mechanical energy that is transmitted into the fluids of the inner ear (Figure 1).

The inner ear is composed of two parts: the balance-sensing system called the vestibular apparatus, which includes the semicircular canals and vestibule (utricle and saccule); and the sensory organ of hearing, known as the cochlea. The cochlea resembles a snail-like structure and is filled with tissue and fluid.



**Figure 1.** Anatomy of the ear.

Source: <http://www.nidcd.nih.gov/health/hearing/Pages/noise.aspx>

Sound waves enter the ear canal and cause the eardrum to vibrate like a drumhead. The vibrations move the ossicles, which amplify and transmit sound to the inner ear. When the stapes vibrates against the inner ear, the fluid within the cochlea moves and stimulates the thousands of tiny sensory structures called hair cells that line the inner surface of the cochlea. The hair cells then transform the sound vibrations into electrical impulses, which travel along the auditory nerve from the cochlea to the brain. The brain translates these signals and allows us to comprehend speech and recognize various sounds. Sounds can vary in terms of intensity (volume) and frequency (pitch).

## Types and Degree of Hearing Loss

There are three main types of hearing loss:

- **Conductive hearing loss** is caused by problems in the outer and/or middle ear that prevent sound waves from being carried, or conducted, efficiently into the inner ear. Conductive hearing loss can be caused by, among other conditions, fluid in the middle ear, a middle ear infection, excessive wax accumulation in the outer ear canal, and a hole in the eardrum. Although uncommon, conductive hearing loss can also be caused by malformation of the ossicles, the absence of an ear canal at birth (a condition known as congenital aural atresia), or restriction of ossicular movement due to the formation of abnormal scar tissue or bone.
- **Sensorineural hearing loss** typically occurs when the hair cells in the inner ear are damaged and unable to transform sound waves into electrical signals. Common causes of sensorineural hearing loss include genetic predisposition, the aging process, excessive exposure to loud sounds, and certain drugs, such as some chemotherapeutic agents or intravenous antibiotics. Sensorineural hearing loss can also result from damage to or congenital absence of the auditory nerve.
- **Mixed hearing loss** is a combination of conductive and sensorineural hearing loss that involves problems in the outer and/or middle ear as well as the inner ear and/or auditory nerve.

### Good to Know

A **decibel** is a measure of sound intensity.

Soft sounds correspond to low decibel levels (e.g., 0-15 dB HL).

Loud sounds correspond to high decibel levels (e.g., 90 dB HL).

Any patient who experiences hearing loss should be referred to an audiologist, who can perform a hearing test (audiogram) to determine the:

- **Degree of hearing loss**, an indicator of how much hearing loss exists
- **Type of hearing loss** (conductive, sensorineural, or mixed)
- **Configuration of the hearing loss**, or the overall pattern of hearing loss across the test frequency range

There are several measurement methods that, collectively, identify the degree, type, and configuration of hearing loss. These methods include behavioral audiologic tests, otoacoustic emissions tests, and auditory brainstem evoked response tests (ABR, sometimes referred to as BAER). Hearing can be assessed at any age; however, the patient's age and ability to cooperate will determine which methods are appropriate. Several tests and test sessions may be required to clearly characterize the hearing of very young children.

To determine the degree of hearing loss, an audiologist performs a hearing test to identify the softest level of sound a person can detect, known as the *audiometric threshold*, for a variety of pitches (frequencies). In a hearing test, hearing sensitivity is measured in terms of decibels hearing level (dB HL). People who have normal hearing are able to hear sounds as soft as 0-15 dB HL. The degree of hearing loss is classified according to severity:

- **Slight hearing loss**: the softest sound the person can hear ranges from 16-25 dB HL
- **Mild hearing loss**: the softest sound the person can hear ranges from 26-40 dB HL
- **Moderate hearing loss**: the softest sound the person can hear ranges from 41-70 dB HL
- **Severe hearing loss**: the softest sound the person can hear ranges from 71-90 dB HL
- **Profound hearing loss**: the softest sound the person can hear is greater than 90 dB HL

Even minimal hearing loss can negatively impact a child's social and academic development. A slight to mild degree of hearing loss can make it difficult to understand speech that is not presented at close range, or that is obscured by background noise. Moderate, severe, and profound hearing loss impairs the ability to understand speech under any conditions, and will significantly affect

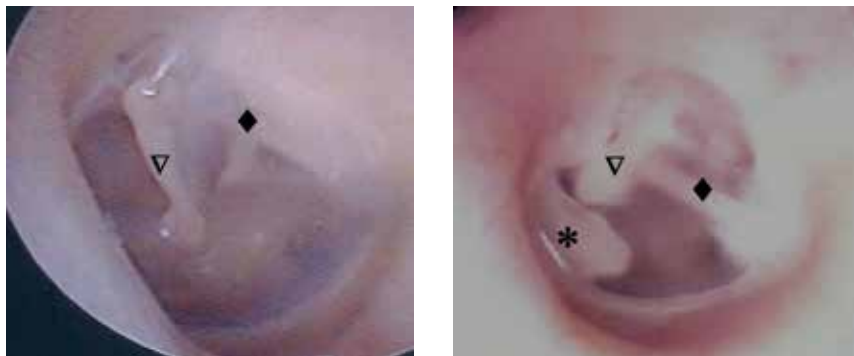
learning and the development of speech and language abilities unless the hearing loss is identified and treated by 6 months of age <sup>(4)</sup>.

## Signs and Symptoms of Ear and Hearing Abnormalities in Patients with FA

Only a few scattered case reports of ear and hearing abnormalities in patients with FA have been reported in the medical literature. To systematically examine and define the ear and hearing abnormalities in patients with FA, a team of researchers at the National Institutes of Health in Bethesda, Md., conducted a study of 31 patients with FA who ranged in age from 3 to 56 years old <sup>(5)</sup>. Out of 62 ears in 31 patients, 4 ears in 4 patients with FA were excluded from the analysis because of prior ear surgery. Thus, the results reflect data obtained from 58 ears.

All patients underwent comprehensive hearing testing and evaluation of the ears, nose, and throat. Microscopic examination of 54 ears revealed abnormalities in 31 ears (57%), and one case of an undeveloped, absent ear canal (aural atresia). Abnormal eardrum findings included a small eardrum, a short malleus that was abnormally positioned on the eardrum, and the presence of abnormal bony islands (bony plate) under the eardrum (Figure 2).

Comprehensive audiologic information was available in 52 ears. Hearing loss was detected in 24 ears (46%), and the majority was classified as mild in degree. The remaining 28 ears had normal hearing. The most common type of hearing loss was conductive, which was found in 11 ears, or 46%. An additional common finding in 8 ears (33%) was the presence of subclinical conductive hearing loss, in which hearing thresholds fell within normal limits, but evidence for a conductive component was still present. Sensorineural hearing loss (which was found in 3 ears, or 13%) and mixed hearing loss (which was found in 2 ears, or 8%) were less commonly observed. These findings suggest that the most common type of auditory dysfunction in patients with FA is mild conductive hearing loss, which is probably due to an abnormally developed eardrum, ossicles, or both.



**Figure 2.** The left eardrums of a healthy individual (left) and a patient with FA (right) and bony plate (\*), manubrium (∇), chorda tympani nerve (◆).

In summary, this research found that hearing loss was present in almost half of the ears (24 out of 52) of patients with FA, and the majority of the ears with hearing loss (19 of the 24, or 79%) had conductive or subclinical conductive hearing loss. Of the 54 ears that underwent microscopic examination, 57% had congenital abnormalities of the tympanic membrane and middle ear ossicles. The incidence of hearing loss and congenital ear malformation observed in this study is much higher than previously reported<sup>(1-3)</sup>. The findings suggest that abnormal features can be present even if hearing is normal or only slightly reduced.

## Consequences of Hearing Loss

Hearing loss in adults can impair an individual's communication abilities, especially if the listening situation is not ideal. It can make a person reluctant to participate in conversation and avoid social situations, and can cause fatigue if visual and contextual clues are required to fill gaps between what was said and what was heard.

Children use their hearing to develop speech, language, and communication skills, and to facilitate learning. Consequently, hearing loss can interfere with language development and learning. Even slight or mild hearing loss makes it difficult to hear a teacher or peers who are not within close range, especially in environments with a lot of background noise, such as a typical classroom. Left untreated, hearing loss can cause delays in language development and gaps in education. Even if the hearing loss only occurs in one ear and the other ear is normal, a child can have enough trouble hearing in school or in other situations that it impairs his or her social interactions and academic potential<sup>(6,7,8,9)</sup>.



## Early Identification and Intervention for Hearing-Impaired Children

Any child diagnosed with FA should undergo comprehensive assessments of his or her ears and hearing by an otolaryngologist (an ENT specialist) and an audiologist, respectively. Newborn hearing screening tests can miss slight or mild degrees of hearing loss; therefore, all children with FA, including those who are not diagnosed with hearing loss at birth, should receive follow-up audiologic testing. The earlier hearing loss is identified and treated, the less severe possible permanent effects may be. Research has shown that early identification and treatment (e.g., speech therapy, amplification devices, and educational accommodations and interventions) within the first 6 months of life can alleviate the long-term adverse effects of hearing loss on learning and language development <sup>(9)</sup>.

Children with hearing impairment often require some form of special education or related services <sup>(10)</sup>. The federal Individuals with Disabilities Education Act (IDEA) <sup>(11)</sup>, Part B, mandates the development of an Individualized Education Plan (IEP) for any student with a disability who needs special education. This document details educational goals for the child, and specifies the services that will be implemented in the school setting. Part C of the IDEA describes early intervention services available for eligible infants and toddlers from birth up to age 3 years, and the development of an Individualized Family Service Plan (IFSP). This document defines the services needed by the child and his or her family to enhance the child's development. The services must be provided in the child's natural environment, which can include the home or childcare center. Early intervention and academic support teams should work in conjunction with health care providers, such as audiologists and speech therapists, to identify intervention and academic needs. Section 504 of the Rehabilitation Act contains provisions for a school-aged child with hearing loss who needs accommodations, such as assistive listening devices, to access the educational curriculum, but who does not need one-on-one special education teaching or therapy services <sup>(12)</sup>. This act also contains provisions for workplace accommodations, which should be sought out as needed by employees with hearing loss.

Examples of accommodations or special education services that a school-aged child with hearing loss might require include the following:

- *Favorable classroom seating located near the teacher and with a clear view of the teacher's face*
- *Assistive listening device*
- *Modifications to the classroom to improve acoustics*
- *Speech and language therapy*
- *Educational audiology consultation with classroom teachers to explain the impact of a student's hearing loss on school performance, and to suggest strategies for communication*
- *One-on-one teaching with a specialist, such as a teacher of the hearing-impaired or special education teacher*

## **Amplification**

If hearing loss is identified in a child or an adult, an audiologist should evaluate the patient's need for hearing aids and/or assistive listening devices (see below). There are many different types of devices available. The audiologist will make a recommendation for the appropriate device based on the patient's lifestyle, type and degree of hearing loss, and the environment in which the device will be used. For example, a school-aged child may need different features on his or her device than an adult in the workforce.

### **Hearing aids**

Hearing aids are devices that make sounds louder, and are worn in or behind the ear. Hearing aids can be beneficial for all types of hearing loss (conductive, sensorineural, or mixed) and almost all degrees of hearing loss. Hearing aids can be used by patients of any age—even babies in their first few months of life<sup>(13)</sup>.

The audiologist programs the hearing aid specifically for a patient's degree and configuration of hearing loss and can reprogram the device later if the patient's hearing changes. Hearing aids differ in technology, size, power, and availability of special features, but all hearing aids have the following components:

- A small **battery** that powers the hearing aid
- A **microphone** that picks up sound
- An **amplifier** that increases or magnifies sounds that are inaudible to the hearing-impaired listener
- A **receiver** (or speaker) that delivers the amplified sound into the ear

A baby or child with hearing loss will be fitted with a hearing aid that sits behind the ear and has the ability to connect with other assistive listening devices if needed. The hearing aid directs amplified sound into the ear canal via the earmold, a plastic piece that is custom-made to fit each ear. Children require frequent replacement of their earmolds—as often as every 2 to 4 weeks during the first year of life, every 1.5 to 4 months as toddlers and preschoolers, and every 6 months to a year until they are teens—due to their growing ear canals.

### **Assistive listening devices**

Assistive listening devices (ALDs) help hearing-impaired individuals function in daily communication situations. They may be used alone or in combination with hearing aids. ALDs are typically only used for specific listening situations, such as environments with a lot of background noise (e.g., school classrooms, restaurants, movie theaters, and conferences). The most common type of ALD, known as a frequency-modulated (FM) system, captures the audio of interest using a microphone (which is often worn by a speaker such as a teacher or presenter) and transmits the sound wirelessly, much like an FM radio signal, to a receiver used by the listener. The receiver can be integrated into a hearing aid or used as a stand-alone listening device similar to a personal music player. If used in a classroom, for example, the device brings the teacher's voice directly to the student's ear at a consistent volume that is above the typical background noise, regardless of the distance between the teacher and student.

An ALD known as a sound-field amplification system can be a good option for children with hearing loss that is mild or only affects one ear, as well as children with stable or fluctuating conductive hearing loss. With this type of ALD, the teacher wears a wireless microphone that transmits sound via FM or infrared waves to a speaker or speakers, which evenly distribute the teacher's voice to all parts of the classroom. A sound-field amplification system can help to ensure that a hearing-impaired student can hear what the teacher is saying, even if the teacher isn't directly facing the student or is speaking from the other end of the classroom.

## Surgical Management of Hearing Loss in FA

### Evaluation

Some types of hearing loss can often be corrected with surgery, though it should be noted that sensorineural hearing loss from inner ear or auditory nerve damage cannot be restored by ear surgery.

Below are a few causes of conductive hearing loss that may be surgically corrected in some patients:

- *Fusion of the malleus to a bony island under the eardrum*
- *Fixation of the ossicles to the bony walls of the middle ear cavity*
- *Discontinuity of the ossicles (one of the ossicles is not attached to the others)*
- *Scarring or bone growth around the stapes*
- *An absent ear canal*
- *Fluid in the middle ear*
- *Hole (perforation) of the eardrum*

Before choosing a middle ear surgery, the otologist, the patient, and the patient's family must consider multiple factors and all of the alternative treatment options, such as hearing aids, to optimize the child's rehabilitation. Surgery is not suitable for every patient with conductive hearing loss. Individuals with serious medical conditions such as heart problems, bleeding tendencies, and a high susceptibility for infection due to bone marrow failure are probably not good candidates for surgery.

To be considered a candidate for middle ear surgery, the patient must have normal inner ear function as demonstrated by a hearing test called bone conduction testing. Patients with moderate, severe, or profound sensorineural hearing loss are typically not candidates for middle ear surgery. The otologic surgeon should carefully evaluate the anatomy of the patient's middle and inner ear using high-resolution thin section CT scanning. This procedure enables the surgeon to determine the possible cause of the conductive hearing loss and gauge the potential success of surgery. In some patients, poor middle ear anatomy or middle ear fluid precludes surgical intervention.

### Timing of surgery

Middle ear surgery can be performed in children ages 7 years or older, who are typically capable of cooperating in the office for the necessary postoperative care and are beyond the age of frequent childhood ear infections. In patients with an ear deformity known as microtia (in which the external part of the ear, known as the pinna, is underdeveloped or absent), the timing of surgery will depend on the family's decision regarding reconstructive surgery for the pinna. The options for management of microtia include the following:

- *Microtia can be repaired using **cartilage** from the patient's ribs, a traditional method that has withstood the test of time. This procedure should be performed prior to middle ear surgery.*
- *Microtia can be repaired using a **synthetic implant**, which is often made of high-density polyethylene. This procedure should be performed after middle ear surgery.*
- *A **prosthetic ear** can be applied before or after middle ear surgery.*

### Middle Ear Surgery

If the middle ear bones are immobile or absent, a surgical procedure called ossicular chain reconstruction can be performed to replace the defective or missing ossicle(s) with a prosthesis. The prostheses are typically made of artificial bone, titanium, or other biocompatible composite materials. Surgery can be done using either local anesthesia and sedation or general anesthesia, and typically takes about 1 to 3 hours.

If the ear canal is absent or very narrow, it can be reconstructed in a surgical procedure called canalplasty. During this procedure, the otologist uses an otologic drill to remove bone, thereby opening or widening the ear canal and freeing the ossicles. To restore hearing to the ear, the surgeon constructs a tympanic membrane using a piece of connective tissue. Then the reconstructed eardrum and bone of the ear canal are carefully lined with a very thin skin graft called a split-thickness skin graft. The outer opening of the ear canal, called the meatus, is widened, and the outer edge of the skin graft is delivered through the meatus and sutured to the native skin of the pinna.

In the general population, middle ear surgery improves conductive hearing loss in 75% to 90% of carefully selected candidates<sup>(14)</sup>, but it is important to understand that not all patients with conductive hearing loss and associated middle ear abnormalities are candidates for surgery. It is through both the

hearing test and the temporal bone CT scan that a patient's candidacy for middle ear surgery or canalplasty is determined.

Complications associated with ear surgery are uncommon but may include:

- ***Further hearing loss or no hearing improvement*** (in less than 10% to 20% of surgeries). Total deafness is extremely uncommon.
- ***Injury to the facial nerve that runs through the ear, which can cause facial paralysis. This is extremely uncommon. Surgeons should use a device called a facial nerve monitor during ear surgery to minimize this risk.***
- ***Altered taste perception on the side of the tongue, which can last for a couple months.***
- ***Persistent post-operative dizziness or ringing in the ears, both of which are quite uncommon.***
- ***Renarrowing (stenosis) of the ear canal, which requires additional surgery.***

### **Bone conduction hearing devices**

A bone conduction hearing device may be useful for patients with conductive hearing loss who cannot use conventional hearing aids due to problems such as a congenitally undeveloped ear canal, or for individuals who are not good candidates for traditional middle ear surgery<sup>(15)</sup>. For children who fall into this category, such a device can be essential for normal speech and language development<sup>(16)</sup>. A bone conduction hearing device transmits sound waves directly to the inner ear by vibrating the bone of the skull, which transfers the sound energy to the fluids of the cochlea. A traditional bone conduction hearing aid consists of a bone oscillator or vibrator affixed to a fabric or metal headband that is worn around the head with the oscillator tightly applied to the mastoid bone or cortical bone above the ear. Alternatively, a bone conduction hearing device can be surgically implanted into the bone behind the ear in children age 5 years and older. This type of device is known as a bone-anchored hearing device. Bone-anchored sound conduction systems have been used in Europe since 1977 and were approved in the United States in 1996 as a treatment for conductive and mixed hearing losses. Table 1 lists the implantable hearing devices that are currently commercially available. The patient and his or her family should consult with an audiologist and otologist about whether to use a traditional bone conduction device or a bone-anchored hearing device for conductive hearing loss in one ear.

**Table 1.** Bone-implantable hearing devices.

Implantable Hearing Device	Baha	Ponto	Sophono	SoundBite*
Manufacturer	Cochlear Ltd. Sydney, Australia	Oticon, Inc. Somerset, NJ	Sophono, Inc. Boulder, CO	Sonitus Medical, Inc. San Mateo, CA

\*A non-surgical bone conduction device via a dental appliance. This device has been FDA approved for individuals 18 years of age and older.

## Family Members of Patients with Hearing and Ear Abnormalities

When a patient is diagnosed with FA, his or her siblings must also be tested for FA. However, if a sibling of a patient with FA does not test positive for FA via a chromosome breakage test on the peripheral blood but displays classic signs of FA-related ear and hearing abnormalities<sup>(17)</sup>, the hematologist should perform additional genetic tests to rule out FA (see *Chapter 1*).

## Regular Periodic Auditory Monitoring

Children who are diagnosed with FA should be referred for audiologic and otologic consultation as soon as possible. Children of any age can undergo hearing testing by an audiologist. Before the age of 3 years, such testing can rule out hearing loss that may affect speech and language development<sup>(16)</sup>. By the age of 5 or 6 years it is typically possible to obtain very complete testing for each ear to establish hearing thresholds of 15 dB HL or better across the speech frequencies, and therefore rule out a hearing loss that may have subtle effects on communication and learning.

Once hearing loss is identified, the patient's hearing should be monitored regularly<sup>(18)</sup>. Babies and toddlers should be seen by an audiologist every 3-4 months, whereas older children should be seen every 6 months until age 6 or 7, after which an annual audiological assessment may be sufficient. If the child's hearing loss is not stable or if other hearing related issues arise, more frequent monitoring may be recommended. Adults with hearing loss should receive annual audiologic monitoring, or immediate evaluation if they suspect a change in hearing.

It remains unclear whether FA is associated with progressive hearing loss. Therefore, patients with FA who have been diagnosed with normal hearing

should have their hearing monitored regularly (approximately every 2-3 years). Hearing tests should be performed more frequently in children, because they are unable or unlikely to self-report concerns about difficulties hearing or communicating. Patients with FA are likely to undergo medical and surgical treatments that can potentially affect hearing. Many patients with FA will be treated with medications that are potentially ototoxic (having a damaging effect on the ear), such as intravenous antibiotics (e.g., aminoglycosides such as gentamicin), iron-chelating agents (e.g., desferoxamine), and chemotherapy agents (e.g., cisplatin). Furthermore, patients with FA are susceptible to recurrent infections due to neutropenia, multiple blood transfusions for severe anemia, and malignancies of the blood and solid tissues; these conditions increase the risk of exposure to ototoxic medications. It is important to establish the patient's baseline hearing level before he or she is treated with ototoxic medications, and monitor the patient's hearing closely during treatment. Lastly, the genetic instability associated with FA has been associated with premature aging processes <sup>(19)</sup>; therefore, patients with FA may be at risk of developing age-related hearing loss at an earlier age than the general population.

## Conclusions

- Congenital hearing loss and/or malformations of the eardrum and middle ear are more commonly associated with FA than reported previously. The hearing loss is typically mild and conductive.
- All patients with FA should undergo a comprehensive ear examination and audiologic evaluation by an otolaryngologist and audiologist, respectively. Preferably, these medical providers should be familiar with FA.
- FA-related hearing problems can often be successfully treated with either appropriate amplification and/or surgical correction.

## Useful Resources for the Hearing Impaired

***Alexander Graham Bell Association for the Deaf and Hard of Hearing***

3417 Volta Place, NW

Washington, DC 20007

202-337-5220

[www.agbell.org](http://www.agbell.org)



***American Academy of Audiology***

11480 Commerce Park Drive  
Suite 220  
Reston, VA 20191  
800-222-2336  
www.audiology.org

***American Academy of Otolaryngology-HNS***

1650 Diagonal Road  
Alexandria, VA 22314  
703-836-4444 (V)  
www.entnet.org

***American Speech-Language-Hearing Association***

2200 Research Boulevard  
Rockville, MD 20852  
800-638-8255 (V)  
301-296-8580 (TTY)  
www.asha.org

***National Institute on Deafness and Other Communication Disorders***

National Institutes of Health  
31 Center Drive, MSC 2320  
Bethesda, MD 20892-2320  
800-241-1044 (V)  
800-241-1055 (TTY)  
www.nidcd.nih.gov  
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***Descriptions of IEPs and Section 504 of the Individuals with Disabilities Education Act***

Wrightslaw Special Education Law and Advocacy: [www.wrightslaw.com](http://www.wrightslaw.com)  
National Dissemination Center for Children with Disabilities: [www.nichcy.org](http://www.nichcy.org)

## **Chapter Committee**

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## Chapter 9: Dermatologic Issues

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### Introduction

Skin abnormalities, such as altered skin pigmentation either overall or in spots, can be the presenting symptoms of Fanconi anemia (FA). Other skin abnormalities may emerge as patients with FA become adults. Patients who undergo hematopoietic stem cell transplants can develop skin abnormalities if the transplanted donor cells attack the recipient's body (graft versus host disease, GvHD). The risk of developing skin cancer appears to be increased for adult patients with FA, making early education on sun protection and skin cancer prevention essential.

#### Good to Know

To protect against all forms of skin cancers, providers should recommend:

- Applying sunscreen, wearing protective clothing, or avoiding sun exposure altogether. These precautions apply for children age 6 months and older. For babies under 6 months of age, try to keep out of direct sunlight and dress in protective clothing, a hat with a brim, and sunglasses. If sunscreen is needed, only apply a small amount and wash off after use.
- Using sunscreens that contain physical blockers (zinc oxide and titanium oxide)
- Performing annual skin exams for patients age 18 and older. For all patients who have received bone marrow transplants, yearly skin exams should be performed regardless of age. More frequent exams are needed if skin malignancies are detected.
- Performing skin biopsies of suspicious lesions
- Maintaining adequate vitamin D levels, by taking vitamin D supplements if necessary, particularly in young adults

This chapter will describe the most common skin problems that affect patients with FA:

- *Pigmentation changes*
- *Sweet's syndrome*
- *Warts*
- *Basal or squamous cell carcinoma*
- *Actinic keratosis*
- *Melanoma*

This chapter will also describe how certain therapies for FA, such as androgen therapy or hematopoietic stem cell transplantation (HSCT), can affect a patient's skin. Therefore, a patient's clinical care team should include a **dermatologist** to evaluate any problems related to the skin.

## Skin Appearance on Initial Diagnosis

### Pigmentation changes

Changes to pigment, the substance that gives the skin its color, are the skin abnormalities most commonly associated with a diagnosis of FA. A patient with FA can develop both hyper- (increased) pigmentation or hypo- (decreased) pigmentation, typically in sun-exposed areas <sup>(2)</sup>. Hyper- and hypopigmented patches of skin can appear on the neck, trunk, and tops of hands and feet; they can also appear on under arms, genitals, hand palms, or foot soles. Differently colored areas of skin often overlap and can create a freckly appearance: raindrop-like, light-colored patches of skin scattered over darker areas. Some patients also appear to have a dusky or shadow-like skin tone, most notably in joint areas, lower extremities, and on the neck. Smooth-bordered, tan patches of skin (café au lait macules) are also common on young patients with FA.

A diagnosis of FA should be considered in young children with distinct skin discoloration and accompanying disorders but can only be confirmed by blood tests (described in *Chapter 2*). While some patients with FA develop skin abnormalities, others do not, and abnormalities that develop are not unique to individuals with FA. The hypopigmented patches in patients with FA are also found in syndromes such as neurofibromatosis and tuberous sclerosis. Café au lait patches of skin are a relatively common birthmark, and also can appear in multiple locations on patients with neurofibromatosis. For cosmetic appearances, some hyperpigmented lesions such as café au lait macules may be removed by laser treatments.

### Sweet's syndrome

Patients with FA may develop Sweet's syndrome (SS), also called acute neutrophilic dermatosis, which presents as painful red plaques or nodules on the skin (Figure 1). As many as 12% of all patients with FA develop SS, according to one institution's experience <sup>(3)</sup>. The syndrome frequently develops many years after a patient has been diagnosed with FA. A fever typically accompanies the red skin plaques or nodules, and similar lesions may be present in a patient's bones, lungs, or gastrointestinal tract.

SS lesions are often mistaken for sites of active infection and treated as such. Providers should consider the possibility of SS in patients with FA who have painful red skin lesions that do not respond to antibiotics. Because patients with FA can develop SS lesions below the skin, radiographic imaging may be necessary to diagnose the condition. Of note, patients with FA who develop SS also tend to have a high incidence of myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML) which either precedes or follows shortly after the diagnosis of SS. When SS is diagnosed along with characteristic hematologic or skeletal abnormalities, providers should consider a diagnosis of FA. Patients with FA who develop SS should undergo a bone marrow aspiration and biopsy to evaluate the possibility of evolution to MDS or AML.



**Figure 1.** A patient with Sweet's syndrome.

## **Types of Skin Growths Associated with FA**

### **Ultraviolet radiation, DNA damage, and FA**

Ultraviolet radiation from the sun has different subtypes: UVA causes premature aging and wrinkling of the skin; UVB induces DNA damage and is the major source of skin cancer. Individuals with FA have a decreased ability to repair the types of DNA damage induced by UVB (double-strand breaks) and therefore have increased potential vulnerability to the damaging effects of UVB<sup>(4)</sup>. Three types of skin cancer are discussed below.

### **Basal and squamous cell carcinomas and verruca vulgaris (warts)**

The relative risk of developing cutaneous basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) is unknown, although cases of these cancers in individuals of relatively young ages have been reported to the Fanconi Anemia Research Fund.

Basal cell carcinoma is the most common type of skin cancer in the general population and accounts for over 80% of cases. BCC can look like a shiny, waxy, pearly, red or pink bump, but can have other appearances. It almost never metastasizes but grows locally, can be disfiguring, and must be removed.

Squamous cell carcinoma is more aggressive than BCC and can metastasize, especially when on the head and neck. It appears as red, thick, scaly, tender patches of skin. Individuals who are immunocompromised, including anyone post-transplant, are at greatly increased risk of SCC. Actinic keratosis, another type of skin lesion, presents as flat pink or red scaly patches and may progress to SCC.

Warts occur when keratinocytes (the main non-pigmented cells that make up skin) proliferate. Most warts are initiated by human papillomavirus (HPV). FA has been associated with the occurrence of unusual numbers of warts and may signal a decrease or abnormality in cell-mediated immunity <sup>(1)</sup>.

Scaly raised growths in patients with FA may be warts, BCC, SCC, actinic keratosis, or other types of lesions. In a young patient with FA, multiple scaly lesions are likely to be warts and can be frozen off using cryotherapy or treated topically. In an older adolescent or adult, providers should perform a biopsy to determine whether the lesion is related to BCC, SCC, or actinic keratosis.

Dermatologists usually use surgery to remove skin cancers. In addition, photodynamic therapy (PDT) can be used to treat BCC, SCC, and actinic keratosis. PDT uses a drug called a photosensitizing agent and a specific type of light to kill cancer cells. Other therapies include use of a topical chemotherapy such as 5FU to kill cancer cells, and topical drugs that stimulate the immune system to kill cancer and precancerous lesions. Although individual patients have received these treatments without apparent problems, the overall tolerability of these treatments in patients with FA has not been well-studied.

## **Melanoma**

Melanomas are the most dangerous and deadly form of the common skin cancers. The majority are black or brown, are often multicolored, can have irregular edges, and are asymmetrical. They are highly aggressive, and must be removed immediately before they metastasize. Stem cell transplant recipients may have an increased number of melanocytic nevi, or moles, including irregular moles on limbs, fingers, ears, or other acral locations <sup>(8)</sup>. A dermatologist should evaluate notable changes in the size, shape, or color of

preexisting moles, and new moles that are growing rapidly, are asymmetric, or are uneven in color. Whether there is an increased risk of developing melanoma in patients with FA is not known. However, immune compromise and damage from solar radiation are both risk factors for melanoma and these may be of increased relevance in FA. Thus, it is reasonable for providers to conduct annual full body skin examinations for all or any of the common skin cancers beginning at age 18.

## **Skin Cancer Prevention**

Given that the ultraviolet rays from the sun act as an immunosuppressant and patients with FA may be immunosuppressed (especially for at least a year after HSCT), skin protection or sun avoidance should be implemented from an early age. Skin protection should include protective hats and clothing and sunscreen. Sunscreens that contain physical blockers such as zinc oxide and titanium oxide are effective. The SPF must be at least 30 (50 or higher is often recommended in immunocompromised patients), and should be reapplied every 1-2 hours. Recommended products that provide broad-spectrum UV coverage are Neutrogena (helioplex), La Roche Posay, and Blue Lizard (zinc oxide). Skin is the sole source of vitamin D synthesis and sunscreen prevents this process. Diet and vitamin D supplements can provide adequate amounts of vitamin D.

## **Medications and Treatments that Affect the Skin**

### **Androgen therapy**

Androgen therapy (see *Chapter 7*) can increase hair growth in both men and women. Laser treatment may remove unwanted hair, but it is unlikely to have a lasting effect if androgen therapy continues. The risks of laser hair removal are discomfort, temporary pigment changes, and scarring. Laser hair removal has not been associated with an increase in the risk of skin malignancy.

### **Hematopoietic stem cell transplantation**

#### *GvHD*

Graft-versus-host disease (GvHD) may occur in patients with FA. GvHD is thought to result primarily from the reaction of donor T-cells (a type of white blood cell) to the patient's skin. New strategies to deplete or inactivate T-cells before or after HSCT have greatly decreased the occurrence of GvHD in FA patients (see *Chapter 11* and <sup>5,6,7</sup>).



As GvHD's clinical manifestations and histological features closely resemble other conditions seen in post-transplant patients, providers, usually the hematologist or transplant physician, must take care to prioritize the recognition and management of cutaneous GvHD. Treatment for cutaneous GvHD may include the use of topical steroids. GvHD prevention and treatment is discussed in detail in *Chapter 11*.

### *Skin Cancer*

While all stem cell transplant recipients are generally at risk for nonmelanoma and melanoma skin cancer, patients with FA may be at heightened risk, due to their decreased ability to repair damaged DNA<sup>(9,10)</sup>. Skin cancer may also behave more aggressively in this population<sup>(11)</sup>. Risk factors in the general population for nonmelanoma skin cancer include a history of chronic GvHD, prolonged immunosuppression, use of the anti-fungal medication voriconazole (see below), and a history of total body irradiation (particularly greater than 14 grays). Risk factors for melanoma include previous treatment with certain alkylating and antimetabolic chemotherapies and radiation. Fortunately, most of these risk factors are minimized in the current routine approach to FA transplantation.

### *Voriconazole (anti-fungal)*

Voriconazole can increase the skin's sensitivity to sunlight. Voriconazole has been implicated in SCC in transplant patients in the general population when used for over 12 months<sup>(12)</sup>. Due to the increased risk of skin cancers from voriconazole, the use of other anti-fungals should be discussed with a patient's hematologist and transplant team.

### *Vitiligo*

Stem cell transplant recipients may develop localized or generalized loss of skin or hair color<sup>(7)</sup>. The cause of this condition is unclear, though it may be more common in patients with a history of acute or chronic GvHD. These patients should be particularly careful to protect their skin from the sun or to avoid sun exposure altogether.

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# Chapter 10: Oral and Dental Health Care

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## Introduction

The health of the mouth and surrounding craniofacial structures is central to overall health. Thus, the goals of dental care are to prevent and control oral and craniofacial diseases, conditions, and injuries. All patients with Fanconi anemia (FA), regardless of age, should be under the care of a dentist. With a few exceptions, dental treatment is similar for FA patients and healthy individuals. This chapter provides guidance to patients with FA and their families on dental care and oral health maintenance, and educates dental practitioners about particular aspects of FA that can impact dental treatment.

## Importance of Oral Hygiene

The oral cavity harbors a variety of microorganisms, also known as the oral microbiota. This community of microorganisms is predominantly composed of bacteria, though fungi and viruses can also be present. Therefore, it is not surprising that bacteria cause many common oral diseases.

Common oral and dental diseases include:

- ***Tooth decay (caries), pulp infections, and abscessed teeth.*** These are particularly important to identify and treat in patients with FA, who have defects in both innate and adaptive immunity, to prevent the spread of infection throughout the body.
- ***Gingivitis*** is a condition characterized by gums that bleed and are red and swollen, particularly in the areas at the base of the teeth and between teeth (known as dental papilla). Left untreated, gingivitis can increase the risk of periodontitis (described below).
- ***Periodontitis*** is an irreversible condition characterized by the loss of the bone and fibrous tissues that attach the teeth to the gums, the presence of periodontal pockets (deep spaces between the tooth surface and the gums), bleeding gums, and occasionally the loss of periodontal bone, which causes teeth to loosen.

It is never too early for individuals with FA to practice effective oral health care on a daily basis. A person with good oral hygiene has a much lower risk of developing oral health problems, and these problems are likely to be much less severe when they do occur. Patients with FA are susceptible to cancers of the head and neck, so it is especially important to maintain healthy oral microbiota. There is increasing evidence for the potential contribution of oral microorganisms and oral inflammation to head and neck carcinogenesis <sup>(1-5)</sup>. In addition, poor oral hygiene has been linked to increased risk for esophageal carcinoma <sup>(6)</sup>. Furthermore, periodontitis, which is mediated by oral bacteria and inflammation, has been suggested as a possible risk factor for head and neck oral squamous cell carcinoma <sup>(3)</sup>. Even though these associations do not imply causation, it is prudent to control the circumstances that may lead to gingivitis and periodontitis. Therefore, it is important for FA patients to aim for the best possible oral hygiene.

## Oral Hygiene at Home

### **Toothbrushing**

Dental plaque contains a thick film of bacteria that have attached themselves to the tooth's surface. Twice daily toothbrushing is the most effective method to remove plaque, thus preventing gum diseases and tooth decay. Manual and electric toothbrushes are overall equivalent in their ability to remove plaque. If an individual has physical limitations that can impact his or her physical ability to hold onto and use a toothbrush, adaptive aids may need to be constructed. Parents of young children with FA should brush the child's teeth until the child can competently care for his or her own teeth.

The frequency of toothbrushing should be increased in patients who have a high risk for caries, such as individuals with reduced salivary flow, known as xerostomia. Xerostomia can occur in patients with FA <sup>(7)</sup> and may develop as a side effect of certain medications, stress, anxiety, diabetes, dehydration, graft versus host disease (GvHD), or radiation therapy for head and neck tumors.

In the mouth, the surface of the tongue is heavily populated with microorganisms, which can contribute to halitosis and gum diseases. Thus, daily tongue cleaning using a toothbrush is also important.

### **Toothpastes**

Patients should use a toothpaste that contains fluoride, which is the most effective agent for preventing dental decay. Many natural toothpastes do

not contain fluoride and therefore do not help to reduce the risk of caries. Some toothpastes contain the antimicrobial triclosan, which is also used in a number of skin cleaners and scrubs. An increasing number of studies suggest that triclosan may alter hormone regulation, and there are concerns about the emergence of triclosan-resistant bacteria. Although the potential detrimental effects of triclosan remain inconclusive, patients with FA are advised to avoid triclosan-containing products due to their predisposition to endocrine disorders.

Some whitening toothpastes contain abrasive agents and chemical additives, such as sodium bicarbonate or sodium pyrophosphate, to help break down and remove surface stains. Whitening toothpastes might also contain bleaching agents, such as hydrogen peroxide or carbamide peroxide, which may be a concern for patients with FA due the potential carcinogenic effects of peroxide. Therefore, whitening toothpastes are not worth the potential health effects that might be caused by exposure to hydrogen peroxide.

### **Plaque removal devices**

Plaque that forms between teeth is virtually unreachable by toothbrushing, but should be removed at least once daily by flossing to prevent gum disease and cavities. Various plaque-removal devices are available, including floss, tape, electric interdental cleaners, and wooden sticks; the choice of device should be based on the anatomy of the teeth and the dexterity of the patient. Therefore, patients with FA who have hand and arm abnormalities may need to experiment to find a device that works well and is easy to manipulate. Other devices that can be used to remove plaque include interdental and end-tufted brushes.

### **Mouth rinses and topical fluoride treatments**

Mouth rinses containing fluoride can be used to prevent tooth decay, rinses containing antimicrobials can prevent both tooth decay and gum disease, and both types of rinses can be used to improve breath odor. However, many mouth rinses contain alcohol, with concentrations ranging from 6%-26.9%. Some studies suggest that alcohol-containing mouth rinses are associated with cancers of the mouth and throat, whereas other studies have found no association between these mouth rinses and cancer development. ***Despite the contradictions in the research, it seems prudent to recommend that patients with FA avoid the use of mouth rinses that contain alcohol.*** Alcohol-free mouth rinses are available and appear to be as effective as their alcohol-containing counterparts.<sup>(8)</sup>

Mouth rinses that contain compounds to kill bacteria, including chlorhexidine (CHX) or other anti-microbials, can provide effective plaque removal in circumstances where mechanical plaque removal is not possible, such as after oral surgical procedures. In the US, mouth rinses that contain antibiotics are available by prescription only, and generally need to be mixed by a pharmacist. Mouth rinses that contain povidone iodine should not be used by patients who are allergic to iodine, children under 6 years of age, patients with thyroid disorders, or patients taking lithium.

A number of over-the-counter mouth rinses are available to help control plaque accumulation. Some products contain 0.05% cetylpyridinium chloride (CPC), a compound that kills bacteria, or phenolic essential oils, which also reduce plaque and gingivitis. However, patients should be aware that many of these formulations have an alcohol content of 20% or greater, and should be avoided. Alcohol-free formulations are available and appear to be equally as effective <sup>(9)</sup>.

Topical fluoride treatments are available over-the-counter or by prescription, and are suitable for use in children as well as adults. Topical fluoride treatments can be self-applied using gels, mouth rinses, or varnishes. The application method should be selected based on the patient's ability to use the method of application.

## Professional Oral Health Care

All FA patients require professional dental care. The dental health care team should include a **dentist** and a **dental hygienist** who are aware of the complexities of the oral health issues in patients with FA, and, when needed, can include other dental specialists. When appropriate, the dental health care team will work in close collaboration with the primary FA health care specialist to provide coordinated, comprehensive care.

### Oral examinations

Individuals should receive routine oral and dental examinations every 6 months. Examinations can occur more frequently if changes occur in the patient's medical and dental conditions, such as the development of periodontitis, diabetes, or xerostomia. In addition, patients with FA have a 500- to 700-fold increase in the incidence of head and neck squamous cell carcinoma (HNSCC), and an increased prevalence of oral cancer. Therefore, the primary objectives of these exams include the prevention and early

detection of oral diseases such as dental caries, gingivitis, periodontitis, and oral cancer.

During an exam, the dentist evaluates the inside of the mouth as well as the soft tissues of the head and neck; any unusual findings should be further investigated. Caries can be detected by the clinical and radiographic examination of tooth surfaces and restorations. Changes in the color, consistency, and contour of the gums can reveal the development of gingivitis and periodontitis. Furthermore, gingival inflammation and plaque accumulation are involved in the development of periodontal diseases, which has been associated with an increased risk of head and neck cancer. Thus, visits to the dentist also allow the dental team to evaluate the patient's oral hygiene practices and reinforce self-performed plaque control.

- **Radiographs**

Many oral diseases cannot be detected with a visual or physical exam. Dental x-rays can help the dentist find cavities between teeth or under fillings, diagnose gum and bone diseases and some types of tumors, and better plan surgical interventions. These images can help detect and treat these hidden problems at an early stage, before more extensive treatment is necessary (for more information, please see: [www.ADA.org](http://www.ADA.org)). Radiographs and other imaging modalities are used to diagnose and monitor oral diseases, as well as to monitor dentofacial development and the progress or prognosis of therapy. However, x-rays should only be taken when there is an expectation that the additional information they can provide might result in improved patient care. Thus, the dentist must weigh the benefits of a radiographic examination against the risk of exposing a patient to x-rays, the effects of which accumulate from multiple sources over time. Based on the patient's health history and vulnerability to oral disease, the dentist may make this assessment in the interest of each patient.

In 2012, the American Dental Association and the FDA devised recommendations for the selection of patients for dental radiographic examinations (please see: <http://www.ada.org/en/member-center/oral-health-topics/x-raysguidelines>), which can serve as a framework for dentists who treat patients with FA. According to this document, the dentist is advised to conduct a clinical examination, consider the patient's signs, symptoms, and oral and medical histories, as well as consider the patient's age and vulnerability to environmental factors that may affect oral health.

This diagnostic and evaluative information may determine the type of imaging to be used or the frequency of its use.

Once the need for radiographs is determined, a conscious effort should be made by the dentist to reduce the radiation risks of dental x-rays, including limiting the number of radiographs, using protective gear (e.g., leaded aprons and thyroid collars), and using faster speed films and digital imaging.

## Good to Know

### Radiation exposure

When taken properly, dental radiographs provide limited exposure to x-rays. In fact, natural sources of radiation can provide more radiation exposure than dental x-rays. For instance, a panoramic dental x-ray exam may expose a patient to only about 1 millirem (a unit of absorbed radiation dose), whereas a cross-country flight exposes an individual to 5 millirem of cosmic radiation. Moreover, the National Council on Radiation Protection (NCRP) estimates that the average resident of the US receives about 360 millirem of radiation every year. Exposure can be minimized even further with the use of digital radiographs. Additional references for comparison are listed in the table below, and more information on this topic can be found in Linet, 2012 <sup>(15)</sup>.

### Effective radiation doses from various dental x-ray procedures.

	$\mu$ Sv	mSv	mrem
Panoramic	6–11	0.006-0.011	0.6-1.1
Cephalometric	6–11	0.006-0.011	0.6-1.1
TMJ tomogram	2	0.002	0.2
Full-mouth intraoral	10–15	0.01-0.015	1-1.5
Bitewings (4 x-rays)	2–3	0.002-0.003	0.2-0.3
Mandible CT	150–700	0.15-0.7	15-70
PA and lat. chest x-ray (for comparison)	170	0.17	17
Background radiation per year (for comparison)	3,600	3.6	360



Effective radiation doses from various dental x-ray procedures.

	$\mu\text{Sv}$	mSv	mrem
Panoramic	6–11	0.006-0.011	0.6-1.1
Cephalometric	6–11	0.006-0.011	0.6-1.1
TMJ tomogram	2	0.002	0.2
Full-mouth intraoral	10–15	0.01-0.015	1-1.5
Bitewings (4 x-rays)	2–3	0.002-0.003	0.2-0.3
Mandible CT	150–700	0.15-0.7	15-70
PA and lat. chest x-ray (for comparison)	170	0.17	17
Background radiation per year (for comparison)	3,600	3.6	360

Source: <http://hps.org/publicinformation/ate/faqs/dentalpatientissuesq&a.html>

- **Detecting oral and head and neck cancers**

Head and neck cancers, which include cancers of the oral cavity, are of particular concern for patients with FA. As the health care provider who is most familiar with a patient's oral cavity, the dentist is in the unique position to identify subtle changes or lesions in an early stage. Screening for oral and head and neck cancers should begin by age 9-10 years in patients with FA. Screening should be performed every 6 months by an experienced professional, complying with the World Health Organization (WHO) oral cancer examination method as follows:

- Inspect the face, head, ears, and neck, noting any asymmetry or changes on the skin; palpate the lymph node areas on both sides of the head and neck to detect any enlarged nodes.
- Observe the lips with the mouth both closed and open, noting color, texture, and any surface abnormalities.
- Examine the labial mucosa (the inside lining of the lips), noting color, texture, and any swelling or other abnormalities.
- Examine the right and left buccal mucosa (the inside lining of the cheeks).
- Examine the tonsillar region, noting any change in pigmentation, color, texture, mobility, and other abnormalities.
- Examine the upper and lower gingival and alveolar ridges (which contain the sockets of the teeth), including the parts facing the cheeks and lips and the parts facing the tongue.

- With tongue at rest and mouth partially open, examine the dorsum for swelling, ulceration, coating, or variation in size, color, or texture. Note any change in pattern of papillae covering on tongue surface and examine the tip of tongue. Note any abnormality of mobility or positioning of the protruded tongue. Using mouth mirrors, inspect right and left sides of tongue. Grasp the tip of tongue and examine the surfaces of the tongue that face the floor of the mouth. Palpate the tongue to detect growths.
- With the tongue elevated, inspect the floor of mouth for changes in color, texture, swelling, or other surface abnormalities.
- Inspect the hard and soft palate with mouth wide open, head back, and tongue depressed. Examine all soft palate and oropharyngeal tissues. Palpate the floor of mouth for any abnormalities. Palpate all mucosal or facial tissues that appear abnormal.

## Cancer Screening Tools

Two non-invasive tests, **toluidine blue vital staining** and **exfoliative cytology techniques**, are FDA-approved and can help identify malignant cells and serve as a guide for biopsy. These tests are not diagnostic, however. Biopsy remains the only proven way to diagnose cancer.

**Chemiluminescence** and **tissue autofluorescence** can be used to screen for oral pre-malignant and malignant lesions. These techniques only serve to guide or illuminate where a biopsy may be needed. Again, biopsy is the only proven way to diagnose cancer.

- **Chemiluminescence** involves rinsing the mouth with a 1% acetic acid solution and then examining mucosa with a special light (wavelength 490-510 nm); it has been proposed that abnormal mucosa will reflect a white color and normal mucosa will appear blue.
- **Autofluorescence** techniques illuminate oral tissues with a special blue light (400-460 nm). Abnormal (potentially malignant) tissue exhibits a decreased ability to autofluorescence and appears darker when examined.

If an individual with FA is not already under the care of an ear, nose, and throat specialist (ENT), the dentist should refer the patient to an ENT for a flexible fiber optic exam of the nasopharynx, oropharynx, hypopharynx, and larynx, especially if the patient develops any persistent symptoms such as odynophagia (severe pain on swallowing), dysphagia (difficulty swallowing), and/or voice changes (see *Chapter 14*).

## Restorative treatments

- **Fillings and restorative materials**

Dental fillings can be used to restore function to teeth that have become damaged or decayed. There are several dental filling materials available. Amalgam fillings, which are made of mercury, silver, tin, copper, and other trace metals, have been used extensively for many decades. Amalgam fillings are easy to place, strong, and have good longevity. However, it remains unclear whether the mercury in amalgam fillings is harmful to health <sup>(10)</sup>. Therefore, the use of amalgam fillings in patients with FA should be limited until further research is available.

Tooth-colored, synthetic resins known as composite resins can be used as a restorative material or adhesive. Composite resins are approved for use in all teeth and can replace the use of amalgam in molar teeth. However, patients should be warned that composite fillings are associated with an increased occurrence of secondary decay and tooth sensitivity. Composite resins may be of potential concern for patients with FA due to the presence of bisphenol A (BPA), which may have endocrine-disrupting, estrogenic properties. However, the potential harmful effects of BPA remain controversial and no unacceptable risks for the patient have yet been recognized <sup>(11)</sup>. Furthermore, BPA exposure can be reduced by cleaning and rinsing surfaces of sealants and composites immediately after placement <sup>(12)</sup>.

The best way to avoid the need for those restorative materials is to decrease the patients' risk for caries. This can be achieved by aiming for optimal oral hygiene, following a balanced diet (low in sucrose), and having access to fluoride as appropriate.

- **Orthodontic treatment**

The use of braces to reposition the teeth should not pose a problem for patients with FA who are not neutropenic or otherwise immunocompromised. However, the brackets and wires on the braces can cause trauma and chronic inflammation in some patients. Because chronic physical irritation has been reported to be associated with oral cancer in clinical studies <sup>(13, 14)</sup>, efforts should be made to prevent them in patients with FA. Recently, new orthodontic treatment methods such as Invisalign® have been developed that obviate the need for traditional braces in certain cases.

- **Dental implants**

Dental implants are titanium cylinders that are implanted into the jaw bone to replace missing teeth. They act as artificial roots to hold crowns or dentures in place. It should be noted that FA is not a contraindication for dental implants. A patient with FA should be stable (i.e., non-immunocompromised and non-thrombocytopenic) and meet all the normal requirements for implants, such as sufficient bone volume and the ability to maintain good hygiene.

- **Oral surgery**

Oral and maxillofacial surgeons are involved in the diagnosis and management of diseases, injuries, and defects of the oral and maxillofacial region. Common reasons to visit the oral surgeon include tooth removal (including removal of the third molars or “wisdom” teeth), treatment of dental infections, biopsy of oral lesions, or reconstruction with dental implants. Patients may also need to see an oral surgeon for the treatment of trauma to the oral region or facial bones. The majority of procedures can be safely and comfortably done in the oral surgeon’s office, where sedation is often used. The sedation techniques used in an oral surgery office are very similar to those used during an FA patient bone marrow aspirate or biopsy. Patients with FA who are non-immunocompromised and non-thrombocytopenic can usually be treated in a routine fashion. The oral surgeon may need to consult with the patient’s hematologist about any questions or concerns.

## **Developmental and Mucosal Changes Associated with FA**

A number of oral and dental changes have been reported in patients with FA. Many of these changes also occur in healthy children, so it remains unclear whether they are associated with FA itself or rather with treatments for oral and head and neck cancers and marrow disorders, such as high-dose chemotherapy and hematopoietic stem cell transplantation (HSCT), which are known to adversely affect the development of teeth and jaws in children younger than 12 years. Regardless, it is important to recognize, diagnose, and manage these changes because they can complicate oral health and function.

Dental and skeletal developmental changes that have been reported in patients with FA include:

- *Microdontia (teeth that are smaller than normal)*
- *Supernumerary teeth (extra teeth)*
- *Agenesis (teeth that do not develop normally)*
- *Changes in the color of the tooth enamel (e.g., abnormally dark or discolored teeth, or opalescent enamel)*
- *Abnormal tooth shape, rotation, and position of teeth within the mouth*
- *Delayed development of teeth (usually permanent teeth), including delayed loss of primary (baby) teeth and eruption of permanent teeth compared with healthy peers*
- *Micrognathia (underdeveloped jaws)*

Oral changes that have been reported in patients with FA include:

- *Gingivitis (inflammation of the gums) and periodontitis (gum disease)*
- *Macroglossia (an unusually large tongue)*
- *Bleeding abnormalities, including bleeding gums and lesions caused by trauma*
- *Abnormal pigmentation of the tongue, cheek mucosa, floor of the mouth, and gums*
- *Dental caries (tooth decay)*
- *Salivary gland dysfunction, resulting in altered flow or composition of the saliva, which may increase the risks for dental decay and oral infections*
- *Oral ulcers*
- *Oral cancer and head and neck cancers*

Oral ulcers occur frequently in patients with FA and can cause anxiety due to the high risk of oral cancer in these individuals. Oral ulcers or any oral lesions that do not resolve within 10 days need to be assessed by a health care professional. The most serious oral lesion associated with FA is oral cancer, most commonly squamous cell carcinomas (SCCs), which will be discussed in detail in *Chapter 14*.

## Assessing oral ulcers in patients with FA

It is extremely important for clinicians to differentiate between canker sores, ulcerations caused by a condition known as aphthous stomatitis, and oral ulcerations due to other potential causes.

- A **canker sore** is a lesion that often develops after a relatively mild trauma and heals within approximately 4-7 days.
- **Aphthous stomatitis** is characterized by multiple ulcers that occur simultaneously and can recur as often as once a month (just as the previous ulcers are healing). Most cases of aphthous stomatitis can be treated with topical steroids applied directly to the ulcer (Table 1).
- Patients who have **neutropenia** (a low neutrophil count) can develop oral ulcers that are clinically indistinguishable from canker sores. Such neutropenic ulcers can develop spontaneously or after a mild trauma (such as a mild bite injury), but tend to worsen and become painful. Neutropenic ulcers can be an early indication of bone marrow diseases, such as aplastic anemia or leukemia, though additional systemic signs and symptoms of bone marrow disease will often be present. Additionally, cancer therapies such as chemotherapy can cause severe neutropenia and neutropenic ulcerations.
- Recurrent **herpes simplex virus (HSV) infections** can cause ulcerations of the oral mucosa and lip. These lesions are often associated with the immune dysfunction that often accompanies severe AA, MDS, and AML. They can also arise after high-dose chemotherapy or HSCT.

**Table 1.** Management of recurrent aphthous ulcerations.

Treatment	Dose and Treatment Schedule
Topical anesthetics	<ul style="list-style-type: none"> <li>• 2% viscous lidocaine</li> <li>• Doxepin solution</li> </ul>
Topical coating agents	<ul style="list-style-type: none"> <li>• Hydroxypropylcellulose film (Zilactin®)</li> </ul>
Topical corticosteroids	<ul style="list-style-type: none"> <li>• 0.05% clobetasol gel</li> <li>• 0.05% flucinonide gel</li> <li>• mg/ml dexamethasone elixir</li> <li>• Budesonide inhaler</li> </ul>
Intralesional injection	<ul style="list-style-type: none"> <li>• 40 mg/ml triamcinolone (0.1 - 0.3 ml)</li> </ul>
Systemic therapy	<ul style="list-style-type: none"> <li>• 0.5 - 1 mg/kg prednisone</li> <li>• Thalidomide</li> </ul>

**Table 2.** Oral health problems in patients with bone marrow dysfunction.

Oral Health Problem	Cause(s)	Management
Bleeding	<ul style="list-style-type: none"> <li>• Thrombocytopenia (loss of platelets)</li> </ul>	<ul style="list-style-type: none"> <li>• Avoid oral trauma</li> <li>• Prevent infection</li> </ul>
Bacterial infections	<ul style="list-style-type: none"> <li>• Loss of white blood cells, especially neutrophils</li> <li>• Secondary infection of traumatic oral lesions</li> </ul>	<ul style="list-style-type: none"> <li>• Maintain excellent oral hygiene</li> <li>• Antibacterial mouthwashes</li> <li>• Systemic antibiotics for severe infections</li> </ul>
Fungal infections (primarily yeast)	<ul style="list-style-type: none"> <li>• Loss of white blood cells, especially neutrophils</li> <li>• Loss of salivary gland function</li> <li>• Use of systemic antibiotics</li> </ul>	<ul style="list-style-type: none"> <li>• Topical antifungals (nystatin or clotrimazole) for oral yeast infections</li> <li>• Systemic antifungals for extensive infections</li> </ul>
Viral infections (primarily herpes simplex virus (HSV), but also varicella zoster virus (VZV), cytomegalovirus (CMV), or Coxsackie group viruses)	<ul style="list-style-type: none"> <li>• Immune dysfunction, including neutropenia</li> </ul>	<ul style="list-style-type: none"> <li>• Systemic antiviral drugs (acyclovir or valacyclovir)</li> </ul>
Delayed healing of oral tissues	<ul style="list-style-type: none"> <li>• Loss of white blood cells (especially neutrophils), resulting in secondary infections</li> <li>• Severe anemia</li> </ul>	<ul style="list-style-type: none"> <li>• Obtain primary closure of extraction or surgical sites</li> <li>• Reduce risk for trauma and irritation</li> <li>• Prevent secondary infection</li> </ul>
Gum enlargement, bleeding, and pain	<ul style="list-style-type: none"> <li>• Accumulation of leukemic cells in gum tissue, usually in response to gingivitis</li> <li>• Medication-induced gum enlargement</li> </ul>	<ul style="list-style-type: none"> <li>• Maintain excellent oral hygiene</li> <li>• Treat the leukemic disease</li> <li>• Consider medication modification</li> </ul>
Facial and oral neuropathies (nerve damage)	<ul style="list-style-type: none"> <li>• Compression of nerve bundles by leukemic cells, resulting in numbness and tingling</li> </ul>	<ul style="list-style-type: none"> <li>• Treat the leukemic disease</li> </ul>

## Oral Care Before and After Treatment for Bone Marrow Dysfunction and Cancer

The treatment and management of oral cancers and marrow dysfunction can result in a wide spectrum of oral complications for patients with FA. Preventing and controlling oral complications can improve the patient's quality of life, and, in many instances, potentially improve the outcomes of the patient's treatments.

Prior to treatment for oral cancer or bone marrow dysfunction, patients should undergo a complete oral examination and dental evaluation. Dental care should focus on eliminating any oral and dental diseases that could contribute to oral complications during treatment. Teeth with a poor long-term prognosis due to periodontal disease and/or teeth deemed to be non-restorable should be extracted. In situations where extractions are not possible due to the patient's medical status, time-release antibiotics can be placed in deep periodontal pockets to reduce the levels of bacteria in the region for several weeks and thus hopefully reduce the risk of periodontal infections.

Prior to radiation therapy, the dentist should review the details of the proposed radiation therapy plan, paying particular attention to the following:

- *The teeth that are included within the fields of radiation treatment*
- *The total dose of radiation that these teeth (and their surrounding bone) will receive*
- *The salivary glands that will be in the radiation fields and the total dose of radiation that these salivary glands will receive*

Patients must be informed of the potential oral complications of cancer surgery, head and neck radiation therapy, chemotherapy, and hematopoietic stem cell transplantation, including the causes, prevention, and management of the complications. Patients must accept responsibility for maintaining the highest level of oral hygiene and adhering to protocols to reduce the risk of oral complications of treatments for oral cancer and bone marrow dysfunction.

Routine oral care after HSCT is essential to help maintain oral health and prevent infections and bleeding problems associated with gingivitis and periodontal disease. Once dental examinations resume after HSCT, the dentist should carefully examine the patient's teeth and periodontal tissues, and x-ray images should be obtained if pre-transplant images are not available. However, routine elective dental treatment, including dental cleanings and restorations, should wait until the patient's immune system has sufficiently recovered.

If a patient urgently needs dental treatment before the immune system has recovered, the dentist and physician should determine what additional supportive medical care should be given. Supportive care may include prophylactic antibiotics, immunoglobulin G administration, adjustment of steroid doses, and platelet transfusions if the patient has a significant risk for bleeding. Rinsing with chlorhexidine immediately before treatment is



recommended. Prophylactic antibiotic regimens (American Heart Association endocarditis prevention protocols) appear to be efficacious, with regimens being extended if there is ongoing dental infection or if there is concern for delayed healing. Dentists should also utilize techniques such as rubber dams and high-volume suction devices, and minimize the spraying of dental equipment to reduce the chances that the patient will inhale any dangerous substances during dental treatment. The dental care team should also aim to reduce the complexity of treatments and shorten treatment times.

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# Chapter 11: Hematopoietic Stem Cell Transplantation

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## Introduction

### Good to Know

A complete list of definitions is provided at the end of this chapter. Here are a few terms you should know right now:

- **Stem cells:** Cells that can develop into one of many types of specialized cells in the body.
- **Allogeneic hematopoietic stem cell transplantation (HSCT):** A medical procedure that destroys the stem cells in a patient's bone marrow and replaces them with stem cells from a HLA-matched or partially matched related or unrelated donor's bone marrow.
- **Human leukocyte antigen (HLA):** A protein found on the surface of cells in the body; this protein helps the body determine what is "self" and what is "foreign." An HLA-matched donor increases the chances that the patient's body will accept the transplant cells and vice versa.

At the time of publication, allogeneic hematopoietic stem cell transplantation (HSCT) remains the only treatment that can correct the hematologic complications common to most patients with Fanconi anemia (FA). Transplants from human leukocyte antigen (HLA)-identical sibling donors are generally associated with excellent outcomes. Currently, survival rates exceed 85% for children younger than 10 years and 65% for children and adults combined <sup>(1)</sup>. In contrast to those with HLA-matched sibling donors, alternative donor (i.e., HLA-mismatched related or unrelated) transplants are more complex due to increased immunological risks. Over time, however, survival rates are increasingly similar between donor sources <sup>(1)</sup>.

Because of the unique complications associated with HSCT and the late effects associated with FA itself, it is recommended that whenever possible, patients be cared for at selected centers with comprehensive care clinics specific to FA. Though only a few of these specialized centers exist worldwide, patients who travel to these centers help advance FA research as much as they themselves benefit from the centers' comprehensive care. The dramatic improvements in

transplantation for patients with FA over the past decades, for example, would not have been possible without research that benefited from the concentration of patients at a few centers. Treating patients at selected centers may also help clinicians and researchers improve the management of FA-associated conditions that develop later in life, particularly cancer.

This chapter will describe the current state of knowledge in this area and explore the following issues specific to HSCT in patients with FA:

- *Current expectations of patient survival after HSCT*
- *Exploring the possibility of transplant: Indications for HSCT, referral to a transplant center, initial assessments, and donor identification*
- *Addressing the potential risks of HSCT: Pre-transplant conditioning, GvHD immunosuppression, and infectious disease prophylaxis*
- *The transplant: Pre-transplant work-up, the transplant stay, and late effects of FA and HSCT*
- *Alternatives to HSCT*

## Good to Know

**Graft-versus-host disease (GvHD):** This complication occurs when immune cells in the transplanted marrow consider the patient “foreign” and attack the patient’s body.

**Myelodysplastic syndrome (MDS):** A group of conditions that develop when blood cells in the bone marrow begin to look abnormal (e.g., changes in the size and appearance of the nucleus and cytoplasm). Also known as “preleukemia.”

**Umbilical cord blood (UCB):** Blood present in the placenta and umbilical cord of an infant after birth. This blood contains high numbers of stem cells that can be used in transplants.

## Recent Developments in HSCT for FA

The general experience with HSCT for the treatment of FA has been detailed elsewhere<sup>(1-12)</sup>. From the institutional and registry studies performed to date, three important findings emerge:

- 1) Survival rates after HSCT continue to improve, particularly for patients undergoing alternate donor transplant.
- 2) The best outcomes of allogeneic HSCT occur in patients younger than 10 years, patients who test negative for cytomegalovirus (CMV), patients with

no or few blood product exposures, and patients treated with fludarabine in the conditioning regimen prior to HSCT.

- 3) The technologies of in vitro fertilization (IVF) and preimplantation genetic diagnosis (PGD) can be useful for providing a healthy HLA-matched donor. Successful use of these technologies reduces the need for higher dose therapy and exposure to the risks of alternate or HLA-mismatched donor HSCT.

Since the 2003 and 2008 editions of the *Guidelines* were published, survival outcomes have improved significantly for patients with FA, primarily due to refinements in the treatment plan, HLA-matching between the patient and donor, and earlier referral for HSCT prior to the onset of myelodysplastic syndrome (MDS), acute leukemia, and/or systemic infection. Several other observations about HSCT have been made since the previous edition of the *Guidelines* (Box 1).

**Box 1.** Recent observations related to HSCT in patients with FA.

- Patients who avoid transfusions and systemic infections tend to have superior outcomes after unrelated donor HSCT.
- Order of priority: For patients without a 7-8/8 matched related donor, 7-8/8 matched adult unrelated donor and 5-6/6 matched umbilical cord blood (UCB) are superior to a 4/6 matched UCB.
- In transplanted FA patients, the risk of cancer appears to be primarily associated with the development of significant graft-versus-host disease (GvHD) with no clear relationship to any particular conditioning regimen.

## Current Expectations of Patient Survival

### Sibling donor HSCT

In an analysis of 209 FA patients with an HLA-identical sibling donor who were transplanted between 1994 and 1999, the 3-year survival was 81% in patients younger than 10 years (109 patients) and  $69 \pm 10\%$  in older patients (100 patients)<sup>(2)</sup>. Today, fewer patients with an HLA-identical sibling donor receive radiation, a treatment that can be associated with late effects such as low thyroid hormone levels. In the largest single-center study of a radiation-free regimen to date<sup>(5)</sup>, 85 patients with FA (median age 9 years, ranging from 3 to 34 years) were treated between 1999 and 2011. Of these 85 patients, 82 were treated for aplastic anemia and 3 were treated for MDS. The treatment consisted of cyclophosphamide (CY) 15 mg/kg x 4 days (60 mg/kg total dose)

along with methotrexate (MTX) and cyclosporine (CSA) immunosuppression to prevent GvHD. At the time of the last report, approximately 85% of patients had survived 5 years, with a higher (96%) survival rate among patients who were younger than 10 years (48 patients) at the time of transplant. Notably, all patients with MDS relapsed after HSCT and died from progressive disease despite receiving a second transplant. Graft rejection occurred in approximately 7% of patients, with acute GvHD in 17 of 81 patients and chronic GvHD in 23 of 78 evaluable patients.

Because transplants can lead to acute and chronic GvHD, and are associated with cancers later in life, MacMillan et al. modified the transplant procedure to incorporate T-cell depletion of the bone marrow, even in sibling donors. This is known to be the best strategy for minimizing the risk of GvHD<sup>(1,3)</sup>. At the University of Minnesota, patients were conditioned with CY 5 mg/kg x 4 days (20 mg/kg total dose), fludarabine (FLU) 35 mg/m<sup>2</sup> x 5 days (175 mg/m<sup>2</sup> total dose), and antithymocyte globulin (ATG) 30 mg/mg x 5 days (150 mg/kg total dose) followed by the infusion of T-cell-depleted marrow with CSA and either methylprednisolone or mycophenolate mofetil (MMF) to prevent GvHD. Of the 23 patients (median age 8.5 years; ranging from 3.2 to 43.3 years) included in the study, 92% survived at least 5 years. One recipient of cord blood developed acute GvHD and died; this was the only patient with acute GvHD. None of the patients developed graft failure/rejection or chronic GvHD.

In 2008, Pasquini et al. compared transplant outcomes in recipients conditioned with (77 patients) and without (71 patients) irradiation-containing treatment regimens prior to HLA-identical sibling donor transplantation, as reported to the Center for International Blood and Marrow Transplant Research (CIBMTR)<sup>(6)</sup>. With a median follow-up of more than 5 years for both groups, the overall survival rates were 78% and 81% at 5 years ( $p = 0.61$ ), respectively, suggesting that there are no advantages to radiation. Future studies are needed to explore whether radiation helps prevent disease recurrence in patients with MDS or more advanced disease.

### **Unrelated donor HSCT**

As the majority of FA patients do not have an HLA-identical unaffected sibling donor, alternative types of donors must be explored. The two most common donor types are adult volunteers registered with organizations like the National Marrow Donor Program (NMDP) and those who have banked or donated umbilical cord blood (UCB) obtained from the placenta after the birth of a baby.

At the University of Minnesota, 48 patients with FA (ranging from 1.7 to 34.3 years) who had aplastic anemia or MDS received FLU, CY, ATG, and low-dose total body irradiation (TBI) (300 cGy) followed by T-cell-depleted 7-8/8 HLA-matched bone marrow (32 patients) or by HLA-mismatched UCB (16 patients) if an unrelated donor was unavailable. All recipients of marrow engrafted at a median of 11 days (ranging from 9 to 23 days). In contrast, engraftment was only 88% at a median of 19 days (ranging from 10 to 40 days) in recipients of UCB. The incidence of acute and chronic GvHD was low (12% and 6%, respectively), with similar outcomes in patients transplanted with bone marrow and UCB. The overall survival for the entire cohort was 78% at a median of 2.9 years (ranging from 0.6 to 6.3 years). However, patients without a prior history of opportunistic infection or transfusions had a 92% (95% confidence interval is 54% to 99%) chance of survival at 5 years (1; MacMillan, unpublished data).

In a preliminary and multi-institutional study reported by Boulad et al. that explored the safety and efficacy of a new conditioning regimen for patients undergoing unrelated donor HSCT, 27 patients (median age 8.1 years, range 4.3 to 31.8 years), primarily with aplastic anemia and/or MDS, received FLU, CY, and ATG in combination with busulfan (BU) followed by transplantation of T-cell-depleted peripheral blood stem cells. All patients engrafted with 1 losing the graft at a later time point. Grade 2-4 GvHD occurred in only 1 patient. Moderate to severe toxicities included severe pulmonary hypertension and veno-occlusive disease of the liver in 1 patient each. The median follow-up time was 8 months (ranging from 0.5 to 37.8 months), and 19 of 23 patients were living at the time of the report <sup>(12)</sup>.

## Exploring the Possibility of Hematopoietic Stem Cell Transplant

### Indications for HSCT

With improved outcomes, the indications for alternate donor HSCT are increasingly similar to the indications for sibling donor HSCT. Patients with an exceptional risk of transplant-related mortality (e.g., patients with severe organ dysfunction, those who are 35 years or older, and those with pre-existing malignancies or systemic infections) may prefer to explore alternative treatment options first, such as the use of hematopoietic growth factor therapy and androgens. These alternatives are discussed later in this chapter.

<b>Box 2.</b> Eligibility for sibling donor and alternative donor HSCT.
Aplastic anemia (Hgb < 8 g/dL or ANC < 500/μL or platelet count < 30,000/μL)
MDS or acute leukemia
Progressive complex cytogenetic abnormalities*
Absence of active infections
Available HSC donor Order of priority: <ul style="list-style-type: none"> <li>• HLA 8/8 (followed by 7/8) allele-matched sibling</li> <li>• HLA 8/8 (followed by 7/8) allele-matched relative other than sibling</li> <li>• HLA 8/8 (followed by 7/8) allele-matched unrelated adult volunteer</li> <li>• HLA 5-6/6 antigen matched UCB</li> <li>• Other (4/6 UCB or haploidentical relative**)</li> </ul>

\*There is currently a lack of unanimity on this criterion.

\*\*Haploidentical transplants are uncommon in the setting of FA, though there have been some reports of success. Haploidentical transplant should be considered in patients with no other alternative. Some treatment plans using haploidentical transplant incorporate significant doses of CY after transplant. This agent at appreciable dose is generally avoided, as patients with FA are inordinately sensitive to high dose CY and would be expected to be at risk of severe toxicity, although experience to date in the Curitiba program (Bonfim, personal communication) has been favorable.

Patients who develop persistent and severe cytopenia [i.e., hemoglobin (Hgb) < 8 grams/deciliter (normally 12-14); absolute neutrophil count (ANC) < 500/μL (normally 2,500-4,500); and/or platelets (PLT) < 20,000/μL (normally 150,000-450,000)] or evidence of MDS or leukemia, should be considered for allogeneic HSCT provided the patient is not too old, has adequate organ function, and controlled infection (Box 2). Earlier transplantation may be considered for patients with specific genetic mutations, who are deemed to be at particularly high risk for rapid progression to MDS or leukemia, and may face markedly shortened survival times [e.g., breast cancer (*BRC A*)-related genetic mutations<sup>(13)</sup>]. The predictive nature of specific mutations is an active area of clinical investigation.

### Referral to a transplant center

Most transplant centers do not have experience with FA. Some centers might be limited to adult transplantation or to the use of autologous (the patient's own) marrow, versus both autologous and allogeneic (another person's) marrow. Even large centers experienced in treating children and adults with allogeneic marrow frequently have no or little experience caring for patients with FA and the short- and long-term complications unique to this patient population.



To best assess a potential transplant team's experience, specific questions should be asked at the time of the initial phone call or visit (Box 3). Additional information can be found on the NMDP website, available at: [http://bethematch.org/Patient/Transplant\\_Planning/Choosing\\_a\\_Transplant\\_Center/U\\_S\\_\\_Transplant\\_Centers.aspx](http://bethematch.org/Patient/Transplant_Planning/Choosing_a_Transplant_Center/U_S__Transplant_Centers.aspx). It should be noted, however, that information about the center's specific experience with FA is usually difficult to discern because FA is often lumped together with other diseases such as sickle cell disease and Diamond Blackfan anemia under the category "Inherited abnormalities of erythrocyte differentiation." In addition, these data do not describe the center's experience with the specific treatment regimen proposed for a given individual; for example, a patient with FA who has aplastic anemia versus a patient with FA who has MDS or leukemia.

Referring doctors and insurance companies may be associated with certain transplant centers, often based on their experiences with patients who have leukemia. Proximity to home may not be the deciding factor for a patient with FA if FA-specific expertise is not locally available. If the insurance company is associated with a bone marrow transplant (BMT) center that has limited or no expertise in FA, the insurance company will often give approval for the FA patient to travel to an experienced FA center once the insurance company understands the differences in the centers' experience and the importance of experience in patient survival. Insurance denials or less than complete coverage for transplant at a FA-experienced transplant center (because they are "out-of-network") can often be contested successfully.

**Box 3.** Questions to help assess a transplant center's experience with FA.

- What is the total number of transplants that the center has performed specifically in patients with FA?
- How many FA transplants have been performed each year for the past 5 years? How many of those patients are still alive?
- What treatment regimen do you propose? Please tell me the exact doses of each drug and the radiation dose (if applicable). How many patients have been treated with this regimen at this center? How many are still alive?
- What is the risk of acute and chronic GvHD in FA patients using this regimen? How do you plan to prevent GvHD?
- How long will you follow the patient (me/my child/my spouse)? Who will follow the patient (me/my child/my spouse) long term?

**\* IMPORTANT NOTE! \***

The insurance company may indicate that a FA-experienced transplant center is not a “Center of Excellence”. This does not necessarily reflect on the suitability or quality of the center. “Center of Excellence” is the designation made by the insurance company to indicate that a center has met criteria and operates under a negotiated contract with the specific insurance company.

*As a rule, a family should not immediately accept a denial from an insurance carrier without asking the FA-experienced transplant center to directly negotiate with their insurer if such a center is desired.*

**First assessments**

Before the first visit to a FA transplant center, the patient’s physician will be asked to put together a packet of information to help the transplant physician provide the best recommendations specific to the patient, whether that patient is you, your child, or your spouse. This packet should include the information listed in Box 4.

**Past medical history.** The manifestations and complications associated with FA vary dramatically from one patient to the next. Because certain malformations and ongoing treatments could impact the proposed HSCT treatment plan, the physician must obtain a complete medical history, including an evaluation of the severity of the malformations (particularly those of the heart and kidney) and prior or ongoing treatments. All infectious disease complications, prior use of androgens, prior surgeries and cancers must be carefully detailed in the medical history, as these complications may affect the design of the transplant treatment plan. The medical history must detail all past surgeries (e.g., tracheoesophageal fistula, duodenal atresia, or ureteral reflux); medical treatments (e.g., metoclopramide and ranitidine for gastroesophageal reflux, or Bactrim prophylaxis for ureteral reflux); transfusion history (e.g., number of red blood cells and platelets); history of androgen use (e.g., type, dose, and duration), and general issues such as immunizations, allergies, and the patient’s use of vitamins, iron supplements, or herbal remedies.

Box 4. Preparing for a new transplant assessment appointment.
<p>History of Present Illness</p> <ul style="list-style-type: none"> <li>• FA diagnosis (date and place of FA testing)</li> <li>• Presenting symptoms that ultimately led to FA testing</li> <li>• Complementation group/mutation testing results (if performed)</li> <li>• List of organs involved</li> <li>• Most recent blood counts</li> <li>• History of transfusions</li> <li>• History of infections</li> </ul>
<p>Past Medical History</p> <ul style="list-style-type: none"> <li>• Perinatal birth history (i.e., number of pregnancies and miscarriages prior to the patient's birth); complications during the pregnancy and delivery; APGAR scores; presence of birth defects</li> <li>• Growth records (height and weight charts)</li> <li>• Developmental history</li> <li>• Surgeries</li> <li>• Hospitalizations</li> <li>• Immunization record</li> </ul>
<p>Current Medications and Allergies</p> <ul style="list-style-type: none"> <li>• Include over-the-counter drugs so that the physician can determine which drugs might damage the bone marrow</li> <li>• List of current medications associated with reactions and severity of reactions</li> </ul>
<p>Family Medical History</p> <ul style="list-style-type: none"> <li>• Number of siblings; have they been tested for FA?</li> <li>• Medical histories for parents of the patient and for other first- and second-generation relatives, particularly noting cancers, anemias, and birth defects</li> </ul>
<p>Social History</p> <ul style="list-style-type: none"> <li>• Home environment, exposure to chemicals, types of pets</li> <li>• School experience (e.g., learning challenges)</li> </ul>

**Family medical history.** The family medical history is extremely important. ***Without exception, all full siblings (i.e., siblings with the same mother and father), regardless of appearance, blood counts, HLA, or blood types, must be tested for FA.*** It has been repeatedly shown that siblings who appear to be completely healthy and without any manifestation suggestive of FA may still have FA. Further, it is important to reveal if there are full siblings not living with the family or, because of donor compatibility issues, if the child with FA is adopted.

**Social history.** Behavioral, school, and work performance issues should be reviewed with the clinician. An open discussion of alcohol consumption and smoking history (cigarette and cannabis) is very important because of the risks of cancer and infection in the early transplant period. Additionally, the

physician should inquire about the use of other drugs that could potentially interfere with the patient's liver function or drug metabolism during and after the transplant.

**Concurrent medications.** The patient's use of complementary medications should be assessed by the transplant team. Some agents, like echinacea, which is believed to help the immune system and prevent colds, flu, and infections, may cause rashes or diarrhea that resemble the symptoms of GvHD. Other supplements, like ginkgo, which is believed to treat asthma and bronchitis as well as improve memory, may cause bleeding problems. St. John's wort, which is believed to treat anxiety and depression, may interfere with the metabolism of cyclosporine A, an important drug used in the early transplant period. A summary of published results of various complementary medications and potential side effects can be found at <http://nccam.nih.gov>.

**Physical examination.** Prior to HSCT, the physician will assess potential factors that may alter the risk or plan of transplant therapy. Careful attention will be paid to the oropharyngeal area (to check for precancerous lesions, infection, and dental health); ears (to check hearing); nose and sinuses (to check for infection); respiratory system (to check for infection or reactive airway disease); and urogenital system (to check for infection, bladder anomalies, or cervical/vulvar precancerous/cancerous lesions). The general examination should carefully document pre-existing cutaneous changes (e.g., *café au lait* spots, areas of hyper- or hypopigmentation, nail abnormalities, nevi, and lesions characteristic of squamous cell carcinoma or melanoma), heart sounds/murmurs, liver and spleen sizes, and scars from prior surgeries.

### **Donor identification: The search process and HLA typing**

Physicians should embark on an extended family and/or unrelated donor search well before the patient develops severe bone marrow failure, MDS, or AML, so that delays are minimized once HSCT is required. According to the NMDP, the average time from search initiation to HSCT is approximately 3-4 months; therefore, a search should be initiated before the need for transfusions or development of leukemia. In general practice, the NMDP will allow the transplant center to "reserve" a donor for several months without having received a request for a marrow harvest or a peripheral blood stem cell collection date. After that time, the NMDP will request more specific information about the proposed timing of the transplant procedure. In some cases, the NMDP and medical director of the collection center will permit an exception and allow the donor to be kept on "reserve" without a specific

date. This is decided on a case-by-case basis. It is important to recognize that a donor on “reserve” may still appear in other patient searches. Though uncommon, it is possible that a patient with an urgent need could request that same donor, in which case the NMDP will work to seek an equitable solution. Some patients or parents ask if it is possible to collect and store bone marrow, either from a related or unrelated donor, for future use so that it is available at the time it is needed. This is generally not recommended and, in the case of unrelated donors, rarely permitted. In some cases, a donor may not be reserved for years in the hope that the “perfect” donor will be available in the future.

A search should be performed with urgency if the patient has advanced bone marrow failure that requires recurrent transfusions or hematopoietic growth factor therapy, or if the patient shows evidence of MDS or acute leukemia. The search should include both adult volunteer and cord blood donor registries. While use of adult volunteers has generally been the preferred source of transplants, urgency and lack of an HLA-matched adult volunteer donor have resulted in the growing use of cord blood for transplants in patients with FA.

For alternate donors (any donors other than an HLA-matched sibling), high-resolution typing at HLA-A, B, C, and DRB1 of the patient must be obtained. Most transplant centers will require confirmatory HLA typing at their institution if HLA typing was originally performed elsewhere. The results of HLA typing are typically available within 7-10 business days.

A search of the bone marrow and UCB registries requires submission of the patient’s HLA type and, in the case of UCB, the patient’s weight. A preliminary search can be performed by any physician at no cost. A formal search and the pursuit of a potential donor, however, must be performed by an approved transplant center with the consent of patients who are at least 18 years old or the patient’s parent/legal guardian if the patient is younger than 18 years. A formal search will result in charges to your insurance plan, so the patient should obtain insurance approval prior to the initiation of the search. The cost will vary depending on the number of donors identified and evaluated.

**\* IMPORTANT NOTE! \***

Even if a formal search has been initiated by a transplant center, the patient is not obligated to have the transplant performed at that center—or even to have a transplant at all.

Transfer of the donor search only requires notification of the National Marrow Donor Program or other coordinating center (policies vary by country) and a newly signed consent from the patient or family.

Other potential considerations in the donor selection process are the age of the donor, CMV serostatus, female parity (i.e., number of pregnancies), and sex match between the donor and patient. Additional factors that are sometimes included in the choice of a specific UCB unit may include the quality of the cord blood bank, the presence in the recipient of anti-HLA antibodies directed against the UCB unit, and the ability to confirm unit identity.

## Addressing the Potential Risks of HSCT

Once the patient and donor meet the transplant center's eligibility criteria, the patient will be scheduled for the transplant admission. The exact timing and therapeutic plan may vary depending on the source of the HSC (i.e., from bone marrow, peripheral blood, or UCB), the degree of donor and patient HLA match, the patient's age, the presence of specific end-organ dysfunction, the stage of disease (e.g., aplastic anemia, MDS, or acute leukemia), institutional preferences, and other personal factors (e.g., school, employment).

### Pre-transplant conditioning

The pre-transplant conditioning regimen works to destroy the diseased FA marrow and to suppress the patient's immune system so that the healthy HSCs from the donor are less likely to be rejected. Pre-transplant conditioning therapy in FA patients is significantly reduced in dose compared to that used in patients who do not have FA. This is because of their unique hypersensitivity to alkylating agents and irradiation, as a result of the DNA repair defect present in nearly all individuals with FA (the notable exception may be the patient with *BRCA2* genetic mutations). The generic side effects of the most commonly used pre-transplant conditioning agents are detailed in Table 1.

**Table 1.** Side effects of the most common pre-transplant conditioning agents.

Busulfan		
Common	Less Common	Rare
<ul style="list-style-type: none"> <li>• Hair loss or thinning, including face and body hair (usually grows back after treatment)</li> <li>• Long- or short-term infertility (inability to have children) in men and women</li> </ul>	<ul style="list-style-type: none"> <li>• Tiredness (fatigue)</li> <li>• Sores in mouth or on lips</li> <li>• Fever</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Rash</li> <li>• Loss of appetite</li> <li>• Diarrhea</li> <li>• Liver damage/veno-occlusive disease</li> </ul>	<ul style="list-style-type: none"> <li>• Allergic reaction with hives, itching, headache, coughing, shortness of breath, or swelling of the face, tongue, or throat</li> <li>• Scarring of lung tissue, with cough, difficulty breathing, and shortness of breath that may occur after prolonged use, or even months or years after stopping the drug</li> <li>• Leukemia (several years after treatment)</li> <li>• Darkened skin</li> <li>• Heart problems with high-dose treatment, most often in people with thalassemia</li> <li>• Problems with the hormone system that cause weakness, tiredness, poor appetite, weight loss, and darker skin</li> <li>• Death due to lung or liver damage, or other causes</li> </ul>

Cyclophosphamide		
Common	Less Common	Rare
<ul style="list-style-type: none"> <li>• Hair loss or thinning, including face and body hair (usually grows back after treatment)</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Loss of appetite</li> <li>• Sores in mouth or on lips</li> <li>• Bleeding from bladder, with blood in urine</li> <li>• Diarrhea</li> <li>• Long-term or short-term infertility in women and men</li> </ul>	<ul style="list-style-type: none"> <li>• Darkening of nail beds</li> <li>• Acne</li> <li>• Tiredness</li> <li>• Infection</li> </ul>	<ul style="list-style-type: none"> <li>• Heart problems with high doses, with chest pain, shortness of breath, or swollen feet</li> <li>• Severe allergic reactions</li> <li>• Skin rash</li> <li>• Scarring of bladder</li> <li>• Kidney damage (renal tubular necrosis) which can lead to kidney failure</li> <li>• Heart damage with trouble getting your breath, swelling of feet, rapid weight gain</li> <li>• Scarring of lung tissue, with cough and shortness of breath</li> <li>• Second cancer, which can happen years after taking this drug</li> <li>• Death from infection, bleeding, heart failure, allergic reaction, or other causes</li> </ul>

Figure 1 continued on next page.

Fludarabine		
Common	Less Common	Rare
<ul style="list-style-type: none"> <li>• Tiredness (fatigue)</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Fever and chills</li> <li>• Infection</li> </ul>	<ul style="list-style-type: none"> <li>• Pneumonia</li> <li>• Diarrhea</li> <li>• Loss of appetite</li> <li>• Pain</li> </ul>	<ul style="list-style-type: none"> <li>• Numbness and tingling in hands and/or feet related to irritation of nerves</li> <li>• Changes in vision</li> <li>• Agitation</li> <li>• Confusion</li> <li>• Clumsiness</li> <li>• Seizures</li> <li>• Coma</li> <li>• Cough</li> <li>• Trouble breathing</li> <li>• Intestinal bleeding</li> <li>• Weakness</li> <li>• Death due to effects on the brain, infection, bleeding, severe anemia, skin blistering, or other causes</li> </ul>

Total Body Irradiation		
Common	Less Common	Rare
<ul style="list-style-type: none"> <li>• Nausea and vomiting</li> <li>• Diarrhea</li> <li>• Cataracts</li> <li>• Sterility</li> <li>• Endocrinopathies</li> <li>• Growth failure</li> <li>• Intestinal cramps</li> <li>• Mucositis</li> </ul>	<ul style="list-style-type: none"> <li>• Parotitis (inflammation of major salivary glands)</li> <li>• Interstitial pneumonitis</li> <li>• Generalized mild erythema</li> <li>• Veno-occlusive disease</li> </ul>	<ul style="list-style-type: none"> <li>• Dysphagia (difficulty swallowing)</li> <li>• Vertebral deformities</li> <li>• Nephropathy</li> <li>• Death from infection, lung injury, or other causes</li> </ul>

### GvHD immunosuppression

GvHD results when the transplanted immune system of the donor recognizes the patient as “foreign” and tries to reject the foreign tissues. This disease sometimes occurs after HSCT because the donor’s immune system is transplanted along with the donor’s HSCs, which are responsible for marrow recovery and reconstitution of the blood cells. While GvHD can occur in any patient undergoing an allogeneic HSCT, the disease tends to be more common and severe in mismatched donor recipients. The signs and symptoms of the two types of GvHD (acute and chronic) are detailed in Table 2A. The side effects of the most commonly used drugs to prevent and treat GvHD are shown in Table 2B.



**Table 2A.** Signs and symptoms of acute and chronic GvHD.

Graft-versus-Host Disease	
Acute GvHD	Chronic GvHD
<ul style="list-style-type: none"> <li>• Skin rash (blistering with more severe disease)</li> <li>• Diarrhea</li> <li>• Jaundice (high bilirubin)</li> <li>• Marked predisposition to infections</li> </ul>	<ul style="list-style-type: none"> <li>• Skin rash/discoloration</li> <li>• Hair loss</li> <li>• Dry mouth/tooth decay</li> <li>• Dry eyes</li> <li>• Sores in the mouth/thrush</li> <li>• Steatorrhea (diarrhea that is oily)</li> <li>• Ridged/fragile nails</li> <li>• Shortness of breath/exercise intolerance</li> <li>• Marked predisposition to bacterial infections</li> </ul>

**Table 2B.** Side effects of common GvHD immunosuppression regimens.

Cyclosporine A and Tacrolimus	
Common	Rare but possibly serious
<ul style="list-style-type: none"> <li>• Headache</li> <li>• Diarrhea</li> <li>• Heartburn</li> <li>• Gas</li> <li>• Increased hair growth on the face, arms, or back</li> <li>• Excessive growth of gum tissue</li> <li>• Acne</li> <li>• Flushing</li> <li>• Uncontrollable shaking of a part of the body</li> <li>• Burning or tingling in the hands, arms, feet, or legs</li> <li>• Muscle or joint pain</li> <li>• Cramps</li> <li>• Pain or pressure in the face</li> <li>• Ear problems</li> <li>• Breast enlargement in men</li> <li>• Depression</li> <li>• Difficulty falling asleep or staying asleep</li> </ul>	<ul style="list-style-type: none"> <li>• Unusual bleeding or bruising</li> <li>• Pale skin</li> <li>• Yellowing of the skin or eyes</li> <li>• Seizures</li> <li>• Loss of consciousness</li> <li>• Changes in behavior or mood</li> <li>• Difficulty controlling body movements</li> <li>• Changes in vision</li> <li>• Confusion</li> <li>• Rash</li> <li>• Purple blotches on the skin</li> <li>• Swelling of the hands, arms, feet, ankles, or lower legs</li> </ul>

Figure 2B continued on next page.

Mycophenolate Mofetil	
Common	Rare but possibly serious
<ul style="list-style-type: none"> <li>• Constipation</li> <li>• Stomach pain or swelling</li> <li>• Nausea</li> <li>• Vomiting</li> <li>• Difficulty falling asleep or staying asleep</li> <li>• Pain, especially in the back, muscles, or joints</li> <li>• Uncontrollable shaking of a part of the body</li> <li>• Headache</li> <li>• Rash</li> </ul>	<ul style="list-style-type: none"> <li>• Diarrhea</li> <li>• Swelling of the hands, arms, feet, ankles, or lower legs</li> <li>• Difficulty breathing</li> <li>• Chest pain</li> <li>• Fast heartbeat</li> <li>• Dizziness</li> <li>• Fainting</li> <li>• Lack of energy</li> <li>• Pale skin</li> <li>• Black and tarry stools</li> <li>• Red blood in stools</li> <li>• Bloody vomit</li> <li>• Vomit that looks like coffee grounds</li> <li>• Yellowing of the skin or eyes</li> </ul>

Prednisone/Methylprednisolone		
Common	Less Common	Rare
<ul style="list-style-type: none"> <li>• Increased appetite</li> <li>• Trouble sleeping</li> <li>• Upset stomach</li> <li>• Excess fluid or swelling in the face, hands, or feet</li> <li>• Weight gain</li> <li>• Slowed wound healing</li> <li>• Increased blood glucose levels</li> </ul>	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Feeling dizzy</li> <li>• Mood swings (shifts between euphoria, anxiety, depression, and others)</li> <li>• Low blood potassium level</li> <li>• Muscle weakness</li> <li>• High blood pressure</li> <li>• Feeling restless</li> <li>• Feeling depressed or anxious</li> <li>• Skin rash</li> <li>• Nausea/vomiting</li> <li>• Hot flashes</li> <li>• Menstrual changes</li> <li>• Sweating</li> <li>• Bone or muscle pain</li> <li>• Increased risk of infection due to suppressed immune system</li> <li>• Fewer and milder symptoms of infection</li> <li>• Skin thinning or bruising easily (with long-term use)</li> <li>• Cataracts (with long-term use)</li> <li>• Glaucoma (with long-term use)</li> <li>• Thinning of bones (osteoporosis) (with long-term use)</li> <li>• Aseptic necrosis of the major joints (hips &gt; knees &gt; shoulders)</li> </ul>	<ul style="list-style-type: none"> <li>• Bleeding or ulcers in the digestive tract</li> <li>• Vision changes</li> <li>• Confusion, losing touch with reality</li> <li>• Change in heart rhythm</li> <li>• Congestive heart failure (can cause shortness of breath or swelling in hands or feet)</li> <li>• Acne (with long-term use)</li> <li>• Thinning hair growth (with long-term use)</li> <li>• Bone fractures (with long-term use)</li> </ul>

GvHD can occur regardless of the prophylactic approach used. The more severe the GvHD (e.g., grade 3-4 disease), the higher the risk of death, mostly due to infection. If GvHD occurs, the mainstay of treatment is methylprednisolone. Other agents successfully used in the management of acute and chronic GvHD include ATG, MMF, and psoralen with ultraviolet light (PUVA). PUVA is *not* recommended for patients with FA, however, as it may be more toxic in this population.

### **Infectious disease prophylaxis**

Infectious complications after alternate-donor HSCT are a major problem for all transplant patients, regardless of FA status, but may pose a greater risk to FA patients due to 1) the unique sensitivity of FA patients to chemoradiotherapy with the resultant breakdown of mucosal barriers after treatment; 2) the extensive prior period of neutropenia; and 3) considerable transfusion exposure prior to HSCT and the resultant exposure to infectious agents.

Prophylactic antibiotic regimens are commonly used after HSCT to reduce the risk of infection. Most patients will be on trimethoprim/sulfamethoxazole (Bactrim or Septra) for 1 year after transplant and other antibacterial and antifungal drugs through day 100, or longer if they develop GvHD.

### **Good to Know**

**Neutropenia:** A condition characterized by abnormally low levels of neutrophils in the blood. Neutrophils are immune cells that fight off bacterial and yeast infections. Therefore, neutropenia can lead to more frequent or severe infections.

**Prophylactic therapy:** Therapy given before symptoms are present, to reduce the patient's risk of developing a certain complication, such as infection or GvHD.

The length of prophylactic therapy to prevent infection depends upon the degree of immunosuppression, the patient's absolute CD4 T-cell level, the development of acute or chronic GvHD, and the patient's prior history of infectious complications.

## The Transplant

### **The pre-transplant work-up**

If a patient with FA appears to be a good candidate for transplant, based on history and physical examination, a number of routine tests should be performed immediately prior to transplant to verify eligibility for transplant and to determine if any adjustments are needed in the treatment. For example, poor kidney function could result in important drug dose adjustments or an anomaly on chest CT might result in additional evaluations, antibiotics, or delay in transplant until resolved. A list of the types of tests performed at most transplant centers is shown in Box 5.

### **The transplant stay**

Most transplant centers will expect the patient to remain near the facility for a minimum of 100 days. While major complications can occur after this period, the first 100 days are considered the highest risk period for the development of immunologic complications (i.e., graft rejection, GvHD, and opportunistic infection) associated with HSCT. During the initial hospitalization for the transplant procedure, all patients are kept in a single occupancy room equipped with a high-efficiency air filtration system to reduce exposure to infectious agents. Once the marrow has recovered sufficiently, patients are allowed out of their hospital rooms unless intervening problems prevent this. After discharge, patients are expected to avoid crowded enclosed spaces and often encouraged to wear masks in an attempt to reduce exposure to viral, bacterial, and fungal pathogens. Specific restrictions and suggestions will vary modestly between different centers.

Patients treated with HLA-matched sibling donor marrow or UCB may be discharged earlier in some cases. Factors that influence the time of discharge include the number of transplant complications such as GvHD and infections, access to a BMT facility closer to the patient's home, the comfort of the referring physician, and evidence of immune recovery. These factors should be discussed on a case-by-case basis.

**Box 5.** Pre-transplant laboratory tests.

- Confirmatory diagnostic testing for FA (DEB or MMC most commonly)
- Confirmatory HLA typing
- Bone marrow aspirate and biopsy with cytogenetic evaluation
- Infectious disease assessments
  - Prior exposures (cytomegalovirus; hepatitis A, B and C; HIV; HTLV1/2; EBV; syphilis)
  - Presence of active infections (CT scan of sinuses, chest, and abdomen; dental evaluation)
- Organ function assessments
  - Lung (pulmonary function tests, oxygen saturation)
  - Heart (EKG, echocardiogram)
  - Liver (liver enzymes, ultrasound)
  - Kidney (chemistries, nuclear medicine studies such as glomerular filtration rate or GFR, ultrasound)

**Late effects of FA and BMT**

All recipients of chemoradiotherapy and allogeneic HSCT are subject to health complications that develop long after the transplant. These are known as “late effects” and they are not necessarily unique to patients with FA (see *Chapter 11*). These effects include late graft failure, recurrent acute and chronic GvHD, and the effects of prolonged steroid therapy such as hypertension (high blood pressure), hyperglycemia (high blood sugar), and aseptic necrosis of bone (loss of bone primarily in the hip, knee, and shoulder joints). Other late effects such as short stature and sterility have not been formally evaluated with respect to the effect of HSCT in patients with FA since these are pre-existing problems in most FA patients. As survival improves for FA patients after HSCT, greater research is now being focused on reducing the risk of late effects, such as malignancy, sterility, or endocrinopathies (hormonal deficiencies), to improve quality of life.

Patients with FA have a high incidence of squamous cell carcinoma (SCC; see *Chapter 14*)<sup>(14,15)</sup>. Some studies suggest that the risk of SCC may be higher after HSCT, although the factors responsible for this relationship remain a topic of debate. Studies suggest that the development of acute or chronic GvHD or the therapy to control GvHD may be the primary risk factor for the subsequent development of SCC, rather than the conditioning therapy or the transplant itself. Because of this association between cancer and GvHD, the use of T-cell depletion of the marrow or peripheral blood, which is recognized as the best approach for reducing GvHD risk, has been incorporated into many protocols. Although there is no proven method of cancer prevention in patients with FA,

recognition of the patient's risk and close monitoring of the head and neck region in particular, via frequent dental and ENT evaluations for example, are important strategies for reducing the morbidity and mortality associated with this late effect (see *Chapters 10 and 14*). The relationship of head and neck cancer with the HPV observed in non-FA adults has inspired the general recommendation that both males and females with FA should receive the HPV vaccine (Gardasil® or Cervarix®).

## Alternatives to HSCT

Recent cloning of the FA genes has provided new insights into the molecular basis of FA, and has unveiled new opportunities to improve the care of FA patients. For example, knowledge of a patient's complementation group or genetic mutation not only allows the physician to predict the course of the patient's disease in some cases <sup>(1)</sup>, but it may also allow for the potential use of gene therapy. Numerous research teams are currently working on the possibility of gene therapy using the patient's own HSC. Thus far, gene therapy has not cured a patient with FA; however, the techniques are being continually optimized and there is hope that this therapy may prove effective in the future (see *Chapter 13*). Most gene therapy protocols would exclude patients who have MDS, leukemia, or those with a high expectation of survival, such as a patient with a 7-8/8 HLA-matched sibling or unrelated donor based on today's outcomes.

Other alternatives are the use of hematopoietic growth factor, such as G-CSF (Neupogen), androgens, or chronic transfusions with iron chelation therapy for patients who receive red blood cells. While transplant is generally recommended as first-line therapy for bone marrow failure, MDS, or leukemia in patients with FA, patients who are considered to be too "high risk" to undergo transplant therapy may be good candidates for an alternative treatment plan. For example, patients with SCC or organ failure might be considered poor candidates for transplant but potential candidates for alternative treatments.

Notably, there has been resurgence in the use of androgens as first-line therapy for FA. In the late 1990s and 2000s, this practice was nearly eliminated because of its side effects and negative impact on transplant outcome in patients with FA. However, some clinicians are considering it as a means to delay or prevent the use of transplant on an investigational basis. The patient and family should discuss the risks and benefits of this approach with the hematologists at a FA comprehensive care center for updates as those studies progress. Additional

approaches that take advantage of new knowledge in FA, such as the effect of aldehydes or the role of various modulators of metabolism or oxidative stress, are also in development. Some are moving into trials now and others may become therapeutic alternatives in the not so distant future.

## Abbreviations and Important Terms

**AA:** *Aplastic anemia.* A condition that occurs when the bone marrow fails to produce the proper amount and type of blood cells. Patients with Fanconi anemia can develop aplastic anemia, but this disorder can occur in other settings as well.

**ANC:** *Absolute neutrophil count.* The number of neutrophils in one microliter of blood. Neutrophils are immune cells that fight off certain infections.

**Antibodies:** Proteins produced by the immune system to attack foreign material—such as bacteria, viruses, or transplants—that the body does not recognize as part of its self.

**Aseptic Necrosis of Bone:** Loss of bone primarily in the hip, knee, and shoulder joints.

**ATG:** *Antithymocyte globulin.* Animal-derived antibodies that attack a patient's immune cells. Treatment with ATG helps prevent the patient's immune system from rejecting the transplanted blood-forming stem cells. ATG is also used as a therapy for aplastic anemia (not Fanconi anemia).

**BMT:** *Bone marrow transplant.* A medical procedure in which a patient's bone marrow is replaced with healthy bone marrow from a suitable donor. In most cases, a patient's bone marrow will be destroyed by medication or radiation therapy before the transplant is performed.

**BU:** *Busulfan.* A drug used to destroy the patient's diseased marrow and treat some forms of leukemia.

**CIBMTR:** *Center for International Blood and Marrow Transplant Research.* An organization that supports research to discover, apply, and improve therapies for bone marrow failure. Read more at <http://www.cibmtr.org>.

**CMV:** *Cytomegalovirus.* A relatively common virus in the herpes family that causes mild symptoms in healthy people, but can pose a serious health risk to immune-compromised individuals.

**CSA:** *Cyclosporine*. A drug that suppresses the immune system after transplant and is used to prevent transplant rejection.

**CY:** *Cyclophosphamide*. A drug used to suppress the immune system before the transplant to prevent rejection of the new blood-forming stem cells, and is also used to treat certain cancers.

**FA:** *Fanconi anemia*. An inherited disease that affects the bone marrow's ability to produce blood cells.

**FLU:** *Fludarabine*. A drug capable of suppressing the immune system before transplant to prevent rejection of the new blood-forming stem cells, and is also used to treat some cancers.

**GvHD:** *Graft-versus-host disease*. This is a relatively common complication that occurs when immune cells in the transplanted material identify the patient as “foreign” and attack the patient's body. It most often involves the skin, gastrointestinal tract, and liver.

**HgB:** *Hemoglobin*. A red blood cell protein that is responsible for transporting oxygen to various parts of the body through the bloodstream.

**HSCT:** *Allogeneic hematopoietic stem cell transplantation*. A medical procedure that destroys the patient's blood and marrow followed by the infusion of bone marrow (as in bone marrow transplant), mobilized peripheral blood stem cells, or umbilical cord blood. All three are sources of hematopoietic (or blood-forming) stem cells.

**HLA:** *Human leukocyte antigen*. A protein found on the surface of all nucleated cells in the body that helps the body determine what is “self” and what is “foreign.” An HLA-matched donor increases the chances that the patient's body will accept the transplant.

**IVF:** *In vitro fertilization*. A treatment for infertility, in which an egg is removed from a woman's ovary and fertilized by one sperm in a laboratory setting. The resultant embryo is then implanted into the woman's uterus.

**“Late Effects”:** Health conditions that manifest more than 100 days after the transplant day.

**MDS:** *Myelodysplastic syndrome*. This is a disease that is diagnosed when the cells of the marrow have an abnormal appearance. Chromosomal abnormalities



are frequently present when this occurs and are often a prelude to full-blown leukemia. This syndrome is commonly thought of as a “preleukemia.”

**MMF:** *Mycophenolate mofetil*. A drug used to suppress the immune system in patients after transplant as a way to prevent graft-versus-host disease.

**MTX:** *Methotrexate*. A drug used to suppress the immune system in patients after transplant as a way to prevent graft-versus-host disease. It can also be used to treat some forms of leukemia and other types of cancer.

**Neutropenia:** A health condition characterized by abnormally low levels of neutrophils in the blood. Neutrophils are immune cells that fight off infections. Therefore, neutropenia can lead to more frequent or severe infections.

**Neutrophils:** A type of white cells that fight off bacterial and yeast infections.

**NMDP:** *National Marrow Donor Program*. This US-based program operates the Be the Match Registry® of volunteer bone marrow, hematopoietic cell, and umbilical cord blood donors.

**Opportunistic Infection:** This type of infection is common in immune-compromised patients who are unable to fight off microbes that do not normally cause disease in humans.

**PGD:** *Preimplantation genetic diagnosis*. A technology for examining the genes of in vitro-derived embryos before they are implanted in a woman’s uterus.

**PLT:** *Platelets*. Disc-like fragments of cells that circulate in the bloodstream and help promote clotting at the site of a cut or injury.

**TBI:** *Total body irradiation*. Treatment delivered in a controlled way to destroy the patient’s immune system and diseased marrow prior to transplantation. It can also be used to treat leukemia and lymphoma that is resistant to chemotherapy.

**T-Cells:** White blood cells that play a key role in the immune response by searching out and destroying material that is considered “foreign.” These cells are also responsible for protecting the patient from viruses and fungal infections.

**UCB:** *Umbilical cord blood or cord blood*. Blood present in the placenta and umbilical cord of an infant after birth. This blood contains high numbers of blood-forming stem cells that can be used in transplants.

## Chapter Committee

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# Chapter 12: Long-Term Follow-Up After Transplantation

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## Good to Know

**Hematopoietic stem cell transplantation**, also called bone marrow transplantation, is performed to treat the blood disorders that often occur in patients with FA.

These disorders may include aplastic anemia (bone marrow failure), myelodysplastic syndrome (improper and insufficient blood cell formation), and a type of cancer known as acute myelogenous leukemia.

## Introduction

Patients with Fanconi anemia (FA) who undergo hematopoietic stem cell transplantation (HSCT) face much brighter prospects today than in years past, thanks to major advances in donor matching, supportive care, treatments that prepare the patient's body for transplantation, procedures that prevent the patient's immune system from rejecting the transplanted cells, and procedures that remove or modify immune cells known as T-cells from the donated bone marrow prior to transplantation.

For patients, a successful transplant is a major milestone. However, it must be thought of as a first step. The next step, known as the continuation phase, is of the utmost importance; it is absolutely critical that the patient receives appropriate and systematic long-term follow-up during this phase.

This chapter will describe the importance of long-term follow-up care, potential adverse effects in patients with FA who have undergone HSCT, and the key elements of a long-term follow-up plan.

### **The Importance of Long-Term Follow-Up Care**

Long-term follow-up of patients with FA is *essential*. It must be thought of as an indispensable part of the patient's routine medical care. Failure to complete long-term follow-up may lead to complications that potentially could have been avoided.

Guidelines for the long-term care of survivors of childhood cancer have been developed by the Children's Oncology Group (*available at:* <http://www.survivorshipguidelines.org>). In addition, the European Group for Blood and Marrow Transplantation (EBMT), the Center for International Blood and Marrow Transplant Research (CIBMTR), and the American Society of Blood and Marrow Transplantation (ASBMT) recently developed joint recommendations (*available at:* <http://www.nature.com/bmt/journal/v37/n3/pdf/1705243a.pdf>) which include suggested screening and preventive practices for adult survivors of HSCT. Many of these recommendations also apply to patients with FA who have undergone HSCT.

The long-term follow-up for patients with FA is considerably more complex than the long-term follow-up for patients with acquired illnesses. Patients with FA require lifelong care for FA and other potential complications caused by FA-associated blood disorders (e.g., aplastic anemia, myelodysplastic syndrome, and leukemia), HSCT, or treatments received prior to HSCT. All of these conditions can cause adverse effects (Table 1) that may negatively impact the patient's physical and mental health, quality of life, growth, development, education, and employment. Therefore, the development of long-term adverse effects must be assessed on an ongoing basis <sup>(1-10)</sup>.

**Table 1.** Possible long-term adverse effects and their causes in patients with FA.

Organ or system affected	Adverse effects	Causes
General	Short stature	FA
	Primary or secondary malignancies	FA, HSCT, GvHD
Skin	Pigmentation	FA, GvHD
	Dryness	FA, GvHD
	Thickening	FA, GvHD
Central nervous system	Side effects of radiation	HSCT
Eyes	Cataracts	HSCT
	Extremely dry eyes (Sicca, or Sjögren's, syndrome)	GvHD
	Retinitis	HSCT
Ears, nose, and throat	Chronic sinusitis	GvHD
	Hearing loss	FA
	Extremely dry mouth (Sicca, or Sjögren's, syndrome)	GvHD
Heart	Congenital anomalies	FA
	Iron overload	FA treatment
Lungs	Side effects of HSCT	GvHD
Liver	Chronic liver disease (transaminitis or cholestasis)	HSCT, GvHD
	Iron overload	FA treatment
Kidneys and genitourinary system	Congenital anomalies	FA
	Chronic renal insufficiency	HSCT
GI tract	Congenital anomalies	FA
	Failure to thrive	FA, GvHD
Endocrine	Diabetes	FA
	Hypothyroidism	FA, HSCT
Gonadal	Masculinization	FA treatment
	Infertility	FA, HSCT
	Early menopause	FA, HSCT
Musculoskeletal	Hand and arm anomalies	FA
	Hip dysplasia	FA
Psychological	Psychosocial issues	FA, HSCT

*Abbreviations:* Fanconi anemia, FA; hematopoietic stem cell transplantation, HSCT; graft-versus-host disease, GvHD

## Practical Considerations for Long-Term Follow-Up Care

Long-term follow-up care must be led by one specific physician who has experience with both FA and HSCT, such as the **transplant physician** or the **primary hematologist**. The overall long-term follow-up care can be performed with the help of the patient's local physicians and subspecialists if those clinicians have experience with FA and HSCT. The patient's medical team should work in close collaboration to provide comprehensive care. The involvement of multiple types of care providers in the care of patients with FA introduces the risk that medications prescribed by one physician might adversely interact with those prescribed by another. Therefore, it is essential that all subspecialists communicate with the primary physician, usually the hematologist/oncologist, to coordinate care.

Long-term follow-up care of patients with FA who have undergone transplantation should strive to:

- **Identify existing adverse effects**, and treat them efficiently to prevent further complications. For example, it is important to diagnose hemochromatosis (iron overload), which can lead to chronic liver disease if left untreated.
- **Proactively screen for adverse effects** so that if they develop, they can be diagnosed early and treated accordingly. In particular, screening for primary or secondary cancers is of the utmost importance.
- **Prevent the development of adverse effects** that may result in additional complications. For example, patients should be counseled to avoid sun exposure, because it could result in malignancies.

The long-term follow-up plan should include the following elements:

### Regular check-ups

- Assess patient's history since the previous visit
- Assess the adverse effects of FA or HSCT on the patient's organs and systems
- Perform a physical examination, with close attention to the adverse effects of FA and HSCT

**Evaluation of growth and development** <sup>(11,12)</sup>

- Assess the patient's height and weight; measure growth hormone levels and refer to a growth specialist if needed
- Perform a neuropsychological evaluation; suggest interventions if needed

**Evaluation of skin**

- Evaluate nevi (birthmarks and moles) and screen for skin cancers yearly
- A HSCT specialist should perform testing to rule out graft-versus-host disease (GvHD) if needed

**Neurological and psychological evaluations** <sup>(13)</sup>

- Perform a neuropsychological evaluation
- Perform a psychological evaluation to screen for psychosocial issues related to living with a chronic disease, late effects of androgen therapy, and post-traumatic stress syndrome

**Ophthalmologic (eye) evaluation** <sup>(14,15)</sup>

- Screen for cataracts
- Screen for Sicca, or Sjögren's, syndrome (extremely dry eyes, caused by GvHD) and keratoconjunctivitis (inflammation of the eyes)
- Evaluate the patient's vision

**Evaluation of ears, nose, and throat** <sup>(16,17)</sup>

- Screen for hearing loss after HSCT
- Screen for FA-associated neurosensory hearing loss
- Screen for Sicca, or Sjögren's, syndrome (extremely dry mouth, caused by GvHD)
- A head and neck specialist should screen for head and neck malignancies (every 6 months)
- Perform testing to rule out chronic sinusitis

**Dental exam** <sup>(18)</sup>

- Screen the oral cavity carefully every 6 months (see *Chapter 10*)

**Cardiac (heart) evaluation** <sup>(19)</sup>

- Evaluate FA-associated anomalies
- Screen for late effects of radiation or chemotherapy by electrocardiogram (EKG) and echocardiogram



**Pulmonary (lung) evaluation** <sup>(20, 21)</sup>

- Test pulmonary function to rule out obstructive or restrictive disease
- Screen for late effects of radiation or chemotherapy
- Screen for bronchiolitis obliterans with organizing pneumonia (BOOP)

**Gastrointestinal and nutrition evaluation**

- Monitor nutrition, food intake, and weight gain
- Perform testing to rule out FA-associated failure to thrive
- Perform testing to rule out chronic GvHD

**Hepatic (liver) evaluation** <sup>(22)</sup>

- Screen for overall FA-associated anomalies, including chronic transaminitis
- Screen for anomalies associated with treatment of FA (after androgen therapy has ceased), including transaminitis
- Screen for iron overload by measuring ferritin levels; perform T2\*MRI (magnetic resonance imaging) if needed
- Screen for chronic cholestasis and chronic GvHD
- Evaluate need for liver biopsy

**Renal (kidney) evaluation**

- Assess overall kidney function
- Screen for late effects of chemotherapy and radiation therapy

**Genitourinary evaluation**

- Follow-up of congenital renal or genitourinary anomalies with a urologist
- Yearly gynecologic evaluation for females, including Pap smear (the recommendations for Pap smear have changed for individuals in the general, non-FA population, raising questions about the right frequency for either post-HSCT or FA patients)
- HPV (human papillomavirus) vaccination

**Evaluation of endocrine system and metabolism** <sup>(23-27)</sup>

- Screen for FA- and/or HSCT-associated anomalies
- Screen for hypothyroidism and thyroid malignancies
- Screen for growth hormone deficiency (if the patient has a short stature)
- Screen for diabetes, including tests for insulin resistance and glucose intolerance
- Screen for dyslipidemia
- Screen for osteoporosis and osteopenia
- Screen for avascular necrosis
- Test for vitamin D deficiency and biochemical rickets (abnormal labs without signs)

**Gonadal evaluation** <sup>(28, 29)</sup>

- Monitor pubertal development
- For male patients: measure levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone; evaluate sperm; prescribe hormonal replacement therapy as needed
- For female patients: measure levels of FSH, LH and estradiol; prescribe hormonal replacement therapy as needed
- Counsel about sex and pregnancy

**Musculoskeletal evaluation**

- Follow-up of FA-associated congenital anomalies
- Evaluation of scoliosis (curvature of the spine)
- Screening for contractures (tightening of muscle, tendon, ligaments, or skin that prevents movement) associated with chronic GvHD

**Hematology (blood) evaluation** <sup>(4)</sup>

- Evaluate complete blood count
- Evaluate bone marrow
- Chimerism testing (to evaluate the success of HSCT): This test measures the percent of donor versus host cells in the blood or the bone marrow
- Assess iron and ferritin levels; if needed, perform T2\*MRI for more precise iron level; discuss treatment recommendations

**Immunology evaluation** <sup>(4, 30)</sup>

- Monitor the restoration of immune function, including assessments of the phenotype (observable characteristics) and function of T- and B-cells (cells involved in innate and acquired immunity)
- Administer immunizations
- Assess titers and response to vaccines
- Revaccinate for high-risk infections, including pneumococcus, *Haemophilus influenzae* type B (HIB), meningococcus, and influenza
- Vaccinate with HPV vaccine in patients older than 9 years; revaccinate patients after HSCT
- Revaccinate for other infectious diseases, such as tetanus and diphtheria

**Malignancy surveillance** <sup>(31)</sup>

- Perform strict lifelong surveillance for cancers of the oropharynx, anogenital area, and skin, with close attention to patients with mutations in the *BRCA2* gene (which can increase the risk for multiple secondary cancers) and patients with GvHD

**Quality of life evaluation** <sup>(32, 33)</sup>

- Counsel patients about the need to adopt a healthy diet; get regular exercise; avoid alcohol, smoking, and second-hand smoke; limit sun exposure; and use sunscreen
- Perform neuropsychological and psychological evaluations and counseling as needed for patients and their families

A guideline for the long-term follow-up of patients with FA is outlined in Table 2. It outlines the evaluations that patients with FA should receive starting at least 1 year after transplant, and is intended as a general guide for physicians; care must be tailored to each individual patient with FA.

**Table 2.** Long-term follow-up evaluations for post transplant patients with FA.

	1 year	2 year	3 year	4 year	5 year	Yearly
Regular check-ups, including patient history and physical exam	X	X	X	X	X	X
<b>HEMATOLOGY</b>						
Complete blood counts	X	X	X	X	X	X
Bone marrow aspiration Chimerism testing Cytogenetics studies	X	X	X			
Measure levels of ferritin and iron Perform T2*MRI if ferritin levels are high	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	
<b>IMMUNOLOGY</b>						
Assess immune phenotype and function	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal			
Measure levels of immunoglobulins G, A, and M	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	
Administer immunizations (including HPV vaccine)	X	As per schedule				Administer boosters as needed
<b>CARDIAC</b>						
Measure fasting lipid profile (levels of total cholesterol, LDL, HDL, and triglycerides)	X	Repeat if previous test was abnormal	X	Repeat if previous test was abnormal	X	Repeat if previous test was abnormal
EKG	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	X	Repeat if previous test was abnormal
Echocardiogram	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	X	Repeat if previous test was abnormal

	1 year	2 year	3 year	4 year	5 year	Yearly
<b>PULMONARY</b>						
Perform pulmonary function testing to rule out obstructive or restrictive disease	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	X	
<b>HEPATIC</b>						
Measure liver function panel	X	X	X	X	X	X
If liver function panel values are high: Perform MRI Evaluate the need for liver biopsy	Only if previous test was abnormal					
Measure levels of ferritin and iron Perform T2*MRI if ferritin levels are high	X	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	
<b>RENAL</b>						
Measure levels of electrolytes, BUN, and creatinine in the urine	X	X	X	X	X	X
Perform urinalysis	X		X		X	
<b>ENDOCRINE and METABOLISM</b>						
Perform an oral glucose tolerance test (OGTT)	X	X	X	X	X	X
Measure levels of TSH and FT4	X	X	X	X	X	X
Measure levels of FSH and LH in patients younger than 10 years Measure estradiol levels in female patients older than 10 years Measure testosterone levels in male patients older than 11 years	X	X	X	X	X	As needed
Measure levels of IGF-1 and IGFBP3 in patients younger than 18 years	X	X	X	X	X	

Table 2 continued on next page.

	1 year	2 year	3 year	4 year	5 year	Yearly
Measure levels of 25-OH vitamin D and calcium	X	X	X	X	X	X
Assess bone age in patients between the ages of 5 and 18 years	X	X	X	X	X	
DXA scan (with adjustment for height; see <i>Chapter 7</i> )	X	As needed	As needed	As needed	As needed	As needed
<b>GROWTH and DEVELOPMENT</b>						
Plot patient's height and weight on a growth chart	X	X	X	X	X	X
Neuropsychological evaluation	X	As needed	As needed	As needed	As needed	
<b>HEAD and NECK</b>						
Ophthalmology evaluation	X	As needed	As needed	X	X	As needed
Screen for head and neck cancers (performed by a head and neck specialist)	Every 6 months	Every 6 months	Every 6 months	Every 6 months	Every 6 months	Every 6 months
Hearing evaluation	X		As needed		As needed	
Biannual dental evaluations	Every 6 months	Every 6 months	Every 6 months	Every 6 months	Every 6 months	Every 6 months
<b>GYNECOLOGIC</b>						
General gynecologic evaluation and cancer screening in female patients older than 13 years	X	X	X	X	X	X
<b>DERMATOLOGY</b>						
Evaluate nevi (birthmarks and moles) and check for skin cancers	X	X	X	X	X	X

*Abbreviations:* Magnetic resonance imaging, MRI; human papillomavirus, HPV; low-density lipoprotein, LDL; high-density lipoprotein, HDL; electrocardiogram, EKG; blood urea nitrogen, BUN; thyroid-stimulating hormone, TSH; free thyroxine, FT4; follicle-stimulating hormone, FSH; luteinizing hormone, LH; insulin-like growth factor, IGF-1; IGF-binding protein, IGFBP3; 25-hydroxy-vitamin D, 25-OH vitamin D; dual X-ray absorptiometry, DXA

## Conclusions

Long-term follow-up care is essential in patients with FA who have undergone HSCT. Failure to complete long-term follow-up may lead to avoidable complications. One specific physician who has experience with both FA and HSCT must lead the long-term follow-up. Follow-up care can be performed with the help of the patient's local physicians and subspecialists if those individuals have experience with FA and HSCT.

## Chapter Committee

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# Chapter 13: Novel Stem Cell Treatment Options

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## Introduction

Physicians have made remarkable progress in hematopoietic stem cell transplantation over the last decade, and patients with Fanconi anemia (FA) who need transplantation now have access to dramatically improved care. Some patients with FA, however, have a difficult time with transplantation, fare poorly during or after the procedure, do not have a medical reason for transplantation, or do not wish to pursue this treatment option. This chapter explores emerging therapies that can translate into better care for those patients.

We will describe three of the most promising therapies in this realm: *gene therapy*, *stem cell therapy*, and a combination thereof known as *stem cell gene therapy*<sup>(1)</sup>. With the objective of moving stem cell gene therapy into clinical trials for individuals with FA, and with support from the Fanconi Anemia Research Fund and Fanconi Hope Charitable Trust, the International FA Gene Therapy Working Group was established in 2010<sup>(2,3)</sup>. Through the power of global collaboration, this group encourages the world's top experts in FA to design gene therapy trials that follow a consistent protocol so that the findings can be easily accessed, shared, compared, and expanded on by FA researchers around the globe.

### Good to Know

**Hematopoietic stem cells** are rare blood cells found in the bone marrow and umbilical cord. These cells are unique because they have the potential to develop into any of the various types of blood cells found in the body.

Doctors can harvest and store a patient's **hematopoietic stem cells** before radiation or chemotherapy, or these cells can be obtained from a human donor. A medical procedure called **hematopoietic stem cell transplantation** transfers stored or donated cells to a patient's body.

## Gene Therapy

### Gene therapy vectors

Delivering a gene into a cell is not a simple matter. There are many barriers to successful gene transfer: moving the genetic material into the cell, evading the cell's defenses, moving the genetic material through the shell of the nucleus, and finally prodding it to integrate into the cell's own genetic code, or genome. To overcome these challenges, researchers have used viruses as so-called “vectors” to deliver genetic material into cells. Viruses naturally have their own means of delivering genes into cells—after all, this is how viruses cause illnesses such as the common cold. Researchers have simply borrowed these properties to insert genes of interest into the patient's cellular genome.

Researchers have traditionally used the gamma retroviral vector in gene therapy studies, although new and improved lentiviral vectors boast the advantage of being able to transduce non-dividing cells. Small DNA viruses known as pyroviruses—the adenovirus and adeno-associated virus, for example—have also been carefully studied in preclinical gene therapy testing. Among these pyroviruses, adenoviruses are considered advantageous because they deliver the gene into the cell without causing the virus to integrate into the cellular genome. The disadvantage of adenoviruses, however, is that they are more likely than other viruses to elicit an immune response in the recipient <sup>(4)</sup>.

When some of the patient's cells are removed from the body so that this genetic manipulation can take place in a laboratory, the procedure is known as *ex vivo* (Latin for “outside the living”) gene therapy. Conversely, when a viral vector containing the healthy gene is injected directly into the patient, the procedure is known as *in vivo* (Latin for “within the living”) gene therapy.

### Good to Know

**Gene therapy** allows physicians to “correct” a patient's genetic information, or DNA, by replacing a disease-associated gene with a healthy version of the gene.

Since the 1970s, researchers have searched for safe and effective ways to correct disease-related genes in human cells. Researchers are currently testing gene therapies for FA in clinical trials, and hope to bring these therapies to market in the years to come.

### Methods of gene therapy

There are two main methods of gene therapy: **gene replacement** and **gene editing**. In gene replacement, a gene of interest is inserted at an almost random location in the patient's genome. This method predictably causes non-physiological regulation of the delivered gene in its new location, or the inadvertent functional disruption of other genes near the insertion site<sup>(5-7)</sup>. Gene editing, on the other hand, takes advantage of the genome's natural ability to repair itself through a process called homologous recombination, in which the faulty gene is corrected at its original locus without the insertion of new material. Gene editing does not typically result in gene dysregulation, and no other region of the genome is likely to be affected<sup>(8,9)</sup>.

### Side effects of gene therapy

The most noteworthy side effect of gene therapy is insertional mutagenesis—an accidental mutation caused by inserting new DNA. This is an unavoidable side effect of gene replacement. Since 2000, more than 70 people—mostly with fatal genetic disorders—have undergone autologous transplantation, in which the patients' own cells were removed and treated with viral vectors carrying a therapeutic gene, then transferred back to their bodies. This gene correction strategy relied on the ability to deliver a functional gene along with other related elements needed to promote sustained, high-level gene expression. The drawbacks of this approach included loss of physiological regulation of the treated gene, and disruption and possible dysregulation of other genes. In one clinical trial, the therapeutic gene was inserted near, and inadvertently activated, a gene that causes cancer, resulting in leukemia in 5 of 20 individuals with severe combined immune deficiency (SCID). Four of the 5 children with leukemia were successfully treated; 1 died. Even with this unfortunate event, the overall outcome of the trial provided evidence that gene therapy is equivalent or superior to the previous standard of care (hematopoietic cell transplantation), providing superior immune function, improved disease-free survival, and a better quality of life<sup>(5,6,10,11)</sup>.

It is important to note that the effects of insertional mutagenesis may vary from patient to patient. It can take a long time for side effects to occur, as demonstrated by the gene therapy trials performed to date. Furthermore, in patients with FA, the bone marrow cells used for gene correction are few in number, extraordinarily intolerant of ex vivo manipulations, and are already at risk of accumulating pre-leukemic mutations, the impact of which can be increased by gene correction. FA cells are constantly in danger of becoming

genetically unstable and triggering the development of leukemia and other cancers. Correcting the gene in a FA cell that has already accumulated some of the mutations needed for cancer progression could have adverse effects by keeping alive cells that might otherwise have been eliminated from the body. This can, in principle, evolve into full-blown leukemia <sup>(37)</sup>.

## Stem Cell Therapy

### Stem cell therapy vectors

Traditionally, stem cell therapy has entailed the use of **bone marrow cells**; this method has been experimentally and clinically proven in many thousands of successful bone marrow transplants over the last 50 years. Hematopoietic stem cell transplant remains the prototype of cellular therapy and a testament to the consistently remarkable fact that stem cells can be transferred from a donor to a recipient, and that they can reconstitute a fully functional lymphohematopoietic system—a system that produces the body’s white blood cells, red blood cells and platelets—from relatively few starting cells <sup>(12-19)</sup>.

While **embryonic stem cells** provide an opportunity to understand more deeply how stem cells work, their use remains controversial and various biological and legal constraints prevent their therapeutic use.

More relevant to clinical care are **induced pluripotent stem cells**, which are embryonic stem cell-like cells from the skin or blood of adults that have been engineered with the potential to develop into any other type of cell in the body. Induced pluripotent stem cells have become a popular tool for the investigation of tissue formation in health and disease, early stages of cell development, and drug intervention strategies, all of which are relevant to the biology and treatment of FA <sup>(20-24)</sup>.

### Good to Know

**Pluripotent stem cells** are cells capable of developing into almost any type of cell in the body. Stem cells can be found in embryos, in umbilical cord blood, and in the blood and bone marrow of adults.

Through a procedure called **stem cell therapy**, physicians introduce new, healthy stem cells into a patient’s body to help replace, repair, or regenerate diseased tissues.

**Hematopoietic stem cell transplantation** usually uses stem cells from the bone marrow or umbilical cord blood of a matched donor.

**Stromal stem cells**, also known as mesenchymal stromal cells, are non-hematopoietic (non-blood-producing) cells of the bone marrow and other organs in the body. These cells are thought to be located in the walls of the blood vessels and to perform key functions, such as supporting hematopoietic stem cells in the bone marrow and modulating the immune response. These useful properties of stromal stem cells have been harnessed clinically in the therapy of graft-versus-host disease (GvHD) <sup>(25)</sup>.

### Methods of stem cell therapy

There are at least two methods of cell therapy: **traditional hematopoietic stem cell transplantation** and **immunomodulation**. Traditional hematopoietic stem cell transplantation involves replacing the entire blood-producing system of the recipient patient with that of a healthy donor. Immunomodulation, on the other hand, involves modifying the patient's immune response. An example of immunomodulation would be the use of mesenchymal stromal cells to support bone marrow engraftment or to treat steroid-resistant GvHD disease.

### Good to Know

**Graft-versus-host disease** occurs when immune cells in the transplanted tissue attack the patient's own cells. This disease is often treated with steroids to suppress the immune response.

Stem cells, for example mesenchymal stromal cells, can also play a role in tissue repair and healing after injury. This is especially relevant in the setting of bone marrow transplant, particularly in healing tissue damage from chemotherapy and treating immune reactions such as GvHD. Patients with FA have defects in the body's DNA repair system, which cause their injuries to be amplified after transplantation. Mesenchymal stromal cells are known to home to the site of injury and therefore, in principle, may provide an especially appealing modality for FA patients who receive transplants <sup>(25)</sup>.

### Side effects of stem cell therapy

The most notable side effect of stem cell therapy is tumorigenesis, or the uncontrolled growth of stem cells, which can give rise to benign or malignant tumors. Most cancers are thought to originate from so-called "cancer stem cells," which are in many ways similar to normally functioning stem cells in their cellular processes and metabolic pathways. Because of this, some donor stem cells potentially can cause malignancies in the patient; indeed, donor-

derived leukemias have been reported in some recipients of hematopoietic cell transplantation. Multiple researchers have observed this phenomenon in animal models when mesenchymal stromal cells were transplanted from one organism to another and gave rise to cancers <sup>(26)</sup>.

In theory, additional side effects are possible because of the specific functions of stem cells. For example, immunomodulation by mesenchymal stromal cells can suppress the immune system of the transplant recipient, which can reactivate latent infections—especially DNA viral infections—or favor tumor growth and create an environment conducive to leukemia.

## Stem Cell Gene Therapy

An effective gene therapy strategy must target the cell type relevant to the specific disease. In most instances, the effects of gene correction are enhanced by the corrected cells' ability to reproduce and repopulate the body in meaningful numbers. For this reason, many gene therapies have attempted to deliver genes to stem cells. It seems only logical that the parallel tracks of gene therapy and stem cell therapy should be joined in one concerted effort termed “**stem cell gene therapy**.” This effort aims to correct the gene in the stem cells of the recipient *ex vivo* and then return the corrected cells to the patient.

Challenges specific to FA can be viewed as opportunities in the context of stem cell gene therapy. For example, deficits in DNA repair make FA stem cells more sensitive than their healthy, or wild-type, counterparts. This sensitivity can be manipulated to the advantage of the patient by using low-dose chemotherapy to selectively eliminate uncorrected cells *in vivo* in a patient with FA who has received a mixture of cells that are either corrected or not corrected.

For reasons mentioned above, the leading strategy for gene therapy represents a shift away from **gene addition**, in which an entirely new gene is pasted into the genome with the help of viruses or transposons, and a move toward **genome editing**, whereby the pathogenic mutation is corrected in its natural gene location with the aid of newly engineered molecules called zinc-finger nucleases, transcription activator-like effector nucleases, or homing endonucleases. These hybrid molecules are engineered to target a specific location in the genome, where they introduce a break in the strand of DNA near the targeted mutation. The break in the DNA is then resolved by homologous recombination between the endogenous genes and an exogenously introduced



fragment from the donor containing the healthy genetic sequence. In this fashion, the pathogenic mutation is permanently changed to the normal sequence. This process also preserves the architecture of the genome and maintains control of the gene by the cell's normal regulatory elements.

One of the advantages of gene editing is its spectacular flexibility and range of use; it can be used for targeted delivery, tissue-specific regulatory sequences, or transduction of cell types committed to tissue-specific differentiation programs. Gene therapy can even be designed to treat diseases that are limited to specific sites in the body, such as for the prevention of head and neck cancers in patients with FA.

The great early promise of stem cell gene therapy comes—as with many advances in medicine—with some risk. Although this risk might be deemed unacceptable to a healthy person, individuals and families who are already living with the perils of a disorder like FA may be willing to accept the risk of emerging therapies when balanced with their potential benefits.

### **Stem cell gene therapy trials in FA**

The first clinical trials of stem cell gene therapy for FA used retroviruses to deliver the *FANCA* or *FANCC* genes. Viral transduction, however, resulted in transient or no correction of hematopoietic cells, an observation consistent with only short-term functional gene complementation<sup>(27-30)</sup>.

Since 2010, the International FA Gene Therapy Working Group has focused on developing a translational platform that can deliver clinically meaningful benefits to individuals with FA. Members of the Working Group share the common goal of accelerating the transition of gene therapy research into clinical trials that follow a consistent protocol so that the findings can be shared among FA researchers around the globe. The current FA stem cell gene therapy platform entails the following: the *FANCA* gene is delivered by a third-generation lentiviral vector pseudotyped with vesicular stomatitis virus, and short viral transduction is achieved without prolonged prestimulation with growth factors. Individuals with a human leukocyte antigen-matched sibling donor, an abnormal karyotype, or a serious infection are not eligible for the trial<sup>(3,31,32)</sup>.

The first FA lentiviral gene therapy trial, led by Dr. Pamela S. Becker (University of Washington, Seattle) and Dr. Hans-Peter Kiem (University of Washington/Fred Hutchinson Cancer Research Center, Seattle), has been

approved by the U.S. Food and Drug Administration (FDA) and was open for enrollment at the time of publication (NCT01331018; *available at*: <http://clinicaltrials.gov>). This trial incorporates the updated transduction procedures and a relatively brief overnight incubation of cells in low oxygen in the presence of a reducing agent. Dr. Juan Bueren (CIEMAT, Madrid, Spain) and his team have opened a hematopoietic stem cell mobilization trial and plan to have the *FANCA* gene therapy trial opened for accrual in 2014. Preparations are under way to open a second U.S.-based trial in Indianapolis (Dr. Helmut Hanenberg and colleagues).

## Challenges Ahead

The ultimate goal of our effort in stem cell gene therapy for FA is to cure bone marrow failure and leukemia safely by preventing unintended effects on surrounding genes and by fine-tuning the expression of FA genes. In addition to the procedures mentioned above, the vector design and treatment of the cells may greatly reduce the risk to the patient. This will likely require the use of genetic components such as weak promoters, strong insulators, and strong polyadenylation sequences to isolate the functions of the inserted genes from the genome and that of the genome from the inserted genes.

A new gene therapy tool involves the use of microRNAs (miRNAs), short segments of ribonucleic acid that bind to and turn off specific products of the genetic code (i.e., transcribed genes, known as RNA transcripts). MicroRNAs are extremely important because they allow researchers to target gene expression accurately in the desired cell population and to avoid cells that should not be targeted by the gene therapy vector, such as antigen-presenting cells that might trigger an undesirable immune response to the vector<sup>(33)</sup>.

As mentioned above, most future efforts will likely focus on combined modalities and attempt to minimize oxidative stress in these cells. For example, a combination of stem cell expansion, correction of hematopoietic stem cells and mesenchymal stromal cells from the same patient, and co-infusion of these cells may provide an ideal environment for engraftment of the gene-corrected hematopoietic stem cells<sup>(34-36)</sup>.

## Summary

Gene therapy, stem cell therapy, and stem cell gene therapy are powerful tools that will improve care for FA patients. Several steps must be taken to achieve this goal. The first step involves the coordination of clinical trials so that individual research centers can pool their collective knowledge and statistical power. The second step involves focusing on a common goal, such as the development of treatments that can be rapidly translated to clinics around the world. The third step involves implementing real-time data exchanges and allowing for the evaluation of these data on the basis of scientific merit. Through these actions, FA researchers can expedite the clinical impacts of basic and clinical gene therapy research.

The field of gene therapy started with a visionary and a daring idea, but suffered from a dearth of preclinical data. The first clinical trials were permitted only because of the high risks of living with such challenging genetic diseases and the risks and incomplete efficacy of alternative therapies such as hematopoietic cell therapy. Through the years, the field of gene therapy has overcome several crises at the collision of public expectations and unintended side effects, and has emerged as an acceptable therapy in the treatment of several genetic disorders.

There is abundant room for optimism that the same outcome will be possible for the treatment of FA. Without doubt, the collective knowledge and unique enthusiasm of FA researchers and clinicians will provide a winning combination of ideas and well-designed experiments that will translate into improved care for people with FA.

## Chapter Committee

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# Chapter 14: Head and Neck Cancers in Patients with Fanconi Anemia

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## Introduction

Head and neck cancers are significantly more common in patients with Fanconi anemia (FA) than in the general population. Although the tumors in patients with FA have a similar microscopic appearance to those in patients without FA, the frequency, distribution, and clinical course differ and must be taken into account when considering cancer management in patients with FA.

### Head and Neck Cancer in the General Population

Head and neck cancer encompasses a wide variety of tumors that typically begin in the squamous cells that line the moist, mucosal surfaces of the oral cavity, nasal cavity, pharynx (throat), and larynx (voice box). These tumors are often referred to as head and neck squamous cell carcinomas (HNSCC). Approximately 30,000 individuals are diagnosed with head and neck cancer in the United States annually, and about 30% of patients with head and neck cancer succumb to their disease. Increasingly, HNSCC is an international health problem, representing the fifth most common cancer type and cause of cancer-related death worldwide <sup>(1)</sup>.

### Good to Know

A **second primary cancer** refers to the presence of an additional, unrelated cancer in someone who was previously diagnosed with another type of cancer.

The vast majority of HNSCC cases (more than 90%) develop following exposure to carcinogens, including tobacco and alcohol <sup>(2,3)</sup>, betel nut (which is commonly chewed in parts of Southeast Asia for its stimulating effects) <sup>(4)</sup>, and sexually transmitted viral pathogens such as human papillomavirus (HPV) <sup>(5)</sup>. Head and neck cancers are prototypic tobacco-related cancers, and the initial risk for the development of cancer and the subsequent risk for the development of second

primary cancers is directly attributable to the duration and intensity of tobacco exposure. Tobacco-related cancers can also occur in non-smokers as a result of secondhand (environmental) smoke exposure. Chronic consumption of alcohol is estimated to increase the risk for HNSCC by 2- to 3-fold in a dose-dependent manner. Moreover, individuals who use both tobacco and alcohol have up to 10-20 times higher risk for HNSCC than people who do not use tobacco or alcohol. Approximately 5% of HNSCC develop in individuals who do not smoke or consume alcohol. Emerging evidence suggests that HPV may play a role in the development of head and neck cancers, with HPV detected in more than 70-80% of cases of oropharyngeal cancer, which develops in the part of the throat that includes the tonsils and base of the tongue<sup>(22)</sup>. Unfortunately, the incidence of oropharyngeal cancer is increasing worldwide.

The incidence of HNSCC varies by geographic region. Southeast Asia has the highest incidence of carcinomas of the oral cavity and oropharynx due to the practice of chewing tobacco containing the betel nut. High rates of oral cancer are also reported in Brazil. The rates of laryngeal and hypopharyngeal cancer, which develops in the bottom part of the throat, are significantly elevated in Italy, France, and Spain due to the high prevalence of alcohol and tobacco use in those countries. Nasopharyngeal carcinoma frequently occurs in southern China and populations residing in nations that skirt the Mediterranean region, possibly due to infection with Epstein-Barr virus (EBV) and/or dietary habits. Because a detailed review of head and neck cancer is not feasible in this chapter, we recommend consulting reference textbooks<sup>(22 and 23)</sup>.

### **Head and Neck Cancer in Patients with FA**

By far, HNSCC is the most common solid tumor in patients with FA. The incidence of HNSCC in patients with FA is 500- to 700-fold higher than in the general population<sup>(6,7,8,9)</sup>. Approximately 1 in 7 (or about 14%) of patients with FA who survive to the age of 40 will be diagnosed with HNSCC during their lifetimes<sup>(10)</sup>. Some cases of FA remain undiagnosed until the appearance of head and neck cancer. Therefore, FA testing should be considered in patients younger than age 40 who develop HNSCC, especially if they have atypical findings such as borderline anemia or an atypical response to cytotoxic treatment.

Compared with the general population, the age of onset, distribution, and course of HNSCC is significantly different in patients with FA. Patients with FA tend to be diagnosed with HNSCC between the ages of 20-40, whereas individuals in the general population tend to be diagnosed between the ages



of 50-60. Patients with FA also have a higher proportion of HNSCC in the oral cavity, the vast majority of which involve the tongue, compared with the general population. Furthermore, a much higher proportion of HNSCC in patients with FA is diagnosed in advanced stages compared with the general population. Despite aggressive treatment, the outcome of HNSCC in patients with FA is significantly poorer than that in the general population. Moreover, even after cure of the primary HNSCC, patients with FA are more likely to develop second primary cancers than the general population (more than 60% vs. ~30%, respectively). The anatomic distribution of second primary cancer is also significantly different in patients with FA compared with the general population. Whereas patients with HNSCC in the general population tend to develop second primary cancers in the lung and esophagus, patients with FA develop second primary cancers in the genitourinary tract and skin. Interestingly, the pattern of second primary cancers in patients with FA resembles that observed in HPV-associated HNSCC in the general population <sup>(11)</sup>.

### **Prevention of Head and Neck Cancer**

Patients with FA have the highest risk for HNSCC amongst all patients with inherited genetic syndromes (e.g., Li-Fraumeni syndrome, Bloom's syndrome). Unlike individuals with an inherited mutation in the retinoblastoma gene (*RB*), nearly all of whom develop tumors of the retina, not all patients with FA develop HNSCC. Like the association between radiation exposure and the development of high-grade sarcomas in patients with an inherited *RB* mutation, a co-factor(s) is likely required for FA patients to develop HNSCC. The precise cause(s) of and co-factor(s) for the increased risk of HNSCC in patients with FA have yet to be defined. The type of FA mutation and severity of manifestations have not been clearly associated with the development of HNSCC. One study <sup>(24)</sup> suggests that bone marrow transplantation increases the risk for HNSCC development in patients with FA, and primarily attributed the increased risk to the development of acute and/or chronic graft-versus-host disease (GvHD). An association between GvHD and HNSCC has also been suggested in patients without FA <sup>(12)</sup>. Tobacco and alcohol consumption are less commonly reported in patients with FA than in the general population, but remain major risk factors for the development of HNSCC in patients with FA. Most studies support a role for HPV in gynecological malignancies, but its precise contributions to HNSCC in patients with FA remain controversial. Some studies <sup>(25,26)</sup> suggest that HPV may be a major contributor to HNSCC development in patients with FA, whereas other studies <sup>(27,28)</sup> dispute these

results. Laboratory studies show that mutations in genes that cause FA increase susceptibility to HPV-induced carcinogenesis<sup>(29, 30)</sup>. Overall, the scientific literature suggests that multiple factors contribute to the development of HNSCC in patients with FA, although the precise contributions of individual factors remain to be defined. The following measures should be considered to minimize the risk of HNSCC:

- ***Abstaining from alcohol and tobacco.*** The causal link between tobacco and alcohol exposure and the development of HNSCC is well-established. Relatively few patients with FA admit to tobacco and/or alcohol use, but this is likely an underestimation of the actual prevalence of tobacco and/or alcohol use in this population. The use of tobacco and tobacco products should be discouraged categorically, including exposure to secondhand smoke. While it is best to abstain from alcohol use, individuals who consume alcohol should restrict their intake to no more than one drink equivalent per month. The chronic use of alcohol-containing mouthwashes should also be discouraged.
- ***Maintenance of oral hygiene.*** Although the evidence is not yet conclusive, several reports suggest that poor oral hygiene and chronic, repeated trauma may promote the development of HNSCC. Therefore, maintenance of proper oral hygiene and routine dental evaluations are recommended. This subject is discussed in detail in *Chapter 10*.
- ***HPV vaccination.*** While there is controversy about the role of HPV in the development of HNSCC in patients with FA, most studies agree that HPV is associated with the development of anogenital cancers as well as non-cancerous conditions such as genital warts. Therefore, all patients with FA should consider HPV vaccination. The timing of vaccination and the need for boosters remains to be defined. In general, HPV is typically transmitted by direct sexual contact; therefore, HPV vaccination is routinely recommended for preteen girls and boys in the general population who have not yet undergone puberty. Both HNSCC and genitourinary tract cancers have been reported in pre-pubertal and sexually inactive patients with FA. Given these factors, patients with FA may need to undergo HPV vaccination at an earlier age than the general population.

Other factors that are associated with the development of HNSCC in the general population include marijuana use and sexual transmission of HPV infection. Therefore, patients with FA should abstain from marijuana use and practice safe sex, including the use of condoms. The use of oral appliances,

braces, and dental X-rays do not need to be restricted in patients with FA given the lack of evidence to suggest a causal association with HNSCC (for more information, see *Chapter 10*).

## Surveillance of Head and Neck Cancer

The high incidence of HNSCC combined with the poor outcome of advanced-stage disease in patients with FA underscores the need for HNSCC surveillance. Surveillance should begin at age 10, which is based on literature reports of the earliest age at diagnosis with head and neck cancer.

### Selection of a medical care provider

The oral cavity of individuals with FA often contains multiple lesions. Distinguishing suspicious lesions from those that are non-cancerous requires the input of a health care provider with significant experience in the evaluation and management of head and neck cancer. Appropriate professionals may have dental, oral surgery, otolaryngology, or general surgery backgrounds supplemented with specialized training in head and neck cancer. Routine oral cancer screening by a general dentist can supplement but should not replace HNSCC screening by an experienced professional.

### Components of examination

The sites at risk for development of HNSCC include all areas of the upper aerodigestive tract. Therefore, all mucosal surfaces of the head and neck region need to be examined thoroughly. The oral cavity, the most common site for HNSCC in patients with FA, and the proximal oropharynx (the back of the tongue) can be effectively evaluated through the mouth by visualization and palpation. Examination of the distal oropharynx (the back of the throat), nasopharynx (the uppermost part of the throat, between the nasal cavity and the soft palate), larynx, and hypopharynx (the bottommost part of the throat) requires the use of either a transoral mirror or a flexible fiberoptic laryngoscope. Although patients with FA have a higher rate of squamous cell carcinomas in the cervical esophagus (the uppermost part of the esophagus) than the general population, the routine use of esophagoscopy (visual examination of the esophagus using an esophagoscope) for screening is not advocated. Symptom-based evaluation for esophageal cancer needs to be considered. Any patient with odynophagia (painful swallowing), dysphagia (difficulty swallowing), or other localizing symptoms merits evaluation with a barium swallow study and/or esophagoscopy.

## Good to Know

A **margin** refers to the amount of normal-appearing tissue surrounding the tumor when it is surgically removed. A positive margin indicates the presence of tumor cells near the edge of the tissue, which suggests that the cancer has not been completely removed.

A **free flap** refers to the transplant of a piece of tissue from one site of the body to another for the reconstruction of a defect.

The **extent or severity of HNSCC** is classified according to the TNM staging system, based on the size and configuration of the primary tumor (T), whether the cancer has spread to nearby lymph nodes (N), and whether the cancer has spread, or metastasized (M), to other parts of the body. For example, **N0** describes a cancer that has not spread to nearby lymph nodes, whereas **N1** indicates lymph node involvement.

The values for T, N, and M are then combined to assign an **overall stage** to the cancer. For most cancers, the stage is a Roman numeral from I to IV, where higher numerals represent more extensive disease.

**Optimized medically** means that a doctor has chosen the best treatment for a patient depending on his or her individual circumstances.

### Frequency of screening

Patients with FA should begin undergoing screening for HNSCC at age 10. A qualified professional should perform a thorough head and neck examination every 6 months. If suspicious lesions are identified, they should be biopsied; further management should be dictated by the results from microscopic evaluation of the tissue. Once a premalignant or malignant lesion has been identified and appropriately treated, the frequency of surveillance examinations should be increased to once every 2-3 months. In patients successfully treated for HNSCC, an annual chest X-ray should be included as part of the screening processes to assess for distant metastasis.

### Approach to biopsy

The oral cavities of patients with FA often have leukoplakia-like lesions (white or gray patches). Many of these lesions often grow bigger and then become smaller, but those that persist or progress require further attention. An experienced examiner should be able to distinguish lesions that need to be biopsied from those that can simply be followed over time. A brush biopsy may be used for screening, but a tissue biopsy is recommended to establish a definitive diagnosis.

## Treatment of Head and Neck Cancer in Patients with FA

Surgery, radiation, and chemotherapy—either alone or in combination—are used to treat HNSCC in the general population. As a general rule, early-stage disease is treated with either surgery or radiation therapy, whereas advanced-stage disease requires combination therapy with surgery followed by radiation with or without chemotherapy or concomitant treatment with chemoradiation therapy. While all of these approaches can be used in the general population, significant negative aftereffects limit the use of chemotherapy and radiation therapy in patients with FA. Therefore, several modifications are required in the management of HNSCC in patients with FA.

### Treatment team

Optimal treatment of HNSCC requires a treatment team that includes not only the **surgeon (cancer and reconstructive specialists), radiation oncologist, and medical oncologist**, but also specialized **dentists, oral surgeons, speech and language pathologists, nurses**, as well as many other professionals. This team should work in close collaboration with other FA specialists to provide comprehensive care. The involvement of multiple types of care providers in the care of patients with FA introduces the risk that medications prescribed by one physician might adversely interact with those prescribed by another. Therefore, it is essential that all subspecialists communicate with the primary physician, usually the hematologist/oncologist, to coordinate care.

### Treatment approach

The following factors complicate the management of HNSCC in patients with FA:

- The tumors of patients with FA tend to be very aggressive and are often present in advanced stages.
- The healthy, non-cancerous cells of patients with FA are highly sensitive to treatments that crosslink DNA, such as the chemotherapeutic drug cisplatin and external beam radiation—two mainstays of HNSCC treatment for the general population.
- HNSCC cells in patients with FA are not as sensitive as non-cancerous cells to DNA-crosslinking agents. Therefore, HNSCC in patients with FA do not respond to sub-therapeutic doses of radiation. Thus, surgery is the preferred therapeutic modality in patients with FA.

## **Surgery**

In contrast to the other treatment modalities, surgical therapy for HNSCC in patients with FA is reasonably well tolerated. Patients with FA exhibit no significant increase in the incidence of complications following surgical therapy, including wound infections or long-term negative side effects associated with surgical scarring. Accordingly, the consensus opinion is that surgical therapy should be considered the primary curative modality in all patients with FA who develop head and neck cancer.

A successful outcome following head and neck surgery requires a multidisciplinary preoperative assessment and optimization of the patient, intraoperative management, and postoperative care. To minimize the risks associated with surgery, patients with FA should be optimized medically by a hematologist who is experienced in the management of patients with FA. Depending on the extent of surgery and the anticipated outcomes, a pain management specialist and a psychiatrist should be consulted prior to surgery to help the patient cope with any negative aftereffects.

Surgery for HNSCC in patients with FA should follow the same parameters that have been established for the general population. In general, a wide complete excision of the primary tumor should be performed with adequate margins. Management of the neck also follows principles established for the management of HNSCC in the general population. The exact type and extent of surgical resection should be dictated by the primary site, size, and the extent of the tumor. In general, tumors of the oral cavity and pharynx should be excised with at least 1-cm margins. The margins for laryngeal tumors need not be as comprehensive, due to the unique anatomy of the larynx.

Reconstruction of the primary site defect should follow the guidelines established for reconstruction in patients with HNSCC in the general population, and should not be limited based on the presence of FA. Therefore, the use of free flaps for reconstruction should be considered as indicated, without restriction. In general, cancers that are classified clinically as N0 disease with high risk for occult metastasis or small volume N1 disease may be managed with a selective neck dissection, whereas modified neck dissection or even radical neck dissection may be required for more advanced disease. The specific details of surgical management are discussed elsewhere<sup>(22, 32)</sup>.

## **Radiation therapy**

Radiation treatment is associated with severe negative aftereffects in patients with FA, and many patients cannot complete a full course of radiation. The risk

of dying from the negative aftereffects of radiation is as high as 50%. Death may be due to local effects, but systemic effects such as bone marrow failure are also major contributors. Those who survive radiation treatment face severe side effects, including xerostomia (dry mouth syndrome), dysphagia (difficulty swallowing), esophageal stenosis (narrowing of the esophagus), laryngeal edema (swelling of the larynx), and wound breakdown. Therefore, radiation therapy should only be used in patients for whom it is absolutely required for disease control. If radiation therapy is to be utilized, patients must be optimized medically and monitored closely for signs for severe toxicity. Aggressive pretreatment optimization, combined with aggressive monitoring and early intervention can allow patients with FA to complete a full course of radiation treatment. It is important to keep in mind that tumor cells in patients with FA do not have increased susceptibility to the effects of radiation (unlike the tumor cells in most individuals in the general population). Therefore, if treatment with radiation is contemplated, it should be planned for the same doses used in the management of patients without FA.

### **Chemotherapy in patients without FA**

Systemic therapy is an integral component of the management for locally advanced and recurrent/metastatic HNSCC in patients without FA. In patients with resected HNSCC, cisplatin (100 mg/m<sup>2</sup> intravenously once every 21 days) administered concurrently with post-operative radiation therapy has been demonstrated to improve locoregional control and overall survival in randomized studies<sup>(13,14)</sup>. A pooled analysis of two phase III clinical trials demonstrated that patients with positive margins and/or extracapsular nodal spread (spread of the tumor beyond the lymph node) benefited the most from the addition of chemotherapy to post-operative radiation therapy<sup>(15)</sup>. Based on these results, treatment guidelines currently recommend adjuvant cisplatin-based concurrent chemoradiation therapy for patients with these high-risk adverse features.

In patients with stage III to IVB disease who are treated non-surgically with curative intent, the integration of platinum-based chemotherapy concurrently with radiation therapy has been demonstrated to improve locoregional control and overall survival in prospective clinical trials and meta-analysis, compared with radiation therapy alone. These studies demonstrated an absolute 5-year survival benefit of approximately 6.5%<sup>(16,17)</sup>. As a result, concurrent platinum-based chemoradiation therapy has become a standard option for non-surgical management of locally advanced HNSCC. However, the addition of cytotoxic

chemotherapy to radiation therapy has been associated with an increased incidence of adverse events, including mucositis (inflammation of the mucous membranes), dermatitis (inflammation of the skin), skin toxicities, and the need for feeding tube placement <sup>(16)</sup>.

Cetuximab (Erbix) is a monoclonal antibody that inhibits the epidermal growth factor receptor (EGFR) and is used for the treatment of patients with locally advanced HNSCC. Erbitux has been shown to improve locoregional control and survival when added to definitive radiation therapy in patients with oropharyngeal, laryngeal, and hypopharyngeal tumors in a randomized phase III trial <sup>(18)</sup>. Based on these results, Erbitux has been approved by regulatory agencies throughout the world to be used in this setting. Erbitux has a more favorable side effect profile than cytotoxic chemotherapy. Clinically relevant Erbitux-induced adverse events include skin rash, hypomagnesemia (abnormally low blood magnesium levels), grade 3-5 hypersensitivity reaction (in approximately 3% patients), and a small increase in the incidence of radiotherapy-induced mucositis. Blood toxicity is not usually observed with Erbitux/radiation therapy. Concurrent Erbitux and radiation therapy has not been directly compared to concurrent cisplatin and radiation therapy in large randomized studies. Studies evaluating the role of Erbitux in the post-operative setting are ongoing.

For patients with recurrent/metastatic disease, the cornerstone of treatment is systemic therapy with single agents (cisplatin, taxanes, 5-fluorouracil, or methotrexate), or platinum-based doublet regimens (the combination of a platinum-based drug with other chemotherapy agents) to ease pain. Erbitux has activity as single agent, and has also been shown to improve survival when added to first-line platinum/5-fluorouracil in a randomized phase III trial <sup>(19)</sup>.

### **Chemotherapy in patients with FA**

The use of chemotherapy—particularly DNA-damaging agents—in patients with FA is challenging, especially as it pertains to bone marrow failure and increased risk for normal tissue injury. The issue is further complicated by the lack of prospective trials, or even large retrospective series evaluating the safety and efficacy of cytotoxic agents in this patient population. Table 1 summarizes the published experience with the use of cytotoxic chemotherapy in patients with FA for treatment of multiple tumor types (the majority of which are HNSCC). Notwithstanding possible publication bias, the limited data demonstrate that standard doses and schedules of chemotherapy do not seem to be feasible in patients with FA. Furthermore, cytotoxic chemotherapy



at both standard and low doses is associated with severe, and in many cases fatal, toxicities and poor treatment outcomes. Kutler et al. recently updated one of the largest retrospective series of HNSCC in patients with FA ever reported. Of the 25 patients included in this report, 3 were treated with chemoradiation (cisplatin/carboplatin) at some point during the course of the disease; all 3 of the patients exposed to cytotoxic chemotherapy developed severe complications, including cytopenia and severe mucositis<sup>(20)</sup>. In addition, 2 patients underwent therapy with targeted chemotherapy (Erbix) after developing non-resectable recurrence of their primary cancer; both tolerated Erbix well, but died of recurrent disease.

The use of biologic agents in patients with FA is an attractive alternative to cytotoxic chemotherapy, given the more favorable side effect profile of biologic agents. Nonetheless, Erbix the only targeted agent approved for HNSCC) has only been used anecdotally in patients with FA. One recent case report describes the use of concurrent Erbix and radiation therapy for the management of a recurrent squamous cell carcinoma of the tongue. The patient was able to complete 8 out of 10 planned doses of the biologic agent; however, the dose had to be reduced to 200 mg/m<sup>2</sup>/week after the patient developed neutropenia (a toxicity not usually seen in non-FA patients) following the initial loading dose of 400 mg/m<sup>2</sup>. The patient also developed grade 3 dermatitis (following 50 Gy of radiation therapy), mucositis (following 45 Gy of radiation therapy), and cholestasis, but all were clinically manageable. Unfortunately, the patient developed a rapid recurrence of HNSCC after completion of treatment and died with the disease<sup>(21)</sup>. Taken together, the data indicate a significant risk of complications in patients with FA receiving cytotoxic agents alone or in combination with radiation therapy.

Cytotoxic chemotherapy serves only as an adjunct to the cornerstone treatment—adequate surgery and/or radiation therapy—for patients without FA who have locally advanced disease. In patients with FA, the highest chance for long-term disease-free survival is achieved with adequate surgery (and/or possibly radiation therapy, as discussed elsewhere in this chapter). Because of the high incidence of complications related to cytotoxic agents in patients with FA, the risks of integrating cytotoxic chemotherapy to the treatment regimen outweigh the potential benefits in most situations. Therefore, the use of cytotoxic agents in patients with FA who have locally advanced or recurrent/metastatic head and neck cancers is strongly discouraged. For selected cases in which chemotherapy and/or biologic therapy are to be considered, it is recommended that treatment is delivered in centers with extensive experience managing head and neck cancers and FA.

**Table 1.** Cytotoxic chemotherapy in patients with Fanconi anemia.

Tumor type	N	Chemotherapy	Cycles	Outcome
SCC tonsil <sup>33</sup>	1 ¶	Cisplatin (40 mg/m2)	X1	Fatal myelotoxicity
SCC hypopharynx <sup>34</sup>	1 ¶	Cisplatin (100 mg/m2)	X1	Fatal myelotoxicity
SCC esophagus <sup>35</sup>	1 ‡	<ul style="list-style-type: none"> <li>• Cisplatin (33 mg/m2)</li> <li>• 5-FU (1000 mg/m2)</li> </ul>	X1	<ul style="list-style-type: none"> <li>• Severe diarrhea and myelotoxicity</li> <li>• Partial response allowing surgery</li> </ul>
SCC tongue <sup>36</sup>	1 ‡	<ul style="list-style-type: none"> <li>• Cisplatin (8 mg)</li> <li>• 5-FU (60 mg)</li> </ul>	X1	<ul style="list-style-type: none"> <li>• Severe toxicity</li> <li>• No tumor response</li> </ul>
SCC lung <sup>37</sup>	1 ‡	<ul style="list-style-type: none"> <li>• Carboplatin (AUC 3 d1)</li> <li>• Gemcitabine (1250 mg/m2 d1,8)</li> </ul>	X2	<ul style="list-style-type: none"> <li>• Pneumonitis</li> <li>• Partial response allowing surgery</li> </ul>
SCC head and neck <sup>10</sup>	3 (2 ¶ + 1 ‡)	N/A	N/A	All died with disease
SCC vulva <sup>38</sup>	1 ¶	Cisplatin (40 mg/m2)	X1	Fatal fungal sepsis

Chemotherapy was given as a single modality (‡) or concurrently with radiation therapy (¶).

*Abbreviations:* AUC, area under the curve; N, number of patients treated with chemotherapy in each report; N/A, not available; SCC, squamous cell carcinomas.

### Rehabilitation and lifestyle modification

The treatment of HNSCC can be debilitating. Rehabilitation should be initiated as needed, to optimize the patient’s functional, psychological, and vocational outcomes. The negative aftereffects of surgical tumor removal on speech and swallowing require intervention by physical and rehabilitation specialists (e.g., neck and shoulder exercises, speech and swallowing therapy, etc.). In addition, paralyzed vocal cords and stricture or obstruction of the pharynx also require intervention. Cosmetic restoration of the face is crucial to psychological rehabilitation. Following radiation therapy, patients may require management of xerostomia (dry mouth syndrome), dental care, and prevention of fibrosis-related complications such as trismus (reduced opening of the mouth due to spasm of the jaw muscles). Patients should be placed on long-term care specifically with respect to dental management. Monitoring of dentition should be maintained, and prevention measures for caries initiated, including the use of fluoride treatments in all patients. Following chemotherapy, patients may require management of kidney function, hearing, and damage to peripheral nerves.

## Conclusions

Patients with FA have an increased risk for developing aggressive head and neck cancer, especially of the oral cavity. Until new therapeutic and preventative measures are available, strict abstinence from tobacco and alcohol, avoidance of second-hand smoke, maintenance of oral hygiene, and aggressive routine screening are the most immediate ways to reduce the development and morbidity of head and neck cancer in patients with FA. Early and frequent head and neck examinations, including careful oral cavity evaluations and flexible fiberoptic laryngoscopy, are important surveillance measures. Appropriate surgical resection remains the mainstay of treatment for patients with FA, because radiation and chemotherapy are poorly tolerated. If radiation and chemotherapy are required for advanced tumors, they should be used with caution and by physicians who have experience in identifying, preventing, and treating associated complications.

## Chapter Committee

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# Chapter 15: Non-Head and Neck Solid Tumors in Patients with Fanconi Anemia

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## Introduction

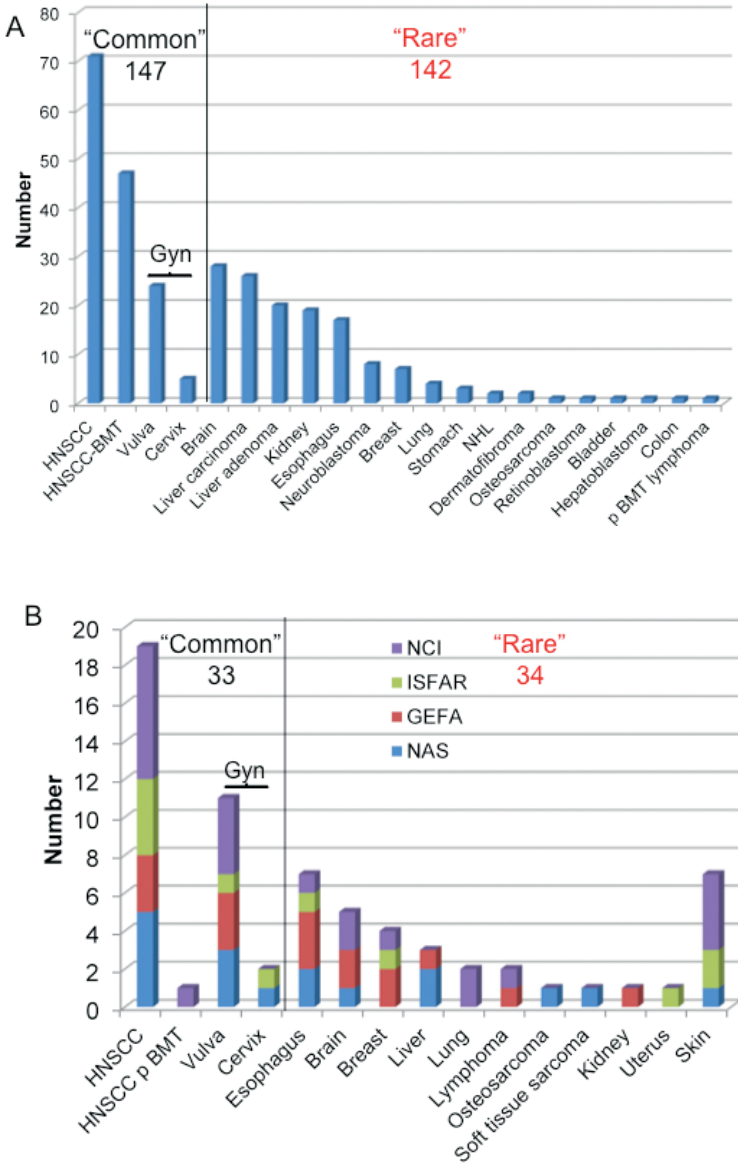
Cancer is a major concern in FA patients. This chapter will describe the most common types of non-head and neck solid tumors in patients with FA, the incidence and risk of developing these tumors, and the influences of age and genetic predisposition on cancer diagnosis. Specifically, cancer types and risks have been determined from case reports and case series in the literature from 1927 through 2012 (Figure 1A), and from follow-up of four cohorts in the US, Germany, and Israel, published from 2003 through 2010 (Figure 1B) <sup>(1-5)</sup>. This chapter will focus on solid tumors, and compare the numbers, ages, and observed/expected risk ratios [adjusted for age, sex, and birth cohort, compared with data from SEER <sup>(6)</sup>] of the more “common” solid tumors with those solid tumors that are considered to be “rare,” in order to provide perspective.

## Types of Solid Tumors

According to case series and case reports, the most common types of solid tumors that occur in patients with FA include head and neck squamous cell carcinomas, as well as gynecologic cancers (primarily vulvar and cervical cancers). These are discussed in *Chapter 14* and *Chapter 6*, respectively. The following types of solid tumors occur less frequently than head and neck cancers and gynecologic cancers in patients with FA:

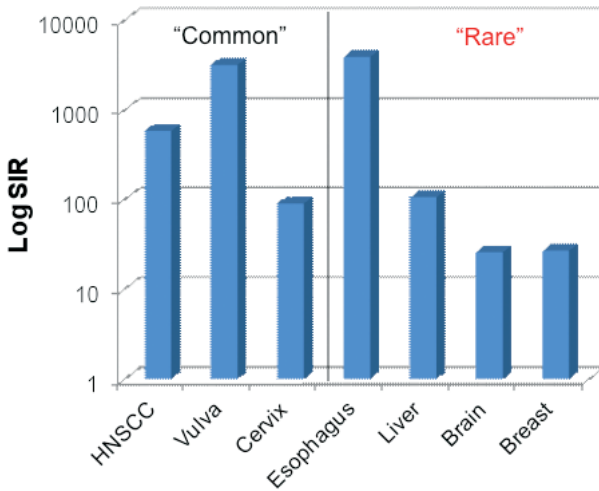
- *Liver carcinomas (sometimes called “hepatocellular”)*
- *Liver adenomas (these tumors are considered to be benign, but are not always clearly diagnosed until a biopsy has been performed)*
- *Brain tumors*
- *Kidney tumors (frequently of a type known as Wilms’ tumor)*
- *Esophageal tumors*
- *Neuroblastomas (tumors that develop from nerve tissue)*
- *Breast tumors*

**Figure 1.** Number of solid tumors in patients with FA. A) 289 solid tumors reported in 2,250 literature case reports and series, from 1927 to 2012. 147 were “common” and 142 were “rare”. Adapted from Shimamura and Alter<sup>(1)</sup>. B) 67 solid tumors reported in 459 patients in 4 cohort studies conducted by the National Cancer Institute (NCI), the Israeli Fanconi Anemia Registry (ISFAR), the German Fanconi Anemia Registry (GEFA), and the North American Survey (NAS)<sup>(2-5)</sup>.





**Figure 2.** Ratio of observed to expected cancers in FA cohorts. The standardized incidence ratio (SIR) compares the observed numbers of cases to those expected from the US national cancer statistics (called SEER, for Surveillance, Epidemiology, and End Results), after adjustment for age, sex, and birth cohort. The SIR data are plotted on a logarithmic scale, because the values range from 10 to more than 1000.



A few additional types of solid tumors have been reported in only 2 to 4 patients with FA:

- Lung tumors
- Stomach tumors
- Lymphomas (tumors that originate from the lymph nodes)
- Dermatofibromas (benign tumors that form on the skin)
- Osteosarcomas (tumors that form in the bones)
- Retinoblastomas (tumors that form in the retina of the eye)
- Bladder cancer
- Hepatoblastomas (tumors that form in the liver)
- Colon cancer

Some patients with FA develop multiple cancers. Of the 2,250 patients described in case series and case reports, 31 patients had 2 or 3 different types of solid tumors, and 22 patients had 1 or more solid tumors in addition to acute myelogenous leukemia (AML) <sup>(1)</sup>.

## Incidence and Risk of Solid Tumors

Approximately 1 out of every 10 patients with FA in case reports, case series, and cohort studies had a solid tumor. However, this statistic does not take age into account. Combined data from the four cohort studies of patients with FA indicate that a solid tumor of any type is a major adverse outcome in FA: One estimate suggests that approximately 1 out of every 4 patients with FA will develop a solid tumor by the age of 45<sup>(2-5)</sup>, and the theoretical risk in patients with normal bone marrow increases to nearly 3 out every 4 patients, since these patients will live long enough to develop a cancer<sup>(2)</sup>. Therefore, solid tumors may be increasingly diagnosed in patients with FA as more patients survive hematopoietic stem cell transplantation (HSCT) and as mild cases of FA, such as patients with hematologic mosaicism (i.e., patients in whom a bone marrow stem cell has undergone a genetic event leading to correction of one of the mutated genes), are recognized more often<sup>(5,9)</sup>.

The most frequent solid tumors in patients with FA appear to be squamous cell carcinomas of the head and neck, and gynecologic cancers. However, the *relative risk* of developing several types of rare cancers is very high. Therefore, patients with FA should be monitored closely for the development of any solid tumor.

Standardized incidence ratios (SIRs) based on the incidences of cancer observed in cohort studies of patients with FA and those expected for the general population<sup>(6)</sup> (after accounting for age and sex) reveal that the “rare” cancers of the esophagus and liver occur with high risks in the FA population. These tumors, as well as brain and breast, are extremely infrequent in the non-FA population, and thus have high ratios of observed to expected, or SIR (Figure 2).

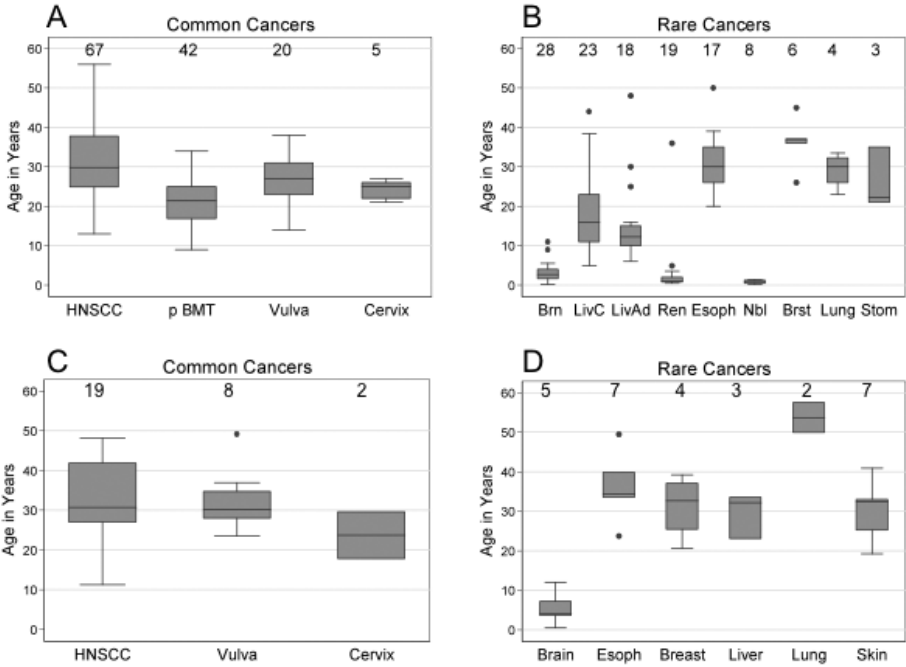
## Age at Cancer Diagnosis

Most of the solid tumors in patients with FA that have been reported occurred when the patient was age 20 or older, although liver tumors were reported in teenage patients with FA and are perhaps related to the use of androgens for bone marrow failure. In addition, neuroblastomas and tumors of the brain and kidney were reported in children below age 10, and were found primarily in patients carrying mutations in both copies of the *FANCD1/BRCA2* gene<sup>(7)</sup>. Cancers of the esophagus, breast, lung, and stomach were reported in patients with FA starting at age 20 (Figure 3A and B). Case series and case reports

suggest that patients with FA who have undergone HSCT tend to develop head and neck squamous cell carcinoma starting in teenage years, whereas patients who have not received a transplant tend to develop head and neck squamous cell carcinoma starting at around age 20. In approximately 35% of the cancer cases reported in patients with FA, the diagnosis of solid tumors or AML preceded the diagnosis of FA; therefore, physicians may sometimes fail to recognize patients with undiagnosed FA who have cancer as their first manifestation<sup>(8,9)</sup>.

As shown in Figure 1B, the types of cancers reported in cohort studies of patients with FA are very similar to those reported in the literature in case series and case reports: Head and neck squamous cell carcinomas and gynecologic cancers are the most common, followed by cancers of the esophagus, brain, breast, and liver. In addition, cohort studies revealed that brain tumors occurred primarily in patients with mutations in the *FANCD1/BRCA2* gene. Of the 459 patients participating in the cohort studies, 15 had multiple cancers. Of these 15 patients, 12 had 2 or 3 solid tumors, and 3 patients had a solid tumor and AML. The ages at diagnosis of cancer were also similar in the case series and case reports and cohort studies: Most of the common and rare solid tumors occurred between the ages of 20 to 40, brain tumors developed at age 10 or younger, and lung cancer occurred after age 40 (Figure 3C and D).

**Figure 3.** Age at cancer diagnosis in patients with FA. A and B, literature case series and case reports. C and D, cohort studies. X-axis abbreviations: HNSCC, head and neck squamous cell carcinoma; p BMT, after bone marrow transplant; Brn, brain; LivC, liver carcinoma; LivAd, liver adenoma; Ren, renal; Esoph, esophagus; Nbl, neuroblastoma; Brst, breast; Stom, stomach. The numbers above the boxes indicate how many cases are in each box. The line in the box is the median, the ends of the lines are the minimum and maximum values, the bottom and top of the boxes mark the first and third quartiles, and the dots above the lines are statistical outliers. Figure shown on next page.



## Genes and Cancer

Recent studies suggest that patients with FA who have mutations in both copies of the *FANCD1/BRCA2* gene have highly predictable patterns of tumor development <sup>(7,10)</sup>. Among 27 patients with mutations in this gene, 2 had no cancer, 19 had 1 cancer, 3 had 2, and 3 had 3 cancers. There were a total of 34 cancers: 12 brain tumors, 10 AML, 7 Wilms’ tumors, 4 acute lymphoblastic leukemia (ALL), and 1 neuroblastoma (Table 1). Five out of 6 patients with at least one copy of a mutation known as the IVS7 variant (either +2T>G or +1G>A) developed AML, whereas only 5 out of 21 patients with other mutations developed AML. Brain tumors were found in 3 out of 3 patients with the 6174delT mutation, 4 out of 4 patients with the 886delGT mutation, as well as 1 patient with both mutations. Two of 19 patients with other mutations also developed brain tumors. A specific mutation was not clearly identified for the 7 patients with Wilms’ tumors.

**Table 1.** Number of cancers in patients with mutations in both FANCD1/BRCA2 genes.\*

	Brain	AML	ALL	Wilms	Neuroblastoma
Total	12	10	4	7	1
As 1st Cancer	8	8	3	6	0
As 2nd Cancer	3	2	0	0	1
As 3rd Cancer	1	0	1	1	0
Median age in years at cancer diagnosis (range)	3.3 (1.3-9)	2 (0.9-6.3)	5.1 (4.9-10)	1 (0.5-6.6)	1.1

\*Adapted from Alter et al. (7)

Abbreviations: Acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL)

## Future Challenges

Although the prognosis for people with FA is better than ever, many challenges remain. Future research should strive to improve strategies for cancer screening and prevention, particularly for cancers to which patients with FA are vulnerable. Avoiding tobacco and alcohol, combined with good oral hygiene, can help mitigate some environmental carcinogens, but these strategies alone are clearly not sufficient to prevent cancers in patients with FA. The vaccines against the human papillomavirus (HPV) that are currently available are prophylactic rather than therapeutic, and while they may help to prevent new cases of gynecologic squamous cell carcinomas, these vaccines may not reduce the incidence of head and neck squamous cell carcinoma, particularly of the oral cavity<sup>(11)</sup>. Screening methods and case management strategies that address the DNA repair defect in patients with FA may help to improve the treatment and prevention of cancer in these patients, but remain open research questions. As the number of patients with defined genotypes and mutations increases, the prognostic value of gene-cancer associations will improve, which may ultimately lead to earlier targeted screening and directed interventions.

*Editor's note:* Screening guidelines for organ-site specific cancers are discussed in previous chapters, including *Chapter 14* (head and neck squamous cell carcinoma) and *Chapter 6* (gynecologic cancers). In addition, *Chapter 20* provides a comprehensive list of all screening recommendations for individuals with FA.

## Chapter Committee

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# Chapter 16: The Adult Patient with FA

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## Introduction

### Good to Know

Fanconi anemia researchers in countries around the world have established programs to collect information about people with FA. This information helps researchers learn more about the condition's diagnosis, natural history, prognosis, treatment, and cancer rates.

The International Fanconi Anemia Registry (**IFAR**), the North American Survey (**NAS**), and the German Fanconi Anemia Registry (**GEFA**) are among these programs.

Thanks to a variety of factors, including increased recognition of disease diversity, greatly increased scientific understanding of Fanconi anemia (FA), improved transplant results, better supportive care options, and early detection, approximately 80% of patients with FA will survive beyond 18 years of age <sup>(1)</sup>. The median survival of all patients with FA is now greater than 30 years [previously estimated to be 33 in 2010 <sup>(2)</sup>], but it should be cautioned that patients with mutations in *FANCD1/BRCA2* have much lower median survivals. As a result, adults ( $\geq 18$  years of age) represent an ever-increasing proportion of the FA population. Fanconi anemia is no longer an exclusive childhood illness, and diagnosis and treatment are no longer exclusively performed by pediatricians.

The major healthcare issues of the adult FA population have been described and discussed in database reports by the International FA Registry (IFAR), the National Institutes of Health (NIH)-based North American Survey (NAS), and the German FA Registry (GEFA) <sup>(3)(4)(5)(6)</sup>. However, the adult subpopulation has not been studied as a group in prospective studies published to date. Many major health issues are unique to this subpopulation of patients with FA and are just beginning to be recognized and evaluated.

This chapter will introduce the three general subgroups of adult patients with FA and describe the following concerns relevant to the adult population:

- *Solid tumors*
- *Bone marrow transplant (BMT)*
- *Gynecologic and fertility issues*
- *Transition from pediatric- to adult-oriented care*
- *Psychosocial issues*

In addition, a list of resources for adults with FA can be found at the end of this chapter.

## Subgroups of Adult Patients with FA

There are three general subgroups of adult patients with FA. These groups have both common and divergent concerns, and often require different strategies for management and follow-up.

### Group 1: Adult patients with FA who were diagnosed in childhood and were not transplanted

#### Good to Know

**Iron overload** is a condition that occurs when excess iron accumulates in a person's organs and tissues. Excess iron can be removed from the body through a process known as **chelation**.

**Note:** For **post-transplant** patients, phlebotomy may also be used to treat iron overload.

This population is becoming smaller due to increased success of bone marrow transplantation. Although a few of these patients have not developed bone marrow failure or hematologic malignancies—and may not do so in their lifetime—all of these patients require scheduled hematologic evaluations. Patients in Group 1 who develop bone marrow failure as adults may require treatment and/or transfusions, along with frequent evaluation for the development of hematologic malignancies. They may also be at risk for iron overload and need chelation, or they may be chronically chelated and require management of chelation side effects. Importantly, with the recent advances in matched sibling and unrelated donor transplants, transplantation remains



an option for many of these adult patients. Patients and clinicians should have ongoing conversations about the potential need for a transplant in the future; these conversations should be informed by the most current transplant results and supplemented by continuing education and counseling. All adult patients with FA, including those in Group 1, are at high risk for the development of solid tumors and require aggressive surveillance by ENT and gynecology specialists. Clinicians should emphasize the need for patients to become educated about this risk.

### **Group 2: Adult patients with FA who were diagnosed in childhood and are transplant survivors**

This population is increasing in number because of the increased success of transplantation. The major issues facing this population are the follow-up and treatment of short- and long-term transplant complications, such as the treatment of chronic graft-versus-host disease (GvHD). These patients face a relatively small risk of hematologic relapse, for which they require continued hematologic evaluation. They also require aggressive surveillance for solid tumors and, in fact, may develop these tumors at a younger age than non-transplanted patients <sup>(7)</sup>. Patients with chronic GvHD of the oral mucosa are at especially high risk for the development of head and neck cancers.

### **Group 3: Adult patients with FA who are diagnosed in adulthood**

#### **Good to Know**

**Cytogenetics** is the study of chromosomes—strands of DNA that contain numerous genes and other genetic material. **Cytogenetic results** such as 1q+ (additional genetic material on the long arm of chromosome 1) describe variations in the normal content of a chromosome.

This is a small but growing population due to increased recognition of the disease diversity. At least 10% of patients with FA are 16 years or older at the time of diagnosis <sup>(8)</sup>. Occasionally, an adult is diagnosed with FA when the family members of an affected sibling are screened. More commonly, an adult is diagnosed with FA because of a clinically atypical cancer diagnosis or an abnormal response to cancer chemotherapy or radiation therapy. One study found that in more than 20% of patients with FA who developed solid tumors, the diagnosis of FA in these patients was made only after the appearance of their cancer <sup>(9)</sup>. Many of these patients were diagnosed as adults and very often had no, or minor, phenotypic abnormalities and normal blood counts.

Hematopoietic somatic mosaicism is a condition that occurs when one of two alleles that carry disease mutations reverts to normal. Other types of cells such as skin cells carry both mutated alleles. Mosaicism may explain some of the cases where a cancer diagnosis precedes the diagnosis of FA <sup>(9)</sup>.

Adult patients should be screened for FA if they have any of the following conditions:

- *Aplastic anemia (AA) or severe cytopenias not responding to standard therapy*
- *Myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) associated with unusual cytogenetic results such as 1q+ or 3q+ <sup>(10)(11)(12)</sup>*
- *Solid tumors that develop at a younger than expected age, in patients without known risk factors*
- *Severely delayed blood count recovery or aplasia after chemotherapy <sup>(13)</sup>*
- *Unusual sensitivity to radiation therapy <sup>(14)(15)</sup>*
- *Decreased fertility or early menopause*

## Solid Tumors in Adult Patients with FA

Solid tumors are the most significant health issues facing the adult patient with FA. In particular, squamous cell cancers of the head and neck, as well as cervical and vulvar cancers in women, occur at remarkably high rates and at younger than expected ages. It is estimated that one-third of patients with FA will develop a solid tumor by the age of 48, most likely in the second and third decades of life <sup>(5)</sup>. These cancers may occur at an even earlier age in transplanted patients <sup>(7)</sup>. The HPV vaccine is prophylactic, not therapeutic, and is currently recommended by the United States Centers for Disease Control and Prevention for males and females, ages 9 to 26. The HPV vaccine may help prevent HPV infections in the cervix and oropharynx, as well as prevent subsequent cancers in these locations. Adults with FA should avoid cigarettes and alcohol, and practice good oral hygiene.

Surveillance for solid tumors is **essential** in all adult patients with FA.

Surveillance should include:

- *Head and neck exam at least every 6 months*
- *PAP smear yearly (for females)*
- *GYN exam yearly (for females)*

- *Dental exam every 6 months*
- *Skin exam yearly*
- *Breast cancer screening (MRI and mammography) beginning at age 25 (for females); see Chapter 6*
- *Esophagoscopy (this surveillance recommendation is controversial because it requires anesthesia)*

Patients must be continually re-educated about the potential for solid tumor development, and should be screened by oncologists specializing in head and neck cancer (see *Chapter 14*.) FA specialists should be consulted when these tumors are diagnosed, as treatment may require different modalities than are used for the same cancers in non-FA patients. Previous reports of the treatment of solid tumors in patients with FA are generally limited to single case reports. The literature contains no prospective studies to date. The largest retrospective study of patients with FA with HNSCC describes the treatment of only 13 patients<sup>(16)</sup>. In general, only early-stage cancers are treatable. Treatment of advanced-stage tumors has been associated with severe toxicity and poor outcomes. Targeted therapies such as Erbitux for head and neck cancers are being studied in patients with FA and may allow for less toxicity and better cancer control<sup>(17)</sup>.

Several FA-related genetic mutations (*FANCD1/BRCA2*, *FANCF*, *FANCG*, *FANCI*, *FANCD2*, *FANCD3*, and *FANCD4*) in heterozygotes (FA carriers) are associated with breast and ovarian cancers. These cancers have been reported in individuals with FA, but the exact risk of developing these cancers in patients with any FA mutation is not known.

## **Bone Marrow Transplant in the Adult Patient with FA**

In patients with FA, transplants yield the best results when performed in the first decade of life and before the onset of myeloid malignancies, solid tumors, or transfusions. Increasingly, however, adult patients with FA are undergoing transplant, made possible by advances such as reduced intensity cytoreduction regimens and T-cell depletion methods designed to decrease the incidence of GvHD. To date, there are no published trials of adult FA transplant; however, data are slowly becoming available. At Memorial Sloan-Kettering Cancer Center (MSKCC), 12 adult patients with FA have received stem cell transplants since April 2001<sup>(18)</sup>. The patients ranged in age from 18 to 36 years (median 24

years). Six of the 12 patients (50%) were post-transplant disease-free survivors, 4 of whom had AML at transplant. However, 2 of the 6 post-transplant, disease-free survivors succumbed to secondary cancers 5 and 8 years after transplant. Although these preliminary data explore a small number of transplants, the results are promising and suggest that BMT for FA adults is a possible therapeutic option.

## **Gynecologic and Fertility Issues in the Adult Patient with FA**

Discussions of fertility and life expectancy are obviously quite different in adults with FA, particularly those diagnosed in adulthood, than in younger patients. Adult women with FA frequently experience early menopause, require high-risk management of pregnancies, and have an increased risk of gynecologic malignancies. Adult FA men are generally azoospermic, meaning that they do not produce measurable levels of sperm, and are therefore infertile. That said, it is important to note that advances in assisted reproduction techniques have led to new possibilities for the prevention and treatment of infertility. Early referral to a fertility clinic may be warranted. A complete discussion of gynecologic and fertility issues in adult patients with FA can be found in *Chapter 6*.

## **Transition of Care**

The transition from pediatric- to adult-oriented care is an important issue facing young adults with complex and chronic illnesses. Although the authors are not aware of specific transition programs for young adults with FA, there is ample evidence to support the benefits of an anticipated and coordinated transition process<sup>(19-21)</sup>. Effective transition programs have been developed for patients with other chronic illnesses, such as cystic fibrosis, diabetes, juvenile idiopathic arthritis, and sickle cell anemia. European countries with comprehensive state-supported healthcare systems have often taken the lead in the development of these transition systems.

Transition of healthcare is particularly important for two reasons. In most centers, patients outgrow pediatric services and are unable to be treated by pediatric subspecialists or in pediatric inpatient facilities. This is obviously dependent on the center and location, and policies vary widely. Furthermore, the transition to adult care is an important step because it helps young adults develop independence and assume a personal responsibility for their healthcare.

Timing is an important issue in the transition to adult care. This transition must be seen as a process, not as an abrupt transfer of services. Current evidence indicates that the most successful transitions are those initiated during the late teenage years, and accompanied by family and patient education about the future transition<sup>(19, 22)</sup>. As this process proceeds and adolescents take on more healthcare responsibilities, the patients should become involved in educational opportunities and decision-making. The timing of this transition should be individualized and not dependent on age, but rather situation-dependent. It would be inappropriate to transition a rapidly deteriorating patient who is facing the end of life, for example.

As an increasing number of patients with FA reach adulthood, the management and development of transition of health care services is becoming increasingly important and must be addressed on a national level. In recent studies, focus groups have identified a number of barriers to the transition to adult care<sup>(19) (21, 23-25)</sup>, including:

- *Reluctance of patients and their families to leave trusted healthcare providers and comfortable clinical settings*
- *Differences in pediatric versus adult approaches to the chronically ill (i.e., family-oriented medicine with support from art therapists, social workers, and psychologists versus the expectation of adult independence and self-reliability)*
- *Concerns about the experience, knowledge base, and quality of care that will be offered by adult medical specialists in childhood-onset diseases*
- *Physician reluctance to transition*
- *Lack of continuing healthcare insurance coverage in the young adult*
- *Lack of an organized detailed history of the chronic complex illness*

The key element to a successful transition is continuous preparation and the identification of a willing and appropriate adult-oriented physician who can become the primary coordinator of healthcare issues. The patient's new and prior teams should work to define necessary subspecialist providers who either have experience in FA or are willing to become educated about the needs of this complicated patient population. Because of the rarity of FA, however, this is often not a realistic option, in which case it is essential that an FA specialist remain involved in the patient care decisions and be available for consultation, especially regarding the screening and treatment of secondary cancers. Patients with FA who have been transplanted at larger centers may have an option to be

followed in long-term survivor clinics, where much of their healthcare needs will be coordinated.

## **Psychosocial Issues in Adult Patients with FA**

The appropriate development of a child through adolescence into adulthood is a monumental process that is complicated significantly by chronic disease. There is a potential risk of parental over-protectiveness given the competing issues of requisite attention to safety and the age-appropriate pursuit of adolescence independence. The inability to fully participate in childhood activities (e.g., school, sports, and leisure) may isolate FA children and delay development of peer relationships. A recent follow-up study of adult survivors of childhood acute lymphoblastic leukemia reveals that these patients experienced more functional impairments in mental health, and limited activities compared with their siblings<sup>(26)</sup>. In addition, rates of marriage, college graduation, employment, and health insurance coverage were all lower compared with controls. It is expected that FA adults may experience similar issues.

For these reasons, the adult FA patient may need extensive vocational, educational, and psychosocial support and guidance. High-risk behaviors, such as alcohol and drug use, are common in patients with chronic illness, just as they are in the general population, and present major challenges for adults with FA<sup>(27)</sup>. Medical compliance may also become a problem, particularly during the transition period. For individuals who are newly diagnosed in adulthood, the ramifications of the diagnosis on established relationships (with spouses, parents, employers, etc.) may be extreme.

The magnitude of these psychosocial problems has not been assessed in FA adults, and should be assessed in contemporary patient cohorts in the future. A complete discussion of psychosocial issues in patients and families affected by FA can be found in *Chapter 18*.

## Summary

### Resources for Adults with FA

**Meeting for Adults with FA:** The Fanconi Anemia Research Fund (FARF) sponsored its fifth Meeting for Adults with FA in March 2014 in Baltimore, MD. Forty-two adults ages 18 to 61 attended. The previous meeting in 2012 was attended by 25 adults with FA. The meeting is held approximately every 18 months.

**FA Family Meeting:** The Fanconi Anemia Research Fund holds its annual FA Family Meeting at Camp Sunshine every summer. Adult patients with FA are well-represented at this event.

**Facebook Support Group:** The FARF also offers an online support group specifically for adults with FA through the social networking site, Facebook.

Today, most patients with FA will survive well into adulthood. This is likely due to earlier diagnosis, improved BMT outcomes, particularly in the area of alternative transplants (non-sibling donors), and better education of patients, their families, and medical staff regarding surveillance for myeloid malignancies and solid tumors.

There is a growing emphasis by the FA community on quality of life, particularly with regards to education, socialization and relationships, and work issues. However, the growing population of adult patients with FA represents a new challenge to FA care providers. These patients have not been studied prospectively, and many of their issues may be poorly defined or understood. The physicians caring for adults with FA must be educated about the nature of the disorder and the particular needs of this patient population. The responsibility lies with the pediatric FA specialist to educate patients and adult care providers, coordinate transitional care, and direct future research to improve outcomes.

## Chapter Committee

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# Chapter 17: Genetic Counseling

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## Introduction

### Good to Know

Genetic counseling is the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease <sup>(1)</sup>.

All individuals with Fanconi anemia (FA), as well as their families, should be encouraged to undergo genetic counseling by a certified genetic counselor who is familiar with FA.

Genetic counseling should be conducted at the time of diagnosis and at various points throughout a patient's life. A genetic counseling consultation should include discussions of the following:

- *Family history of FA*
- *The family's health and pregnancy histories*
- *The process by which FA is inherited*
- *The genetic testing process*
- *The patient's or parents' reproductive options and familial implications*
- *Making decisions and coping with FA*
- *FA-related research opportunities and support groups*

This chapter will discuss the role of family history, the strong recommendation for germline genetic testing, associations between genetic mutations and clinical features, genetic testing for unaffected family members, the risk of cancer in carriers of FA gene mutations, and reproductive issues in patients with FA.

### Family History

A detailed family history should be collected for any individual who is suspected of having, or has been diagnosed with, FA. The patient's family history can be helpful in determining the inheritance pattern as well as provide clues as to the genetic basis of the disease. While obtaining the family history,

the genetic counselor should pay particular attention to any FA-related clinical features, as well as miscarriages and infertility.

In addition, a genetic counselor should conduct a detailed investigation of the patient's family history of cancer, with a special emphasis on leukemia and squamous cell carcinoma of the head and neck, in addition to cancers of the cervix, vulva, anus and other gastrointestinal malignancies, breast, ovaries, and prostate. If the patient's family history of cancer is suggestive of a hereditary breast and ovarian cancer syndrome, the family should undergo a risk assessment and be counseled about genetic testing for mutations in the *FANCN/PALB2* and *FANCD1/BRCA2* genes. Carriers of deleterious mutations in certain FA genes have an increased risk of cancer (see detailed information under "Cancer Risks for Carriers of FA Gene Mutations"). Cancer diagnoses should be verified with medical records whenever possible <sup>(2)</sup>. Features of hereditary cancer syndromes can include the following:

- *Multiple close family members with cancer affecting multiple generations within the family*
- *Onset of cancer at an earlier age than expected*
- *Bilateral breast cancer*
- *Male breast cancer*
- *An individual with multiple cancers*
- *Cancer that occurs in the absence of environmental risk factors*

### **Ethnic background**

Most mutations found in patients with FA occur regardless of ethnicity. However, in certain ethnic groups, some mutations, referred to as "founder" mutations, are found at an increased frequency (Table 1). Identifying if a patient is from one of these ethnic backgrounds can be an important factor in determining the most appropriate genetic testing strategy. If an individual's ethnic background is known to be associated with a particular FA mutation, targeted mutation analysis should be performed for that mutation. However, it is important to remember that individuals with ethnic backgrounds that are associated with specific FA mutations frequently have non-founder mutations. Therefore, such individuals who test negative for FA in a targeted mutation analysis should undergo panel testing (described below, under "Germline Genetic Testing"). If a patient's ethnic background is not associated with a specific mutation, next-generation sequencing and/or duplication/deletion testing should be completed.

**Table 1.** Examples of FA founder mutations in ethnic populations.

Ethnicity	Gene	Mutation(s)	Carrier Frequency	Reference
Ashkenazi Jewish	<i>FANCC</i>	c.456+4A>T (IVS4)	1 of every 90 individuals	(Whitney et al., 1993) <sup>3</sup> and (Verlander et al. 1995) <sup>4</sup>
	<i>FANCD1</i>	c.6174delT	Approximately 1-2 of every 100 individuals	(Roa et al. 1996) <sup>5</sup>
Brazilian	<i>FANCA</i>	c.3788_3790del	Unknown	(Castella et al. 2011) <sup>6</sup>
	<i>FANCG</i>	c.1077-2A>G	Unknown	(Auerbach et al. 2003) <sup>7</sup>
Dutch/Manitoba Mennonites	<i>FANCC</i>	c.67delG (322delG)	Unknown	(deVries et al. 2012) <sup>8</sup>
French Acadian	<i>FANCG</i>	c.1480+1G>C	Unknown	(Auerbach et al. 2003) <sup>7</sup>
Israeli (non-Ashkenazi Jewish)	<i>FANCA</i>	c.2172dupG (Moroccan) c.4275delT (Moroccan) c.2574C>G (Indian) c.890-893del (Tunisian)	Unknown	(Tamary et al. 2000) <sup>9</sup>
Japanese	<i>FANCA</i>	c.2546delC c.3720_3724del	Unknown	(Yagasaki et al. 2004) <sup>10</sup>
	<i>FANCC</i>	c.456+4A>T	Unknown	(Futaki et al 2000) <sup>11</sup>
	<i>FANCG</i>	c.307+1G>C c.1066C>T	Unknown	(Yagasaki et al. 2003) <sup>12</sup>
Korean	<i>FANCA</i>	c.2546delC c.3720_3724del	Unknown	(Park et al. 2012) <sup>13</sup>
	<i>FANCG</i>	c.307+1G>C c.1066C>T	Unknown	(Park et al. 2012) <sup>13</sup>
Saudi	<i>FANCC</i>	c.165+1G>T	Unknown	(Hartmann et al. 2010) <sup>14</sup>
South African	<i>FANCA</i> (Afrikaans)	c.1007-?_3066+?del (Transvaal Province)	Approximately 1 of every 80 individuals	(Rosendorff et al. 1987) <sup>15</sup>
		c.1007-?_1626+?del (Transvaal Province)		(Tipping et al. 2001) <sup>16</sup>
		c.3398delA (Transvaal Province)		(Tipping et al. 2001) <sup>16</sup>
	<i>FANCG</i> (sub-Saharan Africans)	c.637_643del (sub-Saharan Africa)	1 of every 100 individuals	(Morgan et.al. 2005) <sup>17</sup>
Spanish Gypsy	<i>FANCA</i>	c.295C>T	1 of every 70 individuals	(Callen et al. 2004) <sup>18</sup>
Turkish	<i>FANCD2</i>	c.1948-16T>G	Unknown	(Kalb et al. 2007) <sup>19</sup>

## Good to Know

**Autosomal recessive inheritance** is one of several ways that disorders can be passed down through families.

- This type of inheritance involves genes located on one of the chromosomes numbered 1-22, which are called autosomes. Cells have two copies of every autosomal gene.
- If a disorder is **autosomal recessive**, it means that an individual must have two copies of a nonworking gene for the disease to develop.
- Individuals with a single copy of a nonworking gene for an autosomal recessive disorder are known as “**carriers**.” These individuals usually do not develop the disorder, but can pass a copy of the abnormal gene onto their children.
- In the general US population, the chance of being a carrier for any of the FA gene mutations is approximately 1 in 180 (Rosenberg et al. 2011)<sup>20</sup>.
- Individuals with a rare autosomal recessive disease have an increased frequency of parents who descended from the same ancestor, known as consanguinity.
- When both parents are carriers of mutations in the same gene there are three possible outcomes with each pregnancy: a 25% chance the child has two working copies of the FA gene and is unaffected, a 50% chance the child has one nonworking copy of the gene and is a carrier, and a 25% chance the child has two nonworking copies of the gene, causing FA.

**X-linked recessive inheritance** involves genes located on the X sex chromosome. Males have one X chromosome; females have two. In FA, this type of inheritance applies only to the FANCB gene.

- If a disorder is **X-linked recessive**, it means that females must have two copies of a nonworking gene for the disease to develop, whereas males need only one.
- The recurrence risk for families with FANCB mutations is dependent on whether the mother is found to be a carrier of the mutation or whether it occurred sporadically (*de novo*).

## Inheritance of FA

Fanconi anemia is predominantly inherited in an *autosomal recessive* fashion. However, a small fraction of individuals (approximately 2%) have mutations in the *FANCB* gene, which is inherited in an *X-linked recessive* manner. While the majority of FA follows the expected inheritance patterns, there are exceptions

(described later in the chapter) that when present will affect the recurrence risks for that couple. The exact frequency with which these atypical inheritance patterns occur is unknown.

## Germline Genetic Testing

The goal of mutation analysis is to identify the specific gene changes that lead to FA. Genetic test results may help to determine the patient's medical management, prognosis, and reproductive risks, and may help to exclude diseases with similar signs and symptoms. For these reasons, genetic test results should be obtained as soon as possible. Historically, genetic testing involved chromosome breakage studies, followed by complementation group testing (described in *Chapter 2*) and the sequencing of single genes with further testing for gene deletions and duplications as needed <sup>(21)</sup>. This process was expensive and lengthy <sup>(22)</sup> and was not feasible for all families. Modern mutation analysis can include targeted mutation analysis, single gene sequencing, panel testing, whole exome sequencing, or whole genome sequencing. Mutations found by any of these sequencing methods can be used to perform other genetic tests such as carrier testing, prenatal testing, and preimplantation genetic diagnosis, and may in some cases help to guide the patient's medical care and/or enrollment in research studies.

### Targeted mutation analysis

Targeted mutation analysis can be helpful in a variety of circumstances. Once a patient's mutation(s) has been identified, his or her family members can be tested for the same mutation(s), a process known as carrier testing. Targeted mutation analysis can also be used for prenatal testing of an unborn fetus and preimplantation genetic diagnosis of embryos generated through in vitro fertilizations. For an individual with FA, targeted testing may be the fastest and most cost-effective means of identifying mutations if the individual is of an ethnic background with a known founder mutation (Table 1). In addition, any mutations identified during research studies must be confirmed through targeted mutation analysis performed by a clinical laboratory that is certified, as described in *Chapter 2*.

### Single gene sequencing

Historically, single gene sequencing was used following the completion of complementation group testing (described in *Chapter 2*). With the current trend towards increasing panel testing, single gene sequencing will likely become

less frequent in the future. However, single gene analysis may be useful for testing the partners of individuals with FA who are fertile and interested in preconception or prenatal testing. Individuals who are carriers of deleterious mutations in FA genes and who are planning a pregnancy with a new partner should also be offered single gene testing for that partner. Single gene sequencing may also be offered to family members of an individual with FA for whom specific mutations were never identified.

### Panel testing

A panel of all of the known FA genes can be tested simultaneously for mutations using a technique known as next-generation sequencing. Therefore, the families of individuals who have a positive result on a chromosome breakage test (see *Chapter 2*) should be offered panel testing of known FA genes. At the time of this writing, the available panel tests include as many as 15 of the 16 known FA genes; the most recently identified FA gene, *FANCO/XPF/ERCC4*, is not included on panels, but will likely be added soon. Furthermore, due to patent restrictions the *FANCD1/BRCA2* gene may not be included in some panels and must be directly ordered through Myriad Genetics. If the patient's symptoms or family history are suggestive of a mutation in the *FANCD1/BRCA2* gene, targeted mutation analysis or single gene sequencing is recommended.

Panel testing for FA is more efficient for individuals or family members for whom a complementation group or mutations are not known, as it significantly decreases the turnaround time for results. Panel testing may also be able to identify mutations located in regions of genes known as introns, which are not typically sequenced in single gene sequencing tests<sup>(22)</sup>. However, panel testing currently cannot detect large gene deletions, duplications, and insertions. These types of mutations can account for up to 31% of all FA mutations on average, depending on the gene involved. For example, the frequency of these mutations ranges from 4% (for mutations in the *FANCI* gene) to 73% (for mutations in the *FANCF* gene) [data collated from information in the Fanconi Anemia Mutation Database through Leiden Open Source Variation Database (LOVD v 2.0)]. Large deletions account for approximately 40% of the causative mutations that occur in *FANCA*, the most commonly mutated FA gene<sup>(22)</sup>. Therefore, techniques that can detect gene deletions, duplications, and insertions, such as comparative genomic hybridization (CGH) or multiplex ligation-dependent probe amplification (MLPA), are an important part of the genetic testing process. These tests can be performed before or after panel



testing. Identifying large duplications and deletions with next-generation sequencing is currently available in some laboratories.

### **Whole exome sequencing and whole genome sequencing**

In contrast to sequencing tests that analyze a single gene or a small group of genes simultaneously, whole exome sequencing analyzes all of the exons (regions of genes that direct cells to make proteins essential for bodily function) that are present in the human genome's approximately 23,000 genes, whereas whole genome sequencing analyzes the entire genome. Currently, whole exome and whole genome sequencing are available on a clinical and research basis, but may only be warranted in rare instances. For example, whole exome or whole genome sequencing may be warranted for an individual who has a diagnosis of FA based on a positive chromosome breakage test result, but who has no identifiable mutations based on the genetic testing methods discussed above. Whole exome and whole genome sequencing are beneficial for detecting mutations in a very large number of genes, but compared with single gene sequencing or panel testing, these methods are more costly, identify more genetic variants of unknown significance, and may create more ethical dilemmas <sup>(23)</sup>.

### **Benefits, risks, and limitations of genetic testing**

Genetic testing has many benefits, risks, and limitations. As a result, the decision about whether to undergo genetic testing is a personal one. Individuals should be made aware of the possible implications of testing for themselves and family members (Table 2).

## **Associations Between Genetic Mutations and Clinical Features**

In most cases, it is not possible to predict the clinical course of FA, which is a genetically and clinically heterogeneous disease. For example, siblings who have identical FA gene mutations often have radically different clinical signs and symptoms. Medical management for most individuals with FA should be selected according to the patient's clinical features. However, for individuals with mutations in the *FANCD1/BRCA2* and *FANCN/PALB2* genes, the identity of the patient's mutations is essential for proper cancer surveillance and medical management. For patients who have mutations in other FA genes like *FANCA*, *FANCC*, and *FANCG*, the identity of the patient's mutations may be helpful for prognostic purposes in some cases <sup>(24)</sup> and occasionally may lead to

increased monitoring or early intervention. The identity of the patient’s genetic mutations may also indicate the need for detailed assessments of the patient’s clinical features and genetic background <sup>(25)</sup>.

**Table 2.** Some benefits, risks, and limitations of genetic testing.

Benefits	Risks	Limitations
Genetic testing results may give important information that might alter the patient's medical management (e.g., an increase in the frequency of bone marrow biopsies)	Genetic testing information is a part of an individual's medical record and may be examined by health and life insurance providers	Genetic testing results may not give information to guide medical management
Genetic testing results can be used for carrier testing, prenatal testing, and preimplantation genetic diagnosis	Genetic testing could reveal previously unknown family relationships (e.g., non-paternity)	One or both of the patient's mutations may not be identified, or the genetic testing results may be inconclusive
Genetic testing information can be helpful to family members (e.g., the results may help to identify which family members may or may not be at increased risk for having a child with FA or developing cancer)	Genetic information could alter family dynamics (e.g., some family members may prefer not to know about the genetic testing results)	Genetic testing results do not enable exact predictions about future medical complications
Genetic testing results may relieve anxiety	Genetic testing results may create anxiety, distress, and feelings of guilt	
Genetic testing results may be used for inclusion in certain research projects or clinical trials		

### **FANCD1/BRCA2 mutations**

A study published in 2002 reported that individuals with mutations in both copies (known as biallelic mutations) of the *BRCA2* gene had Fanconi anemia <sup>(26)</sup>. Subsequent studies found that individuals with biallelic *FANCD1/BRCA2* mutations develop spontaneous chromosomal aberration at a high rate <sup>(27)</sup>. These individuals also may develop leukemia at a much earlier age than is expected for individuals with mutations in other FA genes and they are also at risk of developing solid tumors such as medulloblastoma, astrocytoma, and Wilms’ tumor which are not commonly seen in individuals with mutations in other FA genes <sup>(28, 29)</sup>. *FANCD1/BRCA2* testing should be considered in all patients with FA who have a medical and/or family history suggestive of *FANCD1/BRCA2* mutations, who do not have an identifiable mutation (as

assessed by next-generation sequencing), and/or who develop leukemia at or before the age of 5 years<sup>(30)</sup>. If a patient has biallelic *FANCD1/BRCA2* mutations or a family history or clinical manifestations that are highly suggestive of *FANCD1/BRCA2* mutations, additional tests such as a brain MRI and kidney ultrasound should be performed immediately to rule out any evidence of tumors.

### ***FANCN/PALB2* mutations**

Mutations in the *FANCN/PALB2* gene are also associated with severe clinical features. Similar to individuals with mutations in *FANCD1/BRCA2*, individuals with mutations in *FANCN/PALB2* develop solid tumors and leukemia at an earlier age than individuals with mutations in other FA genes<sup>(31)</sup>. The cancer surveillance recommendations described above for patients with biallelic *FANCD1/BRCA2* mutations should also be considered for individuals with *FANCN/PALB2* mutations.

### ***FANCA* mutations**

One study reported that individuals with homozygous null mutations (a type of mutation that leads to the production of a nonfunctional protein or no protein at all) in the *FANCA* gene develop anemia at an earlier age and have a higher incidence of leukemia than individuals with *FANCA* mutations that result in an abnormal form of the protein<sup>(32)</sup>. However, a separate analysis revealed that the age of onset of anemia and incidence of leukemia was not altered in patients with homozygous null mutations in *FANCA* or in patients who express an abnormal form of the protein<sup>(6)</sup>.

### ***FANCC* mutations**

A recent study noted that individuals with mutations in *FANCC* had an earlier age of onset of bone marrow failure compared with individuals with mutations in *FANCA* or *FANCG*. One mutation—known as c.456+4A>T (formerly known as IVS4)—in the *FANCC* gene is common to two different ethnic groups, but leads to very different clinical presentations. In the Ashkenazi Jewish population, this mutation leads to bone marrow failure at an earlier age than other patients with FA<sup>(33)</sup>, whereas in the Japanese population, this mutation is associated with significantly milder symptoms<sup>(11)</sup>. Furthermore, mutations located in a region of the gene known as exon 14 are associated with the development of blood abnormalities at an earlier age and poorer survival compared with individuals who have mutations in the region known as exon 1<sup>(33,34)</sup>. Several studies suggest that the c.67delG founder mutation

(formerly known as 322delG), which is common to the Dutch and Mennonite populations, is associated with milder symptoms, but exceptions have been observed<sup>(35)</sup>. Studies in the Saudi population have shown that the founder mutation c.165+1G>T does not prevent the production of the protein encoded by the *FANCC* gene, and therefore may also be associated with a mild form of the disease<sup>(14)</sup>.

### ***FANCG* mutations**

The European FA Research Group reported that individuals with mutations in *FANCG* had more severe cytopenia and a higher incidence of leukemia than patients with mutations in other FA genes<sup>(32)</sup>, but this pattern was not observed in the data set collected by the International Fanconi Anemia Registry (IFAR)<sup>(33)</sup>. The discrepancies between the IFAR and European data may be due to differences in the percentages of individuals with mutations in either gene in the two populations, meaning that the IFAR may have more patients with *FANCA* or *FANCC* mutations and the European group may have more patients with *FANCG* mutations or visa versa. Therefore, mutation-specific risk information, which is more precise than complementation group-specific risk information, is sorely needed.

### ***FANCD2* mutations**

A study of 29 patients with hypomorphic mutations (a type of mutation that reduces the function or amount of protein that is produced from a gene) in the *FANCD2* gene reported that all of the patients in the study had one or more birth defects, which is remarkable because nearly one-third of all individuals with FA have no physical manifestations<sup>(19)</sup>. The study also reported that the median age of bone marrow failure in patients with hypomorphic *FANCD2* mutations was significantly lower than other individuals with FA (2.4 years compared with approximately 7 years, respectively).

## **Genetic Testing for Unaffected Family Members**

If an individual's FA-causing mutations have been identified, his or her family members can then be tested using targeted mutation analysis to determine whether they carry a single copy of the same mutation. This process, known as carrier testing, can be difficult and sometimes impossible if the mutations of the patient with FA are unknown. In such cases, complete sequencing analysis of all the FA genes is technically possible, but it is not appropriate for routine

carrier testing because it could yield results that are difficult to interpret. For example, a negative test result might indicate that the family member does not carry a mutation; however, it might be possible that the individual has a mutation that the test was unable to detect. Therefore, individuals diagnosed with FA should undergo genetic testing prior to carrier testing any of the patient's family members.

### **Parents of children diagnosed with FA**

All parents of children with identified FA-causing mutations should undergo carrier testing to confirm that they carry a copy of the same mutation.

Identifying the parental origin of the mutations enables other family members to have targeted mutation analysis for the appropriate familial mutation.

Although rare, it is possible that a parent of a child with FA will not carry either of the child's FA-causing mutations. Possible explanations for this include the following:

- *The egg or sperm involved in the child's conception had developed a spontaneous mutation (known as a de novo mutation)*
- *Only a fraction of the parent's reproductive cells have the mutation (known as germline mosaicism)*
- *Uniparental disomy in which both mutations are inherited from the same parent*
- *Misattributed paternity (the child was adopted or has a different birth father)*

### **Siblings of children diagnosed with FA**

Due to the wide variability in the clinical symptoms associated with FA, all biological siblings of a child with FA should undergo chromosome breakage analysis (a test that is performed on a sample of blood cells). If the chromosome breakage assay is positive, genetic testing can be ordered to confirm the presence of the mutations found in the child who was originally diagnosed with FA; by contrast, if the chromosome breakage assay is negative, it greatly reduces the chance that the sibling has FA. However, the possibility of FA cannot be fully ruled out until chromosome breakage testing is performed on a second tissue source, such as skin fibroblasts (as reviewed in *Chapter 2*). A healthy sibling of an individual with FA has a 2 in 3 chance of being a carrier for the condition. Carrier testing for an autosomal recessive condition such as FA is a very personal decision and is associated with several benefits and risks (Table 2). Testing guidelines issued by the American Society of Human

Genetics and the American College of Medical Genetics state that carrier testing for children should be deferred until the child is of reproductive age and is capable of providing informed consent <sup>(36)</sup>.

### **Partners of individuals known to carry a FA mutation**

Relatives of individuals with FA, who are known carriers of a FA mutation, are at risk of having a child with FA. For this reason, partners of individuals with FA mutations should be offered genetic counseling and genetic testing for the corresponding FA gene. For instance, if an individual is known to carry a mutation in the *FANCA* gene, his/her partner should be offered genetic testing of the *FANCA* gene (single gene sequencing should be performed first; if those results are negative, duplication/deletion testing should be performed). Because most individuals will not have a known family history of FA, testing should be offered regardless of family history of FA. This is done routinely at some institutions and is often covered by insurance, though coverage varies by plan and provider.

### **Children of individuals with FA**

Although individuals with FA are often less fertile than their healthy peers, some individuals with FA are able to have biological children. The likelihood that a person with FA will have a child with FA depends on whether his or her partner is a carrier of an FA mutation or has FA. To determine the exact chance that a couple will give birth to a child with FA, the partner of an individual with FA should be offered genetic testing to determine whether he or she is a carrier of a mutation in the same gene as the individual with FA. Depending on the genetic testing results, the possible outcomes of the couple's pregnancies are as follows:

- If the partner is not a carrier of a gene mutation in the corresponding gene for FA, none of the couple's children would develop FA but all will be carriers of the condition.
- If the partner is a carrier of a mutation in the same gene as the individual with FA, there is a 50% chance with each pregnancy that the fetus would be affected by FA.
- If both partners have FA and have mutations in the same FA gene, all (100%) of their children will have FA.
- If both partners have FA but have mutations in different FA genes (assuming full sequencing was done of both genes), each of their children

will be a carrier for both FA genes (known as compound heterozygosity) but will not have FA.

Couples who are at increased risk of having a child with FA—including couples in which the partner’s carrier status is unknown—should be offered pre- or post-natal testing.

## Cancer Risks for Carriers of FA Gene Mutations

Data collected by the International Fanconi Anemia Registry indicates that most carriers of mutations in FA genes do not have an increased risk of cancer. However, a few specific gene mutations are associated with an increased risk of cancer<sup>(37)</sup>. For example, the FA genes *FANCD1*, *FANCN*, and *FANCI* are identical to the breast cancer susceptibility genes *BRCA2*, *PALB2*, and *BRIP1*, respectively, and certain mutations in these genes predispose individuals to developing breast cancer. Case control studies have shown that FA-causing mutations in *FANCI/BRIP1* and *FANCN/PALB2* are associated with a moderate risk of breast cancer<sup>(38, 39)</sup>, whereas FA-causing mutations in *FANCD1/BRCA2* are associated with a high risk of breast cancer. Family members of individuals with FA who have a mutation in one of these genes should be referred to a genetic counselor who specializes in cancer and can provide the appropriate risk information and management options.

### Carriers of *FANCD1/BRCA2* mutations

Female and male relatives of individuals with biallelic mutations in the *FANCD1/BRCA2* gene have a significantly increased risk of developing certain cancers. Most carriers of mutations in the *FANCD1/BRCA2* gene will display features that are typical of patients with hereditary breast and ovarian cancer (discussed above, under “Family History”). However, a number of FA-associated mutations in the *FANCD1/BRCA2* gene do not appear to be associated with the same cancer risks that are typically seen in families with harmful *BRCA2* mutations<sup>(29)</sup>. According to recent estimates, approximately 80% of women who inherit a harmful *BRCA2* mutation will develop breast cancer in their lifetimes, with roughly 40% developing breast cancer by age 80, and approximately 10-20% will develop ovarian cancer by age 70. In addition, men who inherit a harmful *BRCA2* mutation have an approximately 7% risk of developing breast cancer and a 20% chance of developing aggressive prostate cancer by age 80<sup>(28, 40, 41)</sup>. About 5% of men and women with *BRCA2* mutations may develop pancreatic cancer in their lifetimes<sup>(39)</sup>. Carriers of *BRCA2*

mutations may also have an increased risk of melanoma <sup>(42, 43)</sup>. Due to the increased risk of these specific cancers, the National Comprehensive Cancer Network has created guidelines that include cancer screening recommendations (Table 3 and Table 4) and surgical options <sup>(44)</sup>. Some individuals may be suitable candidates for enrollment in research studies to help increase the detection of cancers that currently do not have surveillance recommendations.

In addition to cancer screening, which can identify precancerous tumors or tumors that may be amenable to treatment, there are several ways to try to reduce the risks of cancer. The most commonly used risk-reducing procedures are chemoprevention as well as surgery (Table 5). Physicians should talk with carriers of *FANCD1/BRCA2* mutations about the risks and benefits of chemoprevention and surgery, and refer patients to the appropriate medical professionals.

**Table 3.** Cancer screening recommendations for female carriers of *BRCA2* mutations.

Female Screening		Recommendation
Breast	Self exam	Monthly beginning at age 18
	Clinical breast exam	Semi-annually beginning at age 25
	Mammogram	Annually beginning at age 25 or the age of the earliest breast cancer diagnosis in the family
	Breast MRI	Annually beginning at age 25 or the age of the earliest breast cancer diagnosis in the family
Ovarian	Pelvic exam	Every 6-12 months beginning at age 25
	Concurrent transvaginal ultrasound and CA-125 blood test	Every 6 months starting at age 30, or 5-10 years earlier than the age of the earliest onset of ovarian cancer in the family



**Table 4.** Cancer screening recommendations for male carriers of *BRCA2* mutations.

Male Screening		Recommendation
Prostate	Prostate-specific antigen (PSA) test	Consider annual exams beginning at age 40
Breast	Self exam	Provide training and education beginning at age 35
	Clinical breast exam	Every 6-12 months, starting at age 35
	Mammogram	Consider beginning at age 40 and repeating annually thereafter if gynecomastia (enlarged breasts) or high breast density is detected

**Table 5.** Cancer risk reduction recommendations for carriers of *BRCA2* mutations.

Prevention		Specifics
Breast	Chemoprevention	Consider on a case-by-case basis
	Prophylactic surgery (risk-reducing mastectomy)	Discuss the degree of protection afforded by surgery, reconstructive options, and associated risks
Ovarian	Chemoprevention	Consider oral contraceptives on a case-by-case basis
	Prophylactic surgery (risk-reducing salpingo-oophorectomy, which involves the removal of an ovary together with the fallopian tube)	Recommended for individuals between the ages of 35-40 or when childbearing is complete Discussion should include reproductive plans, menopausal symptoms, and the degree of breast and ovarian cancer protection afforded by surgery

### Carriers of *FANCN/PALB2* mutations

Although patients with mutations in *FANCN/PALB2* and *FANCD1/BRCA2* have similar symptoms, carriers of *FANCN/PALB2* mutations may have a lower risk of cancer compared with carriers of *FANCD1/BRCA2* mutations. Recent studies suggest that having a single copy of a truncating mutation (a type of mutation that gives rise to a protein that is shorter than normal) in *FANCN/PALB2* increases the risk of breast cancer by approximately two- to five-fold<sup>(39, 45)</sup>. Another study reported that the risk of breast cancer for a woman with the *FANCN/PALB2* mutation known as c.1592delT, which is common in the Finnish population, is about 2 in 5 (or about 40%) if she lives to be age 70<sup>(46)</sup>.

Truncating mutations in *FANCN/PALB2* have also been reported in patients with familial pancreatic cancer<sup>(47,48)</sup>, but estimates of the exact pancreatic cancer risks for carriers of *FANCN/PALB2* mutations have not been established. Some men with *FANCN/PALB2* mutations have developed breast cancer<sup>(49)</sup>. Carriers of *FANCN/PALB2* mutations should be encouraged to discuss their cancer risks with their health care providers to design a screening plan, which may involve frequent clinical breast exams, mammograms, or breast MRI scans. However, at the time of this writing, there are no formal guidelines describing cancer-screening recommendations for carriers of *FANCN/PALB2* mutations.

### **Carriers of *FANCI/BRIP1* mutations**

The first study to investigate the cancer risk of carriers of *FANCI/BRIP1* mutations analyzed a group of patients with hereditary breast cancer who did not have mutations in the *BRCA1* or *FANCD1/BRCA2* genes, and determined that truncating mutations in *FANCI/BRIP1* double the risk of breast cancer<sup>(38)</sup>. In addition, some missense mutations (a type of mutation that gives rise to a protein containing an incorrect amino acid) in *FANCI/BRIP1* increase the risk for breast cancer while others do not. Carriers of mutations known to increase the risk of breast cancer should be encouraged to discuss their cancer risks with their health care providers to design a screening plan, as again no formal guidelines have been published.

A recent study reported that two frameshift mutations (a type of mutation that results from the addition or loss of DNA from a gene and usually gives rise to a non-functional protein) in *FANCI/BRIP1*, that are common in individuals of Icelandic heritage, are associated with an increased risk of ovarian cancer<sup>(50)</sup>. Furthermore, the same study found that a frameshift mutation in *FANCI/BRIP1* that is common in individuals of Spanish heritage increased risk of breast cancer as well as ovarian cancer. Another study found evidence for a weak association between truncating mutations in *FANCI/BRIP1* and an increased risk of prostate cancer<sup>(51)</sup>.

### **Carriers of *FANCC* mutations**

Mutations in the *FANCC* gene might increase the risk for breast cancer. One study reported that grandmothers who carried a *FANCC* mutation were 2.5 times more likely to develop breast cancer than noncarriers<sup>(37)</sup>, but the molecular basis for the increased risk is not well understood and must be further investigated. Carriers of *FANCC* mutations should be informed of their potential breast cancer risk and encouraged to discuss this risk with their health

care providers. However, the evidence for an association between breast cancer and *FANCC* mutations remains weak <sup>(52)</sup>.

### **Carriers of *FANCO/RAD51C* mutations**

A recent case report described an individual who had an FA-like syndrome and mutations in both copies of the *FANCO/RAD51C* gene <sup>(53)</sup>. Carriers of deleterious mutations in *FANCO/RAD51C* have been reported in families with hereditary breast and ovarian cancer <sup>(54, 55)</sup>.

### **Carriers of *FANCP/SLX4* mutations**

Mutations in the *FANCP/SLX4* gene have been identified in multiple patients with FA <sup>(56, 57)</sup>. To assess the cancer risk for carriers of *FANCP/SLX4* mutations, individuals of German, Italian, or Spanish heritage and hereditary breast cancer of unknown genetic origin were screened for mutations in *FANCP/SLX4*. Truncating and splice-site mutations in *FANCP/SLX4*, which have been predicted to be harmful via computer simulations, were reported to be the cause of cancer in one family with hereditary breast cancer, and one family with hereditary breast and ovarian cancer out of several hundred families <sup>(58, 59, 60, 61, 62)</sup>. Given the weak association, more research is needed to determine the risk for cancer in individuals carrying a *FANCP/SLX4* mutation.

## **Reproductive Issues**

Individuals with FA may seek reproductive counseling for assistance with infertility and/or information on risks for their own children. Health care providers should also talk with parents of individuals with FA about their chances of having additional children with the disorder to permit informed decision-making regarding future pregnancies. Family planning options include natural pregnancy, adoption, birth control, prenatal testing, and various assisted reproductive technologies such as preimplantation genetic diagnosis (PGD).

### **Prenatal testing**

Prenatal testing of fetal cells can be done at various times in pregnancy to determine whether a fetus has FA. Prenatal testing can also be used to determine whether the fetus has the same human leukocyte antigens (HLA) as the sibling with FA (this process, known as HLA typing, reveals whether the child will be a suitable donor of umbilical cord blood and/or bone marrow for the sibling with FA). Prenatal testing options include the following:

- **Amniocentesis**, typically performed between 15-18 weeks of pregnancy, involves inserting a needle through the abdomen to collect a sample of the amniotic fluid surrounding the baby
- **Chorionic villus sampling**, typically performed between 11-13 weeks of pregnancy, involves collecting a sample of fetal cells by a thin, flexible tube inserted through the vagina, or by a long, thin needle inserted through the abdomen

The goal of both procedures is to obtain fetal cells for genetic testing, chromosomal breakage testing, or molecular testing. All samples should be tested to determine whether they contain maternal cells, which will confound the test results. Targeted mutation analysis should be performed on the fetal DNA if the gene mutations are known, whereas chromosome breakage testing should be performed if the familial mutations are not known. Amniocentesis and chorionic villus sampling are associated with a risk of miscarriage. The exact risks will vary between centers; therefore, the procedures and associated risks should be discussed directly with the obstetrician or individual performing the procedure.

### **Preimplantation genetic diagnosis**

Preimplantation genetic diagnosis (PGD) is a genetic screening test used to determine whether embryos produced through in vitro fertilization (IVF) have FA. It can also be used to identify embryos that are HLA matches for siblings. While PGD helps to reduce the likelihood that a family will have a child with FA and increases the chance that the child will be an HLA-match for the sibling with FA, it does not guarantee that the child will not have FA or be a match. There is always a chance (roughly 1-2%) that an error could occur during the process, resulting in a misdiagnosis<sup>(63)</sup>. Therefore, prenatal testing should be performed during all pregnancies that result from embryos produced through in vitro fertilization with PGD.

Parents considering PGD should be advised of the chances of having a healthy, HLA-matched embryo. Theoretically, there is a 3 in 4 chance that an embryo will not have FA, and a 1 in 4 chance that an embryo will be an exact HLA match; thus, the odds that an embryo will be both free of FA and an HLA match is 3 in 16 (18.75%). In actuality, many couples will need multiple rounds of IVF and PGD to obtain a clinical pregnancy resulting in a liveborn baby. The chances of success are also impacted by a woman's age. On average, women younger than age 35 have a greater chance of success (approximately 35%)

with each cycle compared with women older than age 40 (who have a 10% chance of success) <sup>(64)</sup>. Each IVF and PGD center will have statistics on its success rates based on age and on FA gene mutations. Couples considering this procedure should be advised of the unique services and outcomes of the various PGD centers.

Parents should also be counseled on the financial, emotional, and other issues that arise during PGD <sup>(65)</sup>. The procedure can involve multiple doctor appointments, medical treatments, tough decisions, ethical and religious questions, and the addition of a new member to a family. The process has been described as an emotional rollercoaster with alternating high hopes and periods of despair <sup>(66)</sup>. Moral issues and religious beliefs may be important factors for patients' decision making <sup>(67)</sup>. It may be helpful for families to discuss PGD with other families who have gone through the process and can provide a realistic description of their experiences. A poignant memoir has been written on the topic by a mother of a child with FA, entitled *Saving Henry: A Mother's Journey* <sup>(68)</sup>.

Some of the key steps in the PGD process include the following:

- *Consult with a transplantation physician and genetic counselor*
- *Obtain the results of the mutation analysis*
- *Obtain the HLA type information of the individual with FA as well as the mother and father (if applicable)*
- *Consult with IVF center staff and affiliated PGD center staff*
- *Perform the required medical procedures to prepare the individual for PGD*
- *Perform PGD and choose suitable embryos for implantation and, if applicable, embryo preservation*
- *Perform a pregnancy test and prenatal testing*
- *Collect the umbilical cord blood cells*
- *Perform genetic testing on the umbilical cord blood and newborn baby*
- *Transplant HLA-matched umbilical cord into sibling*

## Conclusion

Genetic counseling is an integral part of a comprehensive FA evaluation. Families should be referred to a genetic counselor who specializes in FA and is aware of the many difficult counseling issues that arise in this complex, rare disease. The genetic testing process is complex and continuously evolving. Identifying the genetic basis of the disease is of the utmost importance as it may influence a patient's clinical management, especially for severe cases. Identifying the FA-causing mutations also influences cancer screening, prenatal testing options, and preimplantation genetic diagnosis. However, the decision to proceed with any type of mutation analysis should be at the discretion of the patient or guardian. Genetic testing can have many benefits, risks, and limitations, and as a result, is a personal decision. The individual or guardian should be well informed of the possibility that the child's genetic testing results may impact his/her future reproductive health and ability to obtain life or disability insurance. These issues necessitate a detailed conversation with a genetic counselor who is familiar with FA, because misdiagnosis or misinterpretation of test results can have a significant impact on an individual with FA and his or her family members.

## Chapter Committee

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# Chapter 18: Psychosocial Issues

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## Introduction

Each family confronted with a diagnosis of Fanconi anemia (FA) faces challenges in responding to the illness, from coping with the emotional upheaval of the news to assuming the responsibility of organizing their child's care. A diagnosis of FA often changes the family system, requiring parents to make important healthcare decisions that involve a sophisticated understanding of a complex illness with many treatment options. While any serious illness in childhood can isolate a family from their community, isolation is more likely with a rare condition such as FA. The challenge is for family members to balance their emotions while orchestrating their child's medical care, surrounding themselves with a community of support, maintaining hope, and sustaining some semblance of a normal family life.

Fanconi anemia presents different issues for families depending on the developmental stage of the patient and the patient's individual illness progression. The number of children with FA, the number of unaffected siblings, and their ages will also affect the emotions and needs of each family. This chapter will describe the stages of families' journeys with Fanconi anemia, as well as the unique challenges faced by parents, siblings, partners, and children, adolescents, and adults with FA. This chapter will also discuss stage-related psychosocial issues surrounding hematopoietic stem cell transplantation (HSCT) and end-of-life.

## Stages of the Journey with FA

Living with uncertainty and preparing for a future filled with the medical complexities of FA, while helping children embrace life and establish dreams, career paths, future plans, and hope for longevity places affected families on a unique and challenging journey. This journey can be interwoven with grief, loss, and uncertainty, but it is important for families to note that the course of FA is constantly changing, and that there is ever-increasing room for optimism after the impact of the initial diagnosis fades.

Before FA has been confirmed, most families remain hopeful that this possible diagnosis will be proven wrong. The time of diagnosis itself is an emotional crisis, a period of transition. It takes time before parents can move from shock and disbelief to a more proactive mode of coping.

At the time of diagnosis or soon thereafter, parents of children with FA may begin to face difficult decisions regarding medications or other treatment options. Families need access to up-to-date, clearly presented information to help them navigate this complex illness and make decisions with which they will feel comfortable. They may also need help thinking through their choices and the implications of those choices. Parents, in particular, face a number of uncertainties at the time of diagnosis: Will their child eventually need a stem cell transplant, perhaps from a human leukocyte antigen (HLA)-matched sibling <sup>(1)</sup>? Will they arrange for prenatal diagnosis or HLA typing with subsequent pregnancies?

Once the diagnosis has been established, many families find that emotionally calmer times alternate with more complicated ones. Children with FA can be stable or asymptomatic for long periods of time. As initially described in *The Damocles Syndrome* <sup>(2)</sup>, many parents feel as though they are constantly waiting for the next crisis <sup>(3)</sup>. Families may need help cultivating the ability to live each day to the fullest. Honing this ability is essential, as learning to focus on activities apart from the illness is an effective day-to-day coping strategy. Moments not driven by medical crises are times for families to enjoy life, prepare for the future, and stay abreast of salient treatment options. The information amassed during calmer times will help families feel prepared should their child's condition deteriorate and additional treatment options need to be considered. Education, and a strong support network empower family members to move forward with necessary tasks during times of emotional crisis, when feelings of hopelessness and immobilization may prevail.

For many of the difficult medical choices that face parents and their children with FA, there is no turning back. Therefore, major decisions require that families and older patients know all they can prior to moving forward. Not only should families take time to learn about treatment options, they should also have ample opportunity to integrate the information, and reflect upon and accept the choices they have made. In certain cases, families must make decisions about experimental procedures and protocols. Families may experience vulnerability and anxiety when they know they are traveling on a road that few have traveled before.

## The Parent's Journey with FA

### Coping strategies

Within each family, parents may cope separately and very differently with the diagnosis and course of FA. One parent may prefer to learn as much as possible to create a strategic plan for the future, while the other parent may prefer to focus on each moment. One parent may need to talk and to cry; another parent may be uncomfortable with displays of emotion. Differences in coping styles should be recognized so that each parent can be supported for his or her strengths, insight, and abilities during the course of the illness. Coping differences can create or aggravate marital tension, particularly in relationships that were already stressed before the diagnosis of FA. Alternatively, some couples feel that the magnitude of the illness has helped them forge stronger relationships.

### What Parents Can Do

- Recognize that there is much more to your child—and your family—than FA. Try to enjoy “normal” family activities, encourage your child’s dreams for the future, honor other siblings’ emotional needs, and celebrate each triumph no matter how small.
- Join FARF's online support groups for FA.
- Attend events sponsored by FARF and other organizations.
- Become an expert about FA, its treatments, and options for the future, such as preimplantation genetic diagnosis (PGD).
- Familiarize yourself with techniques for parenting children with chronic illness.
- Forge strong, collaborative relationships with experienced physicians.
- Learn how to explain FA to inexperienced care providers, educators, and others while respecting your family’s need for privacy.
- Advocate for your child’s best interests in education, health care, and elsewhere.
- Recognize the signs of depression and anxiety, and seek out emotional support when you or your family members need it.

Many parents living with FA feel anxious or depressed from the onset, unsure of what to anticipate. The abilities to manage these emotions, make decisions, continue to function, and enjoy life may not be present initially, but are skills

to be mastered as time goes on. Psychosocial support services can greatly assist families who find it difficult to function in the face of their emotional responses; it is important to encourage parents to seek help when they recognize that they need it.

Staying abreast of the ever-growing body of knowledge about FA and its potential treatments can help parents feel calm, focused, and grounded. Talking to other parents, understanding the processes of decision making, and getting support can help parents maintain the emotional balance they need. Information and support are readily available from the Fanconi Anemia Research Fund (FARF) through its website, Facebook pages, e-group, family materials, and communication with FARF staff. These resources support the ongoing and changing needs of children, adolescents, young adults, and adults with FA, and their families. For several years, the FARF has held its annual Family Meeting at Camp Sunshine at Sebago Lake in Casco, Maine (<http://www.campsunshine.org>). The meeting blends educational sessions, presentations about current research, psychosocial support, and recreation.

Support groups offer parents the opportunity to be parents: to compare their child with other children, to seek companionship of other parents in similar situations, to share information, and to join the fight against FA and become empowered in the face of the illness. Facebook, CaringBridge sites, CarePages, and other social media create a global connection among families affected by FA. At times, individuals may feel overwhelmed by the emotional commitment to others and excessive amounts of time spent on the Internet; when this happens, it is important to set personal limits and take a break if needed.

Parents may be incorrectly perceived as aggressive when they advocate for the best interests of their children. There may be moments when families and individual physicians do not agree on treatment options or alternatives (e.g., hematopoietic stem cell transplantation, the use of androgens, or other therapies). The professionals involved in the patient's care must work to make the best decisions *with*, rather than *for*, families. This strategy will help reduce the possibility of future regrets for families and professional staff.

Relationships forged with physicians can be of tremendous value and significance to families affected by FA. The quality of these relationships often influences the family's entire experience of the disease. By helping families navigate the course of the illness and think through decisions, physicians can help those living with FA feel part of a larger system rather than feeling isolated and alone.



Parents, caregivers, and other family members truly become experts about FA. They must integrate tremendous amounts of information while attending to their child's medical needs and managing all other activities of the family. It is not surprising that when parents of children with FA are asked what they have learned about themselves or their children since the diagnosis, they overwhelmingly affirm that they have learned how strong and capable they and their children are <sup>(4)</sup>. Parents describe having a greater appreciation for the things that they do with their children, and they often describe a newfound ability to experience each day to its fullest.

### **Parenting in a family with FA**

When a child is diagnosed with a life-threatening condition, concerns about the child's future often change regular parenting habits and instincts. These changes can profoundly affect the parent-child relationship, and can go on indefinitely in the case of a long-term illness like FA. Parents may turn to physicians for support in returning to normal parenting patterns once the crisis of diagnosis has passed; physicians can also provide help when a child begins to act out and display symptoms of externalizing behaviors, such as tantrums or rebelliousness. Limit-setting and structure make children feel cared for, safe, and secure. Excessive permissiveness by parents who are fearful or sad—or disconnected and inconsistent parenting by those who suffer from depression—unwittingly communicates to children that their behavior doesn't matter.

### **Young Adults' Advice to Parents**

- Don't waste time worrying about what will happen in the future. If it's going to happen anyway, there's no sense in worrying about it right now.
- Don't feel guilty or responsible for the disease. You are not to blame!
- Don't be overprotective.
- Don't forget that my siblings need your attention and support, too.

Parenting siblings without FA—and deciding whether to conceive additional children as potential stem cell donors—can be emotionally challenging as well. Through a process known as preimplantation genetic diagnosis (PGD), parents can determine the genetic makeup of an embryo before it is implanted through in vitro fertilization. With the recent refinements in this process, many families will try to have a child free of FA whose HLA-matched stem cells can be used in a transplant for their child with FA. This process can be financially,

emotionally, and physically draining and, in some cases, all-consuming. Unsuccessful attempts at PGD are disappointing and can create other conflicts for the family, as treatment options as well as additional children stand in the balance. Successful PGD attempts, joyous in nature, create an unusual dichotomy in which the family anticipates the transplant and the birth of a child simultaneously. Discussing concerns with others who have attempted PGD can help families mitigate the intense emotions that can occur during this time. Parents who are beyond childbearing age and unable to benefit from PGD may experience remorse that this technology was not perfected earlier in the course of their child's illness.

## **Siblings in a family with FA**

### **Unaffected siblings of a child with FA**

Siblings care and worry about each other a great deal and, for many children, the universe is defined by their role as either an older or younger brother or sister. The siblings of a child with FA experience their own unique concerns, some visible to other people and some invisible. They may feel guilty that the disorder happened to their sibling and not to them, or they may feel that they are less important, because they are not getting as much attention. Siblings of children with life-threatening illnesses often have as much of an emotional response to the illness as the affected sibling.

### **What Siblings Can Do**

- Ask questions when you don't understand.
- Set aside one-on-one time with your parents.
- Recognize that you are unique, important, and treasured in your parents' eyes—even if they seem distracted at times.
- If you so desire, ask how you can help and become more involved in your sibling's care.
- Learn how to explain FA to curious peers while respecting your need for privacy.
- Recognize when you or others feel sad, frightened, or confused. Tell someone how you feel!

Sadness, anxiety, jealousy, and guilt are common emotions experienced by siblings <sup>(5)</sup>. Providing opportunities to express these emotions, keeping the

lines of communication open, and learning how to process the experience can help siblings work through their emotional responses and find their place in the family system. It is important for families to address their unaffected children's feelings and questions. Siblings are best able to thrive when they can spend quality time alone with their parents, when they are provided with developmentally appropriate medical knowledge, and when they truly feel that they are an integral part of the family <sup>(6)</sup>.

Siblings benefit from having a consistent, designated caregiver in their lives, particularly during times when their sibling with FA is hospitalized. Perceptions of the medical care required by their siblings may be more frightening or more idealized than reality. Inviting the sibling to be a part of the hospital routine can be helpful, and can assist the sibling's ability to cope with the situation.

Unaffected siblings of children with FA will usually be tested for their suitability as donors should transplant become a possibility. Families must make every attempt to appreciate the emotional journey of the sibling donor, a journey that can be markedly different if the sibling is a match or not, or if the transplant is successful or not. Age-appropriate information and emotional support are essential throughout the process. Stem cell donors have their own experiences, which need to be heard and acknowledged.

### **Multiple children with FA**

The already complex relationships of siblings are further complicated when more than one child in the family has been diagnosed with FA. The experience of each affected child will have its own impact on the other affected children. Non-affected siblings may be carriers of FA which creates yet another, often unspoken, dimension in family relationships, especially when they reach child-bearing age. It is important that affected and non-affected siblings have opportunities to talk with each other and with their parents. Sibling relationships can be among the strongest in life and need to be cultivated and nurtured.

## The Child's Journey with FA

### Explaining FA to a child

#### What a Child with FA Can Do

- Ask questions when you don't understand.
- Get involved in activities that you enjoy.
- Recognize that you are unique, important, and treasured—and remember that there's much more to you than FA.
- Learn how to explain FA to curious peers while respecting your need for privacy.
- If you feel ready, ask how you can become more independent and involved in your own health care.
- Recognize when you or others feel sad, frightened, or confused. Tell someone how you feel!

How parents accept and face the illness will influence how children with FA grow and adapt. If parents create an environment that allows for questions, discussions, and an expression of feelings, children will feel free to ask them for information about their illness and treatment options, and become active participants in their own disease management <sup>(7)</sup>.

Children often know much more about what is happening than adults might believe. In addition to what they have been told, children pick up information from ambient conversations, have independent interactions with professionals, and surmise things from the emotional climate around them. Children will ask questions when they want to know about a particular issue, but will often shy away from questions to which they do not want the answers or to which they have not gotten responses in the past. Children are good regulators of their own knowledge base, providing cues to the adults around them at all junctures. Once children are able to read and have access to the Internet, they often perform online searches about their illness.

A major concern of parents is how and when to tell children about FA. At each stage of development, children need age-appropriate explanations of their diagnosis and treatment. These explanations should grow in sophistication as the child grows. Information offered regularly to children will enhance their ability to understand their disease and establish trusting relationships. As they

get older and medical problems emerge, groundwork set in earlier years will encourage affected individuals to rely on health care providers for answers and advice. Providing children with practical knowledge about FA can help them understand what is going on in their bodies, and why a certain treatment or medical test is needed. This information builds trust and engages children as active participants in their own care.

### **School-related concerns**

School is a powerful normalizing environment for children. Learning has been called the “work” of childhood, and brings structure and meaning to children’s lives. Supportive educational environments can make a major difference in a child’s quality of life by building confidence and hope as skills are improved in cognitive, social, and emotional domains. When school attendance is interrupted, or a child’s performance at school is impaired, it can be very disorienting and disruptive. Prioritizing school for children with FA, when medically safe, helps parents and children maintain structure and hope.

Children with FA may face unique challenges in school. Some may have cognitive impairments that require special attention. Others may have no known problems, but may need extra assistance because of illness-related absences. Others may have physical limitations and may need extra support. School is often where children with FA may begin to feel as though they are different from others, whether their differences stem from frequent absences, inability to participate in activities, or other perceived differences. Children may need help learning how to adapt, respond, and connect with their peers.

Visible characteristics of FA, such as short stature or missing thumbs, serve as constant reminders to the outside world that a child with FA is different. At all ages, physical and other differences may set children with FA apart from their peers and cause them to feel anxious, isolated, or depressed. These emotions can affect their self-esteem and their ability to focus on age-appropriate achievements. Children need to be able to confide in their parents and others when they feel physically or socially limited by FA; counseling may be of great benefit during these times.

Fanconi anemia is commonly associated with a range of neurological and developmental issues characterized by mild to significant impairment, such as attention deficit hyperactivity disorder (ADHD), learning disabilities, and developmental delay <sup>(8)</sup>. In addition, treatments for FA, such as anabolic steroids and HSCT, may affect cognition, mood, and behavior. Any child

with FA who is having learning or behavioral issues at school should be formally assessed with an individualized educational plan (IEP) through the public educational system. Treatment centers often provide comprehensive assessments and specific academic recommendations that teachers and administrators at school can follow to personalize the child's educational plan. Children typically struggle in school after returning from HSCT, and transplant teams should help patients and families navigate the special education system and any other resources needed to optimize the child's adjustment and success. Social workers, case managers, child psychiatrists, psychologists, and neuropsychologists can help families advocate for their children.

### **Growing up with FA**

School-age children develop increasingly strong relationships with their peers as they begin to differentiate themselves from their families. Physical limitations that require children to remain dependent on their parents may influence the extent of their social activities. Each child and family must learn to strike a balance in social and family relationships that allows for a blend of independence and dependence, nurturing and differentiation.

Children with FA are invariably exposed to difficult experiences due to the nature of the illness. They face multiple hospitalizations and medical treatments, and may be exposed to the deaths of siblings or other children with FA. These children may therefore come to understand and deal with issues of mortality with which adults may not feel entirely comfortable. Although parents may work hard to "normalize" their children's lives, patients with FA have unique experiences and are confronted with the concept of death at earlier ages than other children. Thus, children with FA often seem more mature than expected for age, and often have more sophisticated attitudes than their peers regarding matters of illness and death. These children may also appreciate life more than others they encounter. However, some children experience a disconnection between what they understand and how to cope with what they experience. An environment of active support and open discussion is helpful for children, but can become complicated if adults do not recognize the need for such discussions.

During adolescence, challenging the rules is age-appropriate and, at times, promotes emotional growth. It allows teens to assert themselves as individuals and begin learning how to take responsibility for their actions. For adolescents with FA, however, this can be a time of rebelling against the "rules" of the disease. Young adults sometimes stop taking their medications and migrate to

activities that have been discouraged, such as sun bathing, drinking alcohol, and smoking. Adherence to medication regimens is a serious concern and should be given particular attention at this developmental phase, as should behaviors that increase the risks of cancer. For adolescents who may already feel socially isolated, foregoing of age-appropriate, yet maladaptive behaviors may pose additional psychosocial issues. During the adolescent years, association with peer groups of others with FA can combat countercultural behaviors, as can the wisdom of adults with FA—particularly if they can recall and share their own adolescent experiences.

As children with FA get older, they should become actively involved in assenting, consenting, and participating in decisions about their medical care. During this transition, parents may feel some relief that they are now making decisions *with*, rather than *for*, their children. Nevertheless, many parents have expressed anxiety about their children's abilities to make complicated and important decisions for themselves as they enter young adulthood. For some young adults, medical decisions will continue to be made in collaboration with their parents; in some cases, cognitive factors may limit the young adult's ability to make decisions. Other young adults will desire full responsibility. When this happens, parents must begin to trust the choices of their grown children. This period of growth for the person with FA also becomes a time of growth for parents, and occasionally creates dissonance between parents and their children.

Living with FA can be a long and arduous journey for many children. Room for continued growth, regardless of medical issues, is a vital part of childhood and prepares children to be successful and motivated in life. Empowering the child with FA inherently helps all family members acknowledge and delight in the child's gains, rather than focusing exclusively on FA. Celebrating achievements—great and small—cultivates growth and satisfaction for both children and their parents, and reminds families that FA is a component of their children's lives, but not what defines them.

## Young Adults and Adults with FA

There is a large and ever-growing population of young adults and adults with FA. Adult FA patients serve as an inspiration to all, yet should be recognized for their own needs, aspirations, and struggles. The medical course of FA is evolving, allowing for a better understanding of emotional and physical

challenges. Emotional connections for this group can also be found in young adults and adults with other rare illnesses who have survived to adulthood.

The transition to young adulthood engenders a more comprehensive understanding of the illness, sometimes producing a new emotional response to FA. During this time, adolescents begin to address salient issues that may have lain dormant during earlier developmental stages. Young adults with FA begin to find their own voices, assume responsibility for managing their own illness, become the primary decision-makers in their care, view their parents as partners or consultants, and truly become independent—all very appropriate and significant steps. It is important to help young adults gain their independence while also letting them know that they can continue to rely on their families for support and assistance. Those who face more severe manifestations of the illness may, of necessity, remain more physically and emotionally dependent on family members. Many young FA adults find that their family connections are stronger than those of their healthy peers. Dependence on parental care and transition to independent ownership of health care can be a major source of empowerment and anxiety. It is best effected over time and with the guidance of adult caregivers.

People with FA approach adulthood from a rather unique perspective, having grown up with uncertainty about the future. These adults face the “normal” challenges of establishing and mastering life goals and forging lifelong commitments, but must also find ways to address the impact of FA on issues surrounding partnership, sexuality, marriage, children, ongoing cancer risks, financial issues, and concerns over medical insurance.

### **Staying on track**

Fanconi anemia affects the whole family—current and future generations—and not just when a child is first diagnosed, but throughout the course of the illness. Ideally, a strong, collaborative relationship between parents and children should be well established long before the transition to young adulthood. Family members should start building this relationship as early as possible by working together to adopt the best decision-making practices for their particular situation.

Ambivalence and anxiety can plague young adults with FA, who need to adhere to unique challenges of living with the illness while struggling to be like everyone else. Normal developmental challenges do not evade young adults with FA, yet age-appropriate experiences may have greater intensity and significance. Relationships, peer pressure, experimentation with drugs



and alcohol, and sexual relationships all pose unique emotional and physical challenges for young adults with FA. Given the inherent increased risks of cancer from a number of these behaviors, young adults with FA are torn between the desire to take care of themselves and the desire to enjoy typical age-appropriate experiences with peers.

Omnipresent are feelings of isolation and distance from adults who are unaffected by FA; thus, relationships among adults with FA often engender an unequalled sense of personal connection. It is easy to see how the multitude of illness-related factors might affect the day-to-day emotional well being of young adults with FA. Beyond the personal aspects of dealing with the disease, these patients may feel accountable for their behavior in the eyes of their peers with FA, parents, physicians, and other professionals with whom they have developed connections. This sense of accountability may encourage young adults to do the “right thing.” Although such connections may increase compliant behavior, online networks can also begin to resemble more typical peer forums that increase the desire to have more “routine,” but risky, social experiences, which ultimately challenge adherence to the patient’s healthcare regimen. Special care should be taken by members of the young adult’s support group to approach these issues with a caring, nonjudgmental stance, understanding that while these behaviors may increase the likelihood of cancer significantly, they are also complex and may have roots in a variety of areas related to family dynamics, desire to have a “normal” life, desire to escape thoughts of FA, or simply lack of understanding about the impact of these behaviors on personal health.

### What Romantic Partners Can Do

- Learn about FA: the causes, treatments, implications for the future, and preventative health strategies.
- Consider joining online support groups.
- Recognize and remember that there is much more to your partner than FA. Focus on activities that you both enjoy!
- Ask your partner if, when, and how you might become involved in his or her care.
- Learn how to explain FA to others while respecting your partner’s need for privacy.
- Recognize the signs of depression and anxiety, and seek out emotional support when you or your family members need it.

### **Dating and relationships**

Deciding when to tell potential romantic partners about FA is an integral part of the dating process for any adult with FA. The issues of *whom* to tell, *when* to tell, and *what* to tell are inextricably tied with concerns about whom to trust and how a relationship might be affected. These issues can silently frame the early stages of relationships with roommates and romantic partners. An open and honest parent-child relationship provides the patient with a model of communication that can help young adults feel comfortable informing others about FA without shame or fear.

As relationships flourish, there is a natural inclination to think about the future. This reflective process evolves as young adults ponder their future goals in the context of what they know about their medical prognosis. All of this may influence their choices in friends, relationships, careers, marriage, and parenthood.

Partners of young adults with FA often need help understanding the disease and its implications for their relationships, as well as the roles of other family members. Partners also need an outlet for information, expression, and support when their partner is not doing well or has to make major life decisions. Many partners understand the disease intellectually, but aren't able to articulate their own concerns until medical concerns arise. Negotiating their roles as partners, particularly when a patient's parents may have nurtured the patient for decades, can be quite challenging. Information, support, and counseling are important tools to help partners navigate this complex journey.

## **Coping with Stem Cell Transplantation**

Stem cell transplantation can be a turning point in the lives of individuals with FA and their families. This procedure may cure the hematological problems of FA, but it also carries risk of illness or death. The perception of HSCT has changed significantly as the outcomes of transplant have improved in recent years. Many families talk about HSCT as less a question of "if," but more often a question of "when." Waiting with uncertainty for long periods of time can be stressful.

### **Preparing for transplant**

Families enter into transplant from a variety of different perspectives. Some patients require HSCT soon after a diagnosis of FA in the context of acute hematologic complications, while others are able to plan in advance, and still

others face the prospect of a transplant in the undefined future. Psychosocial needs differ depending on the patient's perspective and factors related to their family: Are the parents single or partnered? Do other siblings have FA? Are alternate caregivers available? Do the parents have flexible work schedules? How far must they travel to the transplant center? Is the family financially secure?

Many parents experience anxiety, depression, and psychological trauma during the time of transplant. It is critical that they have ongoing access to practical and psychological support from social workers, psychologists, and psychiatrists during and after HSCT. Transplant teams typically include professionals skilled at helping families navigate various challenges, including medical leave from work, childcare for siblings, absence from school, and the practical medical care of their child.

Children of all ages should be prepared for HSCT by their parents, who can work with experienced pediatric professionals to provide explanations appropriate for each child's developmental stage and medical situation. Child life specialists are professionals trained in using play, education, and art to support children in the healthcare setting. Parents often struggle with knowing how much information to share with their children out of a wish to protect them from worry or fear. Children who can communicate openly with their parents about their illness feel safer and experience less anxiety and depression, no matter what their medical prognosis is. Children who have been appropriately prepared tend to cope better with treatment demands and symptoms, and most importantly continue to trust their parents as sources of information and support through hard times <sup>(9)</sup>.

### **Course of transplant**

The days and weeks prior to transplant and through the process of induction chemotherapy are usually the most anxiety-provoking for patients and families. Anxiety tends to peak at this time and decline significantly after the actual transplant infusion, even though patients may remain in isolation awaiting engraftment for several more weeks. The prolonged hospitalization can be marked by significant discomfort and symptoms of nausea, pain, and fatigue, which should be treated aggressively with medication. Patients often find relief in other modalities as well, including hypnosis, behavioral therapy, and relaxation techniques. For many patients, physical symptoms steadily improve over time but may persist past discharge into the outpatient setting, which can be dismaying to patients who have not been adequately prepared. Boredom

commonly causes distress during this time and should be staved off by crafting daily routines with the help of calendars, including structured sessions with physical and occupational therapists, school teachers (as appropriate for the patient's age and time of year), and other supportive members of the multidisciplinary team as well as visits from family and friends. This is the “work” of getting better, and patients need encouragement to stay active in their own recovery. During this period, caregivers need significant support coping with, and keeping track of, extremely complex medical regimens—in some cases, patients take as many as 20-30 medications daily.

Once the patient has been cleared to return to school, children should be involved in discussions and decisions about the re-entry process. School staff can help students by role-playing examples of conversations that might occur on the student's first days back to school. This exercise can help the student find comfortable explanations that balance his or her need for privacy with answers that will satisfy the curiosity of peers. Adolescents and young adults may struggle with adherence to the recovery plan in the post-transplant phase due to a variety of psychosocial factors, including denial, anxiety, developmentally typical struggles with dependency and vulnerability, or post-traumatic stress disorder. Patients should be assessed for these and other issues, and to encourage positive personal care behaviors.

## **Issues Surrounding Death**

When nearing death, the patient and the family need emotional support, space to allow for clear thinking, practical forms of assistance, and tremendous understanding. By this point, the family has likely endured countless struggles with the illness. Continuing the fight and looking towards experimental options are essential pieces of armor that families use to cope and, for some families, it may make sense to search for options as long as possible. No one can determine when a specific family should cease searching for treatment; therefore, physicians can offer invaluable support by providing information and opportunities for discussion, helping families make decisions, accepting their choices, comforting them, and remaining available.

## What Physicians Can Do

- Provide the opportunity for an initial psychosocial assessment of the child and family at the time of diagnosis.
- Refer the family to appropriate counseling and other resources throughout the life of the person with FA.
- Provide developmentally appropriate information to patients to enhance their understanding of and familiarity with FA. Encourage dialogue among children with FA, other bone marrow failure dis-eases, or other life-threatening illnesses.
- Encourage the family to become involved in activities sponsored by FARF. These activities aim to help families develop and maintain an up-to-date knowledge base, gain psychosocial support, and play an active role in supporting FA research.
- Help families forge working partnerships with their physicians, allowing for mutual respect for what each party brings to the situation.
- Enable patients with FA, as they mature, to become responsible and proactive with regard to their medical care.

Support after the death of a child, whether the child was very young or an adult, is essential yet surprisingly difficult to find. Rarely do bereaved parents feel that their loss is understood—and in fact, others find it difficult to understand what they are going through. Grieving parents may find it difficult to accept support, except from people who have endured similar losses. Parental grief does not go away; it changes over time. Certain factors related to the length of the illness tend to complicate the mourning process for families, such as the number of children with FA, a perceived or actual lack of support and the mourner's perception of whether the death might have been prevented. After a long, hard fight, the family may feel a sense of guilt at not having been able to prevent the child's death.

Relationships between clinicians and families should not end abruptly during the bereavement period, as it is a most difficult phase. Explaining to families that intense feelings of anger, regret, loneliness, and depression are part of the natural grieving process is often helpful. Ongoing communication may serve to reflect on the child's life, provide referrals for counseling and support groups, and express empathy about the family's struggle.

The death of a child or sibling is devastating and has lifelong implications for the family. The added complication of a genetic illness—one that a family will continue to deal with for generations to come—adds to the complexity of coping after a child dies. Fanconi anemia will always be an issue for an affected family. Many members of the FA community feel a unique connection with one another, attesting to their resilience and ability to value life and embrace the future. The FA community is strong, active, impressive, and has been greatly empowered by the FARF. Families should be referred to the FARF at the time of diagnosis so that they can avail themselves of the many services provided.

Although the diagnosis of FA can impose great challenges, it can also enable all family members to find great strength, to learn to embrace life to its fullest, and to assess what is valuable in life. The support within the FA community through FARF and its FA family meetings fosters hope in families and enables resilience on the FA journey <sup>(8)</sup>.

## Chapter Committee

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# Chapter 19: The Grieving Process and the Physician's Role: A Mother's Perspective

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## Introduction

When I first wrote reflections on the grieving process more than a decade ago, I described the classic “stages” of grief that were prevalent in the psychosocial literature. I no longer believe people travel through such predictable stages to some ultimate resolution. Furthermore, I failed to appreciate fully that families dealing with a genetic illness grieve a *series* of losses inherent in living with a child or children with a life-threatening illness. These unique challenges greatly complicate the grieving process. I try to address these issues in this updated chapter.

Obviously, no two people confront a profound loss in the very same way. Even within a family, each person experiences emotions with different intensities and at varying times. By necessity, this chapter leans heavily on my personal experience of grief and the stories of others whose lives have been forever altered by Fanconi anemia (FA). I hope that understanding the emotional challenges faced by FA families will enable physicians to better meet the needs of this unique population.

In the 1980s, my husband and I learned that of our five children, all three daughters were born with FA, a life-threatening genetic disorder. We lost our daughter Katie in 1991 at the age of 12, and Kirsten died in 1997 at the age of 24. Our Amy is now 27 and her health is stable, but knowledge of this disease makes us fearful for her future. Living with our unspeakably profound losses has inescapably deepened and altered my understanding of the grieving process. Knowing so many families who have struggled with this disease or have experienced the loss of a child or spouse with FA has magnified my own awareness of the special challenges faced by our grieving families.



### **The Onset of Grief**

The grieving process that affects families dealing with FA can begin during pregnancy or at the moment of a child's birth, when severe physical anomalies signal a serious underlying problem. Some children with FA appear normal at birth, but a significant number are born with abnormal or absent thumbs, absent or shortened radii, small size at birth, small head and eyes, and/or other serious physical problems. Some conditions require immediate or repeated surgical intervention. The loss of the "normal" child one expected and eagerly anticipated can be devastating. The realization that one does not share the unreserved joy that others experience upon the birth of a child can be wrenching.

Parents typically experience intense shock and a range of painful emotions as they realize that their child does not look like other children and may require a series of difficult medical interventions. Parents may learn soon after a child's birth that the cause of various anomalies is FA. With that diagnosis comes the realization that the child has an inherited disorder that results in bone marrow failure, sometimes leukemia and other cancers, and a shortened life expectancy. This knowledge raises the possibility that other children in the family might also have FA. The cumulative impact of this devastating information plunges parents into an immediate and extremely painful grieving process.

FA is highly variable in terms of physical presentation, onset of symptoms, and course of the disease. Many patients are not diagnosed at birth. During the first decade of life, loss of energy, repeated infections, or signs of abnormal bleeding may lead ultimately to the FA diagnosis. Some patients are diagnosed because of an affected sibling. FA also can escape detection for many years and even decades. Infertility, cancers that appear far earlier than one would expect, or other subtle physical findings may suggest FA. But whenever the diagnosis is made, parents will experience the acute loss of the expectation that their child would lead a full and normal life. Learning what might lie ahead, they ache for their precious child and, indeed, for their entire family.

FA often progresses slowly, and patients can live for years and sometimes decades after the diagnosis. As a result, families may endure chronic grief. With every acute crisis such as worsening bone marrow failure or the diagnosis of cancer, loved ones experience again the most painful phases of the grieving process.

## **Characteristics of the Grieving Process**

### ***Shock or denial***

The first expression of grieving is often characterized by numbness and an inability to accept the diagnosis. Parents may tell themselves that the diagnosis is inaccurate, that someone has made a dreadful mistake, or that there must be a magic pill that will make this go away. Some individuals appear calm and can seem to be functioning normally. They carry on with their daily routines, perform regular tasks, and ask appropriate questions. But in fact, they may be functioning on “automatic pilot.” Often they cannot hear, remember, or process information accurately. This phase can last from hours to months and is often intermingled with other characteristics of grief.

### ***Roller coaster of emotions***

Shock and denial give way to a roller coaster of emotionality. Family members commonly experience feelings of crippling sadness, anger, guilt, anxiety, despair, terror, and being out of control. Sudden outbursts of tearfulness or expressions of rage are common. With any loss, we frequently experience some level of guilt. When parents have unknowingly passed lethal genes on to their children, feelings of guilt can be quite intense, even though guilt is entirely unjustified. These intense, painful emotions can wax and wane for months, even years.

## **Living with FA**

### ***Life after diagnosis***

Following the initial diagnosis, there can be long periods of stability when the individual with FA can experience low but stable blood counts and can function normally most of the time. A drug such as danazol can maintain and even improve blood counts for years. Following a successful bone marrow transplant, patients may experience decades of stability. Gradually the intense emotionality described above slows down. Waves of sadness, anger, anxiety, and other disabling emotions are far less intense. For many, there can be extended periods when life returns to almost normal: Families pursue work, school, and pleasurable activities, and FA is not the constant focus of one’s life. But FA parents sometimes characterize this stable period as “waiting for the other shoe to drop.” They frequently feel anxiety and dread about the future. With the appearance of new symptoms and the onset of feared or unexpected medical problems, they must deal, again, with the most painful phases of grief.

### ***The healthy sibling(s)***

Families affected by FA often include a child or children unaffected by this disorder. Parents worry about how this illness will affect the emotional stability and coping abilities of their healthy children. The medical and emotional demands of this illness can absorb much, and at times *all*, of the parents' time and attention, especially during times of medical crisis or extended intervention, such as transplant. Parents can feel guilty, fearing that their physical and emotional absence will negatively affect the entire family. Open and honest communication with all family members is crucial. The family needs to consider ways in which the unaffected siblings can obtain support during the most stressful times. Knowing that one is doing the best one possibly can under extremely difficult circumstances can lessen guilt.

*We have a son with FA and an unaffected daughter. I am always aware that I must not let our daughter feel left out, even inadvertently. She must never feel that our son gets all the attention because he is sick, or that he is loved more due to his illness. But I always wonder if I am doing justice to our daughter.*

—Mahazareen Dastur, FA parent

### ***Social isolation***

Feelings of isolation and loneliness are common, as family members realize that their friends deal with problems of a much different magnitude. Usually, parents know no other person in their community whose child has the same disorder. One feels alone, knowing that the hopes, dreams, and expectations that others have for their children may be drastically different from one's own.

Parents, unaffected children, and the child with FA may grieve the fact that the child's physical appearance sets him or her apart from peers. Short stature or missing thumbs can be the subject of other children's curiosity, and all too often, their cruelty. The ache family members feel for a child's unhappiness can be overwhelming.

### ***Chronic weariness***

Dealing with months and years of medical appointments, medical complications, insurance issues, financial concerns exacerbated by FA, and worry can lead to chronic weariness, including physical and emotional fatigue. Some parents describe feelings of low self-esteem and chronic depression. Most parents feel that part of their role is to protect their children from

dangerous, unhappy experiences. They feel helpless and out of control when confronted with the knowledge that they cannot shield their children from a life-threatening condition.

### ***Coping strategies***

*I must use my energy to do something good for others—to put purpose to the pain.*

— Diane Pearl, FA parent

The loss of control family members experience when dealing with a rare, life-threatening, often unpredictable illness contributes enormously to stress and unhappiness. Learning about this disease, treatment options, comprehensive FA treatment centers and future research directions can help family members regain a sense of hope and control. We advise families to attend FA Family Meetings whenever possible, and use that opportunity to ask questions of FA experts and other families. Use the FA Support Group for information and support. Read the *FA Family Newsletters* and pertinent sections from this *Guidelines* handbook. Many families have found that a focus on fundraising for research is an enormously therapeutic outlet, and one that might hasten life-saving results.

*Parents of children with a life-threatening illness also need to give themselves a break. We don't have to be brave and strong all the time, and it's okay not to think about FA or the future all of the time. That would drive me crazy! I call this "conscious denial." When I need to, I step up to the plate and deal with what is necessary.*

—Lisa Mingo, FA parent

Some families have identified positive aspects of dealing with this life-threatening illness. I have yet to hear a parent proclaim that the benefits outweigh the negatives, yet still, this illness has brought surprising insights and changes in life's focus to many. Families speak of having a greater compassion and empathy for the suffering of others. Realizing that a family member's life expectancy may well be limited can instill a deep appreciation of every minute that each one of us is given. Instead of living in the past or future, some families consciously focus on making the most of the present. Some report deeper and more satisfying relationships with family and friends, and an enhanced capacity to appreciate the things they have taken for granted. They

utilize Make A Wish Foundation, take family trips that otherwise would have been postponed, and pack as much enjoyment as possible into the stable times. They look for every opportunity to “seize the day.”

### ***Loss of a child or spouse***

*If you have ever lost someone very important to you, then you already know how it feels, and if you haven't, you cannot possibly imagine it.*

— Lemony Snicket, *The Bad Beginning*

Even when family members are well prepared for the possibility that a child or spouse might die, they often react with shock and disbelief to the loss of their loved one. The most painful emotions of the grieving process return. The rush of support from caring friends and family, the public or private events that follow the death, and the need to survive this intense period can carry one through the initial days of the grieving process. But the enormity of the loss usually leaves the bereaved with overwhelming sadness, despair, and an intense longing for the child who has died. This most painful period can be very extended.

### ***Marital issues***

Some couples report that struggling with a life-threatening illness and the death of a child brought them closer together. For others, their different coping strategies became a threat to their relationship.

Spouses often react in different ways to the death of their child. Some cry frequently and need to express their emotions constantly. Some are uncomfortable expressing their feelings and believe they must project “strength” to their family and friends. Differences in coping often lead to marital stress, as spouses can feel misunderstood, unappreciated, and resentful of one another. Each may feel that the other spouse is unable or unwilling to provide sufficient emotional support. Some couples report an unhappy disruption of their previously satisfying sex lives together. The grieving process can even threaten a formerly strong marriage. Communication between partners about fears, feelings, and needs is essential. Marriage counseling may be crucial to help couples learn to be more tolerant, understanding, and supportive of one another throughout this extremely painful time.

### ***Guilt***

One of the irrational and truly unfair aspects of grieving the loss of a precious child is the extent to which parents often feel intense guilt. Even those who have learned all they could about this disease, followed the advice of esteemed physicians, and tried their best to make the “right” decision at each step of the way can be riddled with guilt when a child ultimately dies. They may blame themselves for going too early or too late to transplant, for picking one transplant center instead of another, for being too aggressive in trying to influence a physician’s decisions – or not asserting their own beliefs strongly enough. They may remember those times they could not be “there” for their child, and dismiss all the hours they spent, in fact, being there. If they felt responsible for protecting their child, they conclude they have ultimately failed. Parents need to reassure themselves that they made the best decision they could at that particular time, that they can never know the outcome of an alternative decision, and that they must learn to be more compassionate towards themselves.

### ***Crisis in religious beliefs***

Parents with strong religious convictions often state that their faith has brought them peace and comfort, and has enabled them to cope with this illness and the death of a child. Many find solace in the belief that everything happens for a reason, their child is in a better place, and someday they will be reunited with the lost child. They state that their religious community has been a tremendous source of help and support.

For others, the suffering and death of a child have caused them to question their beliefs. Some experience a deeply painful crisis as they try to reconcile their firm convictions and the enormity of their suffering. Those who have always believed that “God does not give us more than we can bear” suspect that they have, in fact, been given more than they can bear. Parents who believe that “everything happens for a reason,” even when we cannot understand the reason, wonder what possible benefit could come from the suffering of an innocent child? Those who believe strongly in miracles question why a miracle did not rescue their precious child. A trusted minister, priest, rabbi, or other spiritual leader may be crucial in helping parents work through and come to peace with these most difficult issues.

### ***Other complications of the grieving process***

A grieving family member frequently experiences cognitive and physical changes. One can suffer forgetfulness, memory loss, slowed thinking, confusion, short attention span, and difficulty in making decisions or problem solving. Common physical symptoms include insomnia, headaches, respiratory problems, higher blood pressure, gastro-intestinal problems, and weight gain or loss. Those experiencing chronic grief are themselves at higher risk for serious health problems.

### ***Grieving multiple losses***

*Grief and trauma are cumulative. We can think of each of us as having a “grief bank” in which we make deposits (adding to our griefs/traumas/losses) and withdrawals (letting go of our griefs/traumas/losses). Every loss has a distinct weight and bundle of emotions, and as you move through life, you deposit each into your grief bank. With many losses, your bank becomes quite full, and as you grieve new losses, the contents mix and begin to spill over. Emotions are not just linked to a single loss, but reflect cumulative losses. You begin to grieve pieces of all of your losses at once.*

—Rev. Tom Harshman (summary of remarks)

Families can have more than one FA child, so families can and do experience multiple losses. It is an unimaginable and devastating tragedy to live for years or decades with multiple children with a complicated disorder; one that can pose a series of life-threatening challenges unique to each child, and that can end in the death of two or more children. Each loss reactivates a previous one as a parent relives the earlier emotions of loving and losing another child or children. The experience of grief is compounded and the work of integrating yet another loss is overwhelming. Families dealing with multiple losses need a tremendous amount of support and strong coping strategies to manage the grieving process.

Many FA families have formed a close supportive network. In addition to giving and receiving advice and emotional support, families are also deeply affected by the ups and downs of others in the support network. They grieve the deaths of children and young adults they have met through the support group and at the FA Family Meetings. Ironically, the many medical challenges and ultimate loss of others in this close network can be threatening to other families and can add to the cumulative losses experienced by this unique group.

### ***What helps, and what doesn't***

*Grief is not a disorder, a disease, or a sign of weakness. It is an emotional, physical, and spiritual necessity, the price you pay for love. The only cure for grief is to grieve.*

—Earl Grollman

What helps one survive the most painful aspects of the grieving process varies greatly from one person to the next. In my experience, anti-depressants and even therapy did not help (although both can help many). I finally concluded that I owned this grief, and if life could ever become more bearable, I had to walk right through the middle of the most painful feelings imaginable. I had to cry (incessantly, my husband would say), and I had to express my deepest feelings if a special friend would listen. I needed to live with my immense sadness and the longing for what I had lost. I had to grieve. I also had to find those caring family members, friends, and physical activities that would bring positive energy to my life. I had to walk, immerse myself in the beauty of nature, ski down a mountain, and listen to the classical music that brought peace and joy into my life.

Some find comfort in creative and artistic pursuits, in journaling, in prayer, and in meditation or mindfulness. Immersion in any special passion can be a great source of support. Reaching out to people in need or devoting energy to a cause that serves others can be therapeutic. Many parents affirm that their religious beliefs have been crucial to their emotional survival. And yet some get “stuck” in the grieving process and find it extremely difficult to function over an extended period of time. In these situations, professional help may be essential to move through the most painful phases of grieving.

### ***Recovery: Is this possible?***

*The reality is that you will grieve forever. You will not ‘get over’ the loss of a loved one; you will learn to live with it. You will heal and you will rebuild yourself around the loss you have suffered. You will be whole again but you will never be the same. Nor should you be the same nor would you want to.*

— Elizabeth Kubler-Ross and John Kessler

Parents frequently believe that they will never experience happiness again and that the depression and deep sadness they feel will be with them forever. This



is very rarely the case. Over a period of months and even years, the pain one initially experiences will lessen. Parents find increased energy to engage with other people, to work with energy and purpose, and to follow new pursuits. There is a time when one can laugh again and experience true joy. But I believe that when a parent loses a child, the parent never really “gets over” the loss. Rather, one integrates the loss—it becomes a part of the parent’s being. A persistent, sometimes gentle ache ties you forever to the person you have lost. Many grieving parents believe that this is as it should be. The special relationship you cherished, the precious time you shared, and the essence of the one you lost is forever a part of you. And in spite of your suffering, you might well admit that you were truly fortunate to be the parent of this wonderful human being. Many acknowledge that, in spite of what they and their child have been through, they would forever choose the time they had, than never to have known this child at all.

*At some point, the pain lessens. The hole in my heart shall always remain, but there is healing around that hole, and I carry my daughter in my heart, always.*

—Beth Janock, FA parent

## The Physician’s Role: What Helps and What Hurts

This section refers to the role of the physician, but often, especially during a prolonged hospitalization, an entire team is involved in caring for the patient, including nurses, social workers, physical therapists, and a wide range of professionals. The comments below apply to all health care providers.

### ***How physicians can help***

A patient’s physician is not expected to “treat” the emotional distress of the grieving parents or spouse, although it may be appropriate for the physician to refer the parents or spouse to a support group, grief counselor, or other professional in one’s local community. The patient’s physician, however, has enormous power to affect the emotional state of the family caregivers. The physician can play a crucial role in helping the family move from the depths of despair, anger, and self-blame into understanding the disease, making and participating in a treatment plan, and maintaining hope.

### ***Physician characteristics that help***

Almost all pediatricians or family doctors and even many hematologists have had no prior experience in treating FA patients. The treating physician needs to be willing to learn, eager to explore current literature and to seek out information from experts. The doctor must be willing to invest the time to learn new therapeutic approaches. FA families can help by providing physicians with this updated *Guidelines* book and with pertinent information from scientific symposia and family meetings.

It is extremely helpful if the physician is a caring, warm individual, concerned about the welfare of the patient and aware of the stress the family is experiencing. Treating physicians must be good at both explaining and listening. They must communicate in a language the family will understand. Physicians need to listen to fears and concerns, and answer questions in understandable terms. It is crucial that they give families the *time* they need to ask questions, and listen to their concerns and feelings. Physicians may be helpful in encouraging the family to ask difficult questions that fear may cause family members to avoid. It is all right for doctors to admit they don't know all the answers and to assure families that they will try to find out.

*After suspecting FA, our wonderful hematologist, Dr. Richard Sills, sat down with us very late one night explaining, reviewing, and answering every single one of our questions and fears. He was amazing, intelligent, and compassionate.*

—Beth Janock, FA parent

### ***Maintaining hope***

The treating physician must be honest, straightforward, and frank in discussing the diagnosis of FA. The family needs to know that this is a very serious, life-threatening disorder. False reassurances do not help, nor does withholding information. At the same time, doctors should encourage families to be hopeful. The literature on FA and its gloomy statistics reflect past treatment approaches. Statistics do not include the high probability that bone marrow transplant outcomes will continue to improve, that new methods of gene therapy could change life expectancies, and that future discoveries will improve overall survival rates. Families need to know that scientific discoveries concerning this rare disorder have progressed at a very rapid pace over more than a decade and that many laboratories are actively pursuing new and hopeful approaches.

When appropriate, they need to know that new discoveries could greatly improve the prognosis for their child or spouse.

Depressed parents (and FA parents have reason to be depressed) must work harder than most to be great parents. They can unwittingly create an atmosphere of sadness and worry which permeates every day and which children immediately sense. As a result, the time that is shared between parent and child may not be “quality time” at all. By emphasizing progress and helping to instill hope, physicians can greatly assist in improving the family's quality of life.

### ***Entering into a partnership with families***

Family members should be encouraged to play an active role in the treatment plan. Making families part of the decision-making process enables them to cope with the anxiety, depression, and loss of control they are experiencing. The relationship between physician and family should be one of mutual respect, shared information, and joint decision-making. Caretakers know the patient well and are aware of subtle or abrupt changes in the patient's condition. They can be an invaluable source of information.

The doctor should encourage family members to voice their concerns or disagreements with the treatment plan. Parents and patients are often intimidated by medical authority, or fear appearing foolish by asking inappropriate questions. But they must live with the results of any medical intervention, so they must understand and agree with decisions. Often, decisions are not clear-cut. Outcomes are unknown and risks are enormous. Family members must believe that the most appropriate decisions were made, given what was known at the time. When they are ill-informed and have never voiced their questions or concerns, they may forever feel guilty if the outcome is not good.

### ***Being responsive to patient needs***

A doctor's responsiveness and empathy with the patient helps foster a good relationship with other family members. When the physician is warm, caring, and concerned about the patient, parents feel positively towards that provider. Whether the patient's immediate concerns are about pain, nausea, fear, or side effects of treatment, these concerns need to be addressed in a caring manner.

Parents are terrified that their child will experience unmanageable pain. I believe that a great deal of pain can be eliminated when pain management is

a priority. Bone marrow aspirations and biopsies can be performed under very short-term, general anesthesia, leaving the patient with a less painful experience. Bone marrow transplant centers have done this routinely for years. But outpatient clinics, aware of the importance of this issue, may be able to offer the same service.

Even though total anesthesia is more costly and the assistance of an anesthesiologist is mandatory, the children and adults who must experience these procedures on a regular basis should not have to endure unnecessary pain. On very rare occasions, a patient's clinical status makes total anesthesia unusually risky. However, in many cases in which patients are not provided with total anesthesia, it is simply because it is not suggested or offered by the physician or care facility, not because it is unavailable.

### ***Communicating diagnostic results promptly***

Family members experience much agonizing distress while waiting for the results of clinical tests. From a simple CBC to a full-body CAT scan or MRI, parents or spouses wait with excruciating anxiety for results which may tell them if their loved one is doomed to die soon or has dodged a terrible diagnosis. For many, the waiting process is more painful than dealing with the results. Once one knows the extent of the problem, he or she can begin to deal with it. The treating physician should make sure that family members get crucial information as soon as possible. If the news is catastrophic, it is important that the patient's primary doctor deliver the bad news if at all feasible.

### ***Encourage normalcy***

When appropriate and within prudent medical guidelines, physicians should encourage patients to live as normally as possible. Sometimes it is necessary to curtail physical activity, but simple measures such as a protective helmet or other modifications might make normal activities possible. When platelets are so low that participating in any contact sport is not wise, there may still be a role for a child in assisting the coach, thereby maintaining involvement with the team. Consideration should always be given to maximizing the quality of a patient's life.

### ***Being "there" for a family when a patient's condition worsens***

When a patient's condition worsens suddenly or when he or she approaches death, a physician should not suddenly withdraw from the family. Many families report that this occurs. They suspect that doctors need to protect

themselves from the family's emotional response and the physician's own feelings of grief. But families desperately need support at this time, and are deeply grateful when physicians are able to empathize with them during the hardest times. When appropriate, physicians should connect families with the palliative care staff if this service is available. Some parents struggle over how or if they should approach the subject of death with a child. The physician, a spiritual counselor, or a palliative care specialist may be able to help parents with this extremely difficult discussion.

***Attitudes and behaviors that do not help***

Family members have openly discussed physicians' behaviors that are not helpful. The doctor who knows little or nothing about FA and has no time to become informed is not helpful. Doctors who appear cold, distant, and unsympathetic do not gain the family's confidence. Physicians who speak only in complicated medical terms, have little time to answer questions, or are rushed or impatient are not helpful. Doctors who deal with families in a condescending way, or do not consider the family's input, contribute to emotional stress. And physicians who have no time or ability to empathize or listen to a family member's distress are perceived as aloof and uncaring.

*Our adult daughter is pretty much housebound now. She grieves that she hasn't been able to pursue her dreams of a career and family. When doctors ask her what she does for work or fun she is upset and embarrassed, and grieves the life she is unable to live. Doctors need first to listen to her, ask what she is able to do, and acknowledge how hard it is to live with FA.*

—Lynn Sablosky, FA parent

One of the most difficult decisions families may face is which medical center to choose for a bone marrow transplant. Families appreciate physicians who help them review their options with unbiased objectivity, focusing only on the needs and best possible outcome for this particular patient.

*I find it extremely upsetting when doctors get defensive when you ask if your child should be transplanted at another medical facility (i.e., one with expertise in transplanting FA patients). The doctor should recommend what's best for the patient. It can be very confusing for a parent trying to make the best decision possible, and a doctor's defensive attitude can add a lot of stress to one's daily life.*

—Lisa Mingo, FA parent

Many parents tell stories of doctors who informed them that their child would probably die within a specific period of time or before reaching a certain age. These comments have devastated parents and have frequently proven to be untrue. Too much is unknown about how any one FA individual will progress. The positive impact of future therapies is obviously unknown and cannot be addressed in the medical literature available today. Doctors who are noticeably missing when bad diagnostic news is delivered or who never come to see a dying patient bring additional pain to a grieving family.

The physician with endless time to research an orphan disease and provide ideal patient care may be difficult to find in these times of work overload, managed care, and pressures from other patients equally in need of quality care. But having dealt with this illness for over thirty years, this writer has observed enormous variance from one physician to another in terms of his or her ability to work with families burdened with a life-threatening, chronic illness. Families should try to identify physicians who can best meet the patient's physical and emotional needs. Physicians should become more aware of and responsive to the needs of this unique group of families.

## **Postscript**

No one should have to endure the devastating, life-long heartache that follows the loss of a beloved child or young adult. In an effort to spare other families what we have experienced, we and others have worked tirelessly to raise funds to advance scientific and medical discovery. In the last 25 years, our combined efforts have greatly extended the lives of individuals with FA. Bone marrow transplant outcomes have improved dramatically since our own children desperately needed healthy marrow. The discovery of FA genes sheds light on the basic science underlying our disorder, and researchers are developing new drugs to prevent and treat the cancers that plague individuals with FA. The discovery that aldehydes are uniquely toxic to the DNA of individuals with FA suggests new therapeutic strategies. We will continue to devote our lives to this cause. We have growing faith in the accelerating pace of scientific progress, justifying our fervent hope that, in the future, families will no longer experience the painful grieving process described in this chapter.

# Chapter 20: Clinical Management Checklist

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## Introduction

Fanconi anemia (FA) is a complex disease that can affect all systems of the body. Patients are at risk for bone marrow failure, leukemia, squamous cell carcinoma, and other types of malignancies. In addition, patients can be affected by other facets of the disease, such as abnormalities of the endocrine, gastrointestinal, and skeletal systems.

This checklist, a compendium of suggestions from many authors of the FA Guidelines, is not all-inclusive and should not take the place of reading the comprehensive information provided in this book. Many of the tests and procedures mentioned in this chapter will not be appropriate for every individual patient, nor does the following checklist present an exhaustive list of possible tests or treatments that each FA patient could or should undergo. Rather, this checklist should be used at the discretion of the patient's physician and should be tailored to the needs of the individual patient and his or her family.

## Diagnostic Testing for FA

### **Who should be tested? (detailed in *Chapter 1*)**

- All children with multiple anatomic abnormalities, possible VACTERL syndrome (birth anomalies affecting several parts of the body that tend to occur together), very short stature, or abnormal thumbs should be tested for FA.
- All full siblings of the FA patient, regardless of whether they show physical signs or symptoms, must be tested to rule out FA and to determine whether they are matched sibling donors for stem cell transplantation.
- All children of individuals with FA.
- Young adults that present at atypical ages for specific malignancies, including squamous cell carcinomas of the head and neck or vulva.

- Individuals with excessive toxicity after treatment with alkylator chemotherapeutics, especially if for an FA-related malignancy such as myeloid leukemia or squamous cell carcinoma of the head and neck.

### **How are patients tested for FA? (detailed in *Chapters 1-2*)**

- Anyone suspected of having FA should be referred to a doctor who specializes in diseases of the blood, known as a hematologist, to arrange for a diepoxybutane (DEB) or mitomycin C (MMC) chromosome fragility test of blood lymphocytes. In the US, this test should be performed at a clinically certified (CLIA) laboratory that has expertise in FA diagnostic testing. Testing can also be performed by analyzing cell cycle arrest using flow cytometry after exposure to a crosslinker, as is used in Germany for the initial testing. The Fanconi Anemia Research Fund (FARF), the United States-based organization that published this book, maintains a website ([www.fanconi.org](http://www.fanconi.org)) with a list of such testing centers.
- If diagnostic test results of blood are not conclusive and there is a high probability of FA based on clinical assessment, skin fibroblasts should be obtained for more complete testing. If the result remains inconclusive, additional diagnostic testing is available, albeit predominantly available through FA Comprehensive Care Centers, and is further described in *Chapter 2*.

## **Good to Know**

**Chromosomes** are strands of genetic material that are passed down from parents to children. Most humans have 23 pairs of chromosomes, including 1 pair of sex chromosomes (females have two 'x' sex chromosomes; males have one 'x' and one 'y' sex chromosome).

**Diepoxybutane and mitomycin C** are chemicals used to break chromosomes in what is called a **chromosome fragility test**.

**Flow cytometry** is a tool used to study the number and types of cells present in a patient's blood sample.



## After an FA Diagnosis: What's Next?

### Good to Know

A **cytogenetic evaluation** examines parts of the patient's cells, including chromosomes.

**Renal dysplasia** refers to abnormal formation of the kidney, along with irregular cysts.

**Hydronephrosis**, or swelling of the kidneys, occurs when urine accumulates and is unable to make its way out of the kidneys.

### Medical management after diagnosis

The care of most patients should be coordinated by a hematologist with expertise in FA, in conjunction with the patient's local physician. See *Chapter 3* for a thorough discussion of ongoing hematological care.

### Complete history and physical

Patients diagnosed with FA should undergo a complete laboratory work up and physical examination that includes the following components:

- **Family history:** Assess consanguinity and history of prior family members with anemia, physical abnormalities, or cancer.
- **Past medical history:** Assess prior blood counts, congenital (present at birth) malformations, prior surgery, and medications previously used.
- **Hematologic (blood) assessment:** Determine the patient's complete blood count and differential, and perform a bone marrow aspiration, biopsy, and cytogenetic evaluation.
- **Hepatic (liver) assessment:** Assess liver enzymes and total bilirubin.
- **Renal (kidney) assessment:** Assess serum electrolytes and creatinine, and perform ultrasound to rule out renal dysplasia, hydronephrosis, and anomalies of the bladder and related areas.
- **Urologic examination:** Assess for external structural abnormalities, genitourinary (GU) reflux, urinary tract infections, and GU malformations. If a renal abnormality is found in a female, the patient should be assessed for reproductive tract malformations.

- **Endocrine (growth and hormone) evaluation:** Assess thyroid function, growth hormone parameters, serum glucose and/or glucose tolerance, lipid assessment, and bone mineral density.
- **Ear and hearing examination:** This exam should be performed by an otolaryngologist (an ear, nose, and throat specialist) to assess for hearing loss and/or structural abnormalities of the ears.
- **Eye examination:** This exam should be performed by an ophthalmologist, a type of eye doctor, if clinically indicated.
- **Examination for head and neck cancer:** This exam should be performed by an otolaryngologist.
- **Gynecological (reproductive) examination:** This exam should be performed by a gynecologist and is recommended for female patients aged 13 (external exam only) and 18 (comprehensive exam) and older. Age as well as menstrual and sexual history will dictate the specifics of the examination. See the *Reproductive Tract* section below for more detail. In addition, the physician should check for reproductive tract anomalies if the patient is known to have kidney anomalies.
- **Examinations by other specialists:** The nature of these exams will depend on the individual needs of the patient.

### **Genetic counseling (detailed in Chapter 17)**

Upon diagnosis, the patient and family should be referred to a genetic counselor who can explain the genetic testing process, clarify the mode of inheritance of FA, and provide reproductive and, if applicable, cancer counseling.

### **Complementation group assignment (detailed in Chapter 2)**

Identification of the FA complementation group and the underlying FA gene defects can guide the patient's medical management and help assess the patient's cancer risk. In the past, complementation group analysis was predominantly performed by FA-specialized laboratories, followed by screening of the FA gene. In the near future, this initial testing will be replaced by high-throughput sequencing approaches that are capable of identifying most genetic defects in patients with FA. When the underlying defect(s) cannot be identified by this approach, or in countries where this technology is not available, retroviral complementation testing, FANCD2 western blotting, or candidate gene sequencing remain viable approaches to further classify patients with FA as described in *Chapter 2*.

### **Mutation analysis (detailed in Chapter 2)**

Mutation analysis—a test to determine a patient’s genetic abnormalities—is available at specialized diagnostic laboratories and can be used to determine or confirm the initial complementation group result. This type of analysis is also used to perform other genetic tests, such as carrier testing or prenatal testing. It can guide family planning efforts, and may prove important for determining whether a patient is eligible to participate in prospective gene therapy trials or other research studies.

### **Prenatal testing and preimplantation genetic diagnosis (detailed in Chapter 17)**

Families wishing to have additional children may be interested in pursuing prenatal or preimplantation genetic diagnosis. Prenatal testing may be performed by amniocentesis or CVS and can be done with a chromosomal breakage test. Before pre-implantation genetic diagnosis can be performed, the mutations(s) in the patient’s FA gene must be identified. The physician should refer such families for appropriate medical and genetic counseling.

## **Living with FA: General Challenges**

### **Good to Know**

**Acute myelogenous leukemia (AML)** is a cancer of the blood and bone marrow. Blood cells are made in **bone marrow**, the spongy material inside bones.

**Cytopenia** refers to an abnormally low number of blood cells.

**Graft-versus-host disease (GvHD)** is a complication that can occur after a bone marrow transplant, when immune cells in the transplanted material consider the patient “foreign” and attack the patient’s body.

**Myelodysplastic syndrome (MDS)** refers to a diverse group of bone marrow disorders where the blood stem cells are abnormal and are unable to produce healthy blood cells. Formerly known as “preleukemia.”

### **Polypharmacy: A warning about potential drug interactions**

The involvement of multiple subspecialists introduces the risk that medications prescribed by one physician will interact adversely with those prescribed by another or that the use of non-prescription drugs may interact adversely with prescribed medication. It is extremely important that all subspecialists communicate with the primary physician to coordinate care. The patient should

take care to share with the primary physician and subspecialists all prescription and non-prescription drugs, dietary supplements and homeopathic agents used.

### **Cancer screening**

Patients with FA are at extraordinary risk for developing cancer at an early age, and therefore require lifelong surveillance, regardless of whether they have undergone a bone marrow transplant. See specific recommendations by organ site below in the section entitled *Living with FA: Body Site-Specific Concerns*.

### **Radiation exposure**

Because patients with FA have increased sensitivity to radiation (depending in part on the affected FA gene), the primary physician involved in managing the patient should work with the patient's family and all of the patient's care providers to reduce exposure to diagnostic radiation as much as possible.

### **Bone marrow failure (detailed in *Chapter 3*)**

Most patients with FA develop bone marrow failure, however, the age of onset can be highly variable, even among affected siblings. All patients should be monitored by a hematologist with experience in FA, regardless of whether they have bone marrow involvement. A detailed schematic for clinical monitoring of bone marrow failure is found in *Chapter 3*.

## **Good to Know**

**Stem cells:** Cells that can develop into one of many types of specialized cells in the body.

**Hematopoietic stem cell transplantation (HSCT):** A medical procedure that destroys the stem cells in a patient's bone marrow and replaces them with stem cells from a donor's bone marrow.

**Human leukocyte antigen (HLA):** A protein found on the surface of cells in the body, this protein helps the body determine what is "self" and what is "foreign." An HLA-matched donor increases the chances that the patient's body will accept the transplant as "self."

- **Myelodysplastic syndrome (MDS) and acute myelogenous leukemia (AML).** Patients with FA are at high risk of developing MDS and AML. They should be monitored closely to assess possible onset of MDS or frank leukemia, and to identify the presence of cytogenetic abnormalities that may warrant immediate intervention. Bone marrow aspiration, with or without biopsy, and cytogenetic evaluation should be done annually in patients with FA who have not received a stem cell transplant to allow comparison of the patient's current marrow to previous specimens. See *Chapter 11* for an individualized schedule for clinical monitoring of bone marrow and timing of referral for discussion with a transplant center.
- **HLA typing.** Early high-resolution HLA typing of the patient and immediate family members is recommended to assess the availability of potential bone marrow donors, should a transplant be necessary. A transplant physician can then decide whether there is a suitable family donor and/or make reasonable estimates of the time required to find a donor in the unrelated donor registries based on the HLA-typing. *In general, however, to ensure prompt and effective medical care, a donor search (if the patient has no sibling donor) should be initiated at least 4 months before the need for transplant and long before the development of MDS or AML.*

### **Hematopoietic stem cell transplantation (detailed in Chapters 11 and 12)**

Hematopoietic stem cell transplantation (HSCT) is currently the only therapy available to cure patients with FA of marrow aplasia, prevent progression to MDS or AML, and cure existing MDS or AML.

- **Pre-transplant precautions in patients with FA.** The FA diagnosis must be confirmed before proceeding to transplant. The donor, if related to the patient, must be tested to rule out the possibility of FA. The physician should take ample time to discuss childbearing options with the patient and family before transplant, as the transplant may affect future fertility.
- **Selecting a transplant center.** Because transplants in patients with FA are so complex, the physicians who developed these guidelines feel strongly that if a local transplant center has performed fewer than 10 transplants in patients with FA, the patient should be referred to a transplant center with greater experience in FA transplants whenever possible.

Post-Transplant Care
<p>Schedule of post-transplant clinical examinations See Table 2 in <i>Chapter 12</i> for a schedule of the clinical examinations needed after transplant.</p>
<p>Early complications</p> <ul style="list-style-type: none"> <li>• Watch for early complications of transplant, such as GvHD, graft failure, organ toxicity, and infections. Provide close follow-up of rashes, diarrhea, liver enzymes, and blood counts, with testing for viruses and monitoring of drug levels.</li> </ul>
<p>Late complications</p> <ul style="list-style-type: none"> <li>• Monitor for chronic GvHD, organ toxicity (cardiac, pulmonary, renal) or endocrinopathies (diabetes, hypothyroidism, gonadal dysfunction), osteoporosis, avascular necrosis, and cancer, particularly HNSCC and anogenital SSC.</li> </ul>
<p>Prophylaxis to prevent infectious disease (yeast/fungal, viral, or protozoal infections)</p> <ul style="list-style-type: none"> <li>• Most transplant centers will expect the patient to remain near the facility for a minimum of 100 days, during which time the patient is at highest risk for developing immunologic complications (i.e., graft rejection, GvHD, and opportunistic infections) associated with transplantation. Prophylactic antibiotic regimens commonly used after HSCT are outlined in <i>Chapter 12</i>.</li> </ul>
<p>Immune reconstitution and immunizations after transplant</p> <ul style="list-style-type: none"> <li>• The patient should be screened for immune reconstitution 1 year after transplant.</li> <li>• The primary care physician should discuss the exact timing of immunizations with the patient's transplant physician.</li> <li>• All patients and their family household members should receive the influenza vaccine on an annual basis. Only the intramuscular formulation should be administered because intranasal influenza vaccine contains live virus, which puts the patient at risk of becoming ill.</li> </ul>
<p>Hematology follow-up care</p> <ul style="list-style-type: none"> <li>• After transplantation, the patient's transplant physician will determine how often blood counts and bone marrow (BM) tests are needed.</li> <li>• In general, BM aspirates and biopsies are performed several times during the first year after transplant. The pattern thereafter varies widely by transplant center.</li> <li>• Subsequent BM examinations are warranted if the patient has mixed chimerism, remains transfusion dependent, or if there are concerns about low peripheral blood counts.</li> </ul>
<p>Ophthalmology follow-up care</p> <ul style="list-style-type: none"> <li>• The three major ocular complications after transplantation are cataracts, dry eyes (usually associated with GvHD), and retinopathy.</li> <li>• Any change in visual acuity should be assessed immediately.</li> </ul>

### **Blood transfusions and iron overload**

- **Transfusions.** Transfusion may adversely affect transplant outcomes and should be avoided if possible. If transfusions are essential, blood products should be cytomegalovirus (CMV)-safe and irradiated. Family members should not be used as blood donors for the patient. Timely consideration of transplant is recommended if regular transfusions are required.
- **Iron overload.** Patients who receive multiple transfusions of red blood cells are at risk for accumulating toxic levels of iron. The liver, heart, and endocrine organs are primary sites of iron accumulation, and end-organ damage may result (e.g., hepatic cirrhosis, heart failure, endocrine dysfunction). For an extensive discussion of the management of iron overload, refer to *Chapter 3*. Referral to a pediatric gastroenterologist or hematologist with expertise in iron toxicity is indicated for monitoring of iron overload.

### **Novel treatments (detailed in *Chapter 13*)**

- If the patient does not qualify for currently available treatment for FA, the patient or family should contact a major medical facility with a Fanconi anemia comprehensive care center to determine if and where novel treatments may be available on a clinical trial basis.
- In addition, the Director of Family Support Services at FARF can assist patients and families in locating possible clinical trials.

## **Living with FA: Body Site-Specific Concerns**

### **Bone health (detailed in *Chapter 6 and 7*)**

The relative risk of low bone density in FA patients remains controversial. However, a stem cell transplant may increase the risk of osteopenia, or reduced bone mass, for any patient regardless of underlying diagnosis. The recommendation for pre-transplant patients is to obtain a bone density screening (DXA scan) at age 14, with follow-up as needed. For patients who have undergone a transplant, a DXA scan should be obtained 1 year post-transplant, with ongoing monitoring as needed. Independent of transplantation, premature menopause is a high-risk factor for osteoporosis/osteopenia and gynecological experts who treat adult women with FA recommend careful monitoring of bone health. Long-term treatment with corticosteroids also increases the risk of osteoporosis/osteopenia. Recent studies suggest that FA men as well as women may be at risk.

### **Ears and hearing (detailed in *Chapter 8*)**

Patients with FA should be examined by an otolaryngologist at diagnosis to assess for possible hearing loss or structural abnormalities of the eardrums and/or middle ear bones. If the patient has structural abnormalities, the otolaryngologist may consider possible surgical intervention to improve hearing.

An audiologist should assess the patient at the time of diagnosis to determine whether an amplification system would be useful if hearing loss is documented. These systems can be used for children as young as 4 months. The audiologist can help the family arrange for speech and language therapy, if needed, and should also contact the patient's school district to inquire about early intervention services (as provided in the US from birth through age 21 by the Individuals with Disabilities Education Act).

If a patient with FA receives potentially ototoxic drugs (i.e., that can impair hearing), such as certain intravenous antibiotics, iron-chelating agents, and/or chemotherapy drugs used during hematopoietic stem cell transplant, the patient's auditory function should be monitored with serial audiograms.

### **Digestive tract (detailed in *Chapter 4*)**

Patients with gastrointestinal or hepatic concerns should be seen by a gastroenterologist. A number of people with FA have gastrointestinal symptoms, such as poor oral intake, nausea, abdominal pain, and/or diarrhea. *These problems may affect nutrition and/or quality of life in patients with FA.* The physician should ask the patient and family about gastrointestinal symptoms during routine clinic visits, as patients do not often disclose these concerns voluntarily.

The hepatic complications of androgens are also a concern in patients with FA. Androgens, which may be used to treat low blood counts in FA, are associated with multiple hepatic complications. Liver enzymes should be monitored every 3-6 months in patients receiving androgens, and a liver ultrasound every 6-12 months is recommended.



## Good to Know

**Osteopenia** refers to reduced bone mass. **Osteoporosis**, a more serious condition, refers to brittle bones that are easily broken.

An **oral glucose tolerance test** measures the body's ability to regulate blood sugar. This test can help determine if a patient has pre-diabetes or diabetes.

A **radial ray** defect is a birth anomaly affecting bones in the hand.

### Growth and hormones (detailed in Chapter 7)

Many children and adults with FA have endocrine problems, including growth hormone deficiency, hypothyroidism, pubertal delay, or diabetes. To ensure optimal care, the patient should consult with an endocrinologist or pediatric endocrinologist—a doctor with experience in growth and puberty—as well as other sub-specialists as indicated.

- **Baseline and ongoing evaluation.** At diagnosis and annually, each FA patient should receive a thorough baseline endocrine evaluation.
- **Growth.** Nutritional and medical causes for poor growth should be identified as early as possible for optimal treatment. Growth in children with FA should be followed clinically. Height, determined on a stadiometer, should be plotted on a growth chart at least annually.
- **Puberty.** Onset of puberty should be evaluated by at least annual physical examinations to evaluate stage and progression. After age 12, pubertal hormone concentrations should be obtained at least every 2 years as needed to assess pubertal progression.
- **Glucose tolerance.** A 2-hour oral glucose tolerance test (OGTT) with insulin levels should be obtained and repeated as determined by the endocrinologist.
- **Diet and exercise.** All persons diagnosed with FA, regardless of OGTT results, should take care to engage in regular exercise and consume a healthful diet that provides adequate calories and follows the guidelines of the American Diabetes Association. Concentrated sweets should be avoided.

### Hands and arms (detailed in Chapter 5)

Patients with hand or arm abnormalities should be assessed at the time of diagnosis by an orthopedic surgeon with experience in congenital limb anomalies. It is very important that the surgeon hold a *Certificate of*

*Added Qualification in Hand Surgery.* Early referral of the patient to an orthopedic upper extremity specialist is important to obtain the best possible surgical outcome.

The orthopedic surgeon should consult with the patient's primary physician. The surgeon should provide emotional support to the patient and family by initiating open discussions about the patient's psychological adjustment to the hand or arm anomalies.

### **Head and neck (detailed in *Chapter 14*)**

Patients with FA are at extremely high risk of developing squamous cell carcinoma of the head and neck (HNSCC). Proper prevention, surveillance, and treatment of HNSCC are essential.

Prevention
<ul style="list-style-type: none"><li>• Beginning at age 10, the patient should obtain a thorough examination every 6 months from an otolaryngologist, oral surgeon, or other doctor who is experienced in head and neck cancer detection and is familiar with FA. The exam should include a careful exploration of the nasopharynx, oropharynx, hypopharynx, and larynx.</li><li>• Maintain good oral hygiene.</li><li>• Minimize exposures to alcohol—including mouthwashes that contain alcohol—and avoid tobacco use and exposure to second-hand smoke.</li><li>• Receive the HPV vaccination series, beginning at age 9 for both boys and girls according to the recommendation of pediatric societies worldwide, to possibly prevent squamous cell carcinoma associated with the HPV.</li></ul>
Treatment and surveillance
<ul style="list-style-type: none"><li>• Suspicious lesions should be immediately examined via inspection, brushes, or biopsies. If a premalignant lesion is found, examinations should increase to every 2 to 3 months, at the physician's discretion. Malignant lesions must be treated immediately, as a cure can best be achieved via early surgical removal. Treatment should be discussed with a hematologist/oncologist with experience in FA.</li><li>• Aggressive monitoring by the surgeon is an absolute must for those already treated for head and neck cancer.</li></ul>

### **Mouth and teeth (detailed in *Chapter 10*)**

All patients with FA should have regular dental examinations at least every 6 months by a dentist who is well versed in FA cancer risks. The examination should include a thorough screening for possible oral cancer.

### Special note for post-transplant patients:

Because of the risk of bacteremia, patients should not have dental cleaning, extraction, or other invasive procedures for at least 1 year after transplantation.

### Reproductive tract (detailed in *Chapter 6*)

Female patients with FA may experience a variety of gynecologic issues, including structural abnormalities, delayed puberty, decreased fertility, early menopause, and a high risk of squamous cell carcinoma of the lower genital tract, which includes cervical, vaginal, vulvar, and anal cancers.

- **Gynecologic exams.** Beginning at age 13, the patient should have annual examinations by a gynecologist for visual inspection of the external genitalia. By age 18, sexually inactive patients should receive comprehensive annual gynecologic exams with cervical cytology testing (Pap smears), along with a discussion of STDs and contraception. Sexually active women with FA should undergo regular comprehensive exams. A colposcopy and biopsy should be done if lesions are identified during the exam or if the patient's cervical cytology test is abnormal.
- **HPV vaccination.** The patient should obtain a human papillomavirus (HPV) vaccination series beginning at age 9 to prevent HPV infection and potentially mitigate HPV-associated cancers.
- **Reproductive tract anomalies.** The physician should check for reproductive tract anomalies if the patient is known to have kidney anomalies.
- **Breast cancer.** Breast cancer surveillance, including annual breast exams, should begin by the patient's early 20s. Screening mammograms can be initiated by age 25 or if a mass is detected; however, the risks and benefits of mammography and its alternatives must be considered in light of FA cells' hypersensitivity to radiation. See *Chapter 6* for more specific recommendations.
- **Pregnancy.** The physician should discuss childbearing options with female patients before transplant, as the transplant may further affect the patient's future fertility. The patient should not take androgens during pregnancy. While pregnancy for women with FA who have not been transplanted is not life-threatening, it nonetheless may impact onset or severity of bone marrow failure, requiring intensified surveillance. The pregnancy

should be considered high risk and should be co-managed by a maternal/fetal medicine specialist and a hematologist. Pregnancies after stem cell transplantation have occurred, but are rare.

- **Menopause.** Patients with FA usually experience premature menopause. Thus, the physician should consider the patient's risk of post-menopausal conditions such as osteoporosis, cardiovascular disease, breast cancer, and the management of hot flashes.

### **Skin (detailed in Chapter 9)**

Patients with suspicious nevi (birthmarks) or other abnormal skin lesions should be examined by a dermatologist. All patients with FA should limit sun exposure and wear sunscreen to reduce the risk of skin cancer. Post-transplant patients should limit sun exposure to reduce the risk of cutaneous chronic GvHD.

## **Living with FA: Transitioning to Adult Medical Care**

Patients with FA are usually diagnosed in childhood, with their medical care managed in the pediatric medical system. As patients reach adulthood, the physician and patient must develop a plan for a seamless transition to adult medical care. This plan should allow for ample time to educate the adolescent patient and his or her family about the transition and to locate appropriate adult medical resources.

### **Creating an adult medical care plan (detailed in Chapter 16)**

The adult medical care plan should include surveillance and treatment of all aspects of the disease, including:

- Preventive health care.
- Ongoing hematological evaluation of patients who have received transplants, as specified by the transplant physicians. Patients who have not yet been transplanted should consult with experts in the transplantation of FA adults.
- Continuation of rigorous cancer prevention and surveillance, especially of head and neck and gynecological SCC.
- Screening for vascular and cardiac disease post bone-marrow transplant (electrocardiogram [EKG] and echocardiogram).

- Screening for endocrine-related conditions, such as abnormal thyroid function, diabetes mellitus, reduced fertility, and osteoporosis.
- Screening for effects of treatment that manifest later in life, such as cataracts. Patients receiving transfusions need to be screened for iron overload or the effects of iron-chelation therapy.
- HPV vaccination to help prevent SCC.
- Gynecological consultations to screen for and prevent cancer, to monitor menses, and to manage fertility and menopause issues.

### **Quality of life in adult patients with FA**

Quality of life varies greatly among adult patients with FA. Some may have neurocognitive deficits and need educational, vocational, workplace, community, or interpersonal relationship assistance. At one time or another, patients with FA may experience anxiety, depression, social withdrawal, difficulty with re-entry into society or school after transplant or cancer treatment, and trouble navigating the complex arena of health insurance. Programs to address these needs are available in many communities. Additionally, the Director of Family Support Services for FARF can provide patients and families with assistance in locating resources to address psychosocial or medical issues.

## **Chapter Committee**

*Margaret MacMillan, MD*

# Abbreviations and Important Terms

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**AA:** *Aplastic anemia.* A condition that occurs when the bone marrow fails to produce the proper amount and type of blood cells.

**Adenocarcinoma:** Cancers that form from cells that line the internal organs.

**ALP:** *Alkaline phosphatase.* An enzyme used to detect liver and bone disease.

**ALT:** *Alanine aminotransferase.* An enzyme used to assess liver function.

**AML:** *Acute myelogenous leukemia.* A cancer of the blood and bone marrow.

**Anal cytology:** Sometimes called an anal Pap test, this is a screening test used to detect anal cancers and precancerous lesions. During the test, cells are collected from the anus and examined under a microscope to identify abnormalities.

**ANC:** *Absolute neutrophil count.* The number of neutrophils in the blood. Neutrophils are immune cells that fight off infections.

**Androgens:** Hormones produced in the body that stimulate the development of male sex characteristics, such as testes formation and sperm production.

**Anorectal malformations:** A spectrum of disorders involving the rectum and anus. These malformations may include a blockage of the anus, a failure of the rectum to connect to the anus, or an abnormal passage between the rectum and another part of the body, such as the urinary tract or reproductive system.

**Anoscopy:** A medical procedure in which the doctor uses a tube-shaped instrument called an anoscope to search inside the anus and rectum for abnormalities.

**Antibodies:** Proteins produced by the blood to attack foreign material—such as bacteria, viruses, or transplants—that the body does not recognize as part of its self.

**Aseptic necrosis of bone:** Loss of bone primarily in the hip, knee and shoulder joints.

**AST:** *Aspartate aminotransferase*. Levels of this enzyme are measured to detect liver damage.

**ATG:** *Antithymocyte globulins*. Animal-derived antibodies that attack a patient's immune cells. Treatment with ATG helps prevent the patient's immune system from rejecting a transplant. ATG is also used as a therapy for aplastic anemia.

**Autosomal recessive condition:** A genetic condition that is passed on when an individual inherits two copies of an abnormal gene: one copy from the mother and another from the father. It's called "recessive" because the person must inherit *both* copies of the gene to develop the condition. This gene is located on one of the chromosomes numbered 1-22, which are called autosomes.

**Autosomal dominant condition:** A genetic condition that can be passed on when an individual inherits only one copy of an abnormal gene. It's called "dominant" because just one copy of the gene is sufficient to pass on the disease.

**B cells:** Type of white blood cell, lymphocyte, that is responsible for antibody production.

**BCC:** *Basal cell carcinoma*. The most common type of skin cancer in the general public.

**Basophil:** Type of white blood cell that is involved in allergic reactions.

**Biallelic mutations:** Genetic changes that are found in both copies (alleles) of the same gene.

**Biopsy:** A medical procedure in which the doctor removes a small piece of tissue, which is then examined under a microscope to determine whether dysplasia (pre-cancer) or cancer is present.

**BMI:** *Body mass index*. A measure of physical fitness that accounts for height and body weight.

**BMT:** *Bone marrow transplant*. A medical procedure in which a patient's bone marrow is replaced with bone marrow from a suitable donor. In most cases,

a patient's bone marrow will be destroyed by medication or radiation therapy before the transplant is performed.

**Bone marrow:** The spongy material inside bones where blood cells are made.

**BU:** *Busulfan*. A drug used to treat chronic myelocytic leukemia.

**Café au lait spots:** Flat, light brown birthmarks.

**Carrier:** An individual who inherits a single copy of an abnormal gene for an autosomal recessive disorder. Carriers usually do not develop the disorder, but can pass a copy of the abnormal gene onto their children.

**Carrier frequency:** The proportion of carriers in a population.

**CBC:** *Complete blood count*. Gives the number, and/or percentage, and/or characteristics of certain blood cells, primary white cells, red cells, and platelets.

**Centralization:** A surgical procedure that moves and centers the wrist over the end of the ulna (a large bone in the forearm).

**Chelation:** The use of a chelator (an organic chemical that bonds with and removes free metal ions) to bind with a metal (such as iron) in the body. Chelation may inactivate and/or facilitate excretion of a toxic metal. In FA patients, most often refers to a method for getting rid of excess iron.

**Chromosomes:** Strands of DNA that are passed down from parents to children. Most humans have 23 pairs of chromosomes, including 1 pair of sex chromosomes (females have two 'x' sex chromosomes; males have one 'x' and one 'y' sex chromosome).

**Chromosome breakage (fragility) test:** Often the first test to diagnose a patient with FA, this test measures the types and rates of breakages and rearrangements found in the chromosomes of cells. It also reveals how well the chromosomes can repair themselves after injury.

**CIBMTR:** *Center for International Blood and Marrow Transplant Research*. An organization that supports research to discover, apply, and improve therapies for bone marrow failure. Read more at <http://www.cibmtr.org>.

**Clastogen:** An agent that induces breaks in chromosomes.



**Clone:** A population of cells.

**Clonal abnormalities:** Changes in the structure or number of chromosomes in certain cells of the bone marrow.

**Clonal evolution:** A process by which cells acquire new abnormalities.

**Clonal expansion:** An increase in the percentage of cells with identical abnormalities.

**CMV:** *Cytomegalovirus*. A relatively common virus in the herpes family that causes mild symptoms in healthy people but can pose a serious health risk to immune-compromised individuals.

**Colposcopy:** A medical procedure in which a doctor uses an illuminated magnifying device called a colposcope to examine the vulva, vagina, and cervix. The procedure allows the doctor to find abnormal tissues that may be missed by the naked eye.

**Complementation Group:** A group of genes that works together to produce a person's physical characteristics. Prior to the identification of the genes and genetic mutations that cause FA, patients with the disease were classified into sub-categories known as complementation groups based on the patient's cellular features. These complementation groups correspond to the various FA genes (e.g., individuals who belong to complementation group A have mutations in the *FANCA* gene, whereas individuals who belong to complementation group B have mutations in the *FANCB* gene).

**Cortisol:** A steroid produced by the body that plays important roles in the stress response, immunity, metabolism of nutrients, and other processes.

**CSA:** *Cyclosporine*. A drug that suppresses the immune system and is used to prevent transplant rejection.

**CY:** *Cyclophosphamide*. A drug capable of killing specific types of cells. This drug is used to suppress the immune system and is also used to treat cancer.

**Cytogenetic evaluation:** A laboratory test that examines parts of the patient's cells, including chromosomes.

**Cytopenia:** An abnormally low number of blood cells.

**DEB:** *Diepoxybutane*. A chemical used in the chromosome breakage test.

**DNA Crosslinks:** Refers to two types of crosslinks. *Interstrand:* when a molecule binds to two positions on the same DNA molecule; *Interstrand:* when a molecule binds to two different DNA molecules.

**Duodenal Atresia:** A condition in which the entrance to the small intestine, known as the duodenum, is incomplete or blocked and does not allow the contents of the stomach to enter the intestines.

**DXA:** *Dual energy absorptiometry.* The primary test used to identify osteoporosis and low bone mass. It uses a low energy x-ray to evaluate bone density in the hip and/or spine and sometimes the wrist.

**Dyslipidemia:** Unhealthy levels of cholesterol and triglycerides.

**EA:** *Esophageal atresia.* A condition in which the lower end of the esophagus—the tube that connects the mouth to the stomach—is incomplete or blocked and does not allow food to pass from the esophagus into the stomach.

**EBV:** *Epstein-Barr virus.* A herpes virus that can be reactivated after bone marrow transplant, resulting in post-transplant lympho-proliferative disease (PTLD) or lymphoma.

**Endocrine:** The endocrine system produces hormones that allow the body to develop and function.

**Erythrocytes:** Also known as red blood cells. They carry oxygen to the body's tissues.

**Erythroplakia:** Also known as erythroplasia. A reddened patch in the oral or genital mucosa that is considered to be a precancerous lesion.

**Esophagoscopy:** Examination of the esophagus by means of a flexible endoscope, a thin, tube-like instrument with a light and a lens for viewing.

**Exons:** Segments of DNA that contain information needed to make proteins.

**Extracorporeal photopheresis:** A procedure used to treat chronic GvHD, in which the patient's blood is treated with drugs that become active when they are exposed to ultraviolet (UV) light.

**FA:** *Fanconi anemia.* An inherited disease that affects the bone marrow's ability to produce blood cells.

**Ferritin:** A protein that binds and stores iron. The levels of ferritin in the blood increase as the amount of iron in the body increases.

**FISH:** *Fluorescence in situ hybridization.* A laboratory technique that allows visualization of the chromosomal abnormalities in cells.

**Flow cytometry:** A laboratory technique used to diagnose blood cancers and other conditions that can separate, count, and evaluate cells with distinct characteristics.

**FLU:** *Fludarabine.* A drug capable of suppressing the immune system before transplant to prevent rejection of the new blood-forming stem cells, and is also used to treat some cancers.

**FSH:** *Follicle stimulating hormone.* A hormone produced by the pituitary gland that stimulates the growth of ovarian follicles in women and sperm-producing cells in men.

**Gastrointestinal system:** This system digests food and absorbs the nutrients the human body needs to function properly.

**G-Banding:** A laboratory technique used to visualize chromosomes.

**Gene therapy:** A novel treatment strategy that attempts to ‘correct’ a patient’s genetic information, or DNA, by replacing a disease-associated gene with a healthy version of the gene.

**Glucose:** A sugar that provides fuel for human cells to function.

**Granulocyte:** Type of white blood cell. It is also called neutrophil or polymorphonuclear leukocyte (poly), which is the infection-fighting cell.

**Growth curves:** Charts that allow physicians to monitor a child’s growth over time in comparison with other children of the same age and gender.

**GvHD:** *Graft-versus-host disease.* This is a complication that can occur after a transplantation if immune cells in the transplanted material identify the patient as “foreign” and mistakenly attack the patient’s body.

**Hepatic transaminases:** Enzymes measured on a liver function test. Elevated levels may indicate liver damage.

**Hematopoietic stem cells:** Rare blood cells found in the bone marrow and umbilical cord. These cells are unique because they have the potential to

develop into any of the various types of blood cells found in the body. Stem cells from umbilical cord can be extracted at birth and either donated to a public bank or stored at a private bank for the family's future use.

**Heterozygotes:** Everyone has two copies of nearly all genes. Heterozygous means that one of the copies of a gene is slightly different from the other copy of the gene. One gene may have an FA mutation and the other may not (i.e., a carrier is heterozygous). An individual with FA may be heterozygous if he or she has two different mutations in FA genes.

**HgB:** *Hemoglobin*. A red blood cell protein that is responsible for transporting oxygen to various parts of the body through the bloodstream.

**HLA:** *Human leukocyte antigen*. A protein found on the surface of cells in the body; this protein helps the body determine what is "self" and what is "foreign." An HLA-matched donor increases the chances that the patient's body will accept the transplant as "self."

**Homozygous:** Both copies of a gene are exactly the same. An individual with FA is homozygous if he or she has the same gene mutation in both copies of the FA gene.

**HPV:** *Human papillomavirus*. The most common sexually transmitted infection.

**HSCT:** *Hematopoietic cell transplantation*. A medical procedure that destroys the stem cells in a patient's bone marrow and replaces them with stem cells from a donor's bone marrow.

**Hydronephrosis:** Swelling of the kidneys; occurs when urine accumulates and is unable to make its way out of the kidneys.

**Hypoplasia:** Underdevelopment or incomplete development of an organ or tissue in the body.

**Hypothyroidism:** A condition caused by low levels of the thyroid hormone. This condition can contribute to reproductive issues, including irregular periods and difficulty becoming pregnant.

**Impaired glucose tolerance:** People with impaired glucose tolerance have trouble breaking down the sugars found in their diets, but they do not yet have diabetes.

**IVF:** *In vitro fertilization*. A treatment for infertility, in which eggs are removed from a woman's ovary and are fertilized by male sperm in a laboratory setting. The fertilized eggs are then prodded to implant in the woman's uterus.

**“Late” effects:** Health conditions that manifest later in life. For example, health problems associated with bone marrow transplant that develop months or years after the procedure.

**Leukemia:** Leukemia is a group of bone marrow diseases involving an uncontrolled increase in white blood cells (leukocytes).

**Leukoplakia:** White patches of epithelium that may occur in the oral cavity. May lead to cancer.

**Lymphocyte:** Type of white blood cell that fights infection by producing antibodies and other protective substances. There are two types: B-cells and T-cells.

**Macrophage:** A white blood cell that helps to destroy invading microorganisms and is involved in the immune response.

**MDS:** *Myelodysplastic syndrome*. This syndrome encompasses a group of health conditions that develop when a certain type of blood cells (known as the myeloid class of blood cells) are not present in sufficient numbers in the bone marrow. This syndrome was formerly known as “preleukemia.”

**Melanoma:** An aggressive form of skin cancer.

**miRNA:** *microRNAs*. Short segments of ribonucleic acid that bind to and turn off specific products of the genetic code (i.e., transcribed genes, known as RNA transcripts).

**MMC:** *Mitomycin C*. A chemical used in the chromosome breakage test.

**MMF:** *Mycophenolate mofetil*. A drug used to suppress the immune system in patients who receive transplants.

**Mosaicism:** Cells in the blood system that are genetically different from others. In FA, mosaicism is mainly used to describe cells where a spontaneous mutation reverts the defective FA gene back to the normal DNA sequence, either in stem cells or in T-lymphocytes.

**MTX:** *Methotrexate*. A drug that prevents the growth of certain types of cells. This drug is used to treat leukemia and other types of cancer.

**Neutropenia:** A health condition characterized by abnormally low levels of neutrophils in the blood. Neutrophils are immune cells that fight off infections. Therefore, neutropenia can lead to more frequent or severe infections.

**Neutrophils:** Immune cells that fight off infection.

**NMDP:** *National Marrow Donor Program*. This United States-based program operates the Be the Match Registry® of volunteer bone marrow, hematopoietic cell, and umbilical cord blood donors.

**Opportunistic infection:** This type of infection is common in immune-compromised patients who are unable to fight off microbes that do not normally cause disease in humans.

**Osteopenia:** Lower-than-normal bone density. Osteopenia often leads to osteoporosis.

**Osteoporosis:** Brittle bones that break easily. This occurs when minerals and protein are depleted from the bones.

**Oxidative stress:** Occurs when the levels of oxygen and its breakdown products, reactive oxygen species, are too high in cells. Oxidative stress may lead to DNA and other cellular damage.

**Pap test:** A gynecological test used to detect cervical cancer and precancerous lesions. Also known as cervical cytology testing.

**PGD:** *Preimplantation genetic diagnosis*. A technology for examining the genetic profiles of *in vitro*-derived embryos before they are implanted in a woman's uterus.

**PH:** *Peliosis hepatis*. A condition that occurs when blood vessels in the liver called sinusoids become excessively dilated and form large blood-filled spaces, like cysts, that are scattered throughout the liver.

**PLT:** *Platelets*. Disc-like fragments of cells that circulate in the bloodstream and help promote clotting at the site of a cut or injury.

**Pluripotent stem cells:** Cells capable of developing into almost any type of cell in the body. Stem cells can be found in embryos, in umbilical cord blood, and in the blood and bone marrow of adults.

**Pollicization:** A surgical procedure that creates a functional thumb by moving the index finger and its nerves, arteries, tendons, and muscles to the thumb position.

**Polypharmacy:** The administration of many different medicines during the treatment for the same disease.

**Pouce flottant:** A so-called “floating” thumb that lacks bones and is composed of skin and soft tissue.

**Pre-axial polydactyly:** A hand with more than one thumb. The thumbs may be fused together or they may be separate digits.

**Radius:** Of the two long bones in the forearm, the radius is the shorter and thicker one.

**Radialization:** A surgical procedure that realigns the patient’s wrist.

**Recessive:** A mutation is said to be recessive if an individual must inherit two copies of the mutant gene, to have the disease. Individuals with one mutant and one normal gene appear normal. They are called “heterozygotes” or “carriers.”

**Renal dysplasia:** Abnormal formation of the kidney, along with irregular cysts.

**SCC:** *Squamous cell carcinoma*. Type of cancer that is derived from squamous cells. Commonly found on the skin and in the oral cavity.

**Short bowel syndrome:** This condition occurs when nutrients from food are not properly absorbed because a large segment of the small intestine is non-functional or has been surgically removed.

**Stem cells:** Cells that can develop into one of many types of specialized cells in the body.

**Stem cell gene therapy:** A novel treatment that combines gene therapy and stem cell therapy in an effort to correct a faulty gene in the stem cells of the recipient. Stem cells are obtained from the patient, grown and “corrected” in a laboratory, and then returned to the patient.

**Stem cell therapy:** A novel treatment strategy that introduces new, healthy stem cells into a patient’s body to help replace, repair or regenerate diseased tissues.

**Sweet's syndrome:** Is also called acute neutrophilic dermatosis. A rare skin condition which presents as painful red plaques or nodules.

**T cells:** White blood cells that play a key role in the immune response by searching out and destroying material that is considered “foreign.”

**TBI: Total body irradiation:** Radiation therapy to the entire body, usually followed by umbilical cord blood, bone marrow or peripheral stem cell transplantation.

**TEF: Tracheoesophageal fistula.** An abnormal passage between the esophagus and the trachea, or windpipe, that may result in food from the esophagus crossing into the airways or air entering the esophagus.

**Transferrin:** A protein in the body that binds and transports iron in the blood.

**Thrombocytopenia:** Low platelet count.

**Transferrin saturation:** The amount of iron carried by the transferrin protein in the blood. Saturation increases as the amount of iron in the body increases.

**Triglycerides:** The building blocks of fats and oils.

**Triphalangeal thumb:** A thumb that has an extra bone (called a phalanx) that can vary in size and shape.

**UCB: Umbilical cord blood; also known as ‘cord blood.’** Blood present in the placenta and umbilical cord of an infant after birth. This blood contains high numbers of stem cells that can be used in transplants.

**Unsaturated iron binding capacity test:** A test that reveals the amount of transferrin that is not being used to transport iron. Binding capacity decreases as the amount of iron in the body increases.

**UV: Ultraviolet light.**

**VACTERL:** A group of birth anomalies that are not necessarily related to each other, but tend to occur together. These include vertebral defects, anorectal malformations, cardiac abnormalities, tracheo-esophageal abnormalities, renal defects, and limb defects such as extra fingers or toes, or abnormally formed forearms.

**Western blot:** A laboratory technique that examines the different types of proteins in a patient's cells.



**Wildtype:** The form of the gene that occurs in nature. It refers to the non-mutated or “normal” copy of a gene.

**X-Linked recessive inheritance:** Genes that are inherited on the X sex chromosome. Males have one X chromosome; females have two. If a disorder is X-linked recessive, it means that females must inherit two copies of an abnormal gene for the disease to develop, whereas males need only inherit one.

*Definitions are reprinted from previous versions of the Guidelines or come from different chapters in this edition.*

## Appendix

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