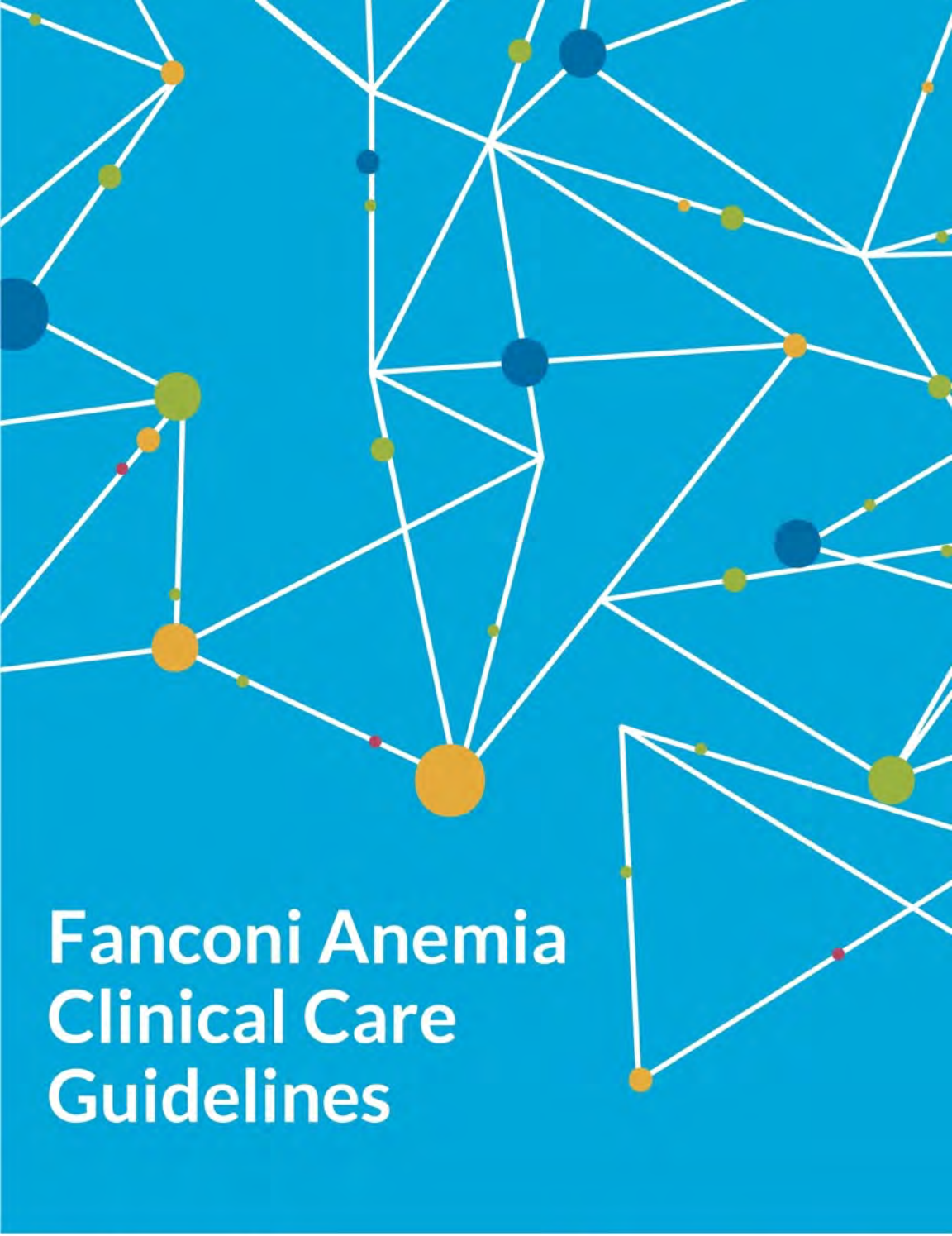

Fanconi Anemia Clinical Care Guidelines

Fifth Edition 2020

FANCONI ANEMIA RESEARCH FUND
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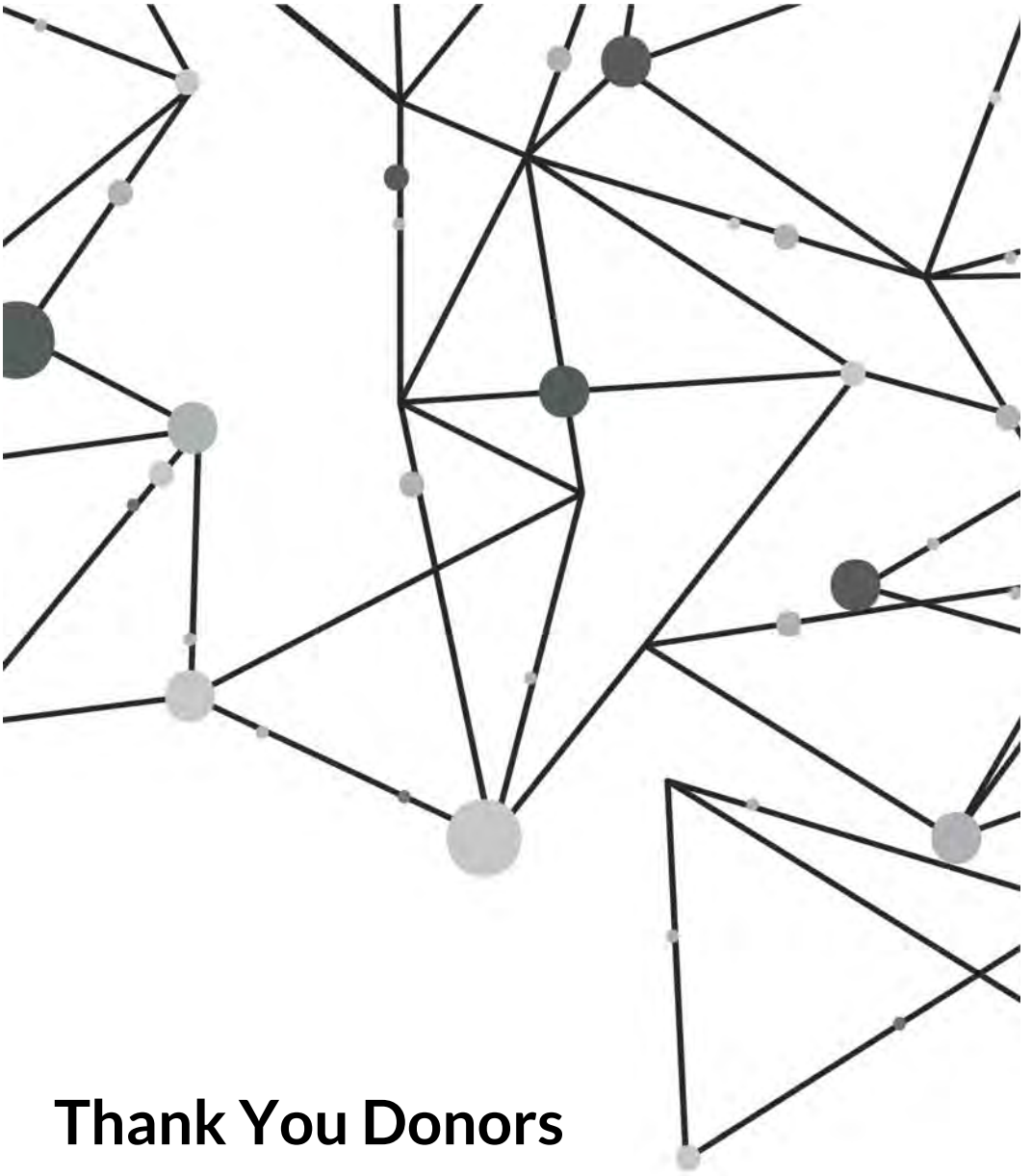

Thank You Donors

We are deeply grateful to the generous donors of the Fanconi Anemia Research Fund, who made this publication possible.

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Fanconi Anemia Clinical Care Guidelines

Fifth Edition 2020

Managing editor: Isis Sroka, PhD, FARF Scientific Director
Editors: Lynn Frohnmayer, MSW, FARF Co-founder
Sherri Van Ravenhorst, MS, FARF Communications Director
Leanne Wirkkula, PhD (Tn Consulting)

Special thanks to all who donated their time and expertise to help write these guidelines. A full list of contributors may be found at the end of this book.

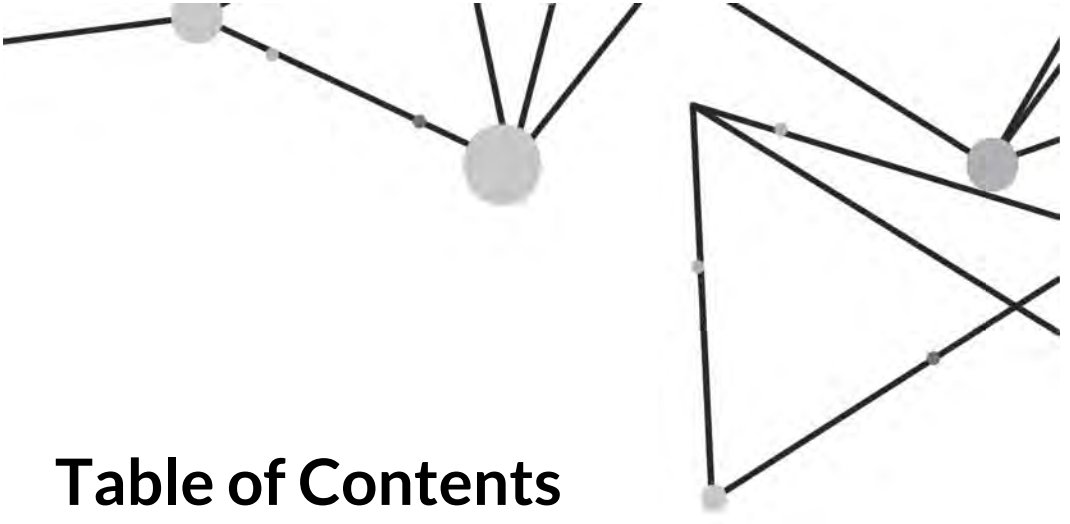
These guidelines are posted on our website www.fanconi.org and are available as a hard copy upon request (email info@fanconi.org).

About the Fanconi Anemia Research Fund

The Fanconi Anemia Research Fund (FARF) is the world leader in advancing research for better treatments and a cure for Fanconi anemia (FA). Founded in 1989 by parents Lynn and David Frohnmayer, FARF's mission is to find better treatments and a cure for Fanconi anemia and to provide education and support services to affected families worldwide. To that end, as of 2020, FARF has supported more than 245 grants to 67 institutions and 163 investigators worldwide. Thanks to our generous and dedicated donors, FARF has funded over $25 million in research grants.

Fanconi Anemia Research Fund
360 E. 10th Avenue, Suite 201
Eugene, OR 97401

www.fanconi.org
541.687.4658
info@fanconi.org



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Preface

Fanconi anemia (FA) is a rare disease caused by pathogenic variants in at least 23 genes that cause faulty DNA repair in every cell of the body. Fanconi anemia is a multi-system disease and the clinical manifestations are highly variable; therefore, the complexities that arise require a comprehensive and interdisciplinary approach to clinical care. In 1999, The Fanconi Anemia Research Fund published the first edition of a clinical care reference guide for people affected by the disease and their families. The clinical reference guide was developed by FA expert physicians with the intent to provide information for care providers with limited knowledge of this rare disease. Since the first edition was published in 1999, three subsequent editions were published by the Fanconi Anemia Research Fund in 2003, 2008, and 2014.

The fifth edition, which is titled *Fanconi Anemia Clinical Care Guidelines*, is a revision of the fourth edition published in 2014. The contributing authors are physicians or clinical care providers with expertise in treating patients with FA. The fifth edition provides evidence-based recommendations from published peer-reviewed medical literature and is geared toward clinical providers as the primary intended audience. Where possible, the chapters have been peer-reviewed and effort was made to provide a balanced view on discordant medical opinions.

The fifth edition starts with a brief summary of the molecular mechanisms of the FA DNA repair pathway (Chapter 1). Over the past few decades, researchers have charted the complexities of the FA DNA repair pathway with the hope that unlocking mechanisms that drive faulty DNA repair in FA cells would enable development of new treatments for the disease. Although research on the FA pathway has expanded knowledge of the coordinated events that lead to FA cell fragility, more work is needed to develop a comprehensive understanding of how targeting the pathway can be exploited as a way to treat the clinical manifestations of FA.

Beyond an overview of the FA pathway, the fifth edition covers the diagnostic testing process for FA (Chapter 2). The chromosome breakage test remains the gold standard diagnostic test for FA; however, molecular diagnostics, such as whole genome or exome sequencing, are quickly becoming important components of the diagnostic cascade. The

inheritance patterns of FA, genetic testing for family members, and updated information regarding cancer risk for carriers of FA variants is also discussed in Chapter 2.

Monitoring the onset of bone marrow failure (BMF) in persons with FA and treatment recommendations for when it occurs are outlined in Chapter 3. To date, hematopoietic cell transplant (HCT) is the only curative treatment option for BMF for persons with FA. The fifth edition provides an overview of recent advancements in HCT published in peer-reviewed clinical research studies. Advancements in HCT protocols and long-term care continue to improve survival rates of persons with FA following HCT. Despite these advancements, the high risk of developing squamous cell carcinoma (SCC) in individuals who have undergone an HCT is a major concern. The development of HCT-related graft-versus-host disease is correlated with increased risk; however, it is unclear whether additional factors associated with the HCT process also confer an increased risk. It is thought that the use of genotoxic chemotherapy and radiotherapy regimens may contribute to increased risk, but more studies are needed to delineate the specifics of each contributing factor. The Fanconi Anemia Research Fund is currently supporting ongoing pre-clinical research focused on using antibody depletion of stem cells as a way to reduce toxic conditioning regimens. Results from these studies may provide a new way to perform HCT that decreases SCC risk. Gene therapy trials are also underway as a curative approach for BMF in patients with FA; however, it is too early to know whether these trials will be successful.

The risk of developing head and neck squamous cell carcinoma (HNSCC) and SCC in anogenital regions is extremely high for persons with FA. There is also an increased risk of developing non-HNSCC solid tumors in other areas of the body (Chapter 4). The risk of solid tumors is age-dependent and associated with undergoing HCT, but risk is also high in patients who have never undergone HCT. Most non-HNSCC and HNSCC tumors develop in patients with FA at a substantially younger age than in the general population (20-50 years vs. 60-70 years). Chapters 5 and 7 cover updated recommendations for early surveillance, prevention, and treatment of HNSCC and anogenital SCC in patients with FA, respectively.

New in the fifth edition is the recommendation to perform comprehensive oral examination combined with brush biopsy of suspicious HNSCC lesions (Chapter 5), to determine whether the presence of pre-cancerous or cancerous lesions warrant further analysis by incisional biopsy. Individuals with FA often have multiple lesions in their oral cavities and use of brush biopsies as an early surveillance tool reduces trauma and leads to early diagnosis of cancer when successful surgical removal is possible. Surgical removal of tumors, both HNSCC and anogenital SCC, remains the best option for curative treatment for persons with FA, although radiation therapy has proved efficacious in some cases. More research is needed to understand the natural history of FA SCC tumors to develop chemopreventive or non-genotoxic treatment modalities. Identifying methods to prevent and treat FA SCC tumors will be a high priority for the Fanconi Anemia Research Fund in the coming years.

Fanconi anemia is a multi-system disease and hematologic manifestations and cancer are not the sole problems for patients with FA. Comprehensive care for FA patients requires an interdisciplinary team that focuses on all body systems simultaneously. The fifth edition covers recommendations for optimal oral health care (Chapter 6), gynecologic care and infertility (Chapter 7), dermatologic issues (Chapter 8), and gastrointestinal and endocrine issues (Chapters 9 and 10, respectively). Expert opinion on how to manage auditory problems (Chapter 11) and skeletal anomalies (Chapter 12) is also covered.

The final chapter (Chapter 13) provides a brief overview of the care recommendations mentioned throughout other chapters. The chapter also provides currently available care recommendations for adults who have FA. Persons with FA are surviving longer due to advancements in HCT and diagnosis of the disease in adults is occurring more often. Filling the gaps that exist around transitioning from pediatric to adult care and specific recommendations for the myriad of issues adults with FA face will be a focus for the Fanconi Anemia Research Fund in the coming years.

Starting in 2021, the *Fanconi Anemia Clinical Care Guidelines*, and all subsequent revisions, will be available on the Fanconi Anemia Research Fund website in an interactive format. The virtual resource guide will enable rapid incorporation of peer-reviewed updates for clinical care recommendations. The FA field changes rapidly and providing timely access to up-to-date recommendations is imperative. Printed editions of content from the website will be made available every five years.

On behalf of the Fanconi Anemia Research Fund, we extend a profound thank you to the many authors who contributed to the *Fanconi Anemia Clinical Care Guidelines* fifth edition. We also extend a heartfelt appreciation for individuals with FA and their families without whom this publication would not have been possible. It is our hope that this resource guide will serve as a valuable resource for physicians who treat patients with FA and ultimately, that it will extend lives and improve the quality of life of those affected by the disease.

Isis Sroka, PhD
Scientific Director
Fanconi Anemia Research Fund

Lynn Frohnmayer, MSW
Co-Founder
Fanconi Anemia Research Fund

Chapter 1

The Fanconi Anemia DNA Repair Pathway

Introduction

Discovery of the genes that cause Fanconi anemia (FA) and the role of FA proteins in regulating DNA repair have been active areas of research over the last 30 years. In the last edition of the clinical care guidelines published by the Fanconi Anemia Research Fund in 2014, 16 FA genes had been discovered. Researchers have now identified 23 genes that, when mutated, cause FA, including *FANCA* [1], *FANCB* [2], *FANCC* [3], *FANCD1/BRCA2 [4]*, *FANCD2* [5], *FANCE* [6], *FANCF* [7], *FANCG* [8], *FANCI* [9-11], *FANCJ/BRIP1* [12], *FANCL* [13], *FANCM* [14-17], *FANCN/PALB2* [18], *FANCO/RAD51C [19, 20]*, *FANCP/SLX4 [21, 22]*, *FANCQ/ERCC4 [23]*, *FANCR/RAD51* [24, 25], *FANCS/BRCA1* [26], *FANCT/UBE2T [27-29]*, *FANCU/XRCC2* [30], *FANCV/REV7* [31], *FANCW/RFWD3* [32], and *FANCY/FAP100* [33].

Fanconi anemia is a multi-system disease caused by defects in the ability of cells to repair damaged DNA. Cells from patients with FA are unable to repair DNA interstrand crosslinks (ICLs), which are lesions that covalently link two strands of DNA and inhibit the essential cellular processes of DNA replication and transcription. This chapter provides a brief

summary of new research advancements on the molecular mechanisms of the FA DNA repair pathway. The relationship between the FA DNA repair pathway and toxins such as aldehydes and stem cell failure are also discussed. This chapter should not be considered a complete overview of all research on the pathway that has been published to date. Readers are encouraged to access references and review articles cited in the chapter for additional details.

The Fanconi Anemia DNA Repair Pathway

The Fanconi anemia (FA) proteins participate in a coordinated set of events that lead to the repair of interstrand crosslinks (ICLs) when the FA DNA repair pathway is activated during DNA replication (Figure 1, reviewed in [34-36]). The key event in the FA DNA repair pathway is the monoubiquitination of the FANCI and FANCD2 proteins (commonly referred to as the I-D2 or D2-I complex) [5, 9-11, 37, 38]. Monoubiquitination of the I-D2 complex depends on FANCL, an E3 ubiquitin ligase which works together with FANCT/UBE2T, an E2 ubiquitin-conjugating enzyme [27-29, 39]. FANCL is a component of a multi-subunit complex called the FA core complex. The core complex contains FANCA, FANCB, FANCC, FANCE, FANCF, FANCG, FANCL, and the FA associated proteins (FAAP) FAAP20 and FAAP100 [40-42]. Deficiency of any of the core complex subunits leads to FA [1-3, 6-8, 13]. FANCM together with FAAP24 associates with the FA core complex, but its absence only partially reduces FANCI and FANCD2 ubiquitination [43, 44] and patients with biallelic mutations in FANCM have distinct presentation from the majority of FA patients (see Chapter 2) [16, 17, 45, 46]. FANCM is thought to participate in the activation of the FA pathway by localizing the core complex to chromatin and also through its role in activation of ataxia telangiectasia and Rad3-related (ATR), a DNA damage responsive kinase that phosphorylates multiple FA proteins [47]. FANCM also has been shown to be necessary for an early event during ICL repair, to promote skipping or “traverse” of the ICL lesion by the replication machinery [48, 49].

The FA core complex is necessary for the activation of its catalytic subunit, FANCL, and also for positioning its two substrates, FANCI and FANCD2, in proper orientation for monoubiquitination [50, 51]. The monoubiquitinated I-D2 complex stably localizes to lesions by encircling the DNA [52, 53]. Monoubiquitinated FANCI and FANCD2 are thought to facilitate the downstream repair events of DNA cutting and repair of the cut DNA [54, 55]. FANCQ/XPF is the essential nuclease that makes incisions around the lesion, a step called “unhooking” [23, 56]. XPF unhooking activity in this step is dependent on FANCP/SLX4, a protein scaffold for three nucleases [21, 22, 56-60]. Once the lesion is unhooked, a specialized translesion polymerase, Polζ, which includes FANCV/REV7 [31, 54], synthesizes DNA across the unhooked lesion creating a substrate for homologous recombination (HR) proteins. FANCD1/BRCA2, FANCJ/BRIP1, FANCN/PALB2,

FANCO/RAD51C, FANCR/RAD51, FANCS/BRCA1, FANCU/XRCC2 and FANCW/RFWD3 are proteins that participate in or regulate HR during ICL repair [4, 12, 18, 19, 24, 26, 30, 32, 61-64]. Some of the HR proteins, FANCR/RAD51 and FANCD1/BRCA2, also work at earlier steps of repair to protect the DNA at the ICL from inappropriate degradation by the DNA2 nuclease-Werner syndrome ATP-dependent helicase (WRN) complex [24, 64]. It is also important to note that the homologous recombination proteins indicated above participate in repair of DNA double-stranded breaks during DNA replication and are major tumor suppressors in the cell (reviewed in [65]). Once the ICL repair is completed, the pathway is turned off by a deubiquitinating enzyme, ubiquitin specific peptidase 1 (USP1) [66].

In addition to participating in ICL repair, FA proteins are also active at other sites in the genome during DNA replication where they respond to replication stress, which is defined as any event that stalls the replication machinery. The FA proteins protect the newly-replicated (nascent) DNA strands when replication is stalled [67, 68] (reviewed in [69]). They function at sites of under-replicated DNA, known as common fragile sites [70-72], and have been shown to play a role in the clearance of DNA:RNA hybrids, which form during transcription and are enhanced by replication and transcription machinery collisions [73, 74].

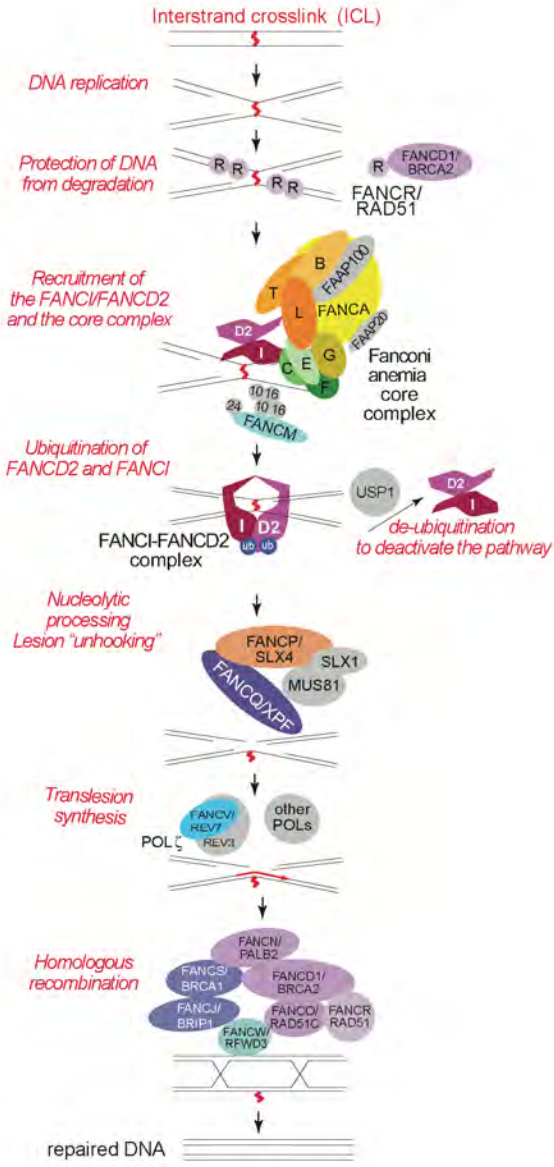

Figure 1. The role of Fanconi anemia proteins in the repair of DNA interstrand crosslinks (ICLs).

This simplified model highlights the activity of Fanconi anemia proteins. It is based on work from many laboratories as referenced in the text. For a more thorough review of the molecular pathway and additional proteins that participate in ICL repair, please see recent reviews [34-36]. For the latest study on the earliest steps of the pathway regulation during replication by the TRAIP protein, see reference [75] and for the studies on ICL traverse see references [48, 49, 76, 77]. See text for details.

The Fanconi Anemia DNA Repair Pathway and Toxic Metabolites

The underlying pathophysiology of Fanconi anemia (FA) is best understood for the hematopoietic system, although more research in this area is needed. Hematopoietic stem cells (HSC) with a faulty FA pathway have increased levels of DNA damage and their attrition is an outcome of activation of the p53 pathway, which initiates apoptosis [78]. It also has been shown that driving quiescent/resting HSCs to enter the cell cycle by chronic bleeding or induction of type I interferon response can trigger bone marrow failure (BMF) in FA-deficient mice [79].These findings are consistent with the FA DNA repair pathway responding to problems encountered during DNA replication. These problems may occur at the sites of replication stress as defined above or may occur at the sites of DNA ICLs caused by metabolites that accumulate when stem cells divide or differentiate.

Endogenous metabolites, especially reactive aldehydes, including acetaldehyde and formaldehyde, have been strongly implicated in the pathogenesis of HSC failure and tumorigenesis in FA [80-83]. Mice deficient in ALDH2, the enzyme which detoxifies acetaldehyde, develop bone marrow failure and leukemia [80, 81], which are common outcomes observed in patients with FA (see Chapter 3). Lack of the ADH5 enzyme, which participates in formaldehyde detoxification, leads to the development of bone marrow failure even faster in a mouse model of FA deficiency [82]. The mouse studies identifying genetic interaction between acetaldehyde and the FA DNA repair pathway have been corroborated in patients with FA. A dominant negative variant in ALDH2 (ALDH2*2, rs671 G>A) is common in East Asian peoples, including Han Chinese, Japanese, and Koreans [84]. Carriers of this variant have greatly diminished enzymatic activity and biallelic variants result in almost absent activity [85, 86]. Hira et al. studied a cohort of Japanese FA patients and showed that the patients who carried the ALDH2*2 variant displayed an increased number of congenital abnormalities, earlier onset of bone marrow failure, myelodysplastic syndrome, and leukemia [83]. Presence of the biallelic ALDH2*2 variants exacerbated the FA-associated phenotypes even more dramatically, leading to a severe disease presentation.

In light of the above studies, it is useful to think of a two-tier system to illustrate how mammalian cells protect themselves from endogenous toxic metabolites (Figure 2, reviewed in [87]). As toxic metabolites are produced by normal cellular metabolism or as a result of ingestion (for example alcohol), enzymes including aldehyde and alcohol dehydrogenases, detoxify the toxic metabolites into non-toxic molecules. Even with a fully-functioning first tier of protection, some toxic metabolites escape detoxification and cause DNA lesions. The FA DNA repair pathway, the second tier of protection, is then needed to remove the resulting DNA lesions to prevent cell death or mutagenesis. In the scenario where more lesions result due to the deficiency of the first tier of protection of enzymatic

detoxification, cells are even more reliant on an efficient DNA repair pathway due to a greater burden of damaging DNA lesions. Thus, deficiency of both tiers of protection leads to severe disease. This paradigm may be used outside of hematopoietic stem cells and for epithelial cells from which squamous cell carcinomas (SCC) develop. This would be an important association considering patients with FA have an increased risk of developing SCC (see Chapters 4 through 7). However, the toxic metabolite implicated in generating DNA lesions likely will be dependent on tissue type. Understanding the sources of the endogenous DNA damage in FA cells will certainly contribute to understanding of the pathogenesis of the disease and may lead to development of new therapies.

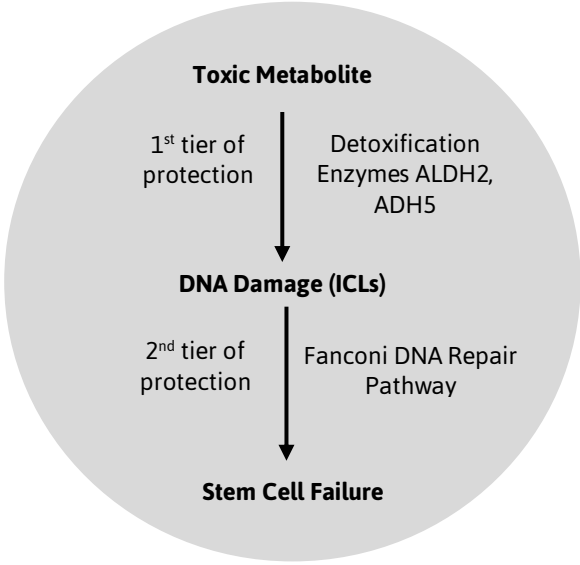

Figure 2. Two-tiered system for protection of hematopoietic stem cells [87]**.**
The first tier, which includes ALDH2 and ADH5, detoxifies metabolites (acetaldehyde and formaldehyde, respectively) that have potential to damage DNA. The Fanconi anemia DNA repair pathway repairs the lesions made by metabolites that escape detoxification.

Summary

Fanconi anemia (FA) is caused by faulty DNA repair of interstrand crosslinks (ICLs) in every cell in patients with the disease. Researchers have discovered 23 genes to date that cause FA and have established many key molecular mechanisms that regulate the FA DNA repair pathway. The absence of functional repair of ICLs can affect stem cells in particular, which results in many of the phenotypic manifestations associated with the disease. Bone marrow failure resulting from hematopoietic stem cells exposed to endogenous or exogenous toxic metabolites in the context of faulty FA DNA repair has been well-characterized. However, more research is needed to develop a comprehensive understanding of how a faulty FA DNA repair pathway causes FA and squamous cell carcinoma and how mechanisms regulating the pathway can be exploited for novel treatments for patients with FA.

The Fanconi Anemia Research Fund recognizes the following author contributions to the 5th edition:

Agata Smogorzewska, MD, PhD

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Chapter 2

Diagnosis of Fanconi Anemia: Testing and Genetic Counseling

Introduction

Fanconi anemia (FA) is a very rare genetic disorder that results from DNA repair defects arising from pathogenic variants in at least 23 genes (*FANCA*, *FANCB*, *FANCC*, *FANCD1*/BRCA2, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCJ/BRIP1*, *FANCL*, *FANCM*, *FANCN/PALB2*, *FANCO/RAD51C*, *FANCP/SLX4*, *FANCQ/ERCC4*, *FANCR/RAD51*, *FANCS/BRCA1*, *FANCT/UBE2T*, *FANCU/XRCC2*, *FANCV/REV7*, *FANCW/RFWD3*, and *FANCY/FAP100*) discovered to play a role in the FA pathway (see Chapter 1). All pathogenic variants in these genes are autosomal recessive, except *FANCB,* which is x-linked, and *FANCR/RAD51*, which is autosomal dominant. The carrier frequency of FA is 1:181 in the general population in North America and 1:93 in Israel [1]. Specific populations have a founder effect with increased carrier frequencies (1 per 100 or less), for example Ashkenazi Jews (*FANCC* and *FANCD1*/BRCA2) [2, 3], Afrikaners (*FANCA*) [4], sub-Saharan Africans (*FANCG*) [5], Spanish gypsies (*FANCA*) [6], and South Asians from India and Pakistan (*FANCL*) *[7]*. The wide spectrum of disease presentation in individuals with FA is closely tied to the relationship between clinical features of the disease and the underlying genetic cause. Early diagnosis and the characterization of patient-specific pathogenic variants (historically called mutations) is

of utmost importance as this information may influence a patient's clinical management, especially for severe cases. This chapter discusses the importance of early diagnosis and the role of genetic counseling and specific cytogenetic and molecular tests used to diagnose FA. Also included are test interpretation considerations for accurate diagnosis that can aid clinical management and facilitate appropriate testing for family members.

Clinical Manifestations and Evaluation for Diagnosis

Most patients with Fanconi anemia have manifestations either at birth or during childhood. The median age at diagnosis is 7 years [8, 9], although it is typically younger if the clinical phenotype is more severe [10]. Those without overt congenital differences may not be diagnosed until adulthood unless they develop bone marrow failure (BMF) (see Chapter 3) or a solid tumor (see Chapters 4 and 5).

Physical Phenotype

The physical phenotype associated with FA is extremely heterogenous and multisystemic, but can offer clues for testing and early diagnosis [9]. The classical congenital abnormalities seen in patients with FA include those described in the VACTERL-H (Vertebral, Anal, Cardiac, Tracheo-esophageal fistula, Esophageal atresia, Renal, upper Limb and Hydrocephalus) association [11]. In a recent comprehensive literature review of FA cases, the proportion of FA patients who met criteria for VACTERL-H association (presence of at least 3 of the 8 common features) was 12% [12], which was similar to prior studies (5% to 30%) [13, 14]. Other abnormalities common to FA were recently grouped with the acronym PHENOS (skin Pigmentation, small Head, small Eyes, Nervous system, Otology, and Short stature) [13]. In the previously mentioned literature review, 9% of the patients with FA had ≥4/6 features of PHENOS [12]. The most frequent abnormalities described are: short stature, skin pigmentary changes, upper limb malformations, male genitalia abnormalities, microcephaly, ophthalmic and renal manifestations [9]; all, except for the male genitalia anomalies, are included in VACTERL-H or PHENOS. Although the majority of patients will have at least one abnormality, between 25-40% will have none, thus the absence of abnormal features does not rule out the diagnosis [13, 14]. The information listed in Table 1 can be used as a guide for evaluating a patient whose appearance suggests a diagnosis of FA. Any combination of the abnormalities listed in Table 1 should raise the level of suspicion for FA.

Table 1. Manifestations that are indicators for Fanconi anemia screening.

Organ, system, or feature	Abnormality
Height	Short stature
Head	Microcephaly
Central nervous system	Small pituitary and stalk interruption; agenesis of corpus callosum; cerebellar hypoplasia; hydrocephalus; dilated ventricles; developmental delay
Eyes	Microphthalmia; epicanthal folds; almond-shaped fissures; ptosis; strabismus; cataracts
Otology	Hearing loss (conductive, sensorineural, or mixed); abnormal pinna; atretic, narrow canal; and abnormal middle ear bones
Facial	FA facies; triangular face; micrognathia; pointed chin; mid-face hypoplasia; facial nerve palsy; microsomia; hypertelorism; hypotelorism; cleft palate
Heart	Patent ductus arteriosus; atrial septal defect; ventricular septal defect; coarctation; situs inversus; truncus arteriosus
Gastrointestinal	Tracheoesophageal fistula Atresias: esophageal, duodenal, jejunal Anal malformations: imperforate or bifurcated anus Annular pancreas Intestinal malrotation
Renal	Horseshoe, ectopic, hypoplastic, dysplastic, absent, hydronephrosis, hydroureter
Male Genitalia	Undescended, small or absent testis; microphalus; hypospadias; micropenis; absent testis; infertility
Female Genitalia	Hypoplastic, absent or bicornuate uterus; gonadal dysgenesis; small ovaries; rectovaginal fistula; vaginal atresia; late menarche; early menopause; infertility
Upper limb	Thumb: absent, hypoplastic, triphalangeal, polydactyly Radius: absent, hypoplastic Thenar-eminence: hypoplastic, absent Others: absent first metacarpal, clinodactyly Ulna: short, dysplastic
Lower limb	Hips: congenital dislocation/dysplasia, malrotation Feet: toe syndactyly, abnormal toes, club feet
Vertebral	Web, hemivertebrae; Klippel-Feil; scoliosis; kyphosis; coccygeal aplasia
Skin	Café au lait macules; generalized hypo- or hyperpigmentation
Bone marrow failure	Anemia; leukopenia; thrombocytopenia; aplastic anemia; myelodysplastic syndrome
Leukemia	Mainly acute myeloid leukemia
Squamous cell carcinoma	Head and neck; esophageal; anogenital (including vulvar, skin)
Other cancers	Skin basal cell carcinoma; medulloblastoma; neuroblastoma; Wilms' tumor; breast; lung

Diagnostic Testing

Any physician who suspects that a patient may have FA should refer the patient to a hematologist and/or clinical geneticist or genetic counselor who can arrange for diagnostic testing.

All laboratories involved in the testing (both the cytogenetic and molecular laboratories) should be accredited by a recognized regulatory body and certified to perform FA testing for clinical care. Recognized accreditation bodies in the United States, Canada, and Europe are as follows:

United States

- Clinical Laboratory Improvement Amendments (CLIA) and the College of American Pathologists (CAP) provide laboratory certification and accreditation.
- The American College of Medical Genetics and Genomics (ACMG) provides detailed guidelines for cytogenetic testing and the interpretation of the results of genetic testing [15].

Canada

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

Europe

- The Belgian Accreditation Council (BELAC), the French Accreditation Committee (COFRAC), the Deutsche Akkreditierungsstelle (DAkkS), the Swiss Accreditation Service (SAS), and the United Kingdom Accreditation Service (UKAS) provide accreditation services.

As FA testing is highly specialized, particularly for evaluation of chromosome breakage in response to DNA damage, only laboratories with extensive experience should undertake this testing.

The recommended testing procedures are outlined in the flow chart in Figure 1. The flow chart presents one potential algorithm for testing, starting with chromosome breakage, and followed by molecular evaluation. However, as genetic testing has become increasingly utilized as a front-line diagnostic test for newborns and pediatric patients with multiple congenital anomalies, the order of testing in these cases may be reversed. Most important, both chromosome breakage and germline genetic testing (described in the following sections) should be applied to each patient for precise diagnosis.

Chromosome Breakage Test in Peripheral Blood Lymphocytes

The chromosome breakage test is the first test that should be performed for an individual suspected of having FA. This assay is performed in a clinical cytogenetics laboratory, often

using a sample of the patient's peripheral blood. Lymphocytes isolated from the blood sample are treated with DNA cross-linking agents; the most commonly used for FA testing are diepoxybutane (DEB) and mitomycin C (MMC) and the chromosomes are examined for evidence of chromosomal breakage [16, 17]. Cells from individuals who do not have FA have relatively few chromosome breaks or other rearrangements detected. In contrast, 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 and Genomics guidelines for cytogenetic laboratories [18], 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.

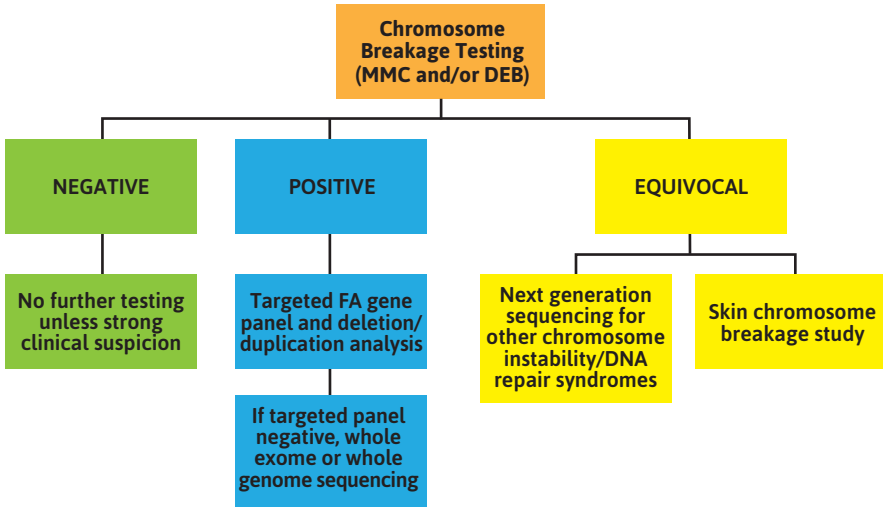

Figure 1. Schematic representing a suggested algorithm for Fanconi anemia testing.

The gold-standard test for diagnosing Fanconi anemia (FA) is the chromosome breakage test (CBT) using the DNA cross-linking agents mitomycin C (MMC) and diepoxybutane (DEB) (orange box). If a patient has a negative CBT (green boxes), no further testing is necessary unless there is strong clinical suspicion. In this case, a skin cell CBT should be performed. If the CBT has a positive result (yellow boxes), targeted FA gene panel should be performed. If the targeted panel is negative, whole exome or whole genome

sequencing can be performed. An equivocal or inconclusive result (blue boxes) will require next generation sequencing for variants that cause other chromosome instability syndromes, or a skin CBT for confirmation of FA.

The laboratory should also measure baseline chromosome breakage by evaluating cells that have not been treated with MMC and/or DEB. The measurements of baseline breakage can vary markedly among patients with different FA variants. For example, patients with variants in the *FANCD1/BRCA2* or *FANCN/PALB2* genes have very high levels of baseline breakage and unusual constellations of abnormalities compared with other groups of patients with FA [19]. The baseline breakage also may 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 premature centromere separation, which are characteristic of Roberts syndrome and Warsaw breakage syndrome [20-25]. Finally, if the breakage is evaluated on G-banded chromosome preparations, it will be possible to rule out constitutional chromosome abnormalities that may provide an alternative diagnosis for the patient's clinical findings. The latter have been documented in approximately 1-2% of patients referred to rule out FA.

Cell Cycle Analysis in Peripheral Blood Lymphocytes

Mitomycin C and/or DEB-induced chromosome breakage analysis is the most common first-line test for the diagnosis of FA. However, a few laboratories measure cell cycle kinetics, rather than chromosome breakage, in peripheral blood lymphocytes treated with mitogen and DNA cross-linking agents [26, 27]. Normal lymphocytes that do not have any DNA damage will progress through all the normal phases of the cell cycle without significant delay. However, cells that have DNA damage will stop at the S/G2 phase of the cycle to repair the damage before they progress to M phase. 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 S/G2 phase when compared to cells from individuals without FA. Some laboratories may use cell cycle analysis in conjunction with a chromosome breakage test for research purposes. Although cell cycle analysis is not currently used in the clinical setting, the principles and flow chart delineated for the chromosome breakage test should be applied. Positive, negative, and equivocal results should be followed as described for the chromosome breakage test results delineated in Figure 1.

Interpreting Chromosome Breakage Test Results

Although chromosome breakage is considered the gold standard for diagnosis of FA, there is still the possibility that a test result is a "false positive" (the test is positive but the patient does not have FA) or that a test result is a "false negative" (the test gives a negative

result but the patient does have FA). Critical to the interpretation of the laboratory results is the establishment of positive and negative control ranges by the laboratory. In order to establish these ranges, the laboratory must have tested a sufficient number of patients (typically 30 or more) with a confirmed diagnosis of FA. Situations that may yield a false negative or false positive test result are described in the following sections.

Positive Test Result

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 compared with their baseline breakage. Typically, more than 90% of the metaphase cells examined in the MMC or DEB treated culture from an individual with FA will show increased breakage, and the rates and types of breakage observed will fall within the laboratory's established FA range. After a positive result, a genetic counselor can help coordinate the necessary follow up. Importantly, follow-up testing should be performed to identify the patient's pathogenic variant(s) using the molecular methods described in this chapter.

In some cases, a diagnosis of FA may be suspected only after the individual has been diagnosed with a cancer, such as leukemia or a solid tumor. The physician may suspect FA because this patient experiences severe side-effects from the therapy that is given to treat the cancer. Evaluating MMC and DEB chromosomal breakage test is warranted.

Negative Test Result

A test result is considered negative if the metaphase cells from the MMC or DEB treated culture do not show increased chromosomal breakage or rearrangement, and if the rates of observed breakage are within the laboratory's established 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 somatic mosaicism, as described below. In addition, there are multiple disorders that have some clinical features in common with FA and are associated with some form of chromosome instability [20-25]. Therefore, patients who have a negative chromosome breakage test should be evaluated by a clinical genetics service as additional genetic testing may be warranted.

Equivocal Test Result

Test results are considered equivocal, or inconclusive, if the percentage of cells that display chromosomal breakage patterns characteristic of FA is lower than the laboratory typically sees for FA, or if there is increased breakage but the types of breakage are not characteristic of FA. The average number of breaks per cell may fall above the upper limit of the normal control range, but below the lower limit of the laboratory's FA range. Underlying causes of inconclusive results include mosaicism in the patient's peripheral

blood cells, hypomorphic alterations, and the possibility that the patient has a condition other than FA that manifests with increased chromosomal breakage.

Mosaicism in Peripheral Blood Cells

Somatic mosaicism can occur in T-lymphocytes and hematopoietic stem cells due to the reversion of an inherited variant in an FA gene. Testing to detect mosaicism should be performed if the clinical evidence that the patient may have FA is strong, but the peripheral blood chromosome breakage test results were reported as negative or equivocal. 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 MMC/DEB chromosome breakage test on fibroblast cells. 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. 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—in either the blood or the bone marrow—does not protect the individual from the development of clonal chromosome abnormalities within the population of cells that retain their FA gene variants, which may lead to the development of hematologic malignancies. In addition, mosaicism in the blood or bone marrow also does not protect against the development of solid tumors.

Germline Genetic Testing

If the results from the chromosome breakage test are positive, genetic testing should be performed to identify the specific FA-causing variants. Genetic testing enables accurate diagnosis and improves clinical care for individuals with anticipated genotype/phenotype manifestations and for relatives who are heterozygous carriers of FA gene variants that confer increased risk for malignancy (see Carrier Cancer Risk section in this chapter).

Further, genetic analysis is useful for preconception screening, prenatal diagnosis, and required for preimplantation genetic diagnosis (see Chapter 7).

Next Generation Sequencing

Until recently, a genetic test known as complementation analysis was the primary method available for determining which *FANC* genes were altered in a given patient. However, complementation analysis is labor-intensive, expensive, and time-consuming. Over the course of the past decade, the development and expansion of next generation sequencing (NGS) technologies, also referred to as massively parallel sequencing or multiplex testing, have transformed the field of genetic testing because they enable detailed analysis of numerous genes simultaneously. Following a positive chromosome breakage test, NGS panel testing for clinically available FA genes should be offered as the next step of testing.

Clinical labs have evolved to offer two types of panel tests: dedicated panels (laboratory pre-selected genes associated with a patient's phenotype) and custom panels (self-selection of desired genes from a large list). When selecting a panel, it is important to consider whether the test has been designed to address variant hotspots and/or gene regions known to present reporting challenges. As an example, the *FANCD2* gene is known to have two pseudogenes that can complicate the accuracy and interpretation of testing [28, 29]. Due to the rapidly evolving knowledge of FA, many laboratories have not yet been able to add the more recently discovered FA genes to their panels. Thus, the majority of panels currently available evaluate only a subset of the 23 known FA genes [30, 31].

In addition to sequencing, testing should always include copy number analysis that will identify large deletions, duplications and insertions [32]. This is critical as 35% of FA patients harbor large deletions that account for 18% of all FA pathogenic variants [33]. Due to the high rate of copy number variants, techniques that can detect gene deletions, duplications, and insertions, such as array comparative genomic hybridization (aCGH), multiplex ligation-dependent probe amplification (MLPA) or NGS-based copy number analysis, are an important part of the genetic testing process; and, it should be determined whether this type of assessment is included in the chosen test platform. Copy number variants (CNV) can be performed in tandem with panel testing or as a reflex test. In cases where the diagnosis of FA is in question, broader panels targeting a specific phenotype such as bone marrow failure or MDS/AML may be considered. Broad panels often are not comprehensive for each of the syndromes they analyze, so an FA-specific panel is still preferred when the diagnosis of FA is considered likely.

Whole Exome and Whole Genome Sequencing

Whole exome sequencing (WES) is an NGS approach that is more expansive than the sequencing of targeted panels of genes. This technique aims to sequence all the exons and splice sites of all known genes, which represent approximately 2% of the human genome. An even more expansive NGS application is whole genome sequencing (WGS), which

analyzes the entire human genome. Clinical WGS recently has been made available; however, the analysis largely remains focused on exons and splice sites, as the ability to interpret the impact of variants outside of those regions is still limited. The high cost of such testing currently prohibits this as a frontline testing tool. It may be warranted to use WES for an individual with a diagnosis of FA based on a positive chromosome breakage test but without causative variants identified on a dedicated FA panel test.

Targeted panels can identify novel variants within known FA genes, but only tests such as WES or WGS can identify novel FA genes since they screen regions of the genome and beyond [29]. Additionally, WGS looks at regions within known FA genes that may not be covered by other methods, such as deep intronic or promoter variants, and, therefore, could detect novel variants in classic FA genes. While WES and WGS are beneficial for detecting variants in a larger area of the genome when compared to panel testing, these methods are not without risks and limitations (See Table 2). Critically, WES/WGS may identify a greater number of variants of uncertain significance, and may create ethical dilemmas in the event of findings not related to the patient's phenotype [29, 34]. These aspects should be presented to the patient/family in advance. Genetic counselors are experienced in conducting informed consent conversations and ordering broad sequencing tests like WES/WGS. They can assist with results interpretation and should be involved in results discussions with providers and families.

Each assay offers different advantages as well as limitations. Table 2 provides an overview of the benefits and limitations for dedicated gene panels, WES, and WGS sequencing.

Table 2. Benefits and limitations of current next generation sequencing platforms.

Platform	Benefits	Risks/Limitations
Dedicated gene panel	• Clinically available genes associated with a patient's phenotype are analyzed in a single test. • Certain regions may be addressed specifically to capture accurate data of known variant/mutation hotspots and sequencing challenges, e.g., *FANCD2* pseudogenes. • Fast turnaround time and lowest cost option.	• Will not detect larger deletions/duplications if copy number analysis is not included. Also will likely fail to detect variants that are deep intronic or in the promoter of a gene. • Variants of uncertain significance may be identified. • Incidental discovery of a hereditary cancer risk in the family not associated with the underlying FA diagnosis is possible.
Whole exome sequencing (WES)	• All coding regions (exons) of the genome are sequenced in a single test. • May provide value for patients not identified with causative variants by dedicated panel testing (may provide opportunity for gene discovery through research). • WES can provide information for conditions other than FA if diagnosis is uncertain and if those conditions have specific clinical management.	• Cannot detect larger deletions/duplications or structural changes like translocations and inversions, distinguish pseudogene regions, or detect deep intronic variants. Overall coverage is poorer, and some exons are not analyzed effectively. • May uncover findings not related to patient's diagnosis, with potential for greater number of uncertain variants than panel testing. • More expensive than panel testing and slow turnaround time.
Whole genome sequencing (WGS)	• All coding and non-coding regions (exons and introns) of the genome are sequenced in a single test. • May provide value for patients not identified with causative variants by dedicated panel testing or WES (may provide opportunity for gene discovery through research). • WGS can provide information for conditions other than FA if diagnosis is uncertain and if those conditions have specific clinical management.	• Standards of what will define a clinical genome are still emerging. Assay cost, turnaround time and variant interpretation are still subject to further refinement to be clinically relevant.

Special Considerations with Genetic Testing

Genetic Discrimination

Fear of discrimination is a common concern for patients when considering genetic testing. Genetic discrimination occurs when people are treated differently because they have a

genetic variant that increases the risk of an inherited condition. The Genetic Information Nondiscrimination Act (GINA) is a U.S. federal law designed to protect people from health insurance and employment discrimination. The GINA does not protect against this discrimination with other forms of insurance such as life, disability, or long-term care insurance.

Variant Interpretation

A major challenge in the interpretation of genetic testing is the identification of variants of unknown significance (VUS). A VUS is a DNA alteration with an uncertain relationship to disease. Although healthy variation in the human genome is expected, the more of an individual's genome that is analyzed, the more likely it is to find sequence alterations that are novel and difficult to interpret. The American College of Medical Genetics and Genomics (ACMG) has recommended that a standard classification system be used to create a common language for clinical variant interpretation [35]. Based on specific criteria, a sequence change may be characterized in terms of its relationship to disease as one of the following: pathogenic, likely pathogenic, VUS, likely benign or benign. While pathogenic and likely pathogenic results are often sufficient to provide a genetic diagnosis, VUS findings should be interpreted with caution. Families should be encouraged to stay in contact with their genetics team annually for updates on the interpretation of their specific variant(s) and enter research studies that can assess pathogenicity.

Variant Confirmation

Although sequencing platforms can detect the presence of genomic variants, they may or may not detect "phase." Phase refers to the positioning of variants affecting the same gene. *In cis* variants are located together on the same copy of a given gene; *in trans* variants are situated on opposite copies of the same gene. Thus, to confirm a diagnosis of autosomal recessive FA, parental testing should be offered to confirm that the variants are positioned *in trans*.

Secondary Findings

As the number of genes in the analysis increases, so does the potential to identify additional findings that may or may not be related to the goal of testing. In addition to identifying the underlying genetic cause of an individual's FA, larger panels, WES, and WGS also may reveal a variant in a gene linked to other health risks. In this scenario, the unanticipated variant is called a secondary finding. For example, testing may detect two *FANCA* gene variants that explain the patient's FA phenotype, and also identify a single pathogenic *BRCA2* variant associated with Hereditary Breast and Ovarian Cancer Syndrome. Patients (and/or their parents or guardians in the case of children) should be told of this potential in advance. In the case of WES and WGS, the ACMG has compiled a specific list of genes for which reporting of secondary findings is recommended [36]. As a critical component toward the acknowledgement of a patient's right "not to know," it is

important to review the opportunity to opt out of receipt of secondary findings during an informed consent discussion for WES and WGS.

Negative Molecular Test Results

Negative molecular test results should be carefully interpreted for an individual with a chromosome breakage test within the FA range. One explanation for a negative result is the presence of a variant(s) in an undiscovered *FANC* gene or a type of variant in a gene that cannot be identified with current technology; another possibility is somatic mosaicism [37, 38]. Analysis of an alternative sample type (such as fibroblasts) may be considered in individuals presenting with an FA phenotype and negative genetic studies on peripheral blood.

Bone Marrow Analysis for Somatic Genetic Variation

Chromosome G-Banding Analysis

Following the diagnosis of FA, a cytogenetic study of the chromosomes of the patient's bone marrow cells should be analyzed using standard G-banding methodology. The goals of such studies are to investigate for the presence of a clone with acquired chromosome abnormalities and, if present, to characterize the observed abnormalities. The identification of a clone, which by definition involves the presence of the same numerical and/or structural chromosomal abnormalities in multiple cells, is an indication of an abnormal hematologic process. The significance of the cytogenetic findings must be interpreted within the context of the clinical findings, bone marrow morphologic findings from hematopathology examination, and immunophenotyping. It also is important to note that the cells of patients with FA demonstrate chromosomal instability and it is likely that some cells will develop random, non-clonal abnormalities. The clinical laboratory performing the chromosome analysis should have expertise in cancer cytogenetics, be familiar with FA and the types of abnormalities associated with the disorder, and be able 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 Abnormalities

Myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and other hematologic malignancies are associated with clonal abnormalities; therefore, the observation of a clonal abnormality may herald the emergence of neoplasms 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 an abnormal clone is observed, then follow-up analyses should be performed more than once per year to monitor the behavior of the clone and evaluate for evolution or expansion. To fully interpret the results of the bone marrow chromosome analysis, a hematopathologist should provide morphologic evaluation and flow cytometry and immunophenotyping should be used to provide additional characterization of the abnormal cells.

Recurring clonal chromosome abnormalities may be found in patients with MDS, AML, and other cancers (see Chapter 3). 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 [39-43]. One study found that gains of the long arms of chromosomes 1 and 3, and loss of chromosome 7 accounted for 75% of the clonal abnormalities observed in patients with FA [39]. The finding of the 3q gain, in particular, is specific to FA, and frequently is associated with cytogenetic evolution that includes monosomy 7 and leads to MDS. In fact, discovery of a 3q gain in a patient with apparent de novo MDS or AML should trigger the recommendation of breakage analysis.

Fluorescence In Situ Hybridization

Because a given clonal abnormality, such as the gain of the long arm of chromosome 3, is often embedded within a more complex structural abnormality (for example, a very small amount of material from 3q may be translocated to another chromosome), it may be difficult to accurately characterize using G-banding alone. In such cases, fluorescence in situ hybridization (FISH), which employs fluorescently labeled chromosome region or gene -specific probes, can be a highly informative addition to G-banded chromosome 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 recent technique that has become a major tool for cytogenetics and/or molecular laboratories. Microarray techniques such as array comparative hybridization and/or single-nucleotide polymorphism 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 conventional chromosomal banding techniques. 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. However, given the now wide availability of microarray testing, in the case of a complex bone marrow chromosome result, microarray analysis is recommended.

Genotype/Phenotype Associations in Fanconi Anemia

Fanconi anemia is a genetically and clinically heterogeneous disease. In some cases, knowing the gene and specific variant(s) can be a critical component of identifying potential risk and attempting to understand clinical course. Medical management for most individuals with FA will be in accordance with their clinical presentation. However, for individuals with variants in genes that have altered phenotypes, genotype identification is essential for proper medical management and for prognostic purposes, particularly as genes with FA-like phenotypes may exclude classic FA symptoms. It is important to recognize that genotype/phenotype information often is based on a limited number of

cases and that outliers to the traditional phenotype have been observed. Several FA variants for which sufficient information is available is included below.

FANCA

One study reported that individuals with homozygous null variants in the *FANCA* gene develop anemia at an earlier age, and have a higher incidence of leukemia than individuals with residual function *FANCA* variants [44]. However, a separate analysis revealed that the age of onset of anemia and incidence of leukemia was not altered in patients with homozygous null *FANCA* variants or in patients who express an abnormal form of the protein [45]. Specific variants may help predict phenotype such as the p.His913Pro and p.Arg951Gln/Trp variants that have been reported in association with a later onset of disease and slow hematologic progression [46].

FANCB

Males with a truncating variant in the *FANCB* gene frequently present with overt findings consistent with VACTERL-H [47], although a milder phenotype has been reported for patients with missense variants or somatic mosaicism [48, 49]. Female *FANCB* carriers do not appear to have associated disease findings [50].

FANCC

The International Fanconi Anemia Registry (IFAR) noted that individuals with variants in *FANCC* had an earlier age of onset of bone marrow failure and poorer survival compared to individuals with variants in *FANCA* or *FANCG* [51]. This finding was not reported by the European FA Research Group, which described the least severe hematologic course and fewer somatic abnormalities in the *FANCC* group when compared to *FANCA* and *FANCG* [44]. Multiple variants in the *FANCC* gene have been associated with specific phenotypes. Variants located in a region of the gene known as exon 15 (historically exon 14) have been reported in association with the development of blood abnormalities at an earlier age, more congenital abnormalities and poorer survival compared with individuals who have variants in exon 2 (historically exon 1) [51, 52]. The variant c.456+4A>T (formerly known as IVS4+4A>T) also was reported in association with a more severe disease presentation in Ashkenazi Jewish individuals [52, 53]. However, this variant has been reported in other populations [54, 55] and may not be associated with a severe phenotype in certain groups [56]. Several studies suggest that the c.67delG founder variant (formerly known as 322delG) is associated with milder symptoms, but exceptions have been observed [52, 53, 57]. A study in the Saudi population reported that the founder variant c.165+1G>T also may be associated with a mild form of the disease [58].

FANCD1/BRCA2

A study published in 2002 reported that individuals with FA and pathogenic biallelic variants of the *BRCA2* gene may develop leukemia, acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), at a much earlier age than expected [59]. They also are at risk of developing solid tumors of the brain (e.g., medulloblastoma, glioblastoma multiforme, astrocytoma) and kidney (e.g., Wilms tumor), which are not commonly seen in FA [60, 61]. If a patient has biallelic *FANCD1/BRCA2* variants, additional screening with brain magnetic resonance imaging (MRI) and kidney ultrasound should be considered [62]. While some studies in this population have demonstrated a severe phenotype, including multiple congenital abnormalities and a 97% risk of developing any malignancy by 5.2 years of age [60], there is a report of older individuals with milder or later onset disease [63, 64].

FANCG

The European FA Research Group reported that individuals with pathogenic variants in *FANCG* had more severe cytopenia and a higher incidence of leukemia than patients with variants in other FA genes [44], but this pattern was not observed in the data set collected by IFAR [51].

FANCM

Overall, more information is needed to better understand the *FANCM* phenotype. *FANCM* was proposed in 2005 to operate as an FA core complex gene and associated with an FA phenotype in a family with affected siblings [65]. Biallelic *FANCA* variants were later identified in the affected siblings, raising the question of *FANCM* as a canonical FA gene [66]. Biallelic loss of function *FANCM* variants have since been identified in individuals diagnosed with FA, and some authors suggest an alternate phenotype associated with an early-onset cancer syndrome rather than a classical FA phenotype, as their cohorts lacked bone marrow failure and congenital anomalies [67, 68]. In 2014 it was reported that a patient with compound heterozygous *FANCM* variants exhibited chromosome fragility, thumb and thenar eminence anomalies of the right hand, and bone marrow failure [69]. Reports of early-onset breast cancer and reduced fertility (primary ovarian insufficiency and mild to severe spermatogenesis in two families) in presumed biallelic carriers without an overt phenotype also have been published [68, 70, 71]. See section on cancer risk for carriers in this chapter.

FANCN/PALB2

Variants in the *FANCN/PALB2* gene typically are associated with a more severe clinical presentation. Similar to the *FANCD1/BRCA2* phenotype, individuals with variants in *FANCN/PALB2* develop solid tumors and leukemia at an earlier age than patients with variants in other FA genes [72]. Commonly reported tumors include medulloblastoma,

Wilms tumor, AML, and neuroblastoma [72-74]. The cancer surveillance recommendations for patients with biallelic *FANCD1/BRCA2* variants also may be considered for individuals with *FANCN/PALB2* variants in the absence of consensus guidelines. Phenotypes outside of this spectrum have been reported [75] indicating that additional cases over time may further expand the phenotypic spectrum of *FANCN/PALB2*-associated FA.

FANCO/RAD51C

Two families with an FA-like disorder and biallelic variants in *FANCO/RAD51C* have been reported [76, 77]. In both families, the affected individuals presented with significant congenital anomalies, including some that are atypical in classical FA such as palate anomalies, holoprosencephaly, and overlapping fingers. Hypersensitivity to diepoxybutane (DEB) and mitomycin C (MMC) and increased radial breaks confirmed the diagnoses of FA. The risk of hematologic features and squamous cell tumors remains unknown.

FANCR/RAD51

While the majority of genes associated with FA require a pathogenic variant on both copies of an FA gene, only a single pathogenic variant in the *FANCR/RAD51* gene is needed to cause disease. In the two reported cases, the *FANCR/RAD51* variant appears to have been de novo in the proband, resulting in an FA-like phenotype that includes congenital abnormalities but has not been associated with hematologic disease or cancers thus far [78, 79].

FANCS/BRCA1

The first confirmed case of biallelic *FANCS/BRCA1* variants was reported in a 28-year-old woman with stage IV papillary serous ovarian carcinoma and severe toxicity to cisplatin treatment, although diagnosis was not confirmed by chromosome breakage analysis [80]. A second case of a 23-year-old woman with ductal breast carcinoma was confirmed to have FA through chromosome breakage studies [81]. Both individuals presented with short stature, microcephaly, dysmorphology, and some degree of intellectual or developmental disability. A recent publication reported two families with four children having chromosome breakage studies consistent with FA, as well as homozygous truncating *BRCA1* variants. All four children had congenital abnormalities and growth deficiency; one child developed T-cell acute lymphocytic leukemia at 5 years and a second child developed neuroblastoma at 2 years. The remaining two children were cancer-free at 5 years and 15.5 years of age [82]. Another case confirmed by chromosome breakage was of a 2.5-year-old female with short stature, microcephaly, neurodevelopmental delay and dysmorphology but without a history of cancer [83]. None of the reported cases have developed bone marrow failure.

FANCQ/ERCC4

In addition to the FA phenotype, biallelic variants in *FANCQ/ERCC4* have been linked to autosomal recessive Cockayne syndrome, xeroderma pigmentosum, and a single case of XFE progeroid syndrome. Affected individuals can present with a single phenotype or concomitant phenotypes, depending on how gene function is impacted [84-87].

FANCR/RAD51

Monoallelic variants in FANCR*/RAD51* have been reported with autosomal dominant congenital mirror movements (CMM) [88, 89]. To date, FA and CMM phenotypes have not been reported in the same individual.

Additional Genetic Counseling Considerations

The decision to proceed with any type of genetic analysis should be at the discretion of the patient or guardian. Genetic testing has benefits, risks, and limitations, which should be reviewed in advance so that an informed decision about testing can be made. The complex challenges of genetic testing necessitate a detailed conversation with a genetic counselor as misdiagnosis or misinterpretation of test results can have a significant impact on the individual and his or her family members. Patients should be counseled by an experienced genetic counselor at the time of diagnosis and at various points throughout their lives. A genetic consultation should include discussions of the following:

- The genetic testing process
- Family, medical, and pregnancy histories
- Inheritance of FA
- Reproductive options for the patients, parents, and relatives
- Research opportunities
- Community support and resources

Inheritance of FA

Fanconi anemia is predominantly inherited in an autosomal recessive fashion, meaning that affected individuals harbor a disease-causing variant in both copies of the same FA gene. However, etiology for a small fraction of affected individuals is due to a single disease-causing variant in either the *FANCB* or *FANCR* gene. *FANCB* is inherited in an X-linked recessive pattern, meaning males with a single pathogenic variant in the *FANCB* gene have FA. *FANCR/RAD51* is inherited in an autosomal dominant pattern meaning both males and females with a single pathogenic variant in *FANCR* would be expected to have FA. The importance of the different forms of inheritance on recurrence risk is described in the section on “Genetic Testing of Family Members.”

Family History

A genetic counselor or family member should collect a three-generation family history. Family history can be helpful in identifying other family members with FA-related clinical features and in determining inheritance pattern. Ancestry and any family history of cancer should be noted since some FA genes have carrier cancer risks. In the event that patterns or clues are identified, testing may be targeted to a single gene or small number of genes of interest.

Ancestry

Most disease-causing variants occur regardless of ancestral background. However, in certain groups, some variants, referred to as "founder mutations," are carried at an increased frequency. Founder variant information can be useful for a few reasons:

Phenotype Predictions:

- For example, the *FANCC* variant (c.67delG) that is common in Northern Europeans [52] and the *FANCA* variant (p.His913Pro) that appears to be common in the Sicilian population [46] are typically associated with a milder FA phenotype. Alternatively, the c.456+4A>T variant in the *FANCC* gene is associated with a severe phenotype in the Ashkenazi Jewish population [53], while this phenotypic severity is not necessarily seen in affected individuals within the Japanese population [56].

Carrier Frequency Predictions:

- While the carrier frequency in the United States general population is predicted to be approximately 1:181 based on the reported incidence of FA, the carrier frequency for FA is higher in certain populations such as Spanish Gypsies, Afrikaners, and Ashkenazi Jews due to known founder events [1]. This information is important for appropriate reproductive counseling for individuals with a personal or family history of FA when his/her partner's ethnic background increases their risk for being a carrier of FA.

Targeted Genetic Testing:

- Historically, founder variant information could be utilized in some cases as a first tier, more targeted genetic test.

Genetic Testing for Family Members

Once an individual's genotype is known, family members can then undergo "targeted" analysis (also called carrier or single-site testing) to determine their carrier status and inform family planning. When possible, efforts should be made to first test the affected individual. However, if the proband is unavailable for dedicated FA testing, panel testing

on relatives to identify their carrier status is a reasonable approach. In this case, results interpretation may be complicated by variants of uncertain significance (VUS), and negative test results for an unaffected relative should be interpreted with caution.

Owing to the clinical variability of FA (even within the same family), all biological siblings of an affected person should undergo a chromosome breakage test. This is particularly important in the setting of transplant where a family member is identified as a potential donor. Pending the breakage study outcome, additional testing may be considered. Subsequent testing options are listed in the diagnostic testing section of this chapter.

As described earlier, most forms of FA follow an autosomal recessive inheritance pattern. Two forms deviate from this with one following X-linked inheritance (*FANCB*) and the other displaying autosomal dominance (*FANCR/RAD51*).

Autosomal Recessive Inheritance

Autosomal recessive inheritance means that an individual must have two copies of a non-working gene to have symptoms of the condition. Biological parents of an affected child should be offered carrier testing. Doing so confirms that each parent carries one of the known variants and proves the variants are *in trans* (on separate gene copies). Each child from parents who are confirmed carriers has a 25% chance of having FA. Unaffected siblings (following negative chromosome breakage studies) have a 67% chance of being an FA carrier. Although rare, it is possible that a parent tests negative. Explanations for this include:

- The egg or sperm involved in the child's conception developed a spontaneous change (known as a *de novo* variant)
- Only a fraction of the parent's reproductive cells has the variant (known as germline or gonadal mosaicism)
- Uniparental disomy (UPD) in which one variant is present on both gene copies and was inherited from only one parent (thus far only reported in *FANCA* and *FANCP* cases) [90]
- Misattributed parentage (the child was adopted, was the product of a donor egg or sperm, paternity or maternity was not accurately reported)

Inheritance also is an important consideration when an individual with FA reaches reproductive age. While reduced fertility is reported, some individuals with FA have conceived biological children. The likelihood of having an affected child depends on the genetic status of a partner. Comprehensive testing that includes full sequencing and deletion/duplication analysis to identify *any* pathogenic variant in the causative *FANC* gene of the partner will best inform risks to future children. For example, when FA is attributed to the *FANCA* gene, comprehensive *FANCA* analysis is needed for the partner, rather than targeted testing for the known *FANCA* variants. Depending on the couple's genetic status, pregnancy outcomes are as follows:

- If the partner tests negative, the chance to have a child with FA is very low. All children will be carriers.
- If the partner tests positive in the same *FANC* gene, there is a 50% chance each child will have FA, and a 50% chance each child will be a carrier of FA.
- If both partners have FA and have variants in the same FANC gene, all (100%) of their children will have FA.

Should both partners have FA due to variants in different *FANC* genes, their children will be carriers for two different forms of FA. The chance for their children to be affected is very low, presuming they had negative carrier testing for one another's FA type. Extended relatives on both sides of the family should be offered carrier testing for the familial *FANC* variants.

X-Linked Recessive Inheritance

With an X-linked condition, the disease-causing gene resides on the X chromosome. In FA, this inheritance applies to the *FANCB* gene. Women have two X chromosomes while men have one X and one Y chromosome. If a woman carries the causative variant, there is a 50% chance of passing on the variant in each pregnancy. Any sons who inherit the variant will be affected. Any daughters who inherit the variant will be carriers. If the mother of an affected boy has negative carrier testing, her son's FA is likely *de novo* although germline mosaicism cannot be excluded. As such, male siblings of an affected male should undergo chromosome breakage analysis. Maternal relatives in these families have an increased chance of carrying or having the condition. Any daughters born to affected men will be obligate carriers. Any sons will be unaffected, since they inherit a Y chromosome from their fathers.

Autosomal Dominant Inheritance

Autosomal dominant inheritance means that an individual need only one non-working copy of a gene to have symptoms of the condition. In FA, autosomal dominant inheritance applies to the *FANCR/RAD51* gene. While affected individuals to date are reported with *de novo* variants (meaning the condition was not inherited from an affected parent), parents should still be offered testing. With negative testing, germline/gonadal mosaicism cannot be excluded. A small chance remains that siblings or a future pregnancy could be affected. All siblings, therefore, should be assessed by chromosome breakage. Anyone who tests positive has FA. Any sons or daughters of a person with autosomal dominant FA would have a 50% chance to have FA, and a 50% chance to be unaffected.

Carrier Cancer Risk

Fanconi anemia and hereditary breast and ovarian cancer genes encode proteins that operate within a common pathway, called the FA DNA repair pathway. These proteins

function together to maintain genome integrity by repairing DNA damage (see Chapter 1) [91]. Variable cancer risks already have been linked to altered protein function of FA genes; however, it is critical for providers and families to understand how information about cancer risk in carriers is evolving and the association of rare variants with cancer susceptibility [92]. In fact, many FA genes are included in large clinical panel tests despite insufficient data to adequately define their cancer risks [93-95]. Currently, for genes listed in Table 3, there are management recommendations published by the National Comprehensive Cancer Network (NCCN) for individuals with positive test results, also known as pathogenic or likely pathogenic test results. The NCCN reviews existing literature annually and provides updated clinical practice guidelines for the detection, prevention, and risk reduction of adult onset cancers as new information is learned [96].

Table 3. Established cancer risks in carriers warranting modified management.

FANC Gene	Established Cancer Risk in Carriers	Additional References
*FANCD1 (*BRCA2)*	Breast, ovary, prostate, pancreas, melanoma	[97-98]
FANCJ (BRIP1; BACH1)	Ovary	[96, 100, 101]
FANCN (PALB2)	Breast, pancreas	[96, 98, 101-105]
FANCO (RAD51C)	Ovary	[101, 106, 107]
*FANCS (*BRCA1)*	Breast, ovary, prostate, pancreas	[97, 98, 101, 108]

**Hypomorphic variants noted.*

Outside of the five genes listed in Table 3, question about increased cancer risk in carriers of the remaining FA and FA-like genes is a topic of great interest and ongoing research. Over the years, data published from FA families have tried to capture the observed number of cancers in carriers versus an estimated cancer incidence in the general population. These studies, limited in scale and to self-reported data collection, did not indicate a significant difference that would warrant modified management [110-112].

All FA carriers should be encouraged to communicate their genetic status with primary providers and to reach out annually for potential health and cancer risk updates. It is equally important to ensure in advance that families are aware of the potential to uncover health risks affecting carriers, and the potential for discrimination of unaffected individuals based on positive findings. Referral to a genetic counselor who specializes in cancer predisposition is recommended for accurate risk assessment and a comprehensive discussion about testing, management options and family planning.

Reproductive Planning

There are multiple reproductive options for parents of a child with FA and individuals with FA. Preconception genetic counseling is available for families to discuss these options in greater detail.

Prenatal Diagnostic Testing

Prenatal diagnostic testing of fetal cells can be done at various times in the pregnancy to determine whether a fetus has FA. Prenatal testing also can 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 for the sibling with FA. Prenatal testing options include chorionic villus sampling and amniocentesis, which are typically available from the 10^{th} and 15^{th} weeks of pregnancy, respectively. The goal of both procedures is to obtain fetal cells for genetic testing or chromosomal breakage analysis. Targeted variant analysis should be performed on fetal DNA if the genetic variants are known, whereas chromosome breakage testing should be performed when the familial variants are not known. Both procedures are associated with a risk of miscarriage and should be discussed in detail with the center performing the procedure.

Preimplantation Genetic Diagnosis

Preimplantation genetic diagnosis (PGD) is a genetic screen used to test embryos produced through in vitro fertilization (IVF). While PGD can attempt to select embryos without FA and those that are an HLA-match for an affected sibling, this technology is not a guarantee and the individual PGD center should inform families of their experience and accuracy. Parents considering PGD should be advised of the chances of selecting a healthy, HLA-matched embryo. Theoretically, for couples who have a child with autosomal recessive form of FA, there is a 75% chance that an embryo will not have FA, and a 25% chance that an embryo will be an HLA match, thus the odds that an embryo will be both unaffected with FA and an HLA match is 18.75% (3/16). Realistically, many couples need multiple rounds of IVF-PGD to achieve a clinical pregnancy resulting in a birth. Further, it is recommended that prenatal testing be performed for all pregnancies resulting from embryos produced through IVF-PGD to confirm the expected genetic status based on PGD.

Other Reproductive Options

Other reproductive options include the use of donor gametes (egg or sperm), adoption, and unassisted pregnancy. Surrogacy also is an option, especially for women with FA who are concerned about the health implications of pregnancy.

Summary

Close communication between physicians, genetic counselors, cytogenetics and molecular genetics laboratories, and hematopathologists is critical for the diagnosis of FA and the optimal care for patients with the disease. Early diagnosis of FA and the characterization of patient-specific FA variants is of utmost importance as this information may influence a patient's clinical management. It is critical that a clinically certified laboratory perform the diagnostic tests to ensure adherence to rigorous standards for quality control and quality assurance. 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. It is strongly recommended that a genetic counselor or other genetics professional help guide the testing. 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 variants 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.

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Evaluation for diagnosis and genotype/phenotype sections:
Jeffrey Lipton, MD, PhD*
Blanche P. Alter, MD, MPH, FAAP
Moises Fiesco-Roa, MD

Diagnostic and somatic testing sections:
Betsy Hirsch, PhD, FACMG*
Kelsey McIntyre, PhD, FACMG
Susan Olson, PhD, FACMG

Genetic counseling, genetic variants, genotype/phenotype, and diagnostic testing sections:
Rebecca Tryon, MS, MA, LGC*
Jennifer Kennedy, MS, CGC

**Section Committee Chair*

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Chapter 3

Clinical Care of Fanconi Anemia Hematologic Issues

Introduction

Most patients with Fanconi anemia (FA) commonly develop hematologic complications that are primarily related to bone marrow failure (BMF). It is thought that the cause of BMF in patients with FA is a faulty DNA repair pathway that damages hematopoietic stem cells (HSCs) (see Chapter 1). This chapter provides an overview of hematologic care for patients with FA, including guidelines for clinical monitoring of patients and the decision process for determining the need for hematopoietic cell transplant (HCT), the only proven curative treatment for BMF. The chapter also outlines HCT care guidelines and provides a discussion of recent advancements in HCT protocols that have led to significant improvements in the survival rates of patients with FA. Alternative therapeutic options beyond HCT, such as gene therapy, also are discussed.

Bone Marrow Failure

Bone marrow failure (BMF) in patients with FA can range from mild, asymptomatic cytopenias to severe aplastic anemia (AA), myelodysplastic syndrome (MDS), or acute myelogenous leukemia (AML). The absence of BMF, however, does not exclude the diagnosis of FA. More than 90% of patients with FA will have macrocytosis starting in infancy or childhood. However, macrocytosis may be masked by concomitant iron deficiency or an inherited blood disorder such as alpha- or beta-thalassemia trait, which can delay diagnosis of FA [1-3].

Definition of Bone Marrow Failure

Bone marrow failure is diagnosed by blood counts that are below standard age-appropriate ranges. While many patients progress to frank aplastic anemia, others may maintain mildly abnormal blood counts for years and even decades. Bone marrow failure is classified into three broad categories depending upon the degree of cytopenia(s) observed (see Table 1). The classification defines points at which different clinical management options should be considered. Importantly, to meet these criteria for BMF, the cytopenia(s) must be persistent and not transient or secondary to another treatable cause, such as infection, medication, peripheral blood cell destruction or loss, or nutritional deficiencies.

Table 1. Severity of bone marrow failure.

	Mild	**Moderate (or hypoplastic or aplastic anemia)**	**Severe (or severe aplastic anemia)**
Absolute neutrophil count (ANC)	<1,500/mm^3	<1,000/mm^3	<500/mm^3
Platelet count	150,000-50,000/mm^3	<50,000/mm^3	<30,000/mm^3
Hemoglobin (Hb) level	≥8 g/dL*	<8 g/dL	<8 g/dL

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

Bone Marrow Failure Age of Onset

The age of onset of BMF in patients with FA is highly variable. Three out of every four patients develop evidence of at least mild BMF within the first decade of life [3-6]. In an analysis of 754 patients in the International Fanconi Anemia Registry (IFAR), the average age of onset was 7.6 years. However, that study analyzed patients who mainly had defects in the *FANCA*, *FANCC*, and *FANCG* genes; therefore, the results may not be representative

of patients with rarer gene defects [5]. In adults, FA is less commonly diagnosed due to primary BMF; instead, diagnosis of FA more commonly occurs as a consequence of presentation with cancer or with severe toxicity after chemotherapy treatment for a malignancy [4-7]. Severe, usually transient, BMF also may develop in non-transplanted female patients with FA during pregnancy.

The cytopenia that most commonly leads to the diagnosis of FA is thrombocytopenia with red blood cell macrocytosis and elevated levels of fetal hemoglobin. When a patient is diagnosed with FA, or when blood counts fall further, a thorough hematologic workup is necessary to rule out additional causes of cytopenias other than primary BMF. Marrow cellularity must be interpreted in the context of changes in peripheral blood counts as it may be variable and subject to sampling variation. Therapeutic intervention should not be based on bone marrow cellularity alone in the absence of clinically significant peripheral cytopenias or clear evidence (usually clonal cytogenetic changes) of a myelodysplastic or malignant process.

Clinical Monitoring of Bone Marrow Failure

Clinical surveillance and therapeutic management are guided by the following:

- Severity of the cytopenia(s)
- Stability or trend of the peripheral blood counts
- Presence or development of morphologic (dysplastic) and cytogenetic bone marrow abnormalities
- Presence of potentially high-risk genotypes (see Chapter 2)
- Other organ system problems
- Patient's quality of life
- Preferences of the patient and their family

At diagnosis, a trephine bone marrow biopsy should be performed in FA patients to evaluate bone marrow cellularity and architecture, and as an aspirate to assess morphology for dysplastic changes and cytogenetics for abnormalities common to FA and MDS (see Chapter 2). Subsequently, annual evaluation of the bone marrow, beginning at age two, allows for serial comparisons of a patient's marrow, and prompt detection of bone marrow progression that may suggest consideration of transplantation.

Recommendations for Clinical Monitoring of Bone Marrow Failure

Peripheral blood counts stable at no more than mild BMF range (Table 1) and no clonal cytogenetic abnormalities present

- For patients with normal blood counts or mild BMF and no cytogenetic clonal marrow abnormalities, peripheral blood counts and differential white blood cell counts should be reviewed every 3-4 months.
- Consider a bone marrow biopsy and aspirate with cytogenetics annually.

Peripheral blood counts stable in the normal to mild BMF range (Table 1) and clonal cytogenetic abnormalities present

- Blood counts and physical findings should be reviewed every three months for patients with a cytogenetic clonal marrow abnormality (in the absence of morphologic MDS) together with normal or mildly low, but stable, blood counts.
- Bone marrow examination should be performed every 3-6 months to evaluate if the patient's status is stable or changing.
- Review appropriate plans for hematopoietic cell 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 by bone marrow biopsy and aspirate with cytogenetics.
- Rising peripheral blood counts may be due to either the development of MDS or AML (requiring discussion of urgent transplantation) or, rarely, reversion of a germ-line mutation in a stem cell called somatic stem cell mosaicism, which repopulates the marrow with normal cells (see Chapter 2). Such patients require ongoing close monitoring, including blood counts every 1-2 months and a bone marrow examination every 3-6 months.
- Discuss and prepare appropriate plans for HCT intervention as adverse clonal progression or worsening BMF may evolve rapidly.

Clonal Abnormalities

The bone marrow of patients with FA can exhibit dysplasia, such as nuclear/cytoplasmic desynchrony, hypolobulated megakaryocytes, and binucleated erythroid cells. These features are difficult to distinguish from truer forms of MDS and the precise diagnosis determines the need for and type of treatment. The presence of dysplasia is not necessarily a harbinger of MDS and AML; therefore, it is important for FA patients to have a baseline bone marrow examination at diagnosis and regular bone marrow cytogenetic analyses for follow up. Bone marrow examination (which includes aspiration, biopsy, and cytogenetic analysis as described in Chapter 2) should be performed by an experienced hematopathologist at the time of diagnosis and in subsequent serial marrow examination annually. The purpose of the serial marrow examination and cytogenetic analysis is to identify clonal evolution to MDS or AML in the context of peripheral blood count changes or physical exam findings. The results of cytogenetics analyses of patients with FA have revealed varying types and frequencies of clones. An early analysis from the International Fanconi Anemia Registry (IFAR) found that the risk of developing MDS or AML within three 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%) [8]. In another cohort, clones were noted to disappear permanently or reappear in serial marrow evaluations [9].

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 [10-13]. The prognostic role of 3qG for predicting progression to MDS or AML was first reported in 18 patients where the three-year risk of MDS/AML was 9 in 10 (90%), compared with 1 in 10 (10%) for patients without aberrations in chromosome 3 [13]. In other studies, the prognostic role of a 3qG has been more difficult to establish. For example, in a study of 119 patients with FA, 32% had clonal aberrations and 20 out of 119 had 3qG [14], although the prognostic power of 3qG could not be evaluated because the chromosome aberration occurred simultaneously with the diagnosis of MDS [14]. Vundinti et al. showed that 10 patients with FA without 3q aberrations progressed to MDS or AML and five of these patients developed other clones [15]. Mehta et al. showed that four of 64 FA patients without MDS and six of 13 with MDS/AML had 3qG, but there was no significant association identified between 3qG and risk of MDS/AML [10]. The results from these studies indicate that 3qG is a common chromosomal abnormality in FA and may be associated with MDS and/or AML, although its prognostic significance is not entirely clear, particularly when it occurs in isolation and different cytogenetic methodologies are used for analysis.

Similar to the non-FA population, the appearance of monosomy 7 and most 7q deletions (7L) is generally associated with a poor prognosis and high risk of developing MDS or 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 combinations of aberrations.

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, some patients may have stable hematopoiesis and possibly a relatively favorable long-term prognosis. Regular marrow examinations before blood count changes offer the best opportunity to diagnose marrow progression and time to discuss treatment options. The interpretation of specific chromosomal abnormalities indicative of clonal progression to MDS and AML is discussed in detail in Chapter 2. The decision on how to proceed should be made by the patient and their family in discussion with an FA physician specialist.

Treatment Guidelines for Patients with Myelodysplastic Syndrome or Acute Myeloid Leukemia

There is no standard therapy for FA patients with MDS or AML. Treatment options include HCT with or without prior induction chemotherapy, and phase I/II trials for MDS or AML. Chemotherapy treatment 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 or 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 [16].

Treatment Options for Bone Marrow Failure

Transfusions

The onset of anemia in patients with FA is insidious. Hemoglobin levels should be monitored closely, at least every 3-4 months from diagnosis, 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 or the patient has other heart or lung disease that requires a higher hemoglobin. Transfusion use should be minimized particularly if the treatment goal is HCT.

All FA patients should receive red blood cells that have been filtered to deplete 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 (GvHD), particularly if transplant is being considered. Extended antigen matching of transfused red blood cells may be important for patients in certain racial groups for whom minor antigen mismatch is more commonly encountered. Patients should not receive blood transfusions from related family members due to the risk of developing alloimmunization that would increase the risk of graft rejection after HCT. Blood from unrelated designated donors offers no increase in transfusion safety and may delay needed transfusion.

Hematopoietic Cell Transplant

The only curative option for bone marrow failure (BMF) in patients with FA is a hematopoietic cell transplant (HCT). Survival outcomes following HCT have improved significantly for patients with FA primarily due to earlier referral for HCT prior to the onset of MDS and/or AML, refinements in treatment plans and HLA-matching between the patient and donor, and better supportive care before, during, and after HCT.

Recent Advancements in Hematopoietic Cell Transplant

From the institutional and registry studies performed to date, six recent developments have occurred:

- Survival rates after HCT continue to improve, particularly for patients undergoing alternate donor transplant.
- Transplant from related and unrelated donors has similar outcomes.

- Transplant without radiation can be successful for patients with FA.
- Radiation during transplant is clearly associated with increased risk of later cancer in larger series of persons without FA. More studies are needed to determine if radiation or a radiation-free conditioning protocol increases the risk of cancer in patients with FA.
- For patients without a 10/10 or 9/10 matched related donor, 10/10 or 9/10 matched adult unrelated donor and 10-8/10 (or perhaps less) matched umbilical cord blood (UCB) are associated with good outcomes.
- Haploidentical transplant can be successful in FA patients with no other donor option.
- In transplanted FA patients, development of chronic or acute GvHD increases the risk of later cancer.

Sibling Donor Hematopoietic Cell Transplant

In the past, limited field total body irradiation (TBI) was given to FA patients with a human leukocyte antigen (HLA)-identical sibling donor; however, today with the use of fludarabine (FLU) conditioning containing regimens, TBI is used much less often for FA patients with BMF who have HLA-matched sibling donors [17]. Bonfim et al. reported that 85 patients with FA (median age 9 years, range 3-34 years) and a matched sibling donor have been transplanted using a radiation-free regimen [18]. 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. The five-year survival rate for all patients was approximately 85%, and 96% among the 48 patients who were younger than 10 years at the time of HCT.

T-Cell Depletion Reduces Risk of Graft-Versus-Host Disease

The Minnesota group reported that T-cell depletion of bone marrow in sibling donors reduced the risk of GvHD [19]. In this report, patients were conditioned with CY (5 mg/kg x 4 days; 20 mg/kg total dose), FLU (35 mg/m^2 x 5 days; 175 mg/m^2 total dose), and anti-thymocyte globulin (ATG) (30 mg/kg 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 - 43.3 years) included in the study, 92% survived at least five years [19]. These results indicate that when possible, T-cell depletion should be used to reduce the risk of GvHD.

Unrelated Donor Hematopoietic Cell Transplant

The majority of FA patients do not have an HLA-identical unaffected sibling donor, so 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 unrelated cord blood (UCB) obtained from the placenta after the birth of a baby.

Recently, the use of haploidentical donors also has been explored as an alternative donor source.

Outcomes of HCT were reported by the Minnesota group on 48 patients with FA (ranging from 1.7-34.3 years) with aplastic anemia or MDS who received FLU, CY, ATG, and low-dose 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 [20]. In this study, recipients of bone marrow engrafted at a median of 11 days (ranging from 9-23 days); in contrast, only 88% of cord blood recipients engrafted at a median of 19 days (ranging from 10-40 days). 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 0.6-6.3 years). However, patients without a prior history of opportunistic infection or transfusions had a 92% chance of survival at five years [20].

In 2017, the Cincinnati group reported results of a multi-institutional study in which a radiation-free conditioning regimen was tested, replacing TBI with busulfan (BU) for patients undergoing alternative donor HCT, including haploidentical transplants. Forty-five patients (median age 8.2 years, range 4.3-44 years), with aplastic anemia and/or MDS, received FLU, CY, and ATG in combination with BU followed by transplantation of T-cell-depleted peripheral blood stem cells. All but one patient engrafted at a median of nine days (range 7-15). The incidence of acute GvHD was low at 7%. Three patients developed limited chronic GvHD and none developed extensive chronic GvHD. The median follow-up time was 41 months and three-year overall survival was 80%. All 19 patients younger than 10 years of age who were transplanted for severe marrow failure and with lower dose BU survived [21]. This group of investigators is now testing a risk-adjusted approach to the use of radiation-free transplant by giving lower doses of BU to those with aplasia and higher doses to those with MDS or AML.

The costs of unrelated donor and cord blood HCT are prohibitive in many countries; therefore, the use of haploidentical donors has been explored as an alternative donor option. Outcomes have improved dramatically for alternative donor HCT with the use of post-HCT (PT) cyclophosphamide (CY) for GvHD prophylaxis, a strategy that raises specific challenges in CY-sensitive FA patients. In 2017, Bonfim et al. reported on the results of this approach in 30 patients with FA after a preparative regimen of FLU, TBI (200-300 cGy), and CY with or without ATG [22]. All patients received PT-CY (25 mg/kg/d x 2 doses) followed by CSA and MMF. All patients engrafted in the subgroup of patients who did not receive ATG (n = 14), but their HCT course was complicated by high rates of acute and chronic GvHD, and only 8 patients survived at time of reporting. In the subgroup that received ATG (n = 16), 14 patients had sustained engraftment, severe GvHD rates were lower, and 13 patients are alive. One-year overall survival for the entire cohort was 73%. These data demonstrate that haploidentical donor transplantation with PT-CY is feasible for FA patients without a matched related or unrelated donor; however, haploidentical

transplants still offer challenges [22] and should be considered in patients with FA only if there are no other alternatives.

In 2018, the Minnesota group compared outcomes of HLA-matched sibling donor (MSD) HCT (n = 17) and alternative donor HCT (n = 57) performed in patients with FA who had severe aplastic anemia between 2001 and 2016 [23]. Overall survival at five years was 94% for MSD-HCT versus 86% for alternative donor-HCT; neutrophil engraftment was 100% versus 95%, and platelet recovery was 100% versus 89%. Acute GvHD was 6% versus 12%, severe acute GvHD was 6% versus 4%, and chronic GvHD was 0% versus 7%, with no statistically significant differences noted by the type of transplant. These data demonstrate that alternative donor-HCT should be considered when a patient is close to transfusion-dependence, similar to timing for MSD-HCT, in patients with FA-associated BMF.

Indications for Sibling and/or Alternative Donor Hematopoietic Cell Transplant

The eligibility criteria to consider for sibling or alternative donor HCT is as follows:

- Aplastic anemia (hemoglobin (Hgb) < 8 g/dL or absolute neutrophil count (ANC) < 500/μL or platelet count < 20,000/μL)
- MDS or AML
- Progressive complex cytogenetic abnormalities known to be associated with malignancy
- Absence of active infections
- Available donor
  Order of priority
  - HLA 10/10 (followed by 9/10) allele-matched sibling
  - HLA 10/10 (followed by 9/10) allele-matched relative other than sibling
  - HLA 10/10 (followed by 9/10) allele-matched unrelated adult volunteer
  - HLA 10-8/10 antigen matched UCB

Indications for Hematopoietic Cell Transplant

With similar outcomes, the indications for alternate donor HCT are the same as the indications for sibling donor HCT. Patients with an exceptional risk of HCT-related mortality (e.g., patients with severe organ dysfunction, those who are 35 years or older, and those with pre-existing malignancies or life-threatening systemic infections) may consider alternative treatment options first, such as the use of androgens.

Patients with FA who develop persistent and severe cytopenias or evidence of MDS or AML should be considered for HCT provided the patient is not too old and has adequate organ function. Clinical investigation is underway to determine whether HCT performed earlier may be considered for patients with specific genetic mutations who are deemed to be at particularly high risk for rapid progression to MDS or AML, and who may face markedly shortened survival times (e.g., *BRCA*-related genetic mutations) [24].

Graft-Versus-Host Disease

Graft-versus-host disease (GvHD) occurs 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 HCT because the donor's immune system is transplanted along with the donor's hematopoietic stem cells (HSC), which are responsible for marrow recovery and reconstitution of the blood cells. While GvHD can occur in any patient undergoing an allogeneic HCT, 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 2. Graft-versus-host disease 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 typical first line treatment is a steroid (methylprednisolone).

Table 2. Signs and symptoms of acute and chronic GvHD.

Graft-versus-host disease (GvHD)	
Acute GvHD	**Chronic GvHD**
Skin rash (blistering with more severe disease) Persistent nausea Diarrhea Jaundice	Skin rash, discoloration Hair loss Dry mouth, tooth decay Dry eyes Sores in the mouth, thrush Ridged or fragile nails Shortness of breath, exercise intolerance Anorexia, weight loss Stiff joints

Infections

Infection following HCT can be a major complication for FA patients due to their unique sensitivity to chemoradiotherapy and, in some cases, the extensive period of neutropenia prior to HCT for some patients. Prophylactic antibiotic regimens are commonly used after HCT to reduce the risk of infection. Most patients are treated with trimethoprim/sulfamethoxazole (Bactrim) for one year after transplant and other antibacterial and antifungal drugs through at least day 100 after HCT. 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.

Long-Term Follow-Up Care for Hematopoietic Cell Transplant

Long-term follow-up after HCT for patients with FA must be thought of as an indispensable part of routine medical care. Guidelines for the long-term care of survivors of childhood cancer have been developed by the Children's Oncology Group [25]. In addition, the American Society of Blood and Marrow Transplantation, the European Group for Blood and Marrow Transplantation, and the Center for International Blood and Marrow Transplant Research recently developed joint recommendations [26] which include suggested screening and preventive practices for adult survivors of HCT. Many of these recommendations also apply to patients with FA who have undergone HCT.

All patients treated with HCT, including those with FA, are subject to health complications known as "late effects" that may develop long after the transplant. These effects include late graft failure, recurrent acute and chronic GvHD, and the effects of prolonged steroid therapy such as hypertension, hyperglycemia, and aseptic necrosis of bone (loss of bone primarily in the hip, knee, and shoulder joints). Other HCT late effects such as short stature and sterility have not been formally evaluated in patients with FA since these are pre-existing problems in most FA patients. Late effects of transplant can negatively impact the patient's physical and mental health, quality of life, growth, development, education, and employment (Table 3). Therefore, the development of late effects must be assessed on an ongoing basis [27-36].

Table 3. Possible long-term adverse effects and their causes in patients with FA.

Organ or system affected	Adverse effects	Causes
General	Short stature	FA, HCT
	Primary or secondary cancers	FA, HCT, GvHD
Skin	Pigmentation	FA, GvHD
	Dryness	FA, GvHD
	Thickening	FA, GvHD
Central nervous system	Side effects of radiation	HCT
Eyes	Cataracts	HCT
	Very dry eyes (Sicca, or Sjögren's syndrome)	GvHD
	Retinitis	HCT
Ears, nose, and throat	Chronic sinusitis	GvHD
	Hearing loss	FA, HCT
	Very dry mouth (Sicca, or Sjögren's syndrome)	GvHD

Organ or system affected	Adverse effects	Causes
Heart	Congenital anomalies	FA
	Iron overload	Blood transfusions
Lungs	Side effects of HCT	HCT, GvHD
Liver	Chronic liver disease (transaminitis or cholestasis)	HCT, GvHD
	Iron overload	FA or HCT treatment (transfusions)
Kidneys and genitourinary system	Congenital anomalies	FA
	Chronic renal insufficiency	HCT
GI tract	Congenital anomalies	FA
	Failure to thrive	FA, GvHD
	Functional problems (e.g., malabsorption)	FA, GvHD
Endocrine	Diabetes	FA, GvHD
	Hypothyroidism	FA, HCT
Gonadal	Masculinization (virilization)	Androgens
	Infertility	FA, HCT
	Early menopause	FA, HCT
Musculoskeletal	Hand and arm anomalies	FA
	Hip dysplasia	FA
Psychological	Psychosocial issues (e.g., anxiety, depression)	FA, HCT, GvHD

Practical Considerations for Long-Term Follow-Up Care

General guidelines for long-term follow-up of FA patients starting at one year post-HCT is outlined in Table 4 [27, 37-39]. Long-term care plans should be tailored to the specific needs of each individual FA patient under the supervision of a long-term care team comprised of the HCT physician, primary hematologist, and a multi-disciplinary team of specialists.

Table 4. General post-HCT long-term follow-up guidelines for 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
HEMATOLOGY						
Complete blood counts	X	X	X	X	X	X

	1 year	2 year	3 year	4 year	5 year	Yearly
Bone marrow aspiration Chimerism testing Cytogenetics studies	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	
Measure levels of ferritin and iron Perform T2*MRI if ferritin levels are high	If clinically indicated	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	
IMMUNOLOGY						
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
CARDIAC						
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 normal
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 normal
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 normal
PULMONARY						
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	
HEPATIC						
Measure liver function panel	X	X	X	X	X	X
If liver function panel values are high, consider 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	If clinically indicated	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	Repeat if previous test was abnormal	

	1 year	2 year	3 year	4 year	5 year	Yearly
RENAL						
Measure levels of electrolytes, BUN, and creatinine in the urine	X	X	X	X	X	X
Perform urinalysis	X		X		X	
ENDOCRINE and METABOLISM						
Perform an oral glucose tolerance test (OGTT)	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated
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 IGFBP-3 in patients younger than 18 years	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	
Measure levels of 25-OH vitamin D and calcium	X	X	X	X	X	X
Assess bone age in patients 5 to 18 years	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	
DXA scan (with adjustment for height)	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated
GROWTH and DEVELOPMENT						
Plot patient's height and weight on a growth chart	X	X	X	X	X	X
Neuropsychological evaluation	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	
HEAD and NECK						
Ophthalmology evaluation	X	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated	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

	1 year	2 year	3 year	4 year	5 year	Yearly
GYNECOLOGIC						
General gynecologic evaluation and cancer screening in female patients older than 13 years	X	X	X	X	X	X
DERMATOLOGY						
Evaluate nevi and check for skin cancers	X	X	X	X	X	X
Testing to rule out GvHD of skin	X	X	X	X	X	X

Alternative Treatments for Bone Marrow Failure

If blood counts decline to severe levels (Table 1) and cure by HCT is not possible or preferred, alternative therapies may maintain blood counts and quality of life in patients with FA.

Androgens

Synthetic androgens, such as oxymetholone and danazol, have been used to treat cytopenias in patients with FA for more than 50 years. Androgens primarily affect red cells and platelets but can also improve neutrophil counts [40, 41]. More than half of patients with FA who are treated with androgens will respond at least transiently, although a subset of patients who initially respond may become refractory over time. As many as 10-20% of patients who receive continuous low dose androgen therapy may never require an HCT, unless MDS and/or AML develop. Thus, androgen treatment may delay a transplant for months and even years in responsive patients [42].

Androgen treatment used to delay HCT may be associated with the following risks and complications:

- Androgens do not prevent progression to MDS/AML
- Androgens may increase the chance of liver or other problems, which may complicate HCT
- Use of androgens may increase the age at which patients with FA undergo HCT
- Patients may have acquired viral infections, which may be problematic during HCT

Patients prescribed androgens should be prospectively monitored for liver function test (LFT) abnormalities and development of liver tumors. Blood LFTs should be performed every 3-6 months, and a liver ultrasound should be performed every 6-12 months. If the

levels of liver transaminases increase to 3-5 times above normal, the androgen dose should be tapered until the blood tests improve. Androgen-associated liver adenomas (benign tumors) may develop with long-term treatment and are predominantly due to the cellular liver toxicities of the 17 alpha-alkylated androgens. 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 HCT. 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 transformation of initially benign hepatic adenomas may occur after years of androgen treatment [43].

Oxymetholone

The most commonly used androgen since 1961 is oxymetholone [40, 41]. The starting dose of oxymetholone is typically ~2 mg/kg/day, but doses as high as 5 mg/kg/day may be required. Most patients who will respond do so within three to four months with stabilization of falling counts or an increase in the hemoglobin or platelet counts. If a response occurs, then the general strategy is to slowly taper the daily dose of oxymetholone in 10-20% decrements every three to four months until the lowest 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 kilogram body weight should be recalculated prior to making dose adjustments.

The patient (both male and female) and family should be counseled about the possible side effects of oxymetholone. Every effort should be made to minimize the side effects by tapering the dose to the minimum effective dose whenever possible. Aggressive acne treatment of facial and back lesions may make the treatment more tolerable. Discussion of the masculinizing side effects, such as hair darkening and development on lip/groin/axilla and deepening of the voice, should occur before prescription. Long-term androgen usage may lead to shrinkage and/or impaired development of the testis in males due to suppression of the hypothalamic-pituitary-gonadal axis.

If no response is seen after three to four months, then—in the absence of other causes of cytopenias such as viral, bacterial, or fungal infection—oxymetholone should be discontinued (although there are anecdotal reports of rare patients responding after six or more months). Stabilization of hemoglobin levels may be seen sooner than improvements in platelet counts; white cell responses may occur later or be nonexistent.

Danazol

A few reports [44-46] in the literature show that both male and female FA patients may benefit from treatment with danazol, an attenuated synthetic androgen that produces fewer virializing effects than oxymetholone and may cause fewer liver complications. 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), including 3 patients (2 females and 1 male) who were treated successfully for more than three years and 1 patient (female) for more than 10 years without exhibiting progressive marrow failure requiring stem cell transplantation [46]. 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/day 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 [47].

Metformin

Metformin is a drug approved by the U.S. Food and Drug Administration for treatment of diabetes mellitus that has shown promise in treating hematologic issues in preclinical FA models. In these studies, metformin increased blood counts and protected cells against DNA damage [48, 49]. Researchers at Harvard University initiated a phase I clinical trial in 2017 to explore whether metformin increases blood counts in patients with FA. As of June 2020, the trial was still recruiting patients and results from the trial had not yet been published.

Quercetin

The University of Cincinnati initiated a phase 1 clinical trial in 2012 to assess the safety profile of oral quercetin therapy in patients with FA. Studies have shown that systemic reactive oxygen species (ROS) contribute to hematopoietic progenitor cells fragility [50]. Quercetin, a naturally occurring flavonoid found in fruits and vegetables, scavenges free radicals and has anti-inflammatory, antioxidant and antineoplastic properties [51, 52]. The goal of the phase 1 pilot study was to determine long-term safety and efficacy of quercetin administration in patients with FA. Secondary endpoints included identifying the effects of quercetin on blood counts. Dose optimization from the phase 1 trial led to development of a phase II quercetin chemoprevention trial that was initiated in 2018 by the Cincinnati group. The goal of the phase II trial is to determine the efficacy of a maximum daily dose of quercetin (4,000 mg/day) in reducing buccal micronuclei as a surrogate marker for DNA damage and susceptibility to squamous cell carcinoma in FA patients post-HCT. As of June 2020, the phase II trial was still recruiting patients and results from the trial had not yet been published.

Cytokines

Several cytokines have been evaluated for their capacity to stimulate failing bone marrow in FA patients, but none has proven entirely successful. The cytokines granulocyte colony-stimulating factor (G-CSF) [53] and granulocyte-macrophage colony-stimulating factor (GM-CSF) [54] can improve the neutrophil count in patients with FA; however, GM-CSF is no longer available for clinical use. Treatment with other cytokines has not shown benefit for

patients with FA. However, newer agents such as thrombopoietin-mimetic drugs are being cautiously tested in patients with FA [55].

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/mm^3 or as a short-term bridge to transplant. There is, however, concern that cytokine therapy will stimulate development or progression of cytogenetic abnormalities. Historically, a few patients also have shown improvements in hemoglobin levels or platelet counts while on G-CSF; these effects most likely are due to the treatment of, or reduction in, infections. Long-term follow-up has not been published. Treatment should generally be discontinued if the neutrophil count fails to improve after eight weeks of G-CSF therapy.

A bone marrow aspirate or biopsy with cytogenetics is recommended prior to the initiation of cytokine treatment, given the risk of stimulating the growth of a leukemic clone. It is recommended that patients being treated with cytokines are monitored for bone marrow morphology and cytogenetics every six months. In the setting of a compelling clinical indication for cytokine therapy, such as an acute infection, there are no findings to support withholding cytokines from patients with clonal abnormalities. In such cases, the use of hematopoietic cytokines should be considered only 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 in patients with the following:

- Anemia and/or thrombocytopenia
- Progressive marrow failure
- Bone marrow failure that precludes all prospect of an early HCT (due to the lack of an acceptable donor, severe organ dysfunction, comorbidities, socioeconomic situations, and/or lack of interest in pursuing HCT 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. However, if HCT is the goal, transfusions should be minimized.

Gene Therapy

Gene therapy has been employed for multiple conditions with a hemopoietic component, including hemoglobinopathies [56], leukemia [57], immunodeficiencies [58], lysosomal storage disease [59], and Fanconi anemia. The first clinical trials of stem cell gene therapy for FA used retroviruses to deliver the *FANCA* or *FANCC* genes. This early protocol, however, resulted in either no correction or only transient correction of hematopoietic cells, an observation consistent with only short-term functional gene complementation [60-63].

Lessons learned from earlier gene therapy clinical trials and preclinical animal model studies [64-67] cumulatively led to development of improved clinical trial protocols. The first successful gene therapy trial for patients with variants in *FANCA* demonstrated that lentiviral-mediated hematopoietic gene transfer into hematopoietic stem cells followed by delivery in non-conditioned patients led to successful engraftment and expansion of *FANCA* gene-corrected cells [68]. Functional laboratory studies also demonstrated that the normal cells expressed a functional *FANCA* protein, as the cells were resistant to DNA damaging agents. Importantly, no adverse events have been reported in any of the patients to date in the ongoing study. Additional clinical gene therapy trials for patients with *FANCA* variants also have been initiated. These trials are addressing additional challenges with FA gene therapy, such as the role of conditioning and optimization of the ex vivo hematopoietic stem cell culture.

Gene Editing

Gene editing also is on the horizon as a useful therapy to treat bone marrow failure in patients with FA, but research is currently in pre-clinical stages. A key differentiating feature between gene editing and gene therapy is precise gene modification. Current gene editing systems include zinc finger nucleases (ZFN), meganucleases (MN), transcription activator-like effector nucleases (TALENs), and the clustered regularly interspaced palindromic repeats (CRISPR)/Cas9 system. Each system is unique, but each shares the function that they bind DNA and generate a break in one or both DNA strands. Following this break, the DNA can be repaired through an error-prone process where the DNA ends are reconnected. To date, ZFNs, TALENs, and CRISPR/Cas9 have been used in FA gene modification in the laboratory [69, 70]; however, because gene editing causes DNA breaks and FA proteins are required to repair DNA breaks [71] this method may not be viable for FA patients. More pre-clinical research is needed to determine whether gene editing will be efficacious for patients with FA.

Summary

Fanconi anemia (FA) is a genetic disorder that results in DNA repair defects that adversely affect the stability of hematopoietic stem cells (HSCs). This results in the high likelihood that patients with FA will develop bone marrow failure (BMF) and/or clonal progression to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). The only cure for BMF at the present time is a hematopoietic cell transplant (HCT). Recommendations for clinical monitoring of BMF are based on the stability of peripheral blood counts and clonal abnormalities observed in serial bone marrow examinations. The decision to use HCT for FA patients with BMF and/or clonal abnormalities, MDS, or leukemia should be made in consultation with an FA physician specialist. Recent advancements in HCT protocols continue to improve survival rates. These advancements include, but are not limited to, knowledge that HCT without total body radiation is successful, T-cell depletion should be used when possible, and that HCT from mis-matched related, unrelated and haploidentical donors can be successful for patients without any other donor options. Transplants in general, because of graft-versus-host disease, the conditioning regimens, and long periods of immunosuppression, confer an increased risk of earlier onset cancer. This indicates that close follow up during long-term care following HCT is imperative. Emerging therapies such as gene therapy also hold promise as curative options for BMF in patients with FA and the future of BMF treatment for patients with FA will undoubtedly shift as gene therapy and gene editing technology matures and efficacy is established.

The Fanconi Anemia Research Fund recognizes the following author contributions to the 5th edition:

Bone marrow failure section:
Zora R. Rogers, MD*

Hematopoietic cell transplant section:
Margaret L. MacMillan, MD*
Stella Davies, MBBS, PhD, MCRP
John E. Wagner, MD

Long-term follow up section:

Eva Guinan, MD*
Farid Boulad, MD
Maria Cancio, MD
Stella Davies, MBBS, PhD, MCRP

Gene therapy section:
Mark J. Osborn, PhD*
Christen L. Ebens, MD, MPH

**Section Committee Chair*

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Chapter 4

Non-HNSCC Solid Tumors in Patients with Fanconi Anemia

Introduction

Cancer risk and management is a major concern for patients with Fanconi anemia (FA) due to the DNA repair defects associated with the disease. The most frequently diagnosed solid tumor cancers in FA patients include head and neck squamous cell carcinoma (HNSCC) and gynecologic squamous cell carcinoma (SCC). In addition to gynecologic SCC, patients with FA also develop other non-HNSCC solid tumors. This chapter describes the type and incidence of non-HNSCC solid tumors in 2,600 cases and case series of patients with FA reported in the medical literature from 1927 through 2018, as well as from other cohorts totaling more than 5,500 patients with FA. The numbers of FA patients with any type of cancer were more than 500 in the case reports and series, and more than 200 in the cohort reports. Cancer risks updated in an FA cohort within the National Cancer Institute's (NCI) Inherited Bone Marrow Failure Syndromes Program also are discussed [1]. Comparison data include cancer cases published by the American Cancer Society (ACS) in 2019 and the Surveillance Epidemiology and End Results (SEER) U.S.-based cancer registry [2, 3]. Most of the data on non-HNSCC were from patients with FA who did not receive a

hematopoietic cell transplant (HCT), although this status was not always clear from the reports, and thus some of the analyses include a combination of non-transplanted and transplanted patients.

Non-HNSCC Tumors in Patients with Fanconi Anemia

The frequencies of rare cancers in patients with FA compared with the general population reported by the American Cancer Society (ACS) in 2019 are shown in Figure 1 [2]. These rare types of solid tumors in patients with FA do not follow the frequency pattern observed in the general population. For example, the five most frequent non-HNSCC cancers in the general population were breast, lung, prostate, colon, and melanoma (Table 1, Figure 1A), while the top five non-HNSCC in FA case reports and case series were brain, Wilms tumor, liver, esophageal, and vulvar cancers (Table 1, Figure 1B). The most frequently reported cancers in all cohorts of FA patients were similar: liver, vulvar, cervical, esophageal, and brain (Figure 1C). More than 500 of the 2,600 cases reported with FA had at least one cancer; more than 70 had HNSCC, and more than 200 had leukemia, with approximately 200 patients (roughly 1 in 13) with non-HNSCC tumors. More than 80 patients had at least two cancers, although some of those may not have been rare cancers.

Table 1. Non-HNSCC solid tumors in U.S. general population and in patients with FA.*

General Population	Fanconi Anemia Case Reports	Fanconi Anemia Cases in Cohort Reports
Breast; lung; prostate; colon; melanoma; bladder; lymphoma; kidney; uterine; pancreatic; thyroid; rectum; liver; stomach; brain; esophageal; cervical; sarcoma; larynx; testis; vulvar; vaginal; osteosarcoma; Wilms; neuroblastoma	Brain; liver; Wilms; esophageal; vulvar; vaginal; breast; neuroblastoma; sarcoma; cervical; lung; lymphoma; colon; stomach; kidney	Liver; vulvar; cervical; esophageal; brain; breast; Wilms; thyroid; lung; lymphoma; anorectal; osteosarcoma

**More than 40,000 cases from the general population [2] and at least two cases in FA.*

Combinations of one or two of acute myeloid leukemia (AML), brain, Wilms tumor, and neuroblastoma were observed in patients with biallelic mutations in *FANCD1/BRCA2*, as well as in a few patients with mutations in *FANCN/PALB2*, but not in other genotypes. The most frequent cancers that occurred as single cancers in other genotypes were AML, liver, esophageal, vulvar, and breast. A few types of cancer were reported in fewer than 10 patients each (i.e., lung, stomach, lymphoma, colon, and sarcomas (corneal

carcinosarcoma post-HCT and rhabdomyosarcoma)), as well as single cases of osteosarcoma, retinoblastoma, hepatoblastoma, non-Hodgkin lymphoma (NHL), renal clear cell sarcoma, bladder, bronchial, prostate, cricoid, testis, and uterine cancers.

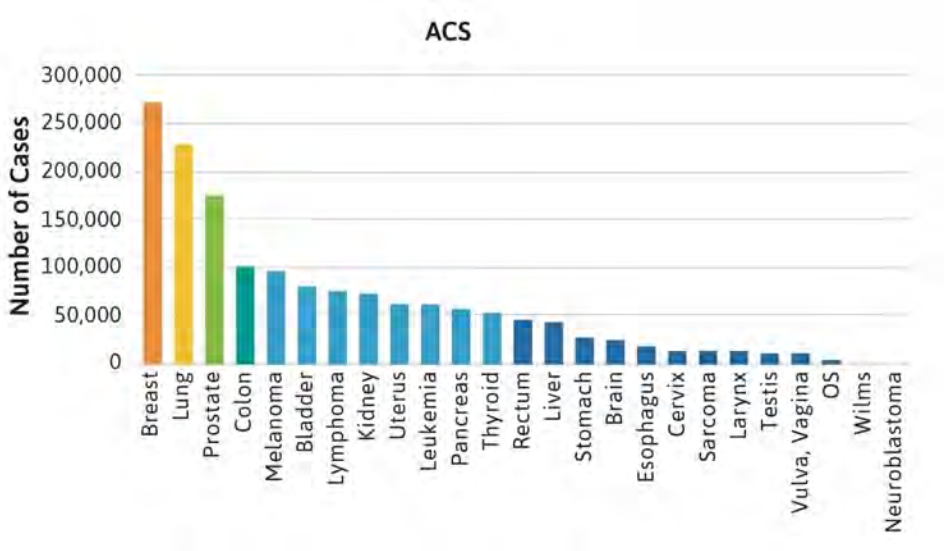

Figure 1A.

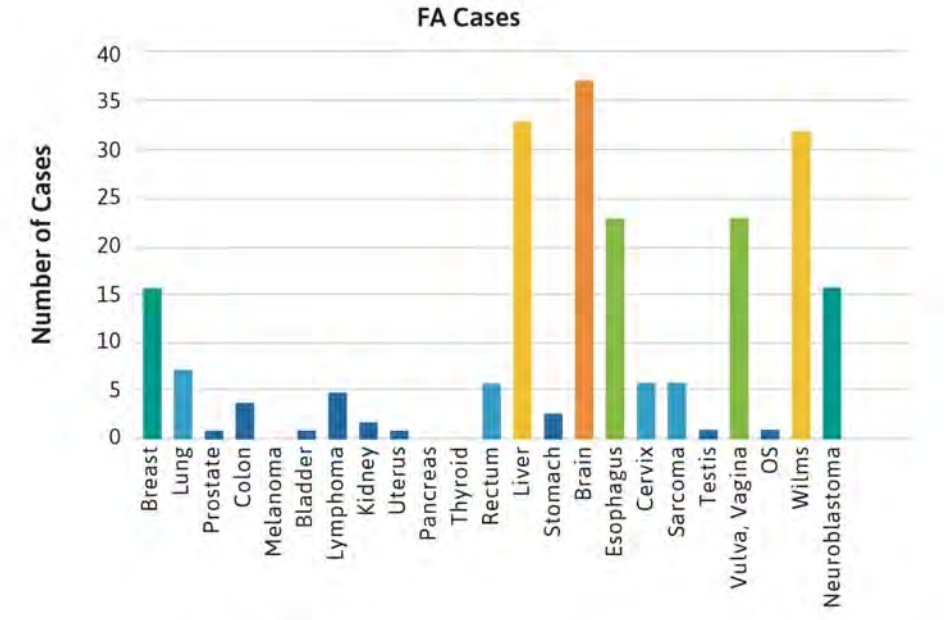

Figure 1B.

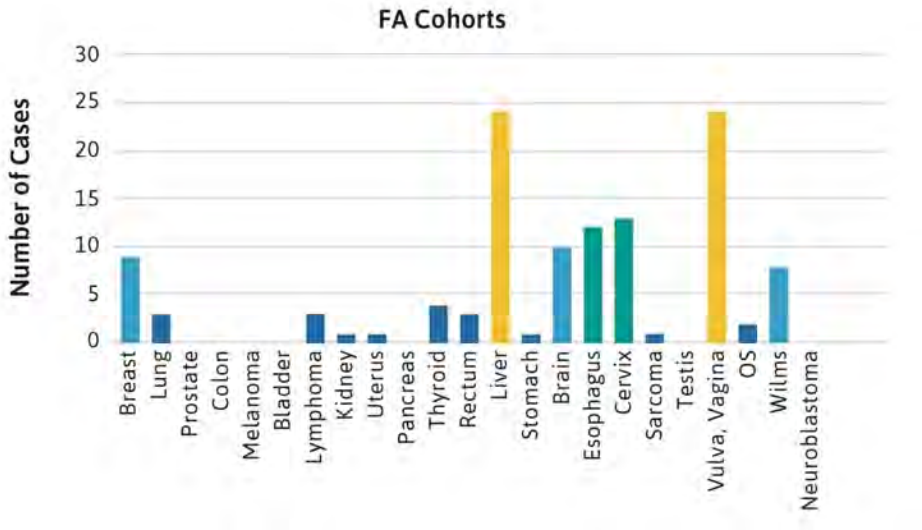

Figure 1C.

Figure 1. **Number of cases of non-HNSCC tumors reported in the U.S. general population or the FA literature from 1927 to 2018.** Cancers are listed on the horizontal axis in order of frequency as reported for the U.S. population. **1A.** Data from the American Cancer Society (ACS) [2]. **1B.** Data from 2,630 cases with FA reported in case reports or case series. Data on non-HNSCC are shown in the same sequence as in Figure 1A. **1C.** Data from more than 5,000 cases with FA included in reports of cohorts, but not discussed individually.

Incidence and Risk of Rare Solid Tumors in Patients with Fanconi Anemia

Most of the rare cancers occurred in FA patients between the ages of 20-40 years, although liver tumors were reported during the teenage years, perhaps related to the use of androgens for bone marrow failure. Brain, Wilms, neuroblastoma and lymphoma cancers typically occurred before age 10 years, primarily in patients with mutations in *FANCD1/BRCA2* and *FANCN/PALB2*. All of the non-HNSCC solid tumors occurred at substantially younger ages than in the general population, where the median age for any type of solid tumors is between 60-70 years (Figure 2). For example, esophageal, breast, lung, and stomach cancers were reported in FA patients at ages between 20-30 years. It is important to note that the diagnosis of a malignancy (solid tumors or AML) preceded the diagnosis of FA in approximately 35% of cases [4]

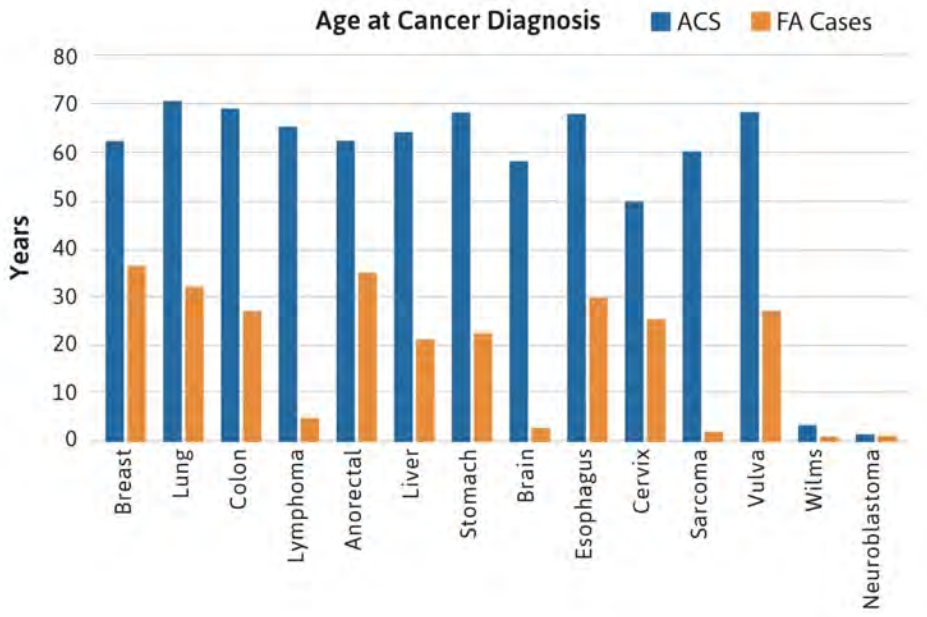

Figure 2. Age at cancer diagnosis in FA cases. The blue bars denote data from the general population, with a median age between 60-70 years in most cancers. The orange bars denote cases with FA reported at the individual level, with median ages below 40 years (most between 20-30 years).

The nature of the descriptive data from case reports and case series does not lend itself to more sophisticated quantitative analyses, such as cumulative incidence or observed to expected ratios. These types of analyses have been published in separate cohorts [5-7] and recently have been updated for the NCI FA cohort [1]. The NCI cohort data were used to reexamine the role of HCT [8] and it was determined that all solid tumors, especially HNSCC, occurred at a higher rate in transplanted patients compared with patients who were not transplanted (Figure 3). The cancer sites following HCT included HNSCC (particularly oral cavity), as well as vulvar, larynx, and brain. In addition, cancers unique to transplanted patients were thyroid cancer and Non-Hodgkin's lymphoma (NHL) [1].

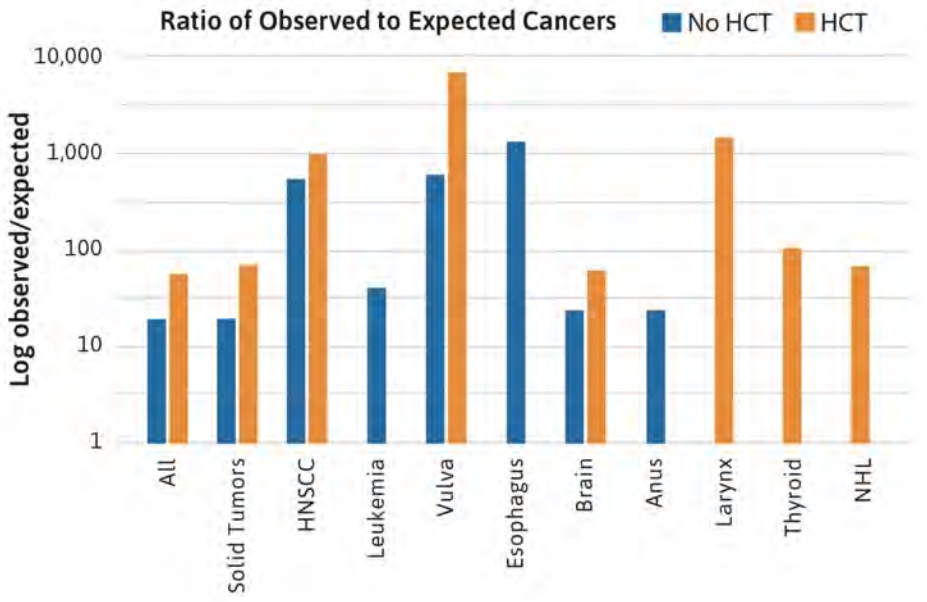

Figure 3. Ratio of observed to expected cancers in the NCI Fanconi Anemia cohort. The bars compare the observed numbers of cases to those expected from the Surveillance Epidemiology and End Results registry, after adjustment for age, sex, and birth cohort. Standard incidence ratio data are log transformed, since the values range from 10 to more than 1000. The blue bars denote patients with FA who did not have a hematopoietic cell transplant (HCT). The orange bars denote patients with FA who had an HCT. The data suggest that the relative risk of most FA-type cancers (particularly HNSCC and vulvar SCC) is higher in the transplanted group. In addition, cases of cancer of the larynx, thyroid, and Non-Hodgkin's lymphoma appeared only in the transplanted group [1].

The NCI cohort data also allowed determination of the ratio of observed (O) to expected (E) cancer cases, adjusted for age, sex, and birth cohort, based on data from the SEER Program. The quantity O/E is often called the standardized incidence ratio (SIR). Accurate SIR calculations are not possible using literature case reports because of the potential for biased reporting of cases (numerators) and the lack of information about how many persons would be reported in the literature were they to develop a cancer (denominators). The NCI cohort enrolled all available patients and followed them consistently and, thus, both numerators and denominators were well defined. Some of the rare cancers occurring in FA patients are extremely rare in individuals of the same ages without FA. It is essential to take age into account when assessing risk. The O/E ratios for rare cancers do not take age into account and were similar to the high ratios observed for HNSCC and gynecologic cancers (e.g., >1000-fold for esophageal cancer). The limited data from the NCI FA cohort suggest that cancers that developed following HCT were higher risk cancers than those that developed in non-transplanted patients; additionally, the types of cancers that

developed in transplanted patients were not typically seen in the non-transplanted patients (Figure 3) [1, 8].

The crude rate of solid tumors in FA patients is approximately 5-20%, based on the numbers of solid tumors reported divided by the total number of patients reported in the literature cases since 1927. The NCI cohort data were used in competing risk analyses to determine that the cumulative incidence or probability of solid tumors as the first adverse event was about 25% by age 50 years. In a hypothetical scenario in which severe bone marrow failure could be excluded, the cumulative incidence of solid tumors was 75% [8]. The most frequent solid tumors appear to be HNSCC and gynecologic SCC. While the absolute numbers of the rare solid tumors are small by contrast, the relative risks for some of them are as high as for HNSCC and gynecologic SCC, and the absolute risk is high enough that patients should be monitored for them closely.

Surveillance and Management of Rare Solid Tumors

Surveillance recommendations for non-HNSCC and non-gynecologic SCC cancers in patients with FA is outlined in Table 2. Surveillance of solid tumors should start on or before the ages listed in the table. Some cancer types have no recommendations for prevention and/or surveillance. Always consult physicians if there are any symptoms of concern.

Table 2: Surveillance for non-HNSCC and non-gynecologic SCC cancers in patients with FA.

Cancers	Prevention	Surveillance	Youngest Age Detected (Years)
Brain		Brain MRI	Newborn
Wilms		Abdominal ultrasound	Newborn
Neuroblastoma		Ultrasound	Newborn
Sarcoma			<1
Lymphoma			<1
Liver	Iron chelation if transfused, avoid alcohol, immunize for Hepatitis A, B	Liver ultrasound, liver enzymes	5
Vulvar, vagina	HPV vaccine	Examination from age 16 or menarche	14
Esophagus	Avoid alcohol and tobacco	Esophagoscopy (usually requires anesthesia)	20
Cervix	HPV vaccine	Examination from age 16 or menarche	21
Breast	Avoid alcohol	Physical exam mammography, ultrasound, MRI	23
Colon	Avoid alcohol	Colonoscopy	21
Stomach		Consider testing for H pylori, treat with antibiotics if found	21
Lung	No smoking	Do not do CT because too much radiation	23
Skin cancer	Limit sun exposure, use sun protection (sun block, long sleeves, hat)	Dermatology exam every 6-12 months or sooner	26
Kidney		Abdominal ultrasound	36

Treatments for solid tumors, including the rare tumors discussed in this chapter, in patients who do not have FA include surgery, radiation, and chemotherapy. Options for treating solid tumors in patients with FA are limited. The best modality is surgery when possible. Radiation may be effective, although it may lead to complications such as skin reactions, mucositis, ulceration, etc.

Study Limitations

The data reviewed in this chapter have several limitations. Some patients may have been reported more than once. Patients reported in the older literature may have been misclassified and may not have had FA. There may have been biased reporting, overreporting of case reports with cancer, and underreporting of those without cancer. Since cancer is age-dependent, and many of the cases were reported as young children and may have developed tumors after they were reported, the cumulative incidence of cancer may be greater than indicated from the published data. This literature review was based primarily on cases reported in English and, thus, cases in other languages may have been overlooked. Cases reported in series for which the focus was the gene and mutation may have had insufficiently detailed description of their clinical problems, including cancer.

Summary

Patients with FA are at high risk for developing head and neck squamous cell carcinoma (HNSCC) (see Chapter 5) and other non-HNSCC cancers, such as gynecologic squamous cell carcinoma (see Chapter 7). This chapter summarizes the type and incidence of all rare non-HNSCC solid tumors in cohorts as well as case reports and series of patients with FA reported in the medical literature from 1927 through 2018. The data show that rare solid tumors in FA patients do not follow frequency patterns observed in the general population. The top five non-HNSCC cancers diagnosed in case reports and case series of FA patients are brain, Wilms, liver, esophageal and vulvar cancer. Importantly, most non-HNSCC tumors that develop in patients with FA occurred at substantially younger ages (20-50 years) compared to the general population (60-70 years). The data also show that patients treated with hematopoietic cell transplant develop higher risk tumors than non-transplanted patients. Therapeutic management of non-HNSCC tumors using modalities currently used in the general population, such as radiation and/or chemotherapy, are generally contraindicated in patients with FA due to issues related to high toxicity. Surgical removal is currently the best approach for treating solid tumors in patients with FA; however, improved screening techniques are needed to identify early neoplastic lesions. Research that focuses on identifying optimal ways to diagnose, prevent, and treat rare solid tumors in patients with FA is desperately needed.

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Blanche P. Alter, MD, MPH, FAAP*
Moises Fiesco-Roa, MD
Philip S. Rosenberg, PhD

**Chapter committee chair*

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Chapter 5

Head and Neck Cancer in Patients with Fanconi Anemia

Introduction

Head and neck squamous cell carcinoma (HNSCC) is significantly more common in patients with Fanconi anemia (FA) than in the general population. This chapter provides an overview of HNSCC in patients with FA. Focus areas include early surveillance, risk factors, diagnosis, and currently available treatment options. Head and neck cancers are diagnosed at a younger age (20-50 years) in patients with FA and often at an advanced stage. The cornerstone treatment for FA patients with HNSCC is surgery; however, outcomes are poor if the diagnosis is at an advanced stage. Patients with FA also have significant toxicity issues from systemic chemotherapies used to treat HNSCC in the general population. The precise risk factors associated with HNSCC for patients with FA have yet to be defined, although studies have shown that DNA repair defects associated with the disease, increased age, and graft-versus-host disease (GvHD) after hematopoietic cell transplant (HCT) correlate with increased risk for HNSCC development. Causative well-defined risk factors in the general population, such as tobacco and alcohol use, should be avoided by patients with FA. It is recommended that early surveillance by oral examination begin at a young age.

Head and Neck Cancer in the General Population

Head and neck cancers encompass a wide variety of tumors that typically begin in the squamous cells that line the mucosal surfaces of the oral cavity, nasal cavity, pharynx, and larynx. These tumors often are referred to as head and neck squamous cell carcinoma (HNSCC). Approximately 30,000 individuals are diagnosed with head and neck cancer in the United States annually, and about 30% of these patients die from their disease. Increasingly, HNSCC is an international health problem, representing the fifth most common cancer type and cause of cancer-related death worldwide [1].

The vast majority of HNSCC cases (more than 90%) develop following exposure to carcinogens, including tobacco and alcohol [2, 3], betel nut [4], Epstein-Barr Virus (EBV), and sexually transmitted viral pathogens such as human papillomavirus (HPV) [5]. Head and neck cancers are prototypic tobacco-related cancers. The risk for the development of HNSCC and the subsequent risk for the development of second primary cancers in the upper aerodigestive tract is directly attributable to the duration and intensity of tobacco exposure. Tobacco-related cancers also can occur in non-smokers as a result of environmental smoke exposure. Chronic consumption of alcohol is estimated to increase the risk for HNSCC by two- to three-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 HNSCC, with HPV detected in more than 70-80% of cases of oropharyngeal cancer.

Head and Neck Cancer in Patients with Fanconi Anemia

Head and neck squamous cell carcinoma (HNSCC) is the most common solid tumor in patients with FA. The incidence of HNSCC in FA patients is 500- to 700-fold higher than in the general population [6-9]. The main cause of death in adulthood for patients with FA is HNSCC and the risk increases with age. In some cases, diagnosis of HNSCC tumors precedes the diagnosis of FA [10]; 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 20-50 years [10], whereas individuals in the general population tend to be diagnosed between the ages of 60-70 years. Patients with FA also

have a higher proportion of HNSCC in the oral cavity (approximately 65%), 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 FA patients is significantly poorer than that in the general population. Moreover, even after cure of the primary HNSCC, patients with FA are more likely than the general population to develop second primary cancers (more than 60% versus ~30%, respectively) [10]. The anatomic distribution of second primary cancers also is 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 head and neck region, 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 [11].

Risk Factors Associated with Head and Neck Cancer in Patients with Fanconi Anemia

Most individuals with FA are now living into adulthood, due to significant improvements in bone marrow transplant outcomes. With increased age, these patients are experiencing a significant escalation in the incidence of cancer, which now represents the major cause of death in the FA adult population. Age alone is a significant risk factor for HNSCC for patients with FA. They are diagnosed with HNSCC earlier than the general population (20-50 years vs. 60-70 years) and the risk increases significantly with age. Cumulative genomic instability from DNA repair defects that are a hallmark of FA also contributes significantly to this age-related risk [12].

Patients with FA have the highest risk for HNSCC amongst all patients with inherited genetic syndromes (e.g., Li-Fraumeni syndrome and 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. A 2004 study [13] 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). However, high numbers of patients with FA who have never undergone HCT also develop HNSCC [14]. An association between GvHD and HNSCC also has been suggested in patients without FA [15]. Tobacco and alcohol consumption are less commonly reported in patients with FA than in the general population; nonetheless,

both 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 [16, 17] suggest that HPV may be a major contributor to HNSCC development in patients with FA, whereas other studies [18, 19] dispute these results. Laboratory studies show that mutations in genes that cause FA increase susceptibility to HPV-induced carcinogenesis [20, 21]. 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.

Prevention of Head and Neck Cancer in Patients with Fanconi Anemia

Abstaining from Alcohol and Tobacco

The causal link between tobacco and alcohol exposure and the development of HNSCC is well-established. The use of tobacco and tobacco products should be discouraged categorically, including exposure to secondhand smoke. Further, marijuana and e-cigarette use also have been associated with the development of HNSCC in the general population [22]; therefore, FA patients are encouraged to abstain from use of these agents. 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 also should be discouraged (see Chapter 6).

Maintenance of Oral Hygiene

Several reports suggest that poor oral hygiene and chronic, repeated physical trauma to the oral cavity may promote the development of HNSCC [23-25], although the evidence is not yet conclusive. Therefore, maintenance of proper oral hygiene and routine dental evaluations are recommended. 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. This subject is discussed in Chapter 6.

Human Papillomavirus Vaccination

The role of human papillomavirus (HPV) in HNSCC development in patients with FA is controversial [16, 17, 19, 26, 27] and more studies are needed. Despite the controversy, it is recommended that both male and female patients with FA receive an HPV vaccination at an early age [28, 29]. See Chapter 7 for detailed vaccination recommendations for female patients with FA.

Surveillance of Head and Neck Cancer in Patients with Fanconi Anemia

The high incidence of HNSCC combined with the poor outcome of this disease in patients with FA underscore the need for careful HNSCC surveillance. Surveillance should begin at age 10, which is based on literature reports of the earliest age of HNSCC diagnosis [8, 10]. The oral cavities of individuals with FA often contain 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 HNSCC for FA patients. Qualified professionals may have dental, oral surgery, otolaryngology, or general surgery backgrounds supplemented with specialized training in detecting and/or treating HNSCC. Routine oral cancer screening by a general dentist can supplement but should not replace thorough HNSCC screening.

Oral Examination

Thorough head and neck examination in patients with FA should occur every six months. 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 should be examined thoroughly. The oral cavity, the most common site for HNSCC in patients with FA, and the proximal oropharynx can be effectively evaluated through the mouth by visual examination and palpation. Examination of the distal oropharynx, nasopharynx, larynx, and hypopharynx requires the use of either a transoral mirror or a flexible fiberoptic laryngoscope. Although patients with FA have a higher rate of SCC in the cervical esophagus than the general population [30], the routine use of esophagoscopy for screening is not advocated. Symptom-based evaluation for esophageal cancer needs to be considered. Any patient with odynophagia, dysphagia, or other localizing symptoms merits evaluation with a barium swallow study and/or esophagoscopy.

Importance of Brush Biopsy for Patients with Fanconi Anemia

The oral cavities of patients with FA often have multiple leukoplakia-like lesions that are typically not malignant. In the past, all suspicious lesions were diagnosed through incisional tissue biopsy only. Early surveillance of tumor development in the head and neck region of individuals with FA is essential; however, conducting numerous incisional biopsies on suspicious lesions is invasive and painful. Patients with FA therefore require alternative and effective early surveillance strategies that do not cause extensive tissue damage. Fourteen years ago, a medical team from Germany initiated a study to see if a non-invasive brush biopsy procedure could accurately determine pre-malignant and malignant tissue in a large cohort of patients with FA. This study, published in 2020, showed that in 713 patients with FA worldwide, careful examination of the oral cavity followed by brush biopsy and cytology identified pre-malignant and malignant lesions with high sensitivity (97.7%) and specificity (84.5%). The addition of DNA ploidy analysis to brush biopsy samples examined by cytology increased the sensitivity and specificity to

100% and 92.2%, respectively [31]. This is a highly significant finding, as 63% of lesions in the study were diagnosed as pre-malignant or early-stage cancer and were curable through surgery.

It is important to point out that once suspicious lesions are identified as precancerous or cancerous by a brush biopsy, they should be biopsied with an incisional biopsy immediately. Suspicious lesions not found pre-cancerous or cancerous by brush biopsy should be closely monitored. Stability or shrinkage in size of the lesion can be used as an indicator to continue observation. Growth or changes in characteristics of the lesion (i.e., thickening or erythroplakia) require further attention.

Treatment of Head and Neck Cancer in Patients with Fanconi Anemia

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 either with surgery or with radiation therapy, whereas advanced-stage disease requires multi-modality 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 side-effects 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 surgeons (cancer and reconstructive specialists), radiation oncologists, and medical oncologists, 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.

Treatment Approach to Head and Neck Cancer in Patients with Fanconi Anemia

The following factors complicate the management of HNSCC in FA patients, making surgery the preferred therapeutic modality in patients with FA:

- The tumors of FA patients tend to be very aggressive and often are present in advanced stages.
- The non-cancerous cells of FA patients are more 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 FA patients are not as sensitive as non-cancerous cells to DNA-crosslinking agents. Therefore, HNSCC in FA patients does not respond to sub-therapeutic doses of radiation. Therefore, surgery is the preferred therapeutic modality in FA patients.

Recommendations for Surgical Treatment of Head and Neck Cancer in Patients with Fanconi Anemia

In contrast to the other treatment modalities, surgical therapy for HNSCC in FA patients is well tolerated and can result in durable local control for small tumors without lymph node metastases [32]. Patients with FA exhibit no significant increase in the incidence of complications following surgery, including wound infections or long-term negative side effects associated with surgical scarring. Accordingly, the consensus opinion is that surgery should be considered the primary curative modality in all FA patients who develop HNSCC.

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, FA patients 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 mental health professional should be consulted prior to surgery to help the patient cope with any negative after-effects.

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. The exact type and extent of surgical resection should be dictated by the primary site, size, and extent of the tumor. Large cancers that involve multiple subsites of the head and neck should be excised via an open approach as in the general population. However, smaller accessible tumors can be resected trans-orally using robotic or laser instruments. 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 biology of laryngeal cancers and anatomy of the larynx.

Management of the neck also follows principles established for the management of HNSCC in the general population. 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 regional disease. A recent study in patients without FA showed that elective nodal dissections in patients with oral cavity cancers with an N0 neck are associated with a significant improvement in overall survival [33]. Therefore, it is recommended that elective nodal dissection be included as part of management in FA patients who have oral cancer as well.

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. Several case reports have described the successful use of free flap reconstruction in FA patients [34-36]. Therefore, the use of free flaps for reconstruction should be considered as indicated, without restrictions. The specific details of surgical management are discussed in other references [37, 38].

Radiation Therapy of Head and Neck Cancer in Patients with Fanconi Anemia

Radiation treatment is associated with severe negative after-effects in patients with FA, and many patients cannot complete a full course of radiation. The risk of dying from the negative after-effects 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, dysphagia, esophageal stenosis, laryngeal edema, and wound breakdown. Therefore, radiation therapy should be used only in FA patients for whom it is absolutely required for disease control.

When radiation therapy is to be utilized, FA patients must be monitored closely for signs of severe toxicity. It is important to keep in mind that tumor cells in FA patients do not have increased susceptibility to the effects of radiation (unlike the tumor cells in most individuals in the general population). Therefore, treatment with radiation should be planned for the same doses used in the management of patients without FA. Radiosensitivity of normal tissues in FA patients is a concern as there have been several case reports of severe mucositis occurring in the oral cavity of FA patients after doses of 10–20 Gy with conventional field sizes encompassing the entire oral cavity. These clinical presentations have usually been associated with conventional fractionation of 1.8–2.0 Gy per day, five days a week, to a target volume that included the entire oral cavity and oropharynx.

An approach has been designed in which a small field of 5 cm x 5 cm is treated for one week (five fractions) at reduced fraction size of 0.5 Gy per day, with daily examination for mucositis and daily peripheral blood counts. Both patients with FA and animal models of FA [39-41] with radiosensitivity have demonstrated significant abscopal bone marrow suppression and leukopenia. Patients tolerating the first week of reduced field and reduced fraction size then can be moved up to a second week of same reduced field size, but now with conventional fractionation of 1.8–2.0 Gy per day. Daily measurements of mucositis by physical exam and peripheral blood counts should be continued. Patients who tolerate this therapy then can move on to the entire clinical target volume with reduced fraction size of 0.5 Gy per day. Subsequently, in the absence of significant mucositis or leukopenia, patients may move on to complete radiotherapy with conventional fraction size and full target volume to the usual post-operative radiotherapy dose of 55–60 Gy. Post-operative radiotherapy for oral cavity cancers is usually indicated if there are positive resection margins and/or positive regional lymph nodes.

Systemic Therapies for Head and Neck Cancer

Systemic therapy using cross-linking agents and other targeted therapies is an integral component of the management for locally advanced, recurrent and/or metastatic HNSCC in the general population. Patients with FA cannot be safely treated with DNA cross-linking

agents due to high toxicity. Other non-cytotoxic targeted therapies may be viable options, but more research is needed to understand their effects on patients with FA.

Platinum-Based Chemotherapy in the General Population

In patients in the general population with surgically resected HNSCC, cisplatin (100 mg/m^2 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 [42, 43]. A pooled analysis of two phase III clinical trials demonstrated that patients with positive margins and/or extracapsular nodal spread benefited the most from the addition of chemotherapy to post-operative radiation therapy [44]. 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 locally advanced 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% [45, 46]. 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, dermatitis, skin toxicities, and the need for feeding tube placement [45].

Epidermal Growth Factor Receptor Inhibition in the General Population

Cetuximab (Erbitux) is a monoclonal antibody that inhibits the epidermal growth factor receptor (EGFR) and is used for the treatment of patients with locally advanced HNSCC. Cetuximab 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 clinical trial [47]. Based on these results, cetuximab has been approved by regulatory agencies throughout the world to be used in this setting. Cetuximab has a more favorable side effect profile than cytotoxic chemotherapy. Clinically relevant cetuximab-induced adverse events include skin rash, hypomagnesemia, grade 3-5 hypersensitivity reaction (in approximately 3% of patients), and a small increase in the incidence of radiotherapy-induced mucositis. Blood toxicity is not usually observed with concurrent cetuximab and radiation therapy. Concurrent cetuximab and radiation therapy recently has been directly compared to concurrent cisplatin and radiation therapy in two randomized studies of patients with HPV-related, locally advanced oropharynx cancers treated non-surgically. These studies have shown inferior locoregional control for the cetuximab-treated patients [48, 49]. As such, concurrent cisplatin with radiation therapy is still considered the standard of care for most

patients with HPV-related and non-HPV-related locally advanced HNSCC treated without surgery. Studies evaluating the role of cetuximab in the post-operative setting are ongoing.

Systemic Therapy for Recurrent or Metastatic Disease in the General Population

For patients with recurrent and/or 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 maintain quality of life and prolong survival. Cetuximab has activity as single agent, and also has been shown to improve survival when added to first-line platinum/5-fluorouracil in a randomized phase III trial [50]. More recently, immunotherapy has emerged as a novel strategy to treat recurrent and/or metastatic disease. Immunotherapy has a different mechanism of action than chemotherapy. It stimulates the patient's own immune system to recognize and eliminate cancer cells. As such, side effects related to immunotherapy are different and usually less severe than chemotherapy, and mostly consist of auto-immune reactions resulting from normal cell injury by the activated immune system. Immunotherapy also benefits a relatively small proportion of patients. However, when effective, immunotherapy may control the disease for longer periods of time when compared to chemotherapy and/or cetuximab. The anti-programmed death-1 (PD-1) immunotherapy drugs nivolumab or pembrolizumab have been shown to improve survival compared to standard therapies in patients who have failed platinum-based treatments [51, 52]. In treatment-naïve patients with recurrent and/or metastatic disease, pembrolizumab alone (in selected patients) or pembrolizumab added to chemotherapy also have been shown to improve survival over the standard-of-care regimen of chemotherapy plus cetuximab.

Systemic Therapies for Head and Neck Cancer in Patients with Fanconi Anemia

The use of chemotherapy—particularly DNA-damaging agents—in FA patients 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 FA patients 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.

The use of biologic agents in FA patients is an attractive alternative to cytotoxic chemotherapy, given the more favorable side effect profile of biologic agents. Nonetheless, cetuximab (the only targeted agent approved for HNSCC) has been used only anecdotally in FA patients and seems to be better tolerated than cytotoxic chemotherapy (Table 1), but efficacy in the FA setting is unknown. The use of anti-PD-1 inhibitors in FA

patients could be an alternative to cytotoxic therapy for management of recurrent and/or metastatic disease, but experience in FA patients also has been limited. Challenges regarding the use of this modality in FA patients include risk of activation of graft-versus-host disease (GvHD) in post-transplant patients [53], and possible lower efficacy compared to the general population, given the presence of immune dysfunction in FA individuals. These concerns, however, remain to be characterized through clinical observations.

Systemic therapies serve 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). 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 FA patients who have locally advanced or recurrent and/or metastatic head and neck cancers is strongly discouraged. For selected cases in which chemotherapy and/or biologic therapy or immunotherapy 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. Systemic therapies for HNSCC in patients with Fanconi anemia.

Tumor type	N	Chemotherapy	Cycles	Outcome
SCC tonsil [54]	1 ¶	Cisplatin (40 mg/m2)	X1	Fatal myelotoxicity
SCC hypopharynx [55]	1 ¶	Cisplatin (100 mg/m2)	X1	Fatal myelotoxicity
SCC esophagus [56]	1 ‡	Cisplatin (33 mg/m2) 5-FU (1000 mg/m2)	X1	Severe diarrhea and myelotoxicity Partial response allowing surgery
SCC tongue [57]	1 ‡	Cisplatin (8 mg) 5-FU (60 mg)	X1	Severe toxicity No tumor response
SCC lung [58]	1 ‡	Carboplatin (AUC 3 d1) Gemcitabine (1250 mg/m2 d1,8)	X2	Pneumonitis Partial response allowing surgery
SCC head and neck [8]	3 (2 ¶ + 1 ‡)	N/A	N/A	All died with disease
SCC vulva [59]	1 ¶	Cisplatin (40 mg/m2)	X1	Fatal fungal sepsis
SCC oral tongue [60]	1¶	Cetuximab	X8	Neutropenia, mucositis, cholestasis
SCC head and neck [32]	1	Carboplatin and paclitaxel	X2	Pancytopenia, colitis, hepatotoxicity
	1¶‡	Cetuximab	Several	Severe toxicity with radiation therapy, well tolerated with tumor response as single agent
	1¶	Cetuximab	Several	Well tolerated
	1	Cetuximab ¶ and nivolumab‡	Several, X3	Tolerated cetuximab well, had nivolumab-induced encephalitis
	1	Cetuximab ¶, paclitaxel (20-80 mg/m2/week)‡, tremelimumab‡, durvalumab‡	Several	Tolerated treatment well, died of disease
SCC head and neck [10]	3¶	Cetuximab	Several	Cytopenia in 1 patient
	3	Conventional chemotherapy	N/A	Severe complications in 1 patient

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 Post-Treatment of Head and Neck Cancer

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, dental care, and prevention of fibrosis-related complications such as trismus. 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.

Summary

Patients with FA have an increased risk for developing aggressive head and neck squamous cell carcinoma (HNSCC), 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 HNSCC in FA patients. 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.

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Bhuvanesh Singh, MD, PhD*
Joel Greenberger, MD
David Kutler, MD
William William, MD

**Chapter committee chair*

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Chapter 6

Oral Health Care for Patients with Fanconi Anemia

Introduction

The health of the mouth and surrounding craniofacial structures is central to overall health. All patients with Fanconi anemia (FA), regardless of age, should seek professional dental care and perform adequate oral hygiene practices at home to prevent and control oral and craniofacial diseases, conditions, and injuries. With a few exceptions, dental treatment is similar for FA patients and individuals in the general population. This chapter provides guidance on dental care and oral health maintenance for patients with FA and educates dental practitioners about particular aspects of FA that can impact dental treatment.

Importance of Oral Hygiene

Good oral hygiene lowers the risk of oral health problems such as tooth decay, gingivitis, and periodontitis. Several reports have suggested that good oral hygiene also reduces the risk of cancers such as head and neck squamous cell carcinoma (HNSCC) [1] and esophageal cancer [2], although the evidence is not yet conclusive. The incidence of HNSCC in patients with FA is 500- to 700-fold higher than the general population (see Chapter 5). Therefore, it is important that patients with FA maintain the recommended oral hygiene and professional dental care routines summarized in this chapter.

The oral cavity harbors a variety of microorganisms, also known as oral microbiota. This community of microorganisms is composed predominantly of bacteria, although fungi and viruses also can be present. There is increasing evidence for the potential contribution of oral microorganisms and oral inflammation in HNSCC development in the general population [3-7]. Elevated levels of bacteria species, such as *Helicobater pylori*, *Neisseria*, *Veilonella*, and *Fusobacteriam nucleatum*, have been associated with cancers, including gastric, esophageal and colon cancer [8-10]. Furthermore, periodontitis, which is mediated by oral bacteria and inflammation, has been suggested as a possible risk factor for HNSCC [5]. Even though these associations do not imply causation, it is prudent to control the circumstances that may lead to gingivitis and periodontitis through adequate and routine oral hygiene practices.

Toothbrushing

Dental plaque on the surface of teeth contains a thick film of bacteria that can be removed only by a dental professional or by brushing with a toothbrush. The surface of the tongue also is heavily populated with microorganisms, which can contribute to halitosis and gum diseases. For home care, twice daily toothbrushing and daily tongue cleaning is the most effective method to remove plaque and bacteria to prevent 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 employed. Parents of young children with FA should brush the child's teeth until the child can competently do so independently.

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 FA patients [11] 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.

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 also is 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 products containing triclosan 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, wooden sticks, and interdental and end-tufted brushes. 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.

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%. Alcohol is known to increase the risk of HNSCC (see Chapter 5) and it is recommended 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 [12].

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 U.S., 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, 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 [13].

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 six months. Examinations can occur more frequently if changes occur in the patient's medical and/or dental conditions, such as the development of periodontitis, diabetes, or xerostomia. In addition, FA patients have increased risk for developing HNSCC or oral cancer; therefore, the primary objectives of professional oral exams include the prevention and early detection of oral diseases such as dental caries, gingivitis, periodontitis, and oral cancer. Oral examination methods for cancer detection in patients with FA and recommendations for biopsy are discussed in Chapter 5.

During an exam, the dentist should evaluate 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 disease, 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. 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.

The American Dental Association and the U.S. Food and Drug Administration have devised recommendations for the selection of patients for dental radiographic examinations [14], which can serve as a framework for dentists who treat FA patients. 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.

Radiation Exposure From Dental Radiographs

When taken properly, dental radiographs provide limited radiation exposure (Table 1). 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, whereas a cross-country flight exposes an individual to 5 millirem of cosmic radiation. Moreover, the National Council on Radiation Protection estimates that the average U.S. resident receives about 360 millirem of radiation every year. Exposure can be minimized even further with the use of digital radiographs [15].

Table 1. Effective radiation doses from various dental x-ray procedures [16].

Type of X-Ray	µSv	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

Restorative Dental 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 [17]. 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 FA patients 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 [18]. Furthermore, BPA exposure can be reduced by cleaning and rinsing surfaces of sealants and composites immediately after placement [19].

The best way to avoid the need for any restorative materials is to decrease the patient's risk for caries. This can be achieved by aiming for optimal oral hygiene at home, 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 [20, 21], efforts should be made to prevent such irritation in FA patients. Recently, new orthodontic treatment methods using clear aligners have been developed that obviate the need for traditional brackets and wires 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

routine requirements for implants, such as sufficient bone volume and the ability to maintain good oral 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), treatment of dental infections, biopsy of oral lesions, or reconstruction with dental implants. Patients also may 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's bone marrow aspirate or biopsy. Patients with FA who are non-immunocompromised and non-thrombocytopenic usually can be treated in a routine fashion. The oral surgeon may need to consult with the patient's hematologist about any questions or concerns.

Oral Manifestations Associated with Fanconi Anemia

Fanconi anemia can manifest in numerous ways in the oral cavity of patients with the disease. Many of these manifestations also occur in healthy children, so it remains unclear whether they are associated with FA itself or rather with treatments for bone marrow failure (BMF), such as chemotherapy and radiation used during hematopoietic cell transplantation (HCT), which are known to adversely affect the development of teeth and jaws in children younger than 12 years. Regardless, it is important that FA patients be evaluated for dental and skeletal developmental issues that include:

- Agenesis, microdentia, or micrognathia
- Supernumerary teeth or delayed development of permanent teeth
- Changes in the color of the tooth enamel or abnormal tooth shape, rotation or position
- Delayed development of teeth (usually permanent teeth), including delayed loss of primary teeth and eruption of permanent teeth compared with healthy peers

Oral Ulcers

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 need to be assessed by a health care professional. The most serious oral lesion associated with FA is oral cancer (see Chapter 5).

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.

Canker sores are lesions that often develop after a relatively mild trauma and heal 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 2).

Table 2. Management of recurrent ulcerations.

Treatment	Dose and Treatment Schedule
Topical anesthetics	2% viscous lidocaine; doxepin solution
Topical coating agents	Hydroxypropylcellulose film (Zilactin)
Topical corticosteroids	0.05% clobetasol gel; 0.05% flucinonide gel; 0.1 mg/ml dexamethasone elixir; budesonide inhaler
Intralesional injection	40 mg/ml triamcinolone (0.1 - 0.3 ml)
Systemic therapy	0.5-1 mg/kg prednisone; thalidomide

Neutropenic Mouth Ulcers

Patients who have neutropenia 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 often will be present. Additionally, cancer therapies such as chemotherapy can cause severe neutropenia and neutropenic ulcerations.

Viral-Induced Mouth Ulcers

Recurrent herpes simplex virus (HSV) infections can cause ulcerations of the oral mucosa and lip. These lesions often are associated with the immune dysfunction that often accompanies severe aplastic anemia, myelodysplastic syndrome, and leukemia. The lesions also can arise after high-dose chemotherapy or hematopoietic cell transplant (HCT).

Oral Health Problems Associated with Bone Marrow Failure

Bone marrow failure (BMF) contributes to significant oral health problems including increased bacterial, viral, and fungal infections, gum enlargement, bleeding, pain and other facial neuropathies. Table 3 describes the underlying causes of these oral health issues in patients with FA and provides recommendations for management.

Table 3. Management of oral health problems during bone marrow failure.

Oral Health Problem	Cause(s)	Management
Bleeding	Thrombocytopenia	Avoid oral trauma; prevent infection
Bacterial infections	Loss of white blood cells, especially neutrophils; secondary infection of traumatic oral lesions	Maintain excellent oral hygiene; antibacterial mouthwashes; systemic antibiotics for severe infections
Fungal infections (primarily yeast)	Loss of white blood cells, especially neutrophils; loss of salivary gland function; use of systemic antibiotics	Topical antifungals (nystatin or clotrimazole) for oral yeast infections; systemic antifungals for extensive infections
Viral infections *(herpes simplex virus, varicella zoster virus, cytomegalovirus or Coxsackie group viruses)*	Immune dysfunction, including neutropenia	Systemic antiviral drugs (acyclovir or valacyclovir)
Delayed healing of oral tissues	Loss of white blood cells, especially neutrophils, resulting in secondary infections; severe anemia	Obtain primary closure of extraction or surgical sites; reduce risk for trauma and irritation; prevent secondary infection
Gum enlargement, bleeding, and pain	Accumulation of leukemic cells in gum tissue, usually in response to gingivitis; medication-induced gum enlargement	Maintain excellent oral hygiene; treat the leukemic disease; consider medication modification
Facial and oral neuropathies (nerve damage)	Compression of nerve bundles by leukemic cells, resulting in numbness and tingling	Treat the leukemic disease

Oral Care Before and After Hematopoietic Cell Transplant

The treatment and management of BMF 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 patient's treatment outcomes.

Pre-Hematopoietic Cell Transplant Oral Examination

Prior to treatment for BMF with HCT, 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.

Patients must be informed of the potential oral complications of HCT, 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 from BMF and HCT.

Post-Hematopoietic Cell Transplant Oral Care

Routine oral care after HCT is essential to help maintain oral health and prevent infections and bleeding problems associated with gingivitis and periodontal disease. Once dental examinations resume after HCT, 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 is needed. 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. Prophylactic antibiotic regimens appear to be efficacious, with regimens being extended if there is ongoing dental infection or if there is concern for delayed healing. Dentists should minimize the spray from dental equipment by using rubber dams and high-volume suction devices to reduce the chances that a patient recovering from HCT will inhale any infectious or dangerous substances during dental

treatment. The dental care team also should aim to reduce the complexity of treatments and shorten treatment times.

Summary

Patients with FA have an increased risk of developing head and neck squamous cell carcinoma (HNSCC). Several studies have highlighted the role of adequate oral hygiene in preventing HNSCC and although the evidence is not yet conclusive, it is recommended that all FA patients follow best practices for oral care and evaluation. All FA patients, including pediatric and adult, should be evaluated by a dental professional every six months. Oral examination for HNSCC should start no later than age 10 (see Chapter 5). Patients with FA are encouraged to develop excellent oral hygiene practices at home, which include twice daily brushing, removal of plaque between the teeth, and avoidance of toothpastes with triclosan or hydrogen peroxide and mouth washes with alcohol. Digital radiographs used for routine dental evaluations do not increase the risk of cancer and support comprehensive dental care for dental caries or additional oral issues common to FA patients. The oral health of FA patients undergoing HCT should be closely monitored before and after transplant.

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Chapter 7

Gynecologic Care for Female Patients with Fanconi Anemia

Introduction

Patients with Fanconi anemia (FA) now have a high likelihood of reaching reproductive age due to advancements in clinical care that have increased life expectancy. As patients with FA reach young adulthood, gender-specific health concerns should be monitored and treated. This chapter provides an overview of clinical problems female patients with FA may face during their reproductive lifetime. These issues include pubertal delay, irregular menarche, primary ovarian insufficiency, early onset of menopause, reduced fertility and reproductive lifespan, and gynecologic cancer. Clinical care guidelines for gynecologic complications that can occur during and after hematopoietic cell transplant (HCT) also are discussed.

Puberty and Menarche

Approximately 9 out of every 10 healthy women experience menarche within three years after breast buds develop, which typically occurs as early as age 11 and before age 16. Most female patients with FA undergo puberty within a normal age range; however, some may experience pubertal delay or not have menarche until their mid-teens. Pubertal delay is defined as breast bud development that is delayed to age 13, or age 14 for individuals

who have low body weight [1, 2]. Pubertal delay in female patients with FA may result from low body mass index or hematopoietic cell transplant (HCT) performed during childhood. Female patients with FA who have no breast development by age 13 or have not started their periods within three years after breast buds develop (by age 15) should be evaluated for hypothalamic dysfunction [1-3]. As discussed in Chapter 10, many female patients with FA experience other endocrine disorders including hypothyroidism and hypothalamic dysfunction [4]. Hypothyroidism, if unrecognized and untreated, may contribute to irregular periods and infertility. Hypothalamic hypogonadism is associated with delayed puberty, amenorrhea, and infertility [3]. If puberty is delayed or does not occur, patients may need hormonal supplementation to optimize growth [4-6].

Menorrhagia

Female patients with FA may experience menorrhagia, or heavy menstrual bleeding, as a result of thrombocytopenia or anovulatory cycles. Menorrhagia can cause anemia and present the need for a blood transfusion. In addition, for female FA patients with normal menses who also have severe anemia, it may be beneficial to suppress menses to limit any blood loss that may worsen anemia. Female FA patients who experience heavy menstrual bleeding should undergo a complete blood count. An ultrasound can be performed to rule out other potential causes of excessive menstrual bleeding, such as polyps or submucosal fibroids that form in the lining of the uterus.

Gynecologic Issues Associated with Hematopoietic Cell Transplant

Menstrual Suppression

Hematopoietic cell transplantation (HCT) regimens typically result in severe anemia and thrombocytopenia; therefore, menstrual suppression is typically recommended for female patients with FA during HCT. Ideally, medications that suppress menstrual bleeding should be initiated one to two months prior to HCT to increase the likelihood that menstruation will cease by the time of the HCT. Options for menses suppression in FA patients include reproductive hormones such as estrogen, progesterone, and a class of drugs known as gonadotropin releasing hormone (GnRH) agonists [7]. Estrogen-containing medications increase the risk of venous thromboembolism, and, depending on the patient's diagnosis or treatment regimen, estrogen-containing medication may be contraindicated. Leuprolide acetate, a type of GnRH agonist, has been shown to be effective in inducing ovarian hormone suppression in female patients scheduled for HCT [8-11]. Patients who are being treated with leuprolide acetate to reduce excessive menstrual bleeding also can take additional oral hormone ("add-back" therapy, usually with the progestin norethindrone) to

manage any menopausal symptoms and to prevent osteoporosis, which is associated with long-term (i.e., more than 6 months) exposure to leuprolide acetate and other GnRH agonists [5].

Genital Graft-Versus-Host Disease

Female patients with FA who have undergone HCT may experience graft-versus-host disease (GvHD) (see Chapter 3) in the anogenital area. The wide range in reported incidence of vulvovaginal GvHD of 3-49% suggests that the true rate is likely unknown [12, 13]. Symptoms include vulvovaginal pain or itching, dysuria, dyspareunia, difficulty with tampon insertion, or postcoital bleeding. Exam findings include vulvar skin erythema and pain on gentle touching, with specific diagnostic mucosal changes (termed lichen planus-like or lichen sclerosis-like features), fissures, erosions, vulvar or vaginal scarring, including loss of the normal vulvar appearance (including vulvar folds). Topical therapies, including steroids and immune modulators, estrogen vaginal rings and dilators, are the mainstays of treatment [14]. Genital exams for female FA patients who have undergone HCT should include examination for the above findings and to distinguish genital GvHD from other conditions, including genital HPV-related disease [12, 15].

Primary Ovarian Insufficiency

On average, menopause typically is diagnosed around age 51 for women in the U.S. Menopause that occurs prior to age 40 is considered premature. By contrast, most female patients with FA experience primary ovarian insufficiency (POI) by their early 30s. The medical diagnosis of POI is sometimes referred to as “premature menopause.” In POI, also described as decreased ovarian reserve, ovarian function can be intermittent. Up to 10% of women with POI experience spontaneous conception. Primary ovarian insufficiency is a spectrum of low ovarian reserve, declining ovarian function, reduced fertility, and estrogen deficiency. Follicle stimulating hormone (FSH) levels measured twice, two months apart, and persistently elevated levels along with irregular menses confirm a POI diagnosis. In girls who underwent gonadotoxic therapy prior to menarche (e.g., in HCT regimens), an absence or arrest of pubertal development together with elevated FSH are indicative of POI. The two main functions of the ovary are to produce the hormones estrogen and progesterone and to release mature oocytes for fertility. In patients with POI, both of these functions are affected.

From a hormone production standpoint, any female FA patient who underwent gonadotoxic therapy prior to or after puberty should be monitored for POI. For pre-pubertal patients, FSH should be measured annually until it is determined whether hormone therapy is indicated to start pubertal development. This monitoring typically is done in consultation with an endocrinologist. Hormone therapy for pubertal development

is comprised of incremental hormone doses during which height (the normal pubertal "growth spurt") also is monitored. For patients who have not undergone gonadotoxic therapy and who are post-pubertal, clinically monitoring for menstrual pattern and periodic monitoring of FSH is suggested.

Hormone Therapy

Optimal hormonal treatment of female FA patients diagnosed with POI serves to replace the hormones that would be produced by the ovary before menopause, making treatment distinctly different from hormonal therapy for menopause that focuses on menopausal symptoms. Two types of hormone therapy can be administered to female FA patients who have POI until they reach age 50: oral contraceptive pills (OCPs) or postmenopausal hormone therapy (also known as hormone therapy, HT), which consists of low to physiologic doses of estrogen and progestins. Either approach to HT is superior to no therapy regarding the effects on bone and other aspects of health [16, 17]. Many clinicians and the American College of Obstetricians (ACOG) favor recommendations of postmenopausal regimens with enough estrogen (slightly higher doses) to maintain bone health [17, 18]. Large studies comparing various doses and types of HT for hormonal contraception have not been undertaken. Given their young age of onset with POI, female FA patients may benefit from taking oral contraceptives rather than HT to prevent pregnancy. The dose in HT is lower and, thus, may not be effective in preventing pregnancy. This is an opportunity for shared decision-making regarding the use of oral contraceptives versus menopausal hormone therapy for optimal bone health. Furthermore, oral contraceptives given to premenopausal women protect against ovarian cancer and likely have a minimal impact on the risk of breast cancer in the general population as well as in patients with variants in the *FANCS/BRCA1* and *FANCD1/BRCA2* genes [16, 19]. Whether the same protective effect of oral contraceptives occurs in individuals with POI or FA who have variants in the *FANCD1/BRCA2* gene is unknown [20, 21].

Women in the general population who experience POI and do not use HT tend to have higher rates of osteoporosis, cardiovascular disease and stroke, general illness and death compared with those who take hormones [22]. It also is not clear that the risks of HT described in postmenopausal women are the same for women with POI who are replacing and receiving physiologic levels of hormone. Therefore, HT should be recommended for female FA patients who have POI and are not using contraceptives. The goals of HT in POI include levels that maintain bone, cardiovascular, and sexual health [16]. Hormone therapy also remains the most effective treatment for the symptoms of menopause (Tables 1 and 2).

Table 1. Medications for management of hot flashes during menopause.

Agent	Type of Drug	Dose	Comments
Combined hormone therapy (HT) [23]	Hormone (estrogen and progestogen)	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, Paroxetine [24]	Selective serotonin reuptake inhibitor (SSRI)	Fluoxetine: 20 mg per day Paroxetine: 10-25 mg per day	Contraindications include neuroleptic syndrome, serotonin syndrome; drug interactions with tamoxifen
Escitalopram or Citalopram [24]	SSRI	Escitalopram: 10-20 mg per day Citalopram: 10-20 mg per day	Contraindications include neuroleptic syndrome, serotonin syndrome; can be used with tamoxifen
Venlafaxine, Desvenlafaxine [24]	Selective norepinephrine reuptake inhibitor (SNRI)	Venlafaxine: 37.5-150 mg per day Desvenlafaxine: 100-150 mg per day	Contraindications include neuroleptic syndrome, serotonin syndrome; can be used with tamoxifen; side effects, including dry mouth, anorexia, and nausea, are more common at higher doses
Gabapentinoids [24]	Anticonvulsant	300 mg by mouth up to three times per day	Improvement in hot flashes; side effects, including dizziness, unsteadiness, and drowsiness, initially experienced, generally improve over time
Megestrol acetate [23]	Hormone (progestogen)	20-40 mg per day	Patients may experience uterine bleeding upon cessation of therapy; may cause bloating; stimulates appetite
Norethindrone	Hormone (progestogen)	NA: 5-10mg per day	Side effects include bloating, weight gain, stomach upset, diarrhea, gas
Conjugated estrogens and bazedoxifene [23, 25, 26]	Hormone (estrogen and selected estrogen receptor modulator (SERM))	0.625mg/20 mg per day	Side effects include muscle spasms, nausea, vomiting, diarrhea, abdominal pain
Pollen extract [24, 27, 28]	Flower pollen, non-hormonal	2 tablets per day	No contraindication, even if bee allergy; always check with MD before starting any medication
Clonidine hydrochloride [24]	Antihypertensive	0.1 mg by mouth twice per day, or 0.1 mg by transdermal patch weekly	Less frequently used; side effects include hypotension, lightheadedness, dry mouth, dizziness, sedation and constipation

Table 2. Hormonal medications for management of vaginal dryness and genitourinary symptoms of menopause.

Agent	Type of Drug	Dose	Comments
Hormone treatments [29]	Hormonal cream (estrogen)	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
Estradiol vaginal ring [30]	Hormonal ring (estrogen)	1 ring 7.5 mcg/24h, inserted into the vagina every 3 months	Minimally absorbed into the general circulation; higher dose rings require progestin use
Estradiol tablets [31, 32]	Hormone (estrogen)	10 mcg tablet 1 tablet inserted into the vagina at bedtime for 14 days; twice per week thereafter for maintenance	Minimal absorption into the general circulation

Findings from the Women's Health Initiative, an ongoing study of health issues in postmenopausal women, initially reported that HT was associated with a slightly increased risk of breast cancer and increased risks of heart attack, stroke, and thromboembolic disease while it protected against bone loss [33]. However, recent re-evaluation of these study data suggests that continuous estrogen treatment alone either decreases or has no effect on breast cancer risk [34]. These observations may not apply to all estrogen preparations since not all estrogens have been studied and the type of estrogen studied may have protective effects on the breast. Importantly, only those women who have undergone hysterectomy are candidates for estrogen-only therapy, and combination therapy with estrogen and progestins resulted in a slightly increased risk of breast cancer. However, as stated above, these risks were observed in postmenopausal women and are not thought to apply to younger women with POI.

Bone Density

Most children and adolescents with FA have a normal bone mineral density when the results are adjusted for stature [35]; however, female patients with FA may have low bone density due to the side effects of HCT treatment. Individuals who undergo POI before peak bone mass at age 30 and who do not use hormone therapy are at risk for bone fractures and may develop osteoporosis with further bone loss. There are many osteoporosis treatment options, including drugs known as bisphosphonates including alendronate and risederonate, which prevent bone resorption, and hormones (estrogen and raloxifene), which build bone. Patients who cannot tolerate oral medications or who are resistant to other treatments may benefit from infusions of zoledronic acid or teriparatide. To prevent

bone loss, most postmenopausal FA patients, including those with POI, should take calcium (1200-1500 mg daily) and vitamin D (400-800 IU daily) supplements. Many women are deficient in vitamin D, possibly due in part to the use of sunscreen, which can reduce the amount of vitamin D that the body produces in response to sunlight exposure. Vitamin D levels can be tested to determine whether supplementation is needed.

Sexual Health

It is important for clinicians to screen for and address sexual health concerns because sexuality is an important aspect of quality of life. Primary ovarian insufficiency can be accompanied by many symptoms that can impair a woman's sexual function, including hot flashes, vaginal dryness, and dyspareunia (suggested hormonal treatments for these symptoms are discussed above and shown in Tables 1 and 2). Conditions related to prior treatments, such as vulvovaginal GvHD, also can impact sexual function.

Treatment for sexual dysfunction is individualized to the patient. Hormone therapy and many non-hormone options exist for managing menopausal symptoms (a sample of available options can be found in Tables 1 and 2**).** For patients with POI, topical estrogen therapy may be needed in addition to systemic HT for the genitourinary symptoms of menopause. Vaginal dryness and pain during intercourse also can be treated with over-the-counter products including long-acting moisturizers, lubricants, vitamin E capsules and suppositories, and vaginal hyaluronic acid [36-38]. Patients with POI or vulvovaginal GvHD also may need management with vaginal dilators if vaginal stenosis is present. Physical therapy, including pelvic floor physical therapy, also may be appropriate for some patients. In addition, women with chronic medical conditions may be at increased risk of depression, body image concerns, or social isolation, which also can impact sexual function. Mental health and/or relationship concerns relative to sexual dysfunction are best addressed, as appropriate, with a psychologist, psychiatrist, or a sexual health therapist.

Reproductive Lifespan, Fertility, and Pregnancy

Female patients with FA may be able to have children, but they often experience reduced fertility and a shortened reproductive lifespan due to delayed menarche, early menopause, and reduced fertility [4, 6, 39, 40].

Some factors that affect fertility and reproductive health in female FA patients include:

- Early menopause
- Infrequent menstrual periods (oligomenorrhea)
- Absence of menstrual periods (amenorrhea)
- Radiation and chemotherapy prior to hematopoietic cell transplantation (HCT)

Contraception

Contraceptive counseling is a central part of gynecologic care for sexually active FA patients who do not desire pregnancy; this counseling includes patients with a diagnosis of POI, as unpredictable, random ovulation can occur in these patients resulting in a 5-10% chance of spontaneous pregnancy. If female FA patients of reproductive age are sexually active and pregnancy is not desired, use of contraception is advised and missing a menstrual period warrants pregnancy testing [41]. Oral contraceptive pills also can be prescribed to improve menstrual regularity in patients with irregular periods. Contraceptive counseling of patients with FA also provides an opportunity to emphasize the importance of safe sex practices and screening for sexually transmitted infection (STI) [42] and vaccination against human papillomavirus (HPV) (see page 129 of this chapter for more details).

Fertility and Pregnancy Rates

Pregnancies have been reported in female patients with FA, both those who were treated with HCT and those who were not [39, 40]. In all reports, very few FA patients become pregnant after age 30; most childbearing in FA patients occurs by the mid-20s. Some women with FA whose pregnancies occurred at older ages may have more mild forms of FA and appear unaffected until worsening anemia related to FA is diagnosed during pregnancy [43].

Most information about fertility in female patients with FA who have not undergone HCT 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 [39]. This low fertility rate is supported by animal models of FA [6]. Women who conceive while taking androgens should immediately discontinue androgen therapy to minimize the risk of masculinizing a female fetus.

Regarding pregnancy after HCT, among 101 female patients with FA over age 16 years who underwent HCT during a 30-year period, only 10 patients (10%) conceived and all infants were delivered prior to age 26 [40]. Of those 10 patients, four had two infants each. Five of these patients showed at least transient signs of gonadal failure prior to pregnancy. In this study, the median age at transplant was 12 years and pregnancies occurred 4-17 years after HCT [40]. This pregnancy rate is somewhat higher than pregnancy rates reported after HCT across the transplant population in general. This higher rate may be due to the lower radiation and chemotherapy doses received by female FA patients and their relatively younger age at transplant.

Monitoring for Primary Ovarian Insufficiency and Infertility

Reproductive endocrinologists and other clinicians currently evaluate anti-müllerian hormone (AMH) as a marker of “ovarian reserve,” or an estimate of the number of

immature follicles that later may be able to become mature oocytes. Anti-müllerian hormone is made by the small, immature follicles in the ovary and does not vary over the menstrual cycle, but slowly declines over a woman's reproductive life. In one study of female patients with FA, the AMH level was extremely low in all patients over age 25, which reflects the known low fertility and primary ovarian insufficiency (POI) in these women [44]. Additionally, chemotherapy treatment has been shown to at least temporarily lower AMH levels [45]. Considering these observations, measuring AMH values over time may allow opportunity for female patients with FA to seek fertility preservation treatments before or when decreasing AMH levels are detected, prior to the onset of POI.

Risks to Fertility and Methods of Fertility Preservation

Female patients with FA have low fertility in general and some treatments involving chemotherapy or pelvic radiation may further impair future fertility. In particular, HCT regimens typically require pre-transplant chemotherapy and radiation that pose a significant risk of infertility. In February 2013, the Ethics Committee of the American Society for Reproductive Medicine issued guidelines for fertility preservation and reproduction in cancer patients [46]. The most important take-home message from these guidelines is that physicians should inform patients about the options for fertility preservation prior to the start of therapies that are gonadotoxic**.** The known risks of infertility and of POI in female FA patients has led to consideration of elective oocyte or embryo cryopreservation before primary ovarian insufficiency occurs.

Cryopreservation of both embryos and eggs has an excellent success rate and may be considered whenever it is clinically available and medically feasible. The process of embryo or egg cryopreservation requires a month or longer. In cancer treatment settings, it does not appear to compromise timely cancer treatment or increase the risk of mortality [47, 48]. However, the patient's medical status and the urgency to complete the next steps in treatment (for example, initiating urgent therapy for a cancer diagnosis) remain the rate-limiting issues. New assisted reproduction protocols are enabling a shorter time to oocyte retrieval.

Other realistic options to achieve motherhood should be discussed with patients, including donor eggs, adoption, and surrogacy. Several options are being actively pursued, including gonadotropin releasing hormone agonists [9], which currently are used to suppress menses and additionally may protect the ovaries from the gonadotoxic effects of radiation and chemotherapy, and ovarian tissue cryopreservation [22]. However, proven methods of fertility preservation are preferred over experimental options.

Some parents of children with FA explore the use of assisted reproductive technologies such as in vitro fertilization with embryo selection and tissue matching to conceive additional children who do not have FA. These children may be able to provide stem cells to assist with the early treatment of their sibling with FA (see Chapter 3). As part of assisted

reproductive technologies, preimplantation genetic diagnosis (PGD) can be performed to identify the FA status of the embryos and implant only those that are FA-negative (see Chapter 2). If PGD is not available, amniocentesis or chorionic villus sampling (CVS) can be used to determine the FA status of a fetus during pregnancy.

Risks During Pregnancy and Childbirth

When a female patient with FA does conceive regardless of whether she has undergone HCT, a specialist in maternal-fetal medicine should work closely with the patient's hematologist. Pregnancy risks vary based on a woman's current health status, prior diagnoses, and prior treatments; however, some risks may be common to all female FA patients.

In women who have not undergone HCT, the largest case series found that blood cell counts significantly decreased during pregnancy in more than half of the female patients with FA; this decrease was associated with thrombocytopenia and the need for blood transfusions, but did not increase the mother's risk of death [39]. In contrast, similar rates of transfusion and an increased mortality risk were seen in female patients with other types of aplastic anemia, a condition that occurs when the bone marrow does not produce enough blood cells [39]. Compared with female patients in the general population, patients with FA who had not undergone HCT had a higher rate of pregnancy complications, such as pre-eclampsia, eclampsia, and spontaneous abortions [39]. In this same study, female patients 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 FA patients; the patients with FA also had a higher rate of failure to progress during labor [39].

Gynecologic Cancers

High rates of lower genital tract squamous cell cancers (SCC), including cervical, vaginal, vulvar, and anal cancers, have been reported in female patients with FA. Patients who have undergone HCT—especially those who developed graft-versus-host disease (GvHD) (see Chapter 3)—have a higher risk of SCC compared with patients who have not undergone HCT [49, 50]. On average, female patients 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 [51-53]. This age difference means that young female patients 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 [51-53]. Because of this, 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.

Human Papillomavirus and Gynecologic Cancer in Patients with Fanconi Anemia

In individuals with FA, detection of HPV in primary anogenital or head and neck squamous cell cancers was high in one study [54], and low in vulvar or absent in the head and neck cancers in two other studies [55, 56]. Importantly, others reported high rates of HPV detected in oral rinses in adults and children [57, 58] and laboratory studies have shown that the loss of FA pathway components in mucosal and skin cells stimulates proliferation of HPV lesions (via HPV genome amplification). These studies provide some evidence that an intact FA pathway functions to limit the HPV life cycle [59]. The variable prevalence of HPV in squamous cell cancers, high rates of HPV in oral rinses from a wide age range of individuals with FA, and insights into the important role the FA pathway serves in controlling HPV together illustrate that our current understanding of the role of HPV in FA-related tumors is incomplete and indicate that further research is needed. The discrepancies in the role of HPV may be due to many factors, including differences in the amount of virus in the individuals studied, geographic differences in the prevalence of HPV infection, or differences in the mode of squamous cell cancer development among individuals with FA. Testing for HPV in female FA patients can be performed at the same time as the Pap test, although the absence of high-risk HPV types in patients with FA should not change the screening interval. Individuals with genital tract squamous intraepithelial lesion (SIL) also may require anal cytology, anoscopy, and lesion biopsy to identify anal SIL and cancers.

Recommendations for Vaccination Against Human Papillomavirus

Current guidelines from the U.S. Centers for Disease Control and Prevention (CDC) recommend routine HPV vaccination of both females and males [60]. There are many different types of HPV; the current vaccine protects against acquiring the nine HPV types that are most commonly associated with cervical, vaginal, and vulvar cancers, and genital warts. The vaccine is available for ages 9-45 years [61]; ideally, the vaccine should be given before the patient has ever been exposed to HPV through sexual intercourse. Three doses of the vaccine are recommended for healthy individuals age 15 years and older. For healthy individuals age 9-14 years old, only two doses of the vaccine are recommended to achieve the same immune response [62]. The long-term effectiveness of HPV vaccination is unknown, but studies have shown that the vaccine immunity continues for at least 10 years in healthy individuals [62]. Because female patients with FA have an increased risk of squamous cell cancers of the lower genital tract, it is strongly recommended that they receive HPV vaccination starting at age 9. Recent small, cross-sectional studies of individuals with FA after HPV vaccination showed a similar, durable response compared to studies in healthy volunteers, suggesting that female FA patients will respond to vaccination [63, 64]. It currently is unknown whether patients with FA who receive the vaccination will require all three doses of vaccine in the series or booster vaccinations

later in life. Although the HPV vaccines will not treat or cure existing HPV-related disease, they may prevent the acquisition of HPV types not currently present. Because the HPV vaccines do not prevent all lower genital tract cancers observed in female FA patients, vaccinated women should undergo regular gynecologic screening, including Pap test. Re-vaccination (or vaccination) against HPV after transplantation is advised, as this will decrease the risk of acquiring HPV after HCT and may reduce the occurrence of HPV-related disease, which, in turn, may help to minimize the risk of secondary cancers [65]. Female FA patients vaccinated after HCT have similar immune responses to those who have not undergone HCT and healthy women [63, 64].

Gynecologic Cancer Surveillance

Early detection of precancerous lesions in individuals with FA is imperative to maximize survival. There is ongoing debate regarding the gynecologic cancer-screening schedule for female patients 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, and because these patients have a high risk for early vulvar cancer and pubertal delay, female FA patients should begin receiving gynecologic cancer screening at a younger age than is typically recommended for women in the general population. Female FA patients should begin having visual examinations of the external genitalia at age 13. Sexually active FA patients, and all women with FA who are 18 years or older, should undergo regular, comprehensive gynecologic exams, including a Pap test and a careful inspection of the cervix, vagina, and vulva. As a comparison, current guidelines for women without FA recommend beginning Pap testing at age 21 years [66].

Recommendations for Colposcopy and Biopsy

Colposcopy of the vulva, vagina, or cervix should be performed 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 promptly. Clinicians should biopsy even those lesions with a benign appearance, as malignant lesions may have an atypical appearance and biopsy is the only way to exclude precancerous disease needing treatment or cancer. Any female patient with FA who is diagnosed with squamous intraepithelial lesion (SIL, a precancerous condition that increases the risk of developing cancer) should undergo gynecologic exams with biopsy of any identified lesions every four to six months.

Female patients with FA and clinicians may find increased challenges with Pap tests and colposcopy. There may be a higher rate of “Unsatisfactory for evaluation” Pap test results due to insufficient cells, likely related to hypoestrogenism from primary ovarian insufficiency. Hypoestrogenism-associated vaginal atrophy also may cause increased discomfort with speculum exams in these patients. This discomfort can be minimized if

clinicians undertake examinations using either pediatric-sized or very narrow speculums, even in adult patients, and additionally lubricate the speculum with warm water or a thin coating of gel-based lubricant. Procedures under anesthesia may be appropriate for select patients.

With these challenges in mind, clinicians need to weigh the risks and benefits of strict adherence to the above Pap test and colposcopy guidelines, which are based on expert opinion and, at times, develop an individualized follow-up schedule that accomplishes long-term screening goals. For example, for patients whose Pap test results are "Unsatisfactory," current American Society for Colposcopy and Cervical Pathology guidelines recommend a repeat Pap test in 2-4 months; however, for a female FA patient with otherwise normal-appearing external genitalia and speculum exam, a slightly longer interval may be desirable, particularly if an intervention such as vaginal estrogen is initiated to treat hypoestrogenism or if sedation is required to obtain the Pap test. The risks and benefits of colposcopy for a patient with a visually normal cervix and genital tract and a Pap test result of atypical squamous cells of undetermined significance (ASCUS) that is HPV negative, is an opportunity for shared decision-making regarding the options of colposcopic evaluation versus increased frequency of Pap tests for surveillance.

Surgical Treatment of Gynecologic Cancer

The optimal treatment for genital warts or SIL is surgical excision or ablation. Vulvar lesions also may be treated with immune modulating drugs, such as imiquimod, 5-fluorouracil (5-FU), or alpha interferon [67, 68]. 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 SIL may benefit from a combination of surgical and medical treatment as reported in other patient populations [69]. Patients with other immune deficiencies typically respond to immune modulators within a few weeks, and thus female FA patients may benefit from long-term immune modulator treatment due to the likelihood of recurrent or refractory SIL. Patients diagnosed with genital tract cancer should be referred to a gynecologic oncologist immediately.

Breast Cancer Screening in Patients with Fanconi Anemia

Five of the genes implicated in Fanconi anemia (FA) are breast cancer susceptibility genes (see Chapter 2): *FANCD1/BRCA2*, *FANCJ/BRIP1*, *FANCN/PALB2*, *FANCO/RAD51C*, and *FANCS/BRCA1*. Breast cancer risk for individuals with FA who harbor variants in these genes or other FA genes has not been established; therefore, more research is needed to

develop guidelines for breast cancer screening for female patients with FA (regardless of their specific FA variant).

Screening for women in the general population who are carriers of variants in the *FANCD1/BRCA2* and *FANCS/BRCA1* genes starts with annual breast exams and annual breast magnetic resonance imaging (MRI) examination starting at age 25 years. Imaging is increased in frequency at age 30 years to twice a year and includes clinical breast examinations and mammography alternating with MRI [70]. In some instances, both mammography and MRI are performed at the same time, either annually or semi-annually. Ultrasound is recommended by the U.S. Food and Drug Administration in conjunction with mammography, particularly for women with dense breasts [71-73].

It is unclear whether the mammography screening recommendations apply to individuals with FA, as they 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 [74]. Magnetic resonance imaging can reduce radiation exposure for patients with FA and 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 [70]. 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 [75]. Magnetic resonance imaging appears to be more sensitive for detecting tumors in patients who have undergone menopause, even in those on hormone therapy, which causes the breast tissue to become less dense [76, 77]. In the future, MRI may be preferred over mammography in post-menopausal patients with FA as a way to minimize radiation exposure from mammograms [78]; however, this approach has not been studied in the FA population.

Summary

Female patients with FA face gynecologic issues including late onset of puberty, abnormal menstrual bleeding, primary ovarian insufficiency, cancer, and reduced fertility. Gynecologic care for female patients with FA should cover the spectrum of these complications and focus heavily on cancer screening. Gynecologic assessment for pubertal delay and genital lesions for female FA patients should begin at age 13 with complete vulvovaginal examinations and Pap testing once the patient becomes sexually active or by age 18. Screening for gynecologic cancer should be performed every 6–12 months with immediate referral to a gynecologic oncologist when gynecologic cancerous lesions are confirmed by biopsy. Surgical resection is currently the best curative option for gynecologic cancers in FA patients; therefore, early detection is imperative. There are currently no consensus guidelines for breast cancer screening in patients with FA; more research is needed to define the risk for breast cancer in patients with FA.

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Mercedes Castiel, MD*
Lesley Breech, MD
Stephanie Cizek, MD
Melissa Merideth, MD
Pamela Stratton, MD

**Section Committee Chair*

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Chapter 8

Dermatologic Issues in Patients with Fanconi Anemia

Introduction

This chapter describes the most common skin problems that affect patients with Fanconi anemia (FA) that result directly from the disease or treatments associated with the disease. Skin abnormalities, such as altered skin pigmentation, can be the presenting symptoms of Fanconi anemia (FA). Patients with FA who undergo hematopoietic cell transplants (HCT) also can develop skin abnormalities that result from graft-versus-host disease (GvHD) that occurs in the skin. The risk of developing skin cancer may be increased for adult FA patients due to the DNA repair defects associated with the disease, making early education on sun protection and skin cancer prevention essential. Guidelines for screening and treating warts, actinic keratosis, and cutaneous cancers including basal and squamous cell carcinoma and melanoma are also discussed.

Appearance of Skin in Patients with Fanconi Anemia

Pigmentation Changes

Changes to pigment are the skin abnormalities most commonly associated with a diagnosis of Fanconi anemia (FA) (see Chapter 2). A patient with FA can develop either hyperpigmentation or hypopigmentation, typically in sun-exposed areas [1, 2]. Hyper- and hypo-pigmented patches of skin can appear on the neck, trunk, and tops of hands and feet; they also can appear on under arms, genitals, hand palms, or foot soles (Figure 1). Differently colored areas of skin often overlap and can create a freckled 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) also are common. Patients with FA also may be prone to easy bruising due to low blood cell counts, which can present in the skin as small (petechiae) or large (purpura) areas of bruising and may cause locally increased pigmentation as these areas heal [3].

Testing for FA should be considered in young children with distinct hyper- and/or hypo-pigmented discoloration, or café au lait macules and accompanying disorders suggestive of FA (see Chapter 2). While some FA patients develop skin abnormalities, others do not; and such abnormalities are not unique to individuals with FA. The hypopigmented patches in patients with FA are found also in syndromes such as neurofibromatosis and tuberous sclerosis. Café au lait macules are a relatively common birthmark on patients with neurofibromatosis. For cosmetic appearances, some hyperpigmented lesions such as café au lait macules may be removed by laser treatments.

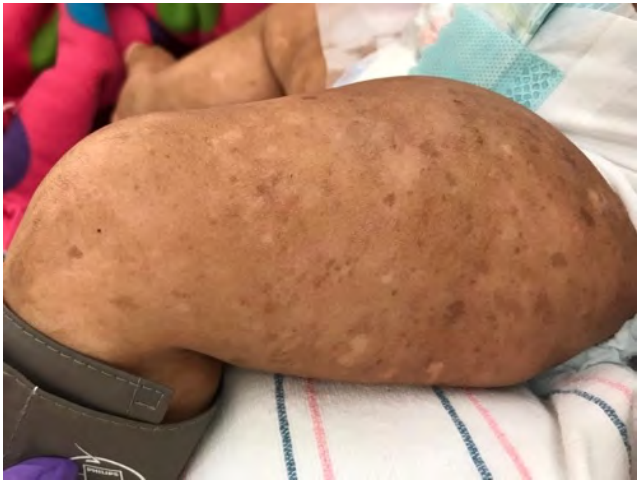

Figure 1. A patient with Fanconi anemia and pigmentary changes in skin.

Sweet's Syndrome

Patients with FA may develop Sweet's syndrome (SS), also called acute neutrophilic dermatosis, which presents as red plaques or nodules on the skin (Figure 2), which may be painful. As many as 12% of all FA patients develop SS, according to one report [4]. The syndrome frequently develops many years after a patient has been diagnosed with FA. Fever typically accompanies the red skin plaques or nodules, and similar lesions may be present in a patient's bones, lungs, or gastrointestinal tract.

Sweet's syndrome lesions are mistaken often for sites of active infection and treated as such; however, when these plaques are biopsied they show no sign of infection and heal very poorly. Providers should consider the possibility of SS in patients with FA who have red skin lesions that do not respond to antibiotics. Because FA patients 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.

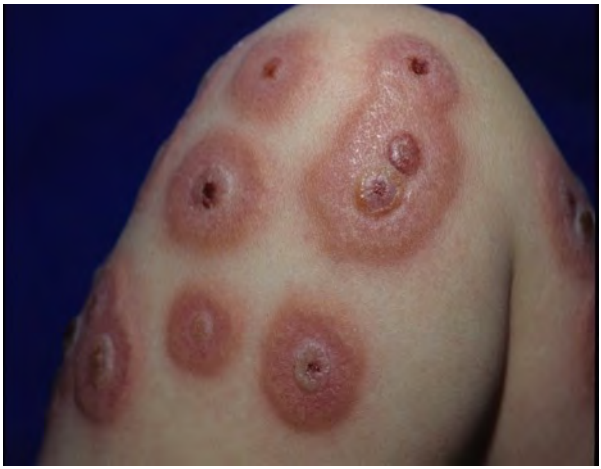

Figure 2. A Fanconi anemia patient with red plaques and nodules characteristic of Sweet's syndrome.

Skin Growths Associated with Fanconi Anemia

Scaly raised skin growths in patients with FA may be warts (verruca vulgaris), basal cell carcinoma (BCC), squamous cell carcinoma (SCC), actinic keratosis (AK), or other types of

lesions. Clinical care providers should carefully monitor all skin growths for changes over time during annual whole body skin examinations.

Non-Cancerous Skin Growths

Patients with FA often have unusually high levels of warts, which may signal a decrease or abnormality in cell-mediated immunity as warts can be initiated by human papillomavirus (HPV) infection [1]. Warts can be treated using cryotherapy or various other topical agents. Actinic keratosis, a non-cancerous growth, presents as flat pink or red scaly patches and may progress to SCC.

Skin Cancers

Ultraviolet (UV) rays emitted by the sun can have multiple damaging effects on the skin, some of which may be heightened in FA patients. Ultraviolet rays induce DNA damage, which increases the potential for skin cancers such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma over time [5]. This risk is underscored by the fact that UV rays can be immunosuppressive in the skin, and immune surveillance is critical for the prevention of skin cancer. Ultraviolet radiation from the sun has different subtypes: Ultraviolet A (UVA) causes premature aging and wrinkling of the skin; Ultraviolet B (UVB) induces DNA damage, such as double-strand breaks, and is the major cause of skin cancer. Individuals with FA have a decreased ability to repair the types of DNA damage induced by UVB (Chapter 1) and therefore have increased potential vulnerability to the damaging effects of UVB and potential to develop BCC and SCC [6].

Basal and Squamous Cell Carcinoma

Basal cell carcinoma manifests typically as shiny, waxy, pearly red or pink bumps that grow slowly with low metastatic potential. Cutaneous SCC appears as red, thick, scaly, tender patches of skin that are highly metastatic, especially when localized on the head or neck. Individuals who are immunocompromised have an increased risk of developing SCC. In a young FA patient, multiple scaly lesions are likely to be warts. In an older adolescent or adult, providers should perform a biopsy to determine whether the lesion is AK, BCC, or SCC.

Dermatologists commonly use surgery to remove skin cancers, although photodynamic therapy (PDT) can be used to treat BCC, SCC, and AK. Other skin cancer therapies used in the general population include topical chemotherapy agents such as 5-Fluorouracil and/or drugs that stimulate the immune system to target precancerous lesions or cancer. The tolerability and efficacy of these treatments in patients with FA has not been well-studied.

Melanoma

Melanoma is highly metastatic and must be removed immediately. The majority of melanoma are black or brown, or multicolored with asymmetrical and irregular edges.

Patients who have received HCT may have an increased number of melanocytic nevi (moles) on limbs, fingers, ears, or other locations [7] and these patients must be followed carefully. It is currently unclear whether FA patients have increased risk for melanoma. However, UV induced immune compromise and DNA damage are both risk factors for melanoma and have relevance in FA; therefore, it is recommended that clinical care providers conduct annual full body skin examinations for melanoma (and non-melanoma cancers) starting at age 18. Similar to BCC and SCC, surgical removal of melanoma is the best curative option for patients with FA.

Skin Cancer Prevention

It is critical that FA patients practice vigilant skin protection or sun avoidance from an early age [8]. Skin protection should include protective hats and clothing in addition to sunscreen. Sunscreens that contain physical blockers, such as zinc oxide and titanium oxide, are effective and tend to be the gentlest on sensitive skin. Chemical absorbers, such as benzophenones and salicylates, also provide broad-spectrum coverage though rates of skin allergies and irritation are higher. Sunscreens of at least 30 SPF should be reapplied every 1-2 hours. UV interaction with the skin is integral to vitamin D synthesis; therefore, sunscreen use can decrease vitamin D levels. Diet and vitamin D supplements can provide adequate amounts of vitamin D (see Chapter 9).

Fanconi Anemia Treatments that Affect the Skin

Androgen Therapy and Laser Hair Removal

Androgen therapy (see Chapter 3) 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. Laser treatment should be performed by a licensed physician with experience in laser therapy.

Hematopoietic Cell Transplant

Cutaneous graft-versus-host disease (GvHD) in patients with FA results primarily from the reaction of donor T-cells to the patient's skin after hematopoietic cell transplant (HCT). The clinical manifestations and histological features of GvHD closely resemble other conditions seen post-transplant in patients with FA. In addition, chronic GvHD can present as pigmentary alteration in the skin, which also is a feature of FA. Therefore, clinical care providers must prioritize the recognition and management of cutaneous GvHD [9, 10]. The prevention and treatment of GvHD is discussed in detail in Chapter 3.

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 [6]. Skin cancer also may behave more aggressively in this population [11]. Risk factors in the general population for nonmelanoma skin cancer include a history of chronic GvHD and/or exposure to prolonged immunosuppression, the anti-fungal medication voriconazole (see below), and radiation therapy. Risk factors for melanoma include previous treatment with certain alkylating and antimitotic chemotherapies and radiation.

Stem cell transplant recipients may develop localized or generalized loss of skin or hair color, termed vitiligo [12]. 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.

Voriconazole is an anti-fungal agent that increases skin sensitivity to sunlight. Voriconazole use has been implicated in SCC development in non-FA patients when used for 12 months [13]; therefore, the use of voriconazole, and other anti-fungal medications, should be discussed with the FA patient's hematologist and transplant team.

Summary

Patients with FA experience high rates of abnormal skin changes, including hyper- or hypo-pigmentation, café au lait spots, the growth of warts, actinic keratosis, and melanoma and non-melanoma skin cancers. Patients with FA may be at increased risk for melanoma and basal and squamous cell carcinomas due to faulty DNA repair associated with the disease; therefore, it is recommended that they undergo annual whole body skin examinations from an early age and no later than 18 years. Patients with FA in all age groups (including infants and those undergoing HCT) also should follow strict guidelines to minimize exposure to UV rays by avoiding direct sunlight through UV blocking clothing or regular application of chemical sunscreens with UV blocking formulations, such as zinc oxide. Hematopoietic cell transplant increases the risk for skin-associated complications such as graft-versus-host disease, which can affect the skin. The patient's clinical care team should continuously monitor the patient for potential cutaneous effects caused by treatments commonly used for patients with FA.

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Arturo Saavedra, MD, PhD, MBA*
Jennifer Huang, MD
Krystal M. Jones, MD
Vinod Nambudiri, MD, MBA

**Committee chair*

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Chapter 9

Clinical Care of Fanconi Anemia Gastrointestinal Issues

Introduction

Fanconi anemia (FA) and medications used to treat the disease can cause gastrointestinal disorders, liver disease, and nutrition-related challenges. Without proper treatment, these complications can interfere with daily living and create hurdles for healthy growth and development.

Concerns related to the gastrointestinal tract that affect patients with FA most commonly include:

- Anatomic 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 cell transplantation (HCT)

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.

Gastrointestinal Tract Anatomic Abnormalities

Approximately 7% of patients with FA are born with anatomic abnormalities in the gastrointestinal tract [1]. The most common abnormalities include esophageal atresia (EA), EA with tracheoesophageal fistula (TEF), duodenal atresia, and other anorectal malformations. 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. Gastrointestinal tract abnormalities may occur in isolation or appear with other birth defects, including the VACTERL-H spectrum of disorders (described in Chapter 2).

Esophageal Atresia and Tracheoesophageal Fistula

Esophageal atresia, with or without tracheoesophageal fistula (EA/TEF), typically is diagnosed during pregnancy. Symptoms of EA/TEF in newborns may include excessive drooling, feeding intolerance, or respiratory difficulties. Infants with EA/TEF who weigh more than 3 pounds 5 ounces (1500 g) at birth and lack major heart defects have a 98% survival rate to childhood and beyond [2]. Recent guidelines for management of this condition have been published elsewhere and can be referred to for additional detail [3].

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 three 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 five or more vertebrae. In this form of atresia, the esophageal segments are very short and it is likely that significant complications will occur. The best practices for treating ultra-long gap EA/TEF are still under debate [2]; however, 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 and swallowing problems such as pain with solid foods, frequent reflux, and vomiting. There also may be a long-term risk of cancer in colon tissue used to reconstruct the esophagus.

Repair of EA/TEF in infancy frequently leads to gastroesophageal reflux disease (GERD), difficulty swallowing, and breathing problems in adulthood [4]. Diagnosis and management of GERD is essential to reduce pain, bleeding, and narrowing of the esophagus. Anti-reflux surgery often is necessary to correct the complication. Respiratory problems, including cough, pneumonia, and wheezing, may suggest the need for bronchoscopy. 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, peptic ulcer, megaduodenum, reflux of fluids from the intestines into the stomach and esophagus, and blind loop syndrome. 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 [5].

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 and constipation with or without encopresis [6]. In most cases, bowel control can be restored with medication, although some patients may require an antegrade continence enema.

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:** Can result from many factors, but often results from 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 also can lead to nausea and abdominal pain, and may worsen existing gastrointestinal complaints.
- **Abdominal Pain:** May result from partial blockage of the digestive tract, which can be caused by complications of structural defects in the gastrointestinal system. Abdominal pain also can 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 for diarrhea.

Initial Evaluation of Gastrointestinal Symptoms

In all cases, the initial evaluation of gastrointestinal symptoms in FA patients begins with a medical 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.

Evaluation of Gastroesophageal Reflux

A recent endoscopic study of eight patients with FA found evidence of reflux esophagitis in all at baseline, with five of the eight patients having moderate or severe disease [7]. All patients with moderate or severe disease were experiencing symptoms of reflux, including difficult swallowing. Age at initial endoscopy ranged from 10-39 years. Two individuals with the most severe esophagitis, including the child in the study, developed esophageal squamous cell carcinoma within two years. Best practice guidelines for evaluation and management of GERD in patients in the general population have been published for both

adults and children [8, 9]. For patients with FA, the symptoms of reflux must be queried at each visit. Common symptoms of reflux include heartburn, chest pain, abdominal pain at the midepigastric area, increased burping or hiccupping, and dysphagia. From a strictly symptomatic standpoint, children with GERD can be treated without further testing if they are old enough to reliably explain their symptoms. Alternatively, reflux can be diagnosed in children with a manometric-placed pH/impedance probe. Treatment begins with proton pump inhibitors (e.g., omeprazole or lansoprazole at a dose of 1 mg/kg/day until adult doses are reached). H2-antagonists should be avoided because these drugs increase the risk of bone marrow suppression. However, a 2019 study suggests that yearly endoscopy, even in young children, must be considered in FA patients to allow early diagnosis of esophageal cancer [7] (see Chapter 5).

Evaluation of Delayed Gastric Emptying

Delayed gastric emptying 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. The test most commonly used to diagnose delayed gastric emptying in the general population is the nuclear medicine gastric emptying study, which involves radiation. To avoid radiation exposure in FA patients, a gastric emptying study can be omitted and a trial of treatment 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 used when available.

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.

The first line of therapy for delayed gastric emptying is dietary. 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.

Gastrointestinal motility may be further enhanced by a trial of medication, such as erythromycin (5 mg/kg/dose, 3 times per day), or—in Canada and Europe—domperidone (0.25 – 0.5 mg/kg/dose, 3-4 times per day; maximum daily dose of 2.4 mg/kg or 80 mg/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 is known to interact adversely with erythromycin. The use of metoclopramide is not recommended because of potentially dangerous side effects including irreversible

tardive dyskinesia, a disorder characterized by repetitive and involuntary movements. The combined use of amoxicillin and clavulanic acid (20 mg/kg amoxicillin and 1 mg/kg clavulanate, 2 times per day, with a maximum of 250 mg of amoxicillin, 3 times per day) 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 [10, 11].

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.

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 two years of age, and measurements of body mass index (BMI) relative to age should be plotted for children more than two 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, multiple hormonal abnormalities [12], 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 height/linear growth.

Malnutrition, whether the result of poor food intake, high energy utilization, or excessive stool loss, initially results in a growth curve demonstrating low weight relative to height or low BMI relative to age. Attention also must 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 [12]. 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 Weight Gain

Parents of children with FA often are 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 also will have proportionately lower weights. Medical providers should discuss with parents of FA

patients the pattern of their child's growth curves, particularly the changes in weight relative to height from birth to two years of age, and BMI after age two. 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 [12].

Poor Food Intake Versus Malabsorption

In patients with documented poor weight gain or weight loss, both poor food intake and/or diarrhea with malabsorption 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 also may 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 on page 168-169).

Vitamin D Deficiency

All patients with FA 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 in Children with Fanconi Anemia

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 third percentile for their age, or who have failed to gain weight over a 3- to 6-month period. Supplemental feeding via feeding tube, known as enteral supplementation, is preferable to supplementation by intravenous infusion, known as parenteral nutrition. Supplemental parenteral nutrition requires 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 supplementation.

Enteral supplementation may be delivered by nasogastric, nasojejunal or gastrostomy tubes. It is recommended that patients with FA have a nasogastric or nasojejunal feeding trial before proceeding to gastrostomy. The nasal route is best for patients who require supplemental feedings for less than three months. Drawbacks of nasal tubes include increased risk of sinus infection and exposure to ionizing radiation during fluoroscopy used for tube placement.

Gastrostomy tubes provide more permanent access to the gastrointestinal tract for administration of enteral feedings. Complications of gastrostomy tubes are limited to local irritation and/or infection, potentially due to low neutrophil counts. In addition, if the patient's platelet level is very low at the time of surgery, excessive bleeding is a risk. Some patients experience heartburn after starting enteral feeding supplementation, particularly with nighttime feeds. Vomiting and diarrhea also may occur. 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.

Appetite Stimulants

Before prescribing appetite stimulants, physicians must first investigate and appropriately manage diagnosable causes of poor appetite and inadequate growth in FA patients. 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.

Nonetheless, several medications have 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—and none has been tested in patients with FA—they have been used to try to prevent unwanted weight loss in patients with cancer, HIV/AIDS, and cystic fibrosis [13, 14].

Megestrol acetate has been shown to increase appetite and weight gain in small trials for relatively short periods [15]. It has a high potential for serious side effects, including adrenal insufficiency [16, 17]. While possibly suitable for situations where short-term treatment is needed (for example, during chemotherapy, palliation therapy), it is not recommended for individuals with FA, who may need long-term appetite stimulation.

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 [14, 18]. However, some physicians elect to try this medication before resorting to nasogastric or gastrostomy feedings. Patients may benefit from cyproheptadine, as it reduces retching [19].

Cannabinoids have been shown to reduce nausea and vomiting in many circumstances [20]. Although some patients try various forms of cannabinoids to stimulate appetite, use should be limited to investigational trials until more is learned.

Overweight and Obesity in Fanconi Anemia

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 also tended to have diabetes [21]. 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.

While a full discussion of the management of overweight and obesity is beyond the scope of this chapter (see references [22] and [23] for more information), modification of lifestyle is an essential starting point. 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 ensure achievement of appropriate weight. Psychological counseling also may help, especially if an eating disorder is suspected. Patients should be urged to avoid fad diets and over-the-counter weight loss preparations and to focus on healthy lifestyle modifications.

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 to assess heart function.

Liver Disease

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

Liver Complications Associated with 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 [24]. 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, three of the 20 patients treated with androgens developed liver tumors [25]. Thus, careful monitoring for hepatic complications of androgen therapy is essential. Figure 1 provides a schematic for liver complication management strategies for FA patients on androgen therapy.

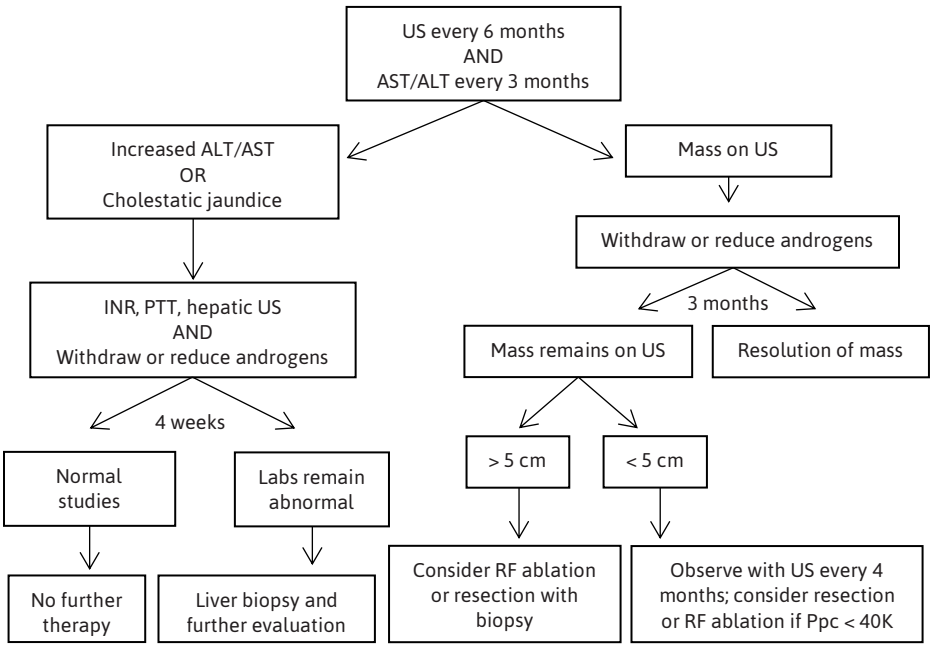

Figure 1. Management of potential hepatic complications in FA patients on androgen therapy. Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; INR, international normalized ratio; PPT, partial thromboplastin time; US, ultrasound; RF, radiofrequency; Ppc, platelet count.

Peliosis Hepatis

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 [18, 19].

Nonspecific Damage to the Cells of the Liver

Androgen therapy can lead to cholestatic jaundice, hypertransaminasemia, or liver cirrhosis in patients on continued androgen therapy [18]. Cessation of androgen therapy usually will 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 Chapter 3 for more information on androgens).

Hepatocellular Adenomas

Androgen therapy also can result in hepatocellular adenoma. An adenoma is a benign tumor that does not invade surrounding tissue; however, it can rupture, leading to life-threatening bleeding. There also is a risk of malignant transformation, particularly in some subsets of adenomas [26]. The risk of bleeding in hepatocellular adenomas is increased in patients with thrombocytopenia. Patients with FA may develop hepatocellular adenomas rapidly, often within 3 months of beginning androgen therapy [27-29]. Hepatocellular adenomas are generally diagnosed by ultrasound. Contrast-enhanced CT scans and MRI are more sensitive than ultrasound in detecting hepatocellular adenomas. Despite the radiation exposure from CT, it is strongly recommend that all patients receive both CT and MRI scans before hematopoietic cell transplantation (HCT) if they have previously undergone androgen therapy [30]. Hepatocellular adenomas may regress after cessation of androgen therapy, but if they persist, surgical removal or radiofrequency ablation may be necessary, particularly prior to HCT.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC), or malignant liver cancer, is reported occasionally 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 α-fetoprotein in the blood,

distinguishing it from other forms of HCC [18]. 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/or 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 and ultrasound examination may reveal the accumulation of fat or scar tissue, impaired blood flow, and obstruction of bile flow in the liver.

Patients with elevated liver enzymes should have a full evaluation of their liver by a hepatologist or pediatric hepatologist. In some cases, liver biopsy may be required to assess severity of liver disease.

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 of cholestatic disease.

Gastrointestinal and Liver Complications of Hematopoietic Cell Transplantation

To treat the blood abnormalities associated with Fanconi anemia (FA), many patients undergo hematopoietic cell transplantation (HCT), a procedure in which abnormal stem cells are replaced with healthy stem cells. Prior to HCT, 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 three months prior to HCT to ensure complete healing of the insertion site. Infections or irritation at the insertion site should be treated prior to HCT. 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 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 HCT is beyond the scope of this work (for a recent review, see [31]).

Historically, patients with FA who undergo HCT had an increased risk of graft-versus-host disease (GvHD) (see Chapter 3), in which the transplanted cells regard the recipient's body as foreign and attack the body, damaging the intestines, skin, and liver [32]. Patients with FA who develop chronic GvHD after undergoing HCT 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 is uncommon, but should be considered in patients with poor absorption of fat.

Patients with chronic liver GvHD typically experience cholestasis in the liver, with elevated levels of the liver enzymes ALT and AST. Both enzymes may increase rapidly if the patient has GvHD and as the doses of immune system-suppressing medications are reduced. It is uncommon for patients to acquire chronic viral hepatitis from HCT, 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, D, E, and K; therefore, levels of these vitamins should be monitored to determine whether vitamin supplementation is needed. Levels of vitamins A, D, and E can be measured via blood tests, and vitamin K levels can be inferred by measuring the clotting tendency of blood [33].

Gastrointestinal System Cancer Screening

Cancers of the gastrointestinal system are potential complications of Fanconi anemia (FA). Only one case of colon cancer in a person with FA has been documented in the literature to date; however, reports from FA adults who attended the Fanconi Anemia Research Fund's annual meeting in 2019 revealed that several adults in the FA community have been diagnosed with colon cancer. The Fanconi Anemia Research Fund is currently evaluating whether colon cancer screening is warranted. Patients with FA are at increased risk for esophageal cancer (see Chapters 4 and 5) and screening guidelines are discussed in Chapter 5. As mentioned on page 157, ultrasound imaging is recommended to screen for hepatocellular carcinoma for patients taking androgens.

Supplementation Risks and Benefits

Currently, no evidence-based studies have shown that large doses of vitamins, antioxidants, or other micronutrients are effective at treating FA. However, it has been shown that products containing supplemental iron, vitamins A (including beta carotene), C, and E, and omega-3 fatty acids may lead to health risks in patients with FA [34]. Large doses of omega-3 fatty acids, commonly found in fish oil supplements, can increase the risk of bleeding due to inactivation of platelets. Because patients with FA have reduced levels of platelets, products that impair platelet function should be avoided. In addition, vitamins A, C, D, and niacin may be toxic in excess.

Micronutrient supplementation to prevent cancer in patients in the general population has shown supplementation may reduce cancer risk in populations with nutrient deficiency, but populations with healthy nutrient levels see no effect or, in some cases, increased cancer risk [35]. In addition, large studies in the general population have shown that both vitamin A and vitamin E supplements are associated with an increased risk of some cancers; therefore, FA patients should avoid additional supplementation with these vitamins until further study indicates otherwise.

Counteracting oxidative damage by using antioxidants may be important for patients with FA [36]; however, research has not conclusively proven that supplementation with oral antioxidants changes the course of the disease. Currently, an ongoing clinical trial at the University of Cincinnati is examining whether oral delivery of quercetin, a naturally occurring flavonoid, reduces reactive oxygen species and DNA damage in cells of patients with FA. Interim results of the phase II prospective squamous cell carcinoma (SCC) chemoprevention study show that oral quercetin led to improved surrogate markers of genomic instability/DNA damage in buccal mucosal cells from the patients and no adverse events have been reported [37]. The preliminary results from the trial are encouraging; however, it is too early to confirm whether quercetin supplementation decreases risk of SCC in FA patients.

Summary

Patients with Fanconi anemia (FA) experience gastrointestinal symptoms such as reduced appetite, nausea, abdominal pain, and diarrhea. These symptoms, in conjunction with anatomical abnormalities of the gastrointestinal tract, can lead to poor weight gain or malnutrition, or in some cases patients being overweight or obese. Common treatments for FA, including hematopoietic cell transplantation (HCT) can cause severe gastrointestinal complications including liver disease, graft-versus-host disease (GvHD), and potentially cancer. Gastrointestinal abnormalities are typically diagnosed and treated via surgery in infancy; however, a comprehensive physical exam is necessary to adequately evaluate gastrointestinal symptom root causes. Similarly, assessment of poor growth should be evaluated in the context of poor intake versus malabsorption issues. Patients with FA who are treated with androgens should be monitored for liver disease and development of hepatocellular carcinoma; prevention of liver disease should include screening and avoidance of substances that cause liver toxicity. Comprehensive and integrated clinical care that adequately addresses gastrointestinal issues for patients with FA is necessary to promote healthy growth, development, and high quality of life.

The Fanconi Anemia Research Fund recognizes the following author contributions to the 5th edition:

Sarah Jane Schwarzenberg, MD

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Chapter 10

Endocrine Disorders in Patients with Fanconi Anemia

Introduction

Fanconi anemia (FA) and treatments used for the disease can adversely affect the endocrine system. Studies have shown that approximately 8 of every 10 patients with FA have at least one endocrine abnormality [1-10], although the origin of these abnormalities is unclear. Patients with FA experience endocrine disorders in myriad ways, including short stature, challenges with weight, abnormal glucose and insulin metabolism, hormonal deficiencies, and low bone mineral density. Endocrine abnormalities influence growth, development, and other aspects associated with the disease and its treatment. It is imperative that the clinical care team include an endocrinologist or pediatric endocrinologist, 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.

Evaluation of Growth

Growth should be closely followed in children with Fanconi anemia (FA) and nutritional and/or medical causes for poor growth should be identified as early as possible. Height

should be measured with a stadiometer and tracked using a growth chart. Children with FA who consistently track low on the growth chart compared with the average in the general population, or whose height gradually falls to a lower percentage, 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 1).

Short Stature

Short stature is a common characteristic of patients with FA. More than half (60%) of patients 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 person in the general population [7]. The average height of adult female patients with FA is about 150 cm (4 feet, 11 inches), while the average adult male patient 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) [4, 7, 10]. However, there are individuals with FA who have a height in the normal range, and about 1 of every 10 patients is taller than the average in the general population [7]. Height is an inherited trait; however, using parental height to predict adult height of children with FA may not be helpful because their stature is influenced by other factors [7].

Endocrine Abnormalities and Short Stature

Patients with FA who have hormone deficiencies tend to be shorter than patients with FA who have normal hormone levels [7, 10]. Adult patients with FA may be even shorter if they were not treated for growth hormone (GH) deficiency or hypothyroidism as children. One study described a patient with FA who had a genetic defect in the growth hormone receptor-signaling pathway that led to low insulin-like growth factor 1 (IGF-1) and primary IGF-1 deficiency, suggesting primary IGF-1 deficiency should be ruled out if clinical features are suggestive [1]. However, it is important to note that endocrine defects are not the only possible reason for short stature. Even FA patients with healthy hormone levels tend to be shorter than average for the general population, with only about half being within the height range considered normal. 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.

Fanconi Anemia Variants and Short Stature

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 variant of the *FANCC* gene have an average height of 4.3 SD less than average for the general population; these patients are significantly shorter than patients with FA who have

other variants [10]. In contrast, patients with variants in the *FANCA* gene are of similar height to patients with other FA variants [7].

Birth Size and Short Stature

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 [7]. 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 25% of FA children who are considered SGA at birth catch up to the normal range [7]. In one series, the median height of children considered SGA at birth was -2.6 SD, while the median height of children considered appropriate for gestational age at birth was -2 SD [7].

Poor Nutrition and Short Stature

Being underweight is linked with short stature in patients with FA [7]. Suboptimal nutrition may predispose children to stunted growth, or growth failure; therefore, dietary changes may be indicated for maintaining optimal growth (see Chapter 9).

Hematopoietic Cell Transplantation and Short Stature

It remains unclear whether hematopoietic cell transplantation (HCT) directly affects growth. However, medications used to treat patients with FA, such as androgens and corticosteroids, may affect growth and bone maturation, and impair adult height. Some medications or radiation used during HCT may affect thyroid or gonadal function, which in turn may negatively impact growth and adult height. In addition, total body, abdominal, or thoracic radiation used in preparation for HCT may directly influence growth of the spinal cord.

Targeted Testing for Short Stature

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 1-2 years in children with FA who have short stature. The results of BA assessments are sometimes used in height prediction algorithms, wherein if BA appears younger than the patient's actual age, then the height prediction algorithm may suggest that normal adult height will be attained over time. 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 HCT [11].

In addition to tracking the patient's bone age, GH secretion can be indirectly evaluated by measuring 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 magnetic resonance imaging (MRI) of the pituitary gland may be performed, along with consultation with a pediatric endocrinologist.

Weight Abnormalities in Patients with Fanconi Anemia

Approximately half of children with Fanconi anemia (FA) are born small for gestational age (SGA) [7]. In one series, infants with FA who were considered SGA were not only shorter but also were 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 [7].

The BMIs of children and adults with FA generally are similar to those of the non-FA population, with average BMIs of -0.2 SD in children and -0.95 SD in adults. One study suggested a lower average BMI of -1.3 +/-0.2 SD in children and in a few adults with FA [10]. Other studies reported that about 25-33% of all patients with FA are thin or underweight, while a few are overweight [4, 7]. The frequency of overweight in children with FA is similar to that in the general population, with a range of 11-27% depending on the group of patients studied [4, 7].

In some cases, being underweight may stem from the nutritional and gastroenterological problems common in patients with FA. Some children may have less than the expected appetite; others have trouble absorbing nutrients from food (see Chapter 9). In addition, illnesses that affect FA patients can raise caloric requirements. Glucose intolerance and insulin deficiency also may contribute to poor weight gain. Excess weight gain, on the other hand, may reflect lifestyle factors and a genetic predisposition to obesity.

Evaluation of Body Weight

Body weight of FA patients should be assessed at least annually, and 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.

Dietary Intervention for Weight Abnormalities

Healthy dietary intake should be encouraged, including sufficient calcium and vitamin D from foods or supplements. Input from a registered dietician may be needed. The underlying causes of under- or overweight should be addressed, including treatment of endocrine or gastrointestinal disorders (see Chapter 9). 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.

Abnormal Glucose or Insulin Metabolism

Diabetes mellitus occurs more commonly in patients with FA than in the general population [12]; moreover, patients with FA have a relatively high incidence of high blood sugars without meeting criteria for diabetes, also known as impaired glucose tolerance. Studies have shown that diabetes was detected in 5-10% of patients with FA, while an additional 24-68% of these patients had impaired glucose tolerance [2, 4, 6, 7, 10]. As many as 34-72% of patients with FA had elevated insulin levels 1-2 hours after eating. Interestingly, in other studies, insulin levels in patients with FA were low 10-45 minutes after an oral glucose test, suggesting slow initial insulin secretion, but became elevated 60-120 minutes after the test [2, 6]. Although the elevated levels suggest that insulin resistance may contribute to diabetes in patients with FA and markers of insulin resistance have been demonstrated in some cohorts [4, 10], these findings also support the possibility that insulin-producing β-cells do not function properly in patients with FA, which could impair first-phase insulin secretion [2, 6]; therefore, the diabetes observed in FA is not typical for either Type 1 or Type 2 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 β-cells that secrete insulin or, alternatively, from iron overload in heavily transfused patients. Insulin resistance also appears to be related to ferritin levels and oxidative stress from iron overload in FA patients [13].

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 [10]. Chronic steroid therapy also predisposes patients to insulin resistance and hyperglycemia [14-16]. The guidelines regarding glucocorticoid use in FA patients 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 (Table 1). 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 two 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 two hours after a meal. Glycosylated hemoglobin (HbA1c) and fructosamine levels may be deceptively normal, presumably due to impaired glycosylation or elevated levels of fetal hemoglobin in patients with bone marrow failure [7].Therefore, HbA1c scores may provide more useful information after HCT compared to before HCT.

In FA 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 two-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 two-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.

Table 1. Endocrine screening recommendations for patients with Fanconi anemia.

	Annual screenings for all patients	Detailed testing for selected patients
Growth	• Plot patient's height and weight on a growth chart	If patient exhibits signs of growth failure: • Test levels of IGF-1, IGFBP-3 • Obtain a BA radiograph • Test levels of FT4/TSH If patient has suspected GHD: • Perform GH stimulation tests • Obtain a pituitary MRI if evidence of pituitary hormone deficiency
Thyroid Activity	• Plot patient's height and weight on a growth chart • Perform early morning TSH and FT4 tests	If patient has suspected central hypothyroidism: • Determine the ratio of early morning TSH to afternoon TSH [17] • Evaluate for other pituitary hormone deficiency
Cortisol Levels		Perform low dose ACTH stimulation test if evidence of: • Any other pituitary hormone deficiency • A pituitary abnormality on MRI
Glucose, Insulin, and Metabolism	• Consider fasting glucose and insulin testing; 2-hr post-prandial glucose and insulin tests • Measure HbA1c (after HCT) • Consider fasting lipid profile in patients older than 10 years	If patient is overweight/obese/has hyperlipidemia: • Perform a 2-hour OGTT test If patient previously had an abnormal OGTT but does not have diabetes: • Repeat OGTT yearly
Puberty and Gonadal Function	• Perform pubertal staging of pubic hair and either breasts (girls) or testes (boys) during physical examination • Assess menstrual history and clinical evidence of hypogonadism in post-pubertal patients	If patient has early/delayed puberty or suspected hypogonadism: • Obtain a BA radiograph • Test LH, FSH, estradiol, or testosterone levels • Serum AMH may be useful as an early marker of ovarian insufficiency in female patients [18, 19]
Bone Mineral Density	• Assess the patient's dietary calcium and vitamin D intake • Measure 25OH-vitamin D level	Consider DXA scan to evaluate BMD: • Every 5 years starting at age 14 • Before HCT and 1 year after HCT • Repeat in 1 year if patient has low BMD • Repeat every 2 years if patient has hypogonadism or premature ovarian failure, or post-HCT.

Abbreviations: adrenocorticotropic hormone, ACTH; anti-müllerian hormone, AMH; bone mineral density, BMD; dual X-ray absorptiometry, DXA; free thyroxine, FT4; follicle-stimulating hormone, FSH; glycosylated hemoglobin, HbA1c; growth hormone, GH; hematopoietic cell transplant, HCT; insulin-like growth factor, IGF-I; IGF binding protein 3, IGFBP-3; luteinizing hormone, LH; magnetic resonance imaging, MRI; oral glucose tolerance test, OGTT; standard deviation units (Z-score) from the mean, SD; Thyrotropin, TSH; 25-hydroxy-vitamin D level, 25OH-vitamin D.

Dyslipidemia and Obesity

In one study of 29 patients with FA, over half (55%) had unhealthy levels of cholesterol and triglycerides, a condition known as dyslipidemia. Of these patients, 21% had elevated levels of low-density lipoprotein (LDL), 31% had low levels of high-density lipoprotein (HDL), and 10% had elevated triglycerides [4]. Another study found 17% of pediatric and adult patients with FA had high cholesterol [7]. An abnormal lipid profile was observed in 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 [4]. Patients with FA are at risk for metabolic syndrome, for which a healthy diet, a regular exercise regimen, and careful screening for blood pressure and lipid abnormalities are recommended.

Bone Mineral Density

Bone mineral density (BMD) in FA has been reported in a few studies with differing conclusions. In 34 children and 3 adults with FA (including roughly equal numbers of patients with prior HCT and no HCT), lumbar spine BMD Z-scores adjusted for height age were in the normal range [8]. However, 3 of 9 children and adolescents <20 years with FA (33%) who were followed at the National Institutes of Health (NIH) had low height-adjusted BMD Z-scores (two of whom had undergone HCT) [20]. These children were older (13-18 years) and had normal height-adjusted BMD Z-score at the lumbar spine, but low values at the femoral neck; one child had vertebral compression fractures. It is recommended that the BMD of children with FA be adjusted for height and that Z-scores be calculated. An online calculator may be used to calculate the height-adjusted Z-score in children with FA [21].

Bone mineral density may decrease after HCT in many patients including those with FA, but the underlying reasons for this remain unclear [22, 23]. In a study of 49 children, including 12 with FA, BMD decreased during the first year after HCT, with the most significant bone loss occurring by six months [24]. The effects of HCT 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 six months after HCT, and the number of patients with a Z-score below –1 increased from 34% at baseline to 52% one year after HCT [1]. The reduction in lumbar BMD at six months correlated with the cumulative dose of glucocorticoids [23]. While BMD remained within normal limits, the average height-

adjusted lumbar BMD Z-score was lower in patients who had undergone prior HCT (-0.9) compared with those who had not had prior HCT (-0.3) [8]. Long-term prospective studies are needed to examine the mechanisms underlying decreased BMD following HCT in FA children.

In adults, HCT is associated with decreased bone formation and increased resorption, and similar mechanisms may apply in children [25]. Medications used during HCT, such as glucocorticoid therapy, also may contribute to low BMD. Long-term prospective studies should explore whether BMD declines further or recovers over time after HCT. Hypogonadism and growth hormone deficiency (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 FA patients before HCT and every two years after HCT [26]. The first DXA evaluation may be performed at about age 14 if the patient has not undergone HCT, 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 HCT recipients and in patients with low BMD [27]. 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.

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 standard recommended dietary 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) [28]. 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 HCT in adults and may be effective in improving the BMD in HCT-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 [29]. 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.

Hypothyroidism

Many children with FA (from 30-60%, depending on thyrotropin or thyroid stimulating hormone (TSH) cut off values) have mildly abnormal levels of serum thyroid hormones, including borderline low levels of thyroxine (T4) or Free T4 (FT4), or borderline high levels of TSH [3, 4, 7, 10]. This combination of test results is consistent with mild hypothyroidism. 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). Central hypothyroidism was noted in 20-25% of patients with FA who were tested with overnight TSH or TSH surge due to low or low normal FT4 [4, 7, 17].

The mechanism causing hypothyroidism in FA patients 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 [10]. Although reduced thyroid hormone binding often is 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 patients with FA receiving androgen therapy [10], suggesting the need to use FT4 and TSH.

Thyroid Evaluation

Thyroid function should be evaluated by obtaining an early morning (e.g., 8:00 am) blood sample and measuring FT4 and TSH levels. All FA patients should undergo screening for hypothyroidism once a year; or more often if clinically indicated. One example would be if the patient shows signs of growth failure (Table 1). Central hypothyroidism is suggested by low levels of FT4 and by a TSH ratio of less than 1.3 at 8:00 am compared to afternoon TSH [17]. 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.

Treatment of 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 FT4 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 0.5-2 mU/L in patients with primary hypothyroidism. In central hypothyroidism, therapy should aim to raise FT4 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 [17]. Some endocrinologists may use a TSH level of 3 mU/L, or even 4.5-5 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 FT4 levels are low [30-32]. 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 [17].

In one study, eight children with FA were treated for seven months with thyroid hormone and for seven months with placebo; the treatment and placebo phases occurred in random order. Children grew significantly better on thyroid hormone than on placebo, and parents reported that their children had better energy levels during the thyroid hormone phase [3]. 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 only a small number of patients were studied.

Growth Hormone Deficiency

Growth hormone deficiency (GHD) has been described in case reports of a few patients with Fanconi anemia (FA) [33-37]. 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 and nearly half of them had a small pituitary gland on MRI [7]. In studies from other centers, nearly half of the patients evaluated for GHD had low GH levels [10]. One in five patients with suspected GHD had a midline defect on the brain MRI [4]. Growth hormone deficiency was more common in patients who had undergone HCT (25%) than in patients who did not have HCT (8%) [7]. The processes that underlie secretion of GH may be abnormal in children with FA during spontaneous overnight GH secretion studies [10], although these results are sometimes difficult to interpret because of the significant overlap with values observed in children without GHD [7]. 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 1 (IGF-1) values may not be as severely affected as the patient's height.

Evaluation for Growth Hormone Deficiency

Screening for GHD in a child with poor growth can be performed by drawing a blood sample and measuring IGF-1 and IGFBP-3 levels (Table 2). If IGF-1 and IGFBP-3 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 radiation. Sex steroid priming should be considered prior to GH stimulation testing in pre-pubertal girls age 10 years and older, and in pre-pubertal boys age 11 years and older or who are in stage two of puberty [38, 39]. 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^2, maximum dose 300 mcg), arginine (0.5 g/kg, maximum dose 20 g), or glucagon (0.3 mg/kg, maximum dose 1 mg) [39-41]. Peak GH levels are considered normal if they rise to 10 ng/mL or greater [42]. Patients diagnosed with GHD should be evaluated for central hypothyroidism, central adrenal insufficiency, and also should undergo an MRI scan of the pituitary gland.

Treatment of Growth Hormone Deficiency

Patients with FA who have 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 patients and 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 HCT. In the absence of safety data, GH therapy in FA patients should be titrated to achieve IGF-1 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 HCT and for at least six months after HCT, as well as during critical illness [43].

One study found positive effects of GH treatment in 75% of children with FA treated with HCT, with at least a 0.5 SDS increase in height [44]. In studies of patients without FA, the response to GH treatment after HCT has varied [45-48]. Ongoing use of glucocorticoids after HCT may limit the patient's growth response. In a study that included HCT recipients, GH treatment was associated with significantly improved adult height (on average, patients treated with GH grew about 4-5 cm taller than untreated children) [49] and did

not increase the risks of recurrent leukemia, secondary malignancies, or diabetes in post-HCT patients treated with GH compared with those who were not treated. A beneficial effect of GH treatment on growth rate after HCT also has been reported by others [50, 51].

Patients with FA are inherently at an increased risk of cancer, particularly for acute leukemia prior to HCT, as well as malignancies of the head and neck, and gynecological cancers [52-54]. 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 [55-61]. 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 [62]. 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. Patients and families should be counseled regarding the predicted adult heights, 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

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 [4]. 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 [9, 33]. 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 [9, 63]. Studies also have shown midline and other central nervous system abnormalities on brain MRI [64]. Three patients with FA at the National

Institutes of Health (NIH) had pituitary stalk interruption syndrome (PSIS) with or without septo-optic dysplasia. This syndrome has previously been reported in eight other patients with FA [34, 65-67], 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 also were 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. 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 low IGF-1 levels [67]. Serial endocrine testing is essential in patients with PSIS because pituitary hormone deficiencies may evolve over time.

Genital Tract Abnormalities

Developmental anomalies of the genital tract are more frequent in patients with FA than in the general population. Male patients with FA 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. Female patients 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 [68].

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. One study suggests this therapy can delay puberty to increase the patient's adult height by an average of 4-5 cm after four years of therapy [69]. More

commonly, children with FA enter puberty later than their healthy peers. Studies have shown that 12-14% of girls with FA had delays in starting their menstrual cycles [4, 7]. 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 (see Chapter 7). Chronic illness also is associated with delayed pubertal maturation. Total body radiation and some chemotherapy agents used during HCT also may 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 1). 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.

Treatment of Delayed Puberty

A boy with FA 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 (see Chapter 7). 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 two years of estrogen replacement therapy. Estrogen therapy is not needed if a female patient with FA has normal pubertal development or is having normal menstrual cycles, even if there is evidence of ovarian hormone deficiency.

Hypogonadism

Hypogonadism is very common in adults with FA. In addition, hypogenitalism with small testes and penis size affects 64% of men with FA, while premature ovarian failure affects 77% of women with FA [4]. In another study, 40% of adults with FA had evidence of hypogonadism [7]. Both hypergonadotropic (either testicular or ovarian) hypogonadism [66] and hypogonadotropic (specific to the hypothalamic-pituitary glands) hypogonadism have been reported in FA patients. 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 HCT, including radiation and chemotherapy [67].

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 pregnancies have been documented (see Chapter 7) [68, 70]. 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 HCT, 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 [71]. Disruption of *FANCA* in mice is associated with hypogonadism and a reduction in fertility [72]. Animal studies also have shown that the *FANCC* protein is required for the proliferation of primordial germ cells [73]. Primary ovarian insufficiency also was observed in a mouse model with *FANCE* mutation [74]. In addition, radiation or chemotherapy with HCT may contribute to decreased fertility after HCT. Cryopreservation of embryos or sperm is being investigated as a reproductive option. Future studies are needed to more fully address the fertility issues in FA patients.

Endocrine Abnormalities Specific to Adults with Fanconi Anemia

Endocrinopathies clearly persist into adulthood, though the treatment of FA with hematopoietic cell transplant (HCT) 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. Thus far, results

from endocrine studies have been reported only for a small number of adults with FA [4, 7, 8, 10].

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 also were 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 [4, 7]. In one study, a low stimulated GH peak was observed in a small number (6 of 16) of adults with FA [4, 7]. 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. In addition, many women with FA experience premature menopause (see Chapter 7).

One study reported decreased BMD (osteopenia or osteoporosis) in 12 of 13 adults with FA [4]. Of the eight females with decreased BMD, seven experienced premature ovarian failure and early menopause [4]. In 15 adult female patients with FA from the same center, five (33%) had osteoporosis and all had hypogonadism, which appears to be the predominant cause of low BMD in adult female patients with FA [20]. 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 [75]. 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 also is unknown. Additionally, many FA adults have hypogonadism, other endocrine deficiencies, and have undergone HCT—all of which may adversely affect bone health and trigger the early development of osteoporosis.

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 (see Chapter 3). 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, in particular with oxymetholone, also may 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.

Hematopoietic Cell Transplantation

Transplantation is inherently associated with a state of illness. Illness is not an optimal time to assess any hormone concentrations, as illness often alters thyroid levels, growth, gonadal function, nutrition, and glucose regulation. The treatments and radiation used during HCT 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 HCT should be closely monitored for hormonal abnormalities [26]. The late effects screening guidelines [26] recommend that a full endocrine evaluation including height/weight measurements, Tanner staging, bone age and growth factors should be assessed after HCT in children. In addition, screening is recommended for diabetes, dyslipidemia, vitamin D deficiency and osteoporosis (DXA scan before HCT and every two years after HCT). Some of these guidelines have been outlined by the Children's Oncology Group [76]. Many agents used in HCT have side effects on the endocrine system. Busulfan can adversely affect thyroid function [77] and sometimes growth [78, 79]. It is highly toxic to gonads and can lead to gonadal failure, particularly in females [80, 81]. Cyclophosphamide has a known dose-related effect on gonadal function in both males and females, particularly when used in combination with busulfan [25, 82-84]. 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 [5]. Methotrexate increases the risk for bone loss [85, 86]. Total body irradiation (TBI) increases the risk of primary hypothyroidism [87, 88], growth impairment [79, 89], hypogonadism [82, 90], and poor bone mineralization [91, 92].

Summary

Endocrine problems are common in FA patients, who often—though not always—are shorter than the general population. Patients 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. Older children and adults with FA tend to have low BMD. Height adjusted BMD Z-scores should be used in children, but it is unclear if BMD should be adjusted for height in adults with FA and short stature, and if these measures correlate with the risk of bone fractures. However, the high incidence of endocrine dysfunction—especially hypogonadism, corticosteroid use, and HCT—may predispose adults with FA to osteoporosis.

The origin of endocrine disorders in FA patients remains unclear. Hypothyroidism generally is 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 generally is thought to arise from pancreatic beta cell dysfunction, but insulin resistance and metabolic syndrome also are 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 radiation with HCT may contribute to endocrine dysfunction.

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Susan R. Rose, MD*
Neelam Giri, MD
Roopa Kanakatti Shankar, MD, MS
Constantine A. Stratakis, MD, DSc

**Committee Chair*

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Chapter 11

Hearing and Ear Issues in Patients with Fanconi Anemia

Introduction

Hearing and ear anomalies are prevalent in patients with Fanconi anemia (FA). Three of every 20 patients with FA have ear malformations [1] and reported prevalence of hearing loss in patients with FA ranges from 11% to 50% [2, 3]. Hearing loss in patients with FA is typically mild; however, it can impair an individual's communication abilities and interfere with language development and learning. This chapter will describe common concerns related to ear abnormalities and hearing loss in patients with FA, routine auditory monitoring, amplification tools, and surgical management. The ear and hearing clinical care team for patients with FA should include an otologist and an audiologist and, when needed, a speech-language pathologist. This team should work in close collaboration with other FA specialists and the primary physician to coordinate care.

Hearing and Ear Abnormalities in Patients with Fanconi Anemia

Researchers at the National Institutes of Health published a study in 2016 on 33 patients with FA who ranged from 3-56 years old to systematically examine and define ear and hearing abnormalities in this patient population [4]. In this study, comprehensive audiologic information available for 31 of the patients showed that hearing loss was detected in 14 (45 %) of the patients: 5 patients had bilateral hearing loss and 9 had unilateral hearing loss. The remaining 17 patients had normal hearing. The majority of hearing loss was classified as mild in degree. Out of the 14 patients with hearing loss, the most common type of hearing loss was conductive, which was found in 9 patients, or 64%. Sensorineural hearing loss (found in 2 patients or 14%) and mixed hearing loss (found in 1 patient or 7%) were less commonly observed.

After detailed microscopic ear examination, structural ear abnormalities were detected in 18 out of the 31 (58%) patients. Narrow ear canals and abnormally shaped pinna were identified in 10 (32%) and 3 (10%) patients, respectively. One patient with FA was born with an absent ear canal, an anomaly known as aural atresia. The most frequent finding was a small tympanic membrane in 18 patients, followed by the short handle of the malleus (manubrium) that was abnormally positioned on the eardrum in 16 patients, and the presence of abnormal bony islands (bony plate) under the eardrum in 12 patients (see Figure 1 as an example). One patient had an underdeveloped auditory nerve and profound sensorineural hearing loss unilaterally. Interestingly, an absent or underdeveloped radius found in 21% of the patients with FA was associated with hearing loss, suggesting a developmental relationship between the radius and structural ear abnormalities [4]. The results from this study indicate the incidence of hearing loss and congenital ear malformation is much higher in patients with FA than previously reported [1-3]. The findings suggest that abnormal features can be present even if the hearing is normal or only slightly reduced.

In a separate retrospective study of 17 FA patients who underwent a speech in noise (SIN) test, speech reception in noises was subnormal in nine subjects (53%) and abnormal in two subjects (12 %). Two patients with an abnormal SIN test and six patients with a subnormal SIN test had normal audiograms [5].

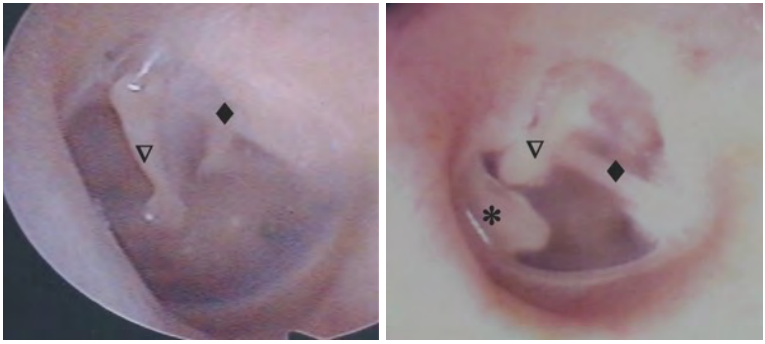

Figure 1. Anatomical differences in eardrums of patients with Fanconi anemia. This figure shows examples of a left eardrum of a healthy individual (left) and a patient with FA (right) with the bony plate (*), manubrium (∇), and chorda tympani nerve (♦) highlighted.

Early and Periodic Auditory Monitoring for Patients with Fanconi Anemia

Any child diagnosed with Fanconi anemia (FA) should undergo comprehensive assessments of his or her ears and hearing by an otolaryngologist 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 pass their newborn hearing screening, 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 six months of life can alleviate the long-term adverse effects of hearing loss on learning and language development [6].

Before the age of 3 years, such testing can rule out hearing loss that may affect speech and language development [7]. By the age of 5 or 6 years it is possible to obtain very complete testing across the speech frequencies to rule out a hearing loss that may have subtle effects on communication and learning. A speech in noise (SIN) test should be included as a part of hearing evaluation.

Once hearing loss is identified, the patient's hearing should be monitored regularly. 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, FA patients 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. 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, such as intravenous antibiotics (e.g., aminoglycosides such as gentamicin), iron-chelating agents (e.g., deferoxamine), and chemotherapy agents (e.g., cisplatin). It is important to establish the patient's baseline hearing level before he or she is treated with ototoxic medications, and to monitor the patient's hearing closely during treatment. Lastly, the genetic instability associated with FA has been associated with premature aging processes [8]; therefore, patients with FA may be at risk of developing age-related hearing loss at an earlier age than the general population.

Consequences of Hearing Loss

Children use their hearing to develop speech, language, communication skills, and to facilitate learning, so 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 [6, 9-11]. 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 [12].

Children with hearing impairment often require some form of special education or related services [13]. The United States' federal Individuals with Disabilities Education Act (IDEA)

[14] mandates the development of an Individualized Education Plan (IEP) for any student with a disability who needs special education. Early intervention and academic support teams should work in conjunction with health care providers, such as audiologists and speech pathologists, to identify intervention and academic needs. Section 504 of the U.S. Rehabilitation Act contains provisions for a school-aged child with hearing loss who needs accommodations, such as remote microphone Hearing Assistive Technology (HAT), to access the educational curriculum, but who does not need one-on-one special education teaching or therapy services [15]. This act also contains provisions for workplace accommodations, which should be sought out as needed by employees with 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.

Amplification

If hearing loss is identified in a child or an adult with Fanconi anemia (FA), an audiologist should evaluate the patient's need for hearing aids and/or hearing assist technologies. 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 worn in or behind the ear that 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. 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.

Hearing Assistive Technology

Remote microphone Hearing Assistive Technology (HAT) helps hearing-impaired individuals function in daily communication situations. They may be used alone or in combination with hearing aids. Hearing assistive technology is 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 personal remote

microphone HAT is a commonly used device that captures sound via a microphone worn by the person speaking. The device then transmits the sound wirelessly to a receiver worn on the ear or attached to a hearing aid. 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.

Another type of HAT known as a classroom audio distribution system (ADS), or sound-field system, can be a good option for children with hearing loss that is mild or only affects one ear. This system requires the teacher to wear a wireless microphone that transmits sound to speakers that evenly distribute the teacher's voice to all parts of the classroom. The classroom ADS system can help to ensure that a hearing impaired student can hear what the teacher is saying, even if the teacher is not directly facing the student or is speaking from the other end of the classroom.

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 [16]. For children who fall into this category, such a device can be essential for normal speech and language development. 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 (anchored) into the bone behind the ear in children age 5 years and older.

Surgical Management of Hearing Loss for Patients with Fanconi Anemia

In the general population, middle ear surgery improves conductive hearing loss in 75% to 90% of carefully selected candidates [17]. It should be noted, however, 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 patients with FA:

- 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
- Perforation of the eardrum

Assessing Candidacy for Surgery

Surgery is not suitable for every patient with conductive hearing loss. Patients with moderate, severe, or profound sensorineural hearing loss are typically not candidates for middle ear surgery. Individuals with serious medical conditions such as heart problems, bleeding tendencies, and a high susceptibility for infection due to bone marrow failure typically are not good candidates for surgery. Candidates for surgery must have normal inner ear function as demonstrated by audiometric thresholds for on bone conduction testing. 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. 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.

Middle Ear Surgery

Middle ear surgery can be performed in children ages 7 years or older who are capable of cooperating with 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. 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.

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 one to three 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.

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 of months.
- Persistent post-operative dizziness or ringing in the ears, both of which are quite uncommon.
- Restenosis of the ear canal, which requires additional surgery.

Summary

Congenital hearing loss and/or malformations of the eardrum and middle ear are more commonly associated with Fanconi anemia (FA) than reported previously, although 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. Hearing problems that are FA-related often can be successfully treated with either appropriate amplification and/or surgical correction.

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H. Jeffrey Kim, MD*
Kalejaiye Adedoyin, MD
Carmen C. Brewer, PhD
Bradley Kesser, MD
Kelly King, PhD
Carter van Waes, MD
Karen L. Wilber, AuD
Christopher Zalewski, PhD

**Section committee chair*

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Chapter 12

Clinical Care of Hand and Arm Abnormalities in Fanconi Anemia

Introduction

Approximately half of all children with Fanconi anemia (FA) have skeletal abnormalities, 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 child's hands and arms. By the time most FA patients reach adulthood they have completed all necessary hand surgeries in childhood 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 with pediatric problems. Thus, patients should ask their pediatric hand surgeon to recommend a physician who cares for similar hand and upper extremity abnormalities in adults.

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

- Underdeveloped, missing, or duplicated thumb
- Shortened or missing radius
- Shortened, curved forearm
- A hand that develops perpendicularly to the forearm
- Impaired movement in the wrist, fingers, and elbow

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 child with Fanconi anemia (FA) should be referred to a hand and upper limb surgeon who specializes in pediatrics.

Many children with upper limb abnormalities require physical or occupational therapy, which may begin after the initial assessment. A therapist can help to stretch and strengthen the affected limb, fabricate splints, 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 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 (see Chapter 2). Some patients with VACTERL-H actually have FA, and a combination of radial and renal anomalies is an important clue in this diagnosis [1]. The precise clinical

indication for FA testing in children with limb anomalies is still evolving; however, every child with isolated thumb or hand abnormalities or deficiencies with the radius should be tested for FA (see Chapter 2).

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

Syndrome or Health Condition	Characteristics
Holt-Oram Syndrome	Heart defects, particularly defects of the cardiac septa
Thrombocytopenia Absent Radius (TAR) Syndrome	• Thrombocytopenia present at birth • May require blood transfusions and can improve over time • Thumbs are present in TAR and may be abnormal in shape
VACTERL Association (also discussed in Chapter 2)	**V**ertebral abnormalities **A**nal atresia **C**ardiac abnormalities **T**racheoesophageal fistula **E**sophageal atresia **R**enal defects **R**adial dysplasia **L**ower limb abnormalities
Fanconi anemia	• Aplastic anemia that usually develops in the first decade of life • Thumbs are often absent if radii are absent
CHARGE Syndrome	**C**oloboma of the eye **H**eart defects **A**tresia of the nasal choanae **R**etardation of growth and/or development **G**enital and/or urinary abnormalities **E**ar abnormalities and deafness

Thumb Anomalies

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

Type I Deficiency

In Type I 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 present. This mild deficiency may go unrecognized and many individuals are not diagnosed until later in life when everyday activities such as buttoning a shirt or tying shoes become more difficult.

Type II Deficiency

Type II deficiency is more involved and is characterized by a narrowing of the web space between the thumb and index finger, absence of the thenar muscle at the base of the thumb, and instability of the metacarpophalangeal joint in the middle of the thumb (Figure 1A and B).

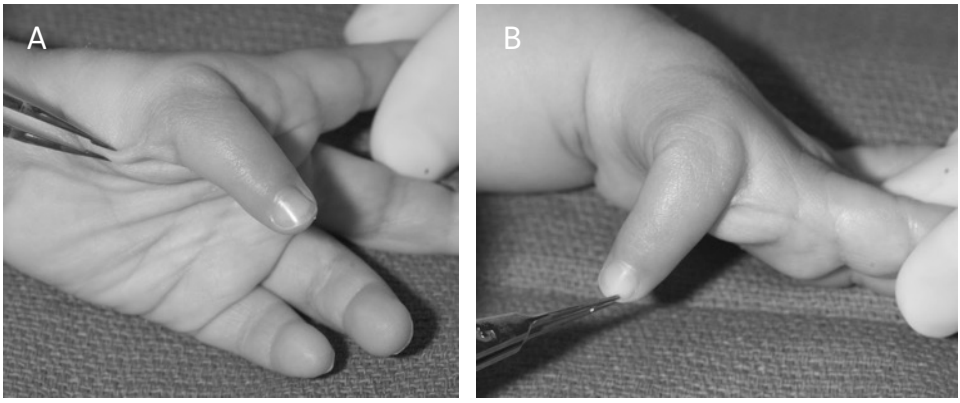

Figure 1. A two-year-old child with Type II thumb hypoplasia. A) Absent thenar muscles; B) Narrowed thumb-index web space with instability of the metacarpophalangeal joint. Source: Shriners Hospital for Children, Philadelphia Unit.

Type III Deficiency

A child with Type III deficiency 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, respectively, of a stable carpometacarpal joint at the base of the thumb.

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

The clinical differentiation between Type III-A and Type III-B can be difficult. The child's pattern of thumb usage often helps discriminate between these types. Type III-B thumb deficiencies produce an unstable thumb that will not be incorporated into pinching and grasping motions; rather, the child will learn to pinch and grasp between the index finger and the long digit, and the index finger will tend to rotate out of the palm toward a thumb position. 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 ossify or become visible on x-ray until 4-6 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 trapezium and trapezoid anatomy without the need for anesthesia. A thumb metacarpal that tapers to a point at the base of the metacarpal on x-ray also is indicative of an unstable carpometacarpal joint.

Type IV Deficiency

Type IV 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. A one-year-old child with severe Type IV thumb hypoplasia (also known as a 'pouce flottant' or floating thumb). Source: Shriners Hospital for Children, Philadelphia Unit.

Type V Deficiency

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

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

Thumb classifications can guide treatment recommendations as shown in Table 2 [3-5]. 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 AND: 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 (Type I) does not require surgical reconstruction. Type II and III-A thumbs can be reconstructed; however, multiple elements need to be addressed during surgery to maximize the thumb's function (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).
- Metacarpophalangeal joint instability can be improved by reconstructing the ligaments using tendon 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 grasp.

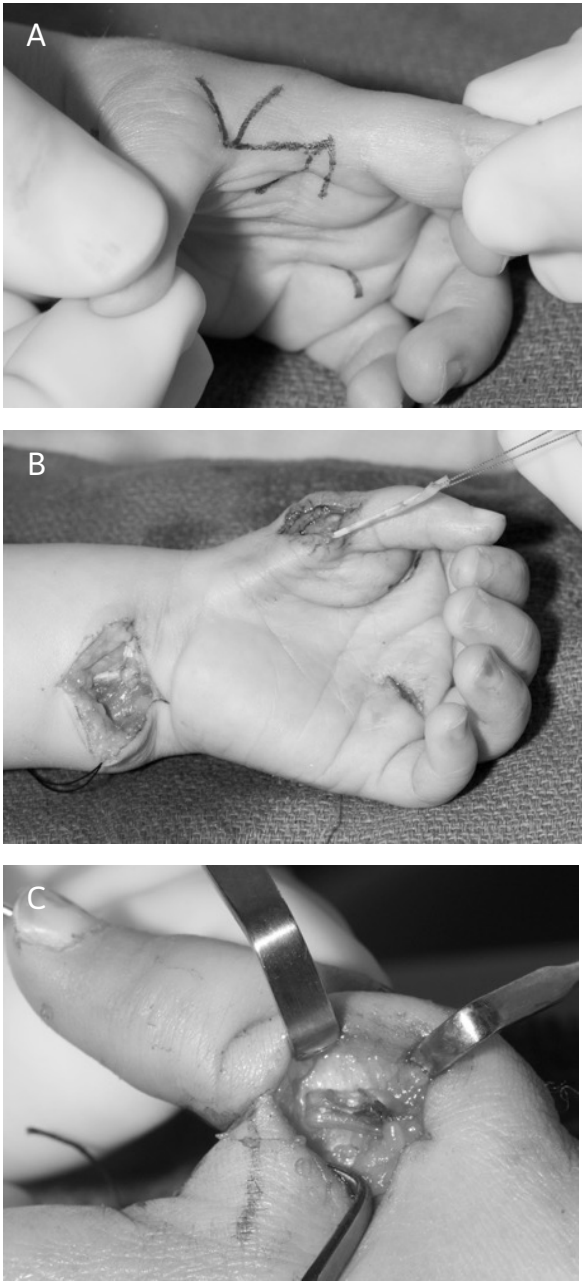

Figure 4. Thumb reconstruction for Types II and III-A requires the surgeon to address all deficient elements. A) Z-plasty of the narrowed thumb-index web space; B) Tendon transfer to overcome the deficient thenar muscles; C) Ligament reconstruction to stabilize the metacarpophalangeal joint instability.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

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 (Figures 5 and 6).

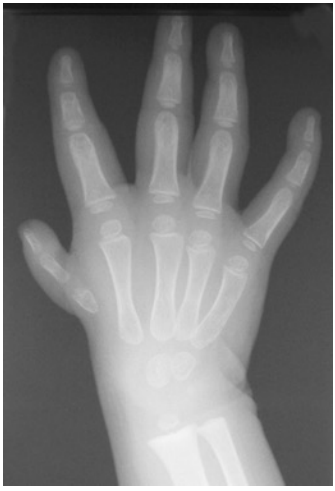

Figure 5. An X-ray of a two-year-old child reveals a thumb metacarpal that tapers to a point, indicative of an unstable carpometacarpal joint. Source: Shriners Hospital for Children, Philadelphia Unit.

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

In addition, Type III-B and IV thumbs are not 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 often is a difficult process for parents and caregivers. Discussions with the

surgeon and conversations with families who have made similar decisions often are helpful to parents tasked with making this decision for their child.

Following removal of a hypoplastic thumb, creation of an opposable thumb is critical for grasp and object manipulation. The preferred procedure is pollicization, which involves moving the index finger and its nerves, arteries, tendons, and muscles to the thumb position. 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. This procedure is generally performed when the child is between 6-24 months of age, depending on the health status of the child, the degree of forearm deficiency, and the surgeon's preference [2, 3]. The general medical health of a child with FA also should 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, though acceptance of a change in the appearance and composition of their hand can be more difficult.

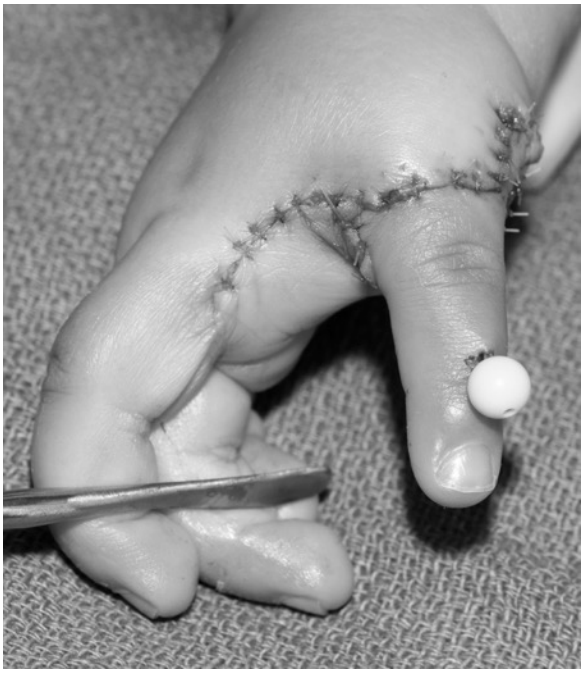

Figure 7. Pollicization of the index finger requires careful surgical technique to give the appearance and function of a thumb. Source: Shriners Hospital for Children, Philadelphia Unit.

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). Good results shortly after pollicization have been shown to persist into adulthood [6, 7].

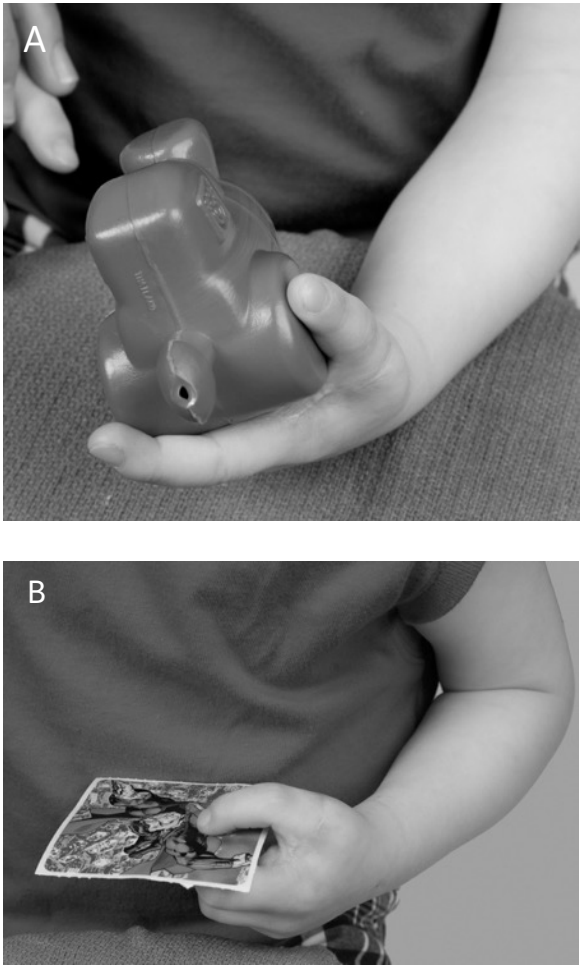

Figure 8. A two-year-old's status post-pollicization of a mobile left index finger. A) Thumb used for grasping large objects; B) Mobile thumb incorporated into fine pinch. Source: Shriners Hospital for Children, Philadelphia Unit.

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.

Triphalangeal thumb

A triphalangeal thumb has an extra phalanx that can vary in size and shape (Figure 9). The alignment and length of this type of thumb must be monitored during growth. 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 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 that causes the thumb to curve and become excessively long should not be removed because joint instability is common following 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 realigns the thumb, shortens the elongated thumb, and eliminates the extra joint.

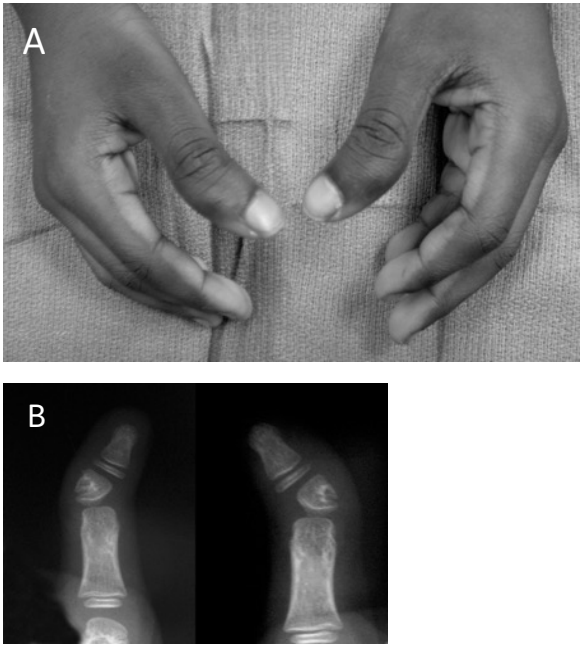

Figure 9. Eight-year-old child with triphalangeal thumbs. A) Clinical appearance with mild angulation; B) X-rays show an extra phalanx that is triangular in shape causing the angulation. Source: Shriners Hospital for Children, Philadelphia Unit.

Pre-Axial Polydactyly

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) [8, 9]. 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) [10]. This procedure is not always straightforward and requires careful intra-operative decision making. 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 and modification via 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.

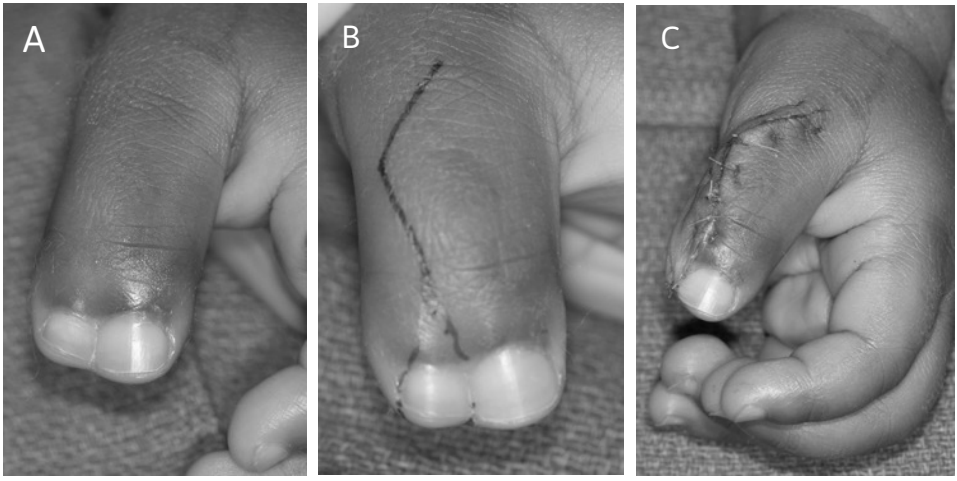

Figure 10. A one-year-old child with a duplicated left thumb. A) Clinical presentation; B) Skin incision designed to incorporate parts of the deleted component; C) Surgical reconstruction using the soft tissues from the deleted thumb to augment the size and girth of the retained thumb. Source: Shriners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

Table 3. Classification of duplicated thumbs.

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 reference [9].

Radial Deficiency

Radial deficiency is a skeletal condition in which the radius 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 [11, 12]:

- **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 substantial 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.

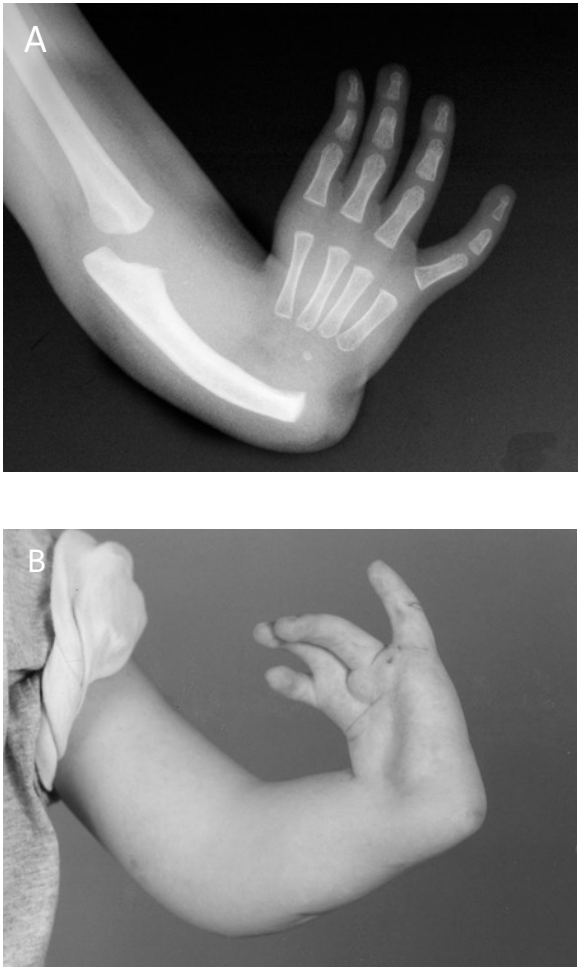

Figure 11. A two-year-old child with complete absence of the radius (Type 4). A) X-ray reveals complete absence of the radius; B) Hand with a perpendicular relationship with the forearm. Source: Shriners Hospital for Children, Philadelphia Unit.

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 three 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, and forearm abnormalities (Table 4).

Table 4. Classification of radial longitudinal deficiency.

Type	Thumb	Carpus	Distal radius	Proximal radius
N	Hypoplastic or absent	Normal	Normal	Normal
0	Hypoplastic or absent	Absence, hypoplasia, or coalition	Normal	Normal, radioulnar synostosis, or congenital dislocation of the radial head
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 absent	Variable hypoplasia
4	Hypoplastic or absent	Absence, hypoplasia, or coalition	Absent	Absent

Modified from references [11] and [12].

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 may be shorter than expected and the elbow may not bend properly. Furthermore, the forearm will always be shortened because the ulna is approximately 60% of the normal length at birth and remains short even after the skeleton has completely grown and matured [13]. The ulna also will 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 often are absent 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 often absent, although the ulnar nerve and artery are normal [13]. 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.

Radial Deficiency Treatment Considerations

The fundamental goals of treatment are to correct the radial deviation of the wrist to balance the wrist and forearm while maintaining range of motion for the wrist and fingers. Treatment also should strive to promote growth or lengthening of the forearm and improve the overall function of the arm. A slightly shortened radius (Type 0 and 1 deficiencies) requires repeated stretching and occasionally requires 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 unilateral radial deficiency may be able to compensate for any functional deficits using their unaffected limb and, therefore, have a lower overall degree of functional impairment compared to children who have bilateral radial 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 abilities to pinch and grasp.

Radial Deficiency Nonsurgical Treatments

The initial treatment for an absent radius should begin shortly after birth and consists of stretching the soft tissues, including the tendons, ligaments, skin, and muscles. This treatment is typically performed by both 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 stretching and splinting treatments.

Radial Deficiency 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 [14, 15]. 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).

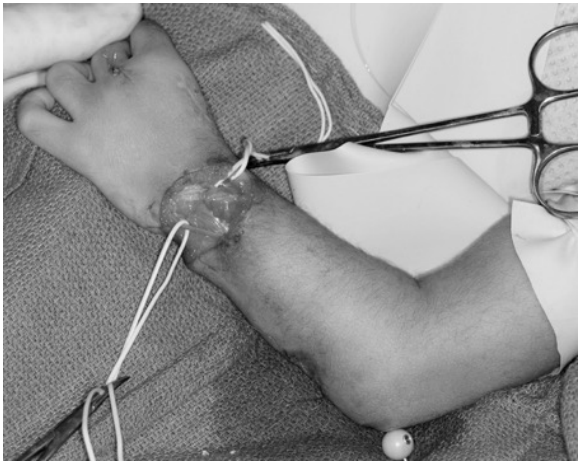

Figure 12. Surgical centralization requires placing the wrist on top of the ulna to realign the carpus onto the distal ulna. Source: Shriners Hospital for Children, Philadelphia Unit.

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 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 8-12 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 at least 4-6 weeks. The splint can be removed for physical therapy exercises, but most surgeons recommend that the splint be worn during sleep until the child has stopped growing.

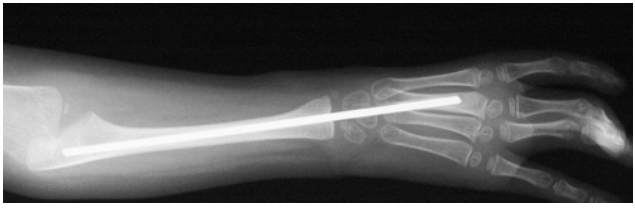

Figure 13. Centralization is maintained by placement of a stout wire across the wrist. Source: Shriners Hospital for Children, Philadelphia Unit.

Centralization typically is performed when the child reaches approximately one 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 best able to pinch and grasp using their palm and the fingers on the

outside edge of the hand, known as an ulnar grasp pattern. In these children, 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.

In an effort to maintain motion and obtain partial correction of the radial deviation, a surgeon may find it useful to use a soft tissue release and skin flap to avoid entering the joint and jeopardizing growth and motion [16]. High satisfaction rates and functionality scores have been reported even though the forearm remained angulated after surgery. This technique involves a bilobed flap to transpose the excess ulnar-sided soft tissue to the radial side of the wrist (Figure 14). All underlying tight fascial bands are released and wrist flexors with a purely radial deviating force are cut or transferred. The ulnocarpal joint is not opened and a formal centralization is not performed. Concomitant ulnar osteotomy is performed if angulation exceeds 30 degrees.

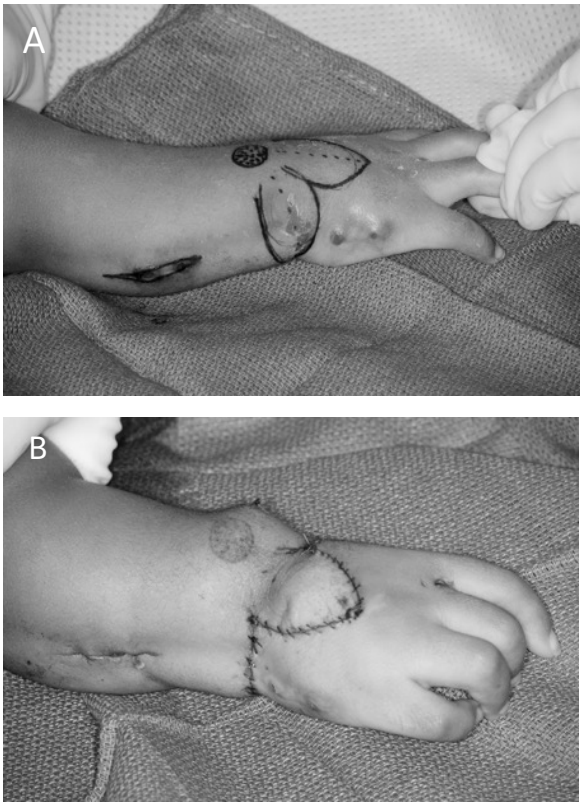

Figure 14. Soft tissue release and skin flap procedure. A) Design of bilobed flap to transpose dorsal skin to the radial side of the wrist and the excessive ulnar-sided skin to dorsum of the wrist for added dermodesis; B) Flap inset and closure after transposition of dorsal and ulnar flaps. Source: Shriners Hospital for Children, Philadelphia Unit.

Contraindications for Surgery

Mild deformities with adequate support for the hand (Type 0 or 1) do not require surgery. Surgery also is not advised for children with limited ability to bend 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 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 [17-19]. The fixator may be unilateral with pins or ringed multiplanar with wires (Figure 15).

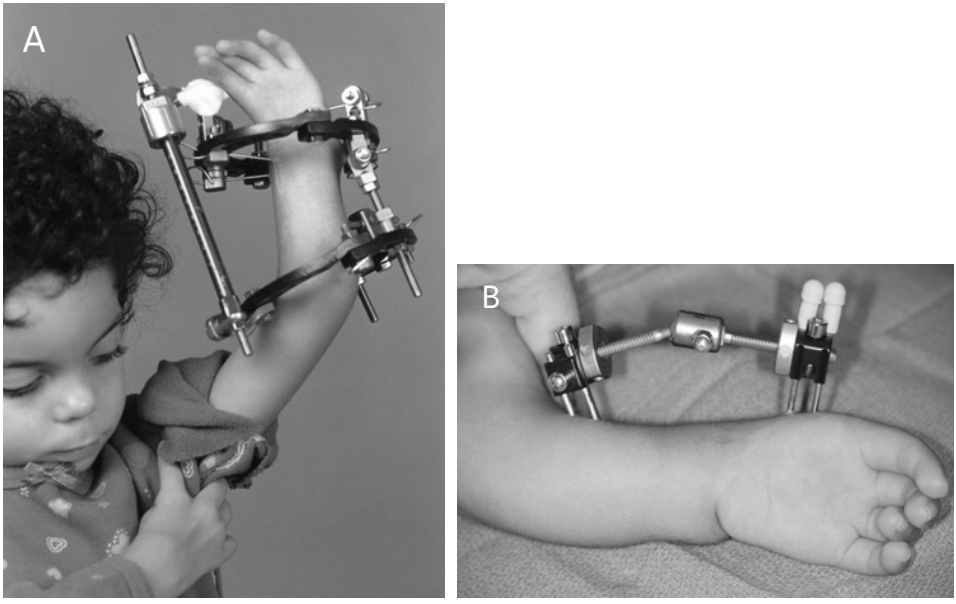

Figure 15. Radial deficiency with rigid deformity is treated with preliminary soft tissue distraction. A) Uniplanar device along the radial side of the forearm; B) Multiplanar device for additional control of hand and forearm. Source: Shriners Hospital for Children, Philadelphia Unit.

Numerous other technical modifications have been proposed to maintain alignment of the wrist position. These include overcorrection of the radiation deviation, tendon transfers to correct the alignment, prolonged wire fixation following centralization (leaving the wire in place for longer than the typical 8-12 weeks), and microvascular free toe transfer.

Overcorrection of the radial deviation requires the patient's hand to be positioned slightly off-center into ulnar deviation to help prevent recurrence of the radial deviation. Microvascular free toe transfer 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 16). 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 [20]. This is a technically demanding operation, however, and complications are common.

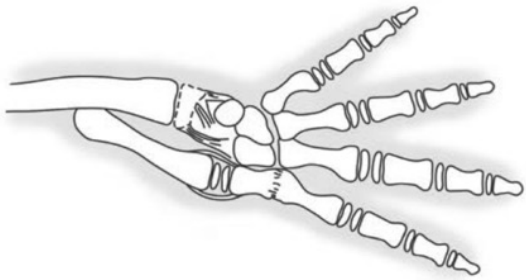

Figure 16. Diagram of free toe transfer to support the radial side of the wrist. The toe proximal phalanx is fused to the base of the second metacarpal and the proximal metatarsal affixed to the side of the distal ulna. Reprinted with permission [21].

Treatment Outcomes for Radial Deviation Correction

Unfortunately, no single treatment method consistently and permanently corrects the radial deviation, balances the wrist, and allows continued growth of the forearm [14, 15]. Recurrence can prove frustrating to the child, parent, and surgeon (Figure 17). 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 minimize 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. Although patients with severe radial deviation may have limitations in their range of motion and strength, long-term studies have found that they function independently and participate in a high number of activities that is comparable to children with less severe deformities [22-25].

Figure 17. An 11-year-old child with recurrent radial deviation following centralization as an infant. Source: Shriners Hospital for Children, Philadelphia Unit.

A 2017 study examined the long-term outcome of surgical or nonsurgical treatment of children with radial deficiency [26]. Non-surgical patients had the most radial deviation and forearm angulation. Soft tissue release and bilobed flap lessened the radial deviation without causing physeal arrest and maintaining good wrist motion. External fixation and subsequent centralization or radialization achieved the best angular correction but resulted in the decreased wrist motion and shortened the ulnar length. Microvascular toe transfer that connected the distal ulna to the carpus resulted in the best motion while maintaining good ulnar length.

The management of recurrent deformity must be individualized to each patient and the specifics of his/her deformity. Similarly, the indication for forearm lengthening to overcome the inherent problem of a shortened forearm have 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 18). 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 [27]. 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 physical therapist is a valuable preoperative tool. Painstaking measures should be taken to ensure that wrist fusion does not lead to loss of function.

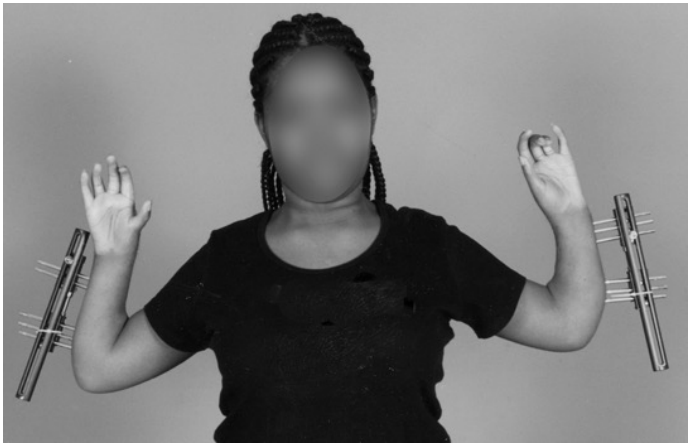

Figure 18. Bilateral forearm lengthening using an external fixator. Source: Shriners Hospital for Children, Philadelphia Unit.

Summary

Upper extremity skeletal abnormalities such as thumb and radial deficiencies are common in patients with Fanconi anemia (FA). Evaluation of skeletal abnormalities typically precedes diagnosis of FA and can be used as criteria for further evaluation during diagnosis of the disease. Mild to severe hypoplastic thumb deficiencies may require surgical intervention depending on the severity of the anomaly and other patient-specific factors. Radial deficiencies are variable and characterized by a radius that can be smaller than average, or altogether absent. The treatment for radial abnormalities ranges from soft tissue stretching for mild cases to surgical intervention for more severe cases. The goals of treatment are to correct the radial deviation while promoting forearm lengthening and improving the overall function of the arm. Treatment for radial abnormalities, regardless of the modality used, may not be permanent and recurrence is possible.

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Scott H. Kozin, MD*
Roger Cornwall, MD
Ann Van Heest, MD

**Chapter Committee Chair*

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Chapter 13

Brief Guide to Clinical Care for Patients with Fanconi Anemia

Introduction

This chapter is a brief clinical guide that is a compendium of information provided in all other chapters in this book. It is not all-inclusive and should not take the place of reading the comprehensive information provided in other chapters. Many of the tests and procedures mentioned in this chapter will not be appropriate for every individual patient, nor does this brief guide present an exhaustive list of possible tests or treatments that each FA patient could or should undergo. Rather, it 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.

The brief guide covers the following areas:

- Diagnosis of FA
- General clinical care
- Bone marrow failure and hematopoietic cell transplant
- Reproductive health and gynecologic cancer
- Head and neck cancer prevention, diagnosis, and treatment
- The adult patient with FA and clinical care transition

Diagnosis of Fanconi Anemia

The following should be used as criteria to perform diagnostic testing for Fanconi anemia (FA) (see Chapter 2):

- All children with multiple anatomic abnormalities, particularly those that are grouped with the acronym PHENOS (skin Pigmentation, small Head, small Eyes, Nervous system, Otology, and Short stature) and those described in the VACTERL-H (Vertebral, Anal, Cardiac, Tracheo-esophageal fistula, Esophageal atresia, Renal, upper Limb and Hydrocephalus) association.
- All children and adults with aplastic anemia.
- All patients with a 3q gain on cytogenetic evaluation.
- All full siblings of patients with FA, 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 hematopoietic cell transplant (HCT).
- Young adults that present at atypical ages for specific malignancies, including squamous cell carcinoma (SCC) of the head and neck or anogenital region.
- Individuals with excessive toxicity after treatment with chemotherapeutics commonly used to treat cancers such as myeloid leukemia and head and neck or anogenital SCC.

Laboratory Tests for Fanconi Anemia

Physicians who suspect that a patient may have FA should refer the patient to a hematologist and/or clinical geneticist or genetic counselor who can arrange for diagnostic testing (see Chapter 2 for complete testing guidelines).

Anyone suspected of having FA should be tested using a diepoxybutane (DEB) or mitomycin C (MMC) chromosome breakage test of blood lymphocytes. The DEB/MMC test should be performed at a clinically certified laboratory that has expertise in FA diagnostic testing.

If diagnostic test results of blood lymphocytes are negative, no further testing is necessary, unless there is strong clinical suspicion. If the result is negative, or equivocal, skin fibroblasts can be used for additional chromosome breakage testing. In addition, molecular testing for other chromosome instability or DNA repair syndromes can be performed.

If the chromosome breakage test is positive, a targeted FA gene panel and deletion/duplication analysis should be performed. If results from this test are negative, whole exome or whole genome sequencing can be performed.

General Clinical Care

Fanconi anemia (FA) leads to numerous bodily complications that require specific clinical care approaches. This section provides an overview of guidelines for monitoring and treating the body systems covered in the chapters of this guide.

Audiologic Care

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 (see Chapter 11).

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.

If a patient with FA receives potentially ototoxic drugs (i.e., that can impair hearing), such as certain intravenous antibiotics and/or chemotherapy drugs used during hematopoietic cell transplant (HCT), the patient's auditory function should be monitored with serial audiograms.

Dermatologic Care

Patients with suspicious nevi or other abnormal skin lesions should be examined by a dermatologist (see Chapter 8). All patients with FA should limit sun exposure and wear sunscreen to reduce the risk of skin cancer. Post-HCT patients should limit sun exposure to reduce the risk of cutaneous chronic graft-versus-host disease.

Endocrine Care

Many children and adults with FA have endocrine problems, including growth hormone deficiency, hypothyroidism, pubertal delay, or diabetes (see Chapter 10). To ensure optimal care, the patient should consult with an endocrinologist or pediatric endocrinologist.

At diagnosis and annually, each FA patient should receive a thorough baseline endocrine evaluation to monitor the following:

- **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, which is often delayed in individuals with FA, 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 two 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 should 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.

Gastrointestinal Care

Patients with gastrointestinal or hepatic concerns should be seen by a gastroenterologist. A number of patients with FA have gastrointestinal symptoms, such as poor oral intake, nausea, abdominal pain, and/or diarrhea resulting in a failure to thrive. 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 often do not disclose these concerns voluntarily (see Chapter 9). The hepatic complications of androgens also are a concern in patients with FA. Liver enzymes should be monitored every 3-6 months in patients receiving androgens, and a liver ultrasound every 6-12 months is recommended.

Hand and Arm Abnormalities

Patients with hand or arm abnormalities should be assessed at the time of diagnosis by an orthopedic surgeon with specific 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 functional and cosmetic outcome for arm and thumb abnormalities that are common in FA.

Oral Care

All patients with FA should have regular dental examinations at least every six months by a dentist who is well versed in FA head and neck squamous cell carcinoma risks. The examination should include a thorough screening for possible oral cancer. Digital dental x-rays provide limited radiation exposure and may be required to monitor for cavities and diagnose gum and bone diseases that cannot be detected by visual inspection. However, because patients with FA have increased sensitivity to radiation, use of dental x-rays should be limited as much as possible.

Other dental procedures (e.g., braces) should be discussed with the FA hematologist. Bone marrow failure (BMF) contributes to significant oral health problems, including increased

bacterial, viral, and fungal infections. Oral care is essential for treating and managing oral complications for patients with FA both pre and post-HCT. Patients with FA should not have dental cleaning, extraction, or other invasive procedures after HCT until the immune system has recovered. If urgent care is required, supportive care may be needed (see Chapter 6).

Polypharmacy

Patients with FA often take several different prescription medication simultaneously throughout their lives. 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 or hematologist to coordinate care. The patient should share all prescription and non-prescription drugs, dietary supplements, and homeopathic agents used with the primary physician and subspecialists.

Skeletal Health

Hematopoietic cell transplantation may increase the risk of osteoporosis/osteopenia for any patient regardless of underlying diagnosis. The pre-transplant recommendation for FA 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 one year post-transplant, with ongoing monitoring as needed. Independent of transplantation, premature menopause is a high-risk factor for reduced bone mass and gynecological experts who treat adult female patients with FA recommend careful monitoring of bone health. Long-term treatment with corticosteroids also increases the risk of osteoporosis/osteopenia in both male and female patients with FA.

Bone Marrow Failure

Most patients with Fanconi anemia (FA) will develop bone marrow failure (BMF); however, the age of onset can be highly variable, even among affected siblings. The absence of BMF does not exclude the diagnosis of FA, however. All patients with FA should be monitored by a hematologist with experience in FA, regardless of whether the patient has bone marrow involvement. Chapter 3 provides a detailed overview for clinical monitoring of BMF in patients with FA.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is currently the only therapy available to cure patients with FA of marrow aplasia and prevent progression to myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML).

Pre-Transplant Precautions for Patients with Fanconi Anemia

The FA diagnosis must be confirmed before proceeding to HCT. 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 HCT, as the procedure may affect future fertility.

After Transplant Care

Table 2 in Chapter 3 provides a comprehensive schedule of the long-term follow-up examinations needed for FA patients after HCT. Long-term care plans should be tailored to the specific needs of each individual FA patient under the supervision of a long-term care team comprised of the HCT physician, primary hematologist, and a multi-disciplinary team of specialists. Early complications, such as graft-versus-host disease (GvHD), graft failure, organ toxicity, and infections should be monitored. Abnormal liver enzymes and blood counts should be monitored. Testing for viruses should be performed early on as well. Late complications should be monitored and include chronic GvHD, organ toxicity (i.e., cardiac, pulmonary, renal), endocrinopathies (i.e., diabetes, hypothyroidism, gonadal dysfunction, growth failure), osteoporosis, avascular necrosis, infertility, and cancer.

Most transplant centers will expect patients 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 HCT. Patients with FA should be screened for immune reconstitution one year after HCT. The primary care physician should discuss the exact timing of immunizations with the patient's transplant physician. All patients and their family household members should receive the intramuscular formulation of the influenza vaccine on an annual basis. After HCT, the patient's hematologist will determine how often blood counts and bone marrow tests are needed (see Chapter 3).

Myelodysplastic Syndrome and Acute Myelogenous Leukemia

Patients with FA are at high risk of developing MDS and AML and should be monitored closely to assess for possible onset. Serial marrow examination and cytogenetic analysis should be performed annually in patients who have not undergone HCT to identify clonal evolution to MDS or AML. There is no standard therapy for FA patients with MDS or AML. Treatment options include HCT with or without prior induction chemotherapy.

Hematopoietic Cell Transplant in Adult Patients with Fanconi Anemia

In patients with FA, HCT yields 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. A multicenter retrospective analysis of 199 adult patients with FA transplanted between 1991 and 2014 was recently published [1]. Non-relapse mortality at 96 months was 56% with an overall survival of 34%, which improved with more recent transplants.

Reproductive Health

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 (SCC) of the lower genital tract, which includes cervical, vaginal, vulvar, and anal cancers. Male patients with FA may have numerous structural abnormalities of the reproductive system and extremely low sperm count that affect fertility.

Gynecologic Cancer

Proper prevention, surveillance, and treatment of anogenital SCC in female patients with FA are essential. Beginning at age 13, female patients with FA should have annual examinations by a gynecologist for visual inspection of the external genitalia. Once sexually active, or by age 18, female patients with FA should receive comprehensive annual gynecologic exams with cervical cytology testing. Clinical experts recommend screening for gynecological cancer every 6-12 months because squamous intraepithelial lesions (SIL) can rapidly progress to cancer. Anal pap smears and anoscopy may be considered in female patients with FA who have vulvar disease.

As with the general population, colposcopy is appropriate in the setting of abnormal cytology or suspicious lesions noted on examination. Suspicious genital tract lesions should be biopsied. Female patients diagnosed with anogenital SCC should be referred immediately to a gynecologic oncologist. Early referral may enable surgical treatment of the cancer, thereby avoiding the risks associated with chemotherapy or radiation for patients with FA (see Chapter 7 for complete guidelines on gynecologic cancer).

Human Papillomavirus Vaccination

It is recommended that patients with FA follow the current guidelines from the U.S. Centers for Disease Control and Prevention, which recommends routine HPV vaccination for both females and males. The currently available vaccine protects against acquiring the nine HPV types that are most commonly associated with cervical, vaginal, and vulvar cancer, and genital warts. Ideally, the vaccine should be given before the patient is exposed to HPV through oral sex or sexual intercourse. It is recommended that patients with FA be vaccinated starting at age 9. Regardless of prior HPV vaccination, patients with FA should be vaccinated after hematopoietic cell transplantation (HCT), when deemed appropriate (see Chapter 7).

Primary Ovarian Insufficiency

Primary ovarian insufficiency (POI) is common in female patients with FA. It is characterized by a spectrum of low ovarian reserve, declining ovarian function, reduced fertility, and estrogen deficiency. It is recommended that female patients with FA be treated either with oral contraceptive pills (if the patient is sexually active and pregnancy is not desired) or postmenopausal hormone therapy, which consists of low to physiologic doses of estrogen and progestins. Either approach is superior to no therapy regarding the effects on bone and other aspects of health.

Fertility and Pregnancy

Pregnancies have been reported in female patients with FA, in both those who were treated with HCT and those who were not. Physicians should discuss childbearing options with female patients with FA before HCT, 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 likely will 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 HCT have occurred, but they are rare.

Menopause

Female 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 using hormone therapy.

Breast Cancer Screening

Five of the genes implicated in Fanconi anemia (FA) are breast cancer susceptibility genes: *FANCD1/BRCA2*, *FANCJ/BRIP1*, *FANCN/PALB2*, *FANCO/RAD51C*, and *FANCS/BRCA1*. However, breast cancer risk for individuals with FA who harbor variants in these genes or other FA genes has not been established; therefore, more research is needed to develop guidelines for breast cancer screening for female patients with FA (regardless of their specific FA variant). It is unclear whether the current mammography screening recommendations for carriers also apply to individuals with FA, as FA 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.

Reproductive Issues in Male Patients with Fanconi Anemia

Developmental anomalies of the genital tract are more frequent in male patients with FA than in the general population. Many male patients with FA may have the following reproductive issues:

- Delayed puberty
- Undescended testicles and hypospadias, a condition where the urethra opens on the underside of the penis
- Small testes for their age and pubertal status, most likely reflecting reduced Sertoli cell mass and spermatogenesis
- Testicles fail to descend
- Low levels of sex hormone production due to underlying problems with the pituitary gland or hypothalamus
- Azoospermia

Head and Neck Squamous Cell Carcinoma

Patients with FA are at extremely high risk for developing cancer at an early age, and in particular, head and neck squamous cell carcinoma (HNSCC). Therefore, implementation of early and lifelong surveillance, regardless of whether the patient has undergone a bone marrow transplant, is essential.

Prevention

- Maintain good oral hygiene and visit a dentist and an expert in head and neck cancer detection every six months.
- Minimize exposure to dietary alcohol and do not use mouthwashes containing alcohol.
- Avoid smoking and exposure to second-hand smoke; vaping also should be avoided.

- Receive the human papillomavirus (HPV) vaccination series, beginning at age 9 for both male and female patients with FA (see Chapter 7 for full guidelines).

Surveillance and Treatment

- Beginning at age 10, patients with FA should be examined every six months by 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.
- Suspicious lesions in the oral cavity should be brushed immediately using a brush biopsy. If pre-cancerous or cancerous lesions are identified via brush biopsy, incisional biopsy must be performed to confirm the diagnosis.
- Malignant lesions must be treated immediately, as cure can best be achieved via early surgical removal. Treatment should be discussed with a hematologist/oncologist with experience in FA.
- Aggressive monitoring by the treating surgeon is required for those previously treated for head and neck cancer.

Adult Patients with Fanconi Anemia

Fanconi anemia (FA) is no longer an exclusive childhood illness. Increased recognition of disease diversity, improved hematopoietic cell transplant (HCT), better supportive care options, and early detection have improved the likelihood that patients with FA will live into adulthood. It is now estimated that approximately 80% of patients with FA will survive beyond 18 years of age [2, 3]. The major healthcare issues of the adult FA population have been described and discussed in database reports by the International Fanconi Anemia Registry, the National Institutes of Health (NIH)-based North American Survey, and the German Fanconi Anemia Registry [4-7]. However, the adult population with FA has not been studied as a patient subgroup in any prospective studies published to date. Many major health issues unique to this subpopulation of patients with FA are just beginning to be recognized and evaluated.

Subgroups of Adult Patients with Fanconi Anemia

The three general subgroups of adult patients with FA have both common and divergent concerns, and often require different strategies for management and follow-up. All adult patients with FA, regardless of which subgroup they are in, are at high risk for the development of head and neck squamous cell carcinoma or anogenital SCC (female patients) and require aggressive surveillance (see Chapters 5 and 7). The three subgroups of FA adult patients are summarized as follows:

Adult Patients Diagnosed in Childhood Who Have Not Had a Transplant

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 this group who develop bone marrow failure as adults may require an HCT.

Adult Patients Diagnosed in Childhood Who Have Had a Transplant

This population is increasing in number because of the increased success of HCT. The major issues facing this population are the follow-up and treatment of non-hematologic FA issues and short- and long-term complications of HCT, 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.

Adult Patients Who Are Diagnosed in Adulthood

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 [8]. Occasionally, an adult is diagnosed with FA when the family members of a newly diagnosed individual 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 [9]. Many of these patients were diagnosed as adults and very often had no, or minor, phenotypic abnormalities and normal blood counts. Mosaicism may explain some of the cases where a cancer diagnosis precedes the diagnosis of FA [9].

Transitioning to Adult Clinical Care

The transition from pediatric- to adult-oriented care is an important issue facing young adults with many 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 [10-12] that is outlined as follows:

- This transition must be seen as a process, not as an abrupt transfer of services.
- Successful transitions are often initiated during the late teenage years, and accompanied by family and patient education about the future transition [11, 12].
- Transition timing should be individualized and not dependent on age.
- Pediatric FA specialists may remain involved in long-term patient care decisions, especially regarding the screening and treatment of secondary cancers.
- Patients transplanted at larger centers may be followed in long-term survivor clinics where healthcare needs are addressed by a multi-disciplinary team.

Creating an Adult Clinical Care Plan

The adult clinical care plan should include surveillance and treatment of all aspects of FA, including:

- Preventive healthcare and wellness check-ups.
- Ongoing hematological evaluation of patients who have not undergone an HCT.
- Continuation of rigorous cancer prevention and surveillance, especially of head and neck and anogenital SCC.
- Screening for vascular and cardiac disease after HCT.
- 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.
- Complete all standard vaccinations including human papillomavirus vaccination to prevent SCC.
- Gynecological consultations to screen for and prevent cancer, to monitor menses, and to manage fertility and menopause issues.

Psychosocial Issues in Adult Patients with Fanconi Anemia

The magnitude of potential psychosocial problems has not been assessed in FA adults and should be assessed in patient cohorts in the future. However, 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 engaged in limited activities compared with their siblings [13]. In addition, rates of marriage, college graduation, employment, and health insurance coverage were all lower in FA patients in comparison to 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. Medical compliance also may become a challenge, 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.

Summary

The brief clinical guide for patients with FA is an overview of clinical recommendations provided in all other chapters in this book. It should be used as a guide only and is not intended to provide comprehensive clinical care guidelines for each unique patient with FA. Fanconi anemia is a heterogenous disease that affects all bodily systems. The complexity of the disease requires a holistic approach to wellness and treatment for each patient. Multi-disciplinary clinical care is essential for patients with FA and should be offered in a coordinated fashion by a team with expertise in FA. This is particularly important for adult patients with FA, who are quickly becoming the largest subpopulation of FA patients. Adults with FA have a unique set of clinical challenges that are still not well understood. Research on this subgroup is desperately needed in order to improve their clinical care.

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John E. Wagner, MD

Adult patient with Fanconi anemia section:
Eva Guinan, MD*
Farid Boulad, MD

**Section committee chair*

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Appendix A: Glossary and List of Abbreviations

5'-nucleotidase test: A test that measures the levels of 5'-nucleotidase, an enzyme produced by the liver.

AA: *Aplastic anemia.* A condition that occurs when the bone marrow fails to produce the proper amount and type of blood cells.

ABR: *Auditory brainstem evoked response test*. Also referred to as BAER.

aCGH: *Array comparative genomic hybridization.* A microarray technique that can detect changes (loss or gains) in DNA.

Adenocarcinoma: A type of cancer that initiates in the mucus-producing glandular cells of the body.

Agenesis: Failure of an organ to develop during embryonic development.

AK: *Actinic keratosis*. Precancerous skin lesion.

Alloimmunization: An immune response to foreign antigens after exposure to genetically different cells or tissue.

Allosensitization: A condition caused by exposure to an alloantigen that induces immunologic memory cells.

ALP: *Alkaline phosphatase*. An enzyme measured in the blood that is used to detect liver and bone disease.

Alpha-thalassemia minor: An inherited blood disorder that affects the alpha chain of hemoglobin. The minor indication reflects mild symptoms.

ALT: *Alanine aminotransferase*. An enzyme measured to assess liver function.

Amenorrhea: Absence of menstruation.

AMH: *Anti-müllerian hormone*. A hormone used as a marker for ovarian reserve.

AML: *Acute myelogenous leukemia.* A cancer of the blood and bone marrow.

Amniocentesis: A medical procedure in which amniotic fluid is removed from the uterus for testing.

ANC: *Absolute neutrophil count*. The number of neutrophils in the blood. Neutrophils are immune cells that fight infection.

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 the 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 the reproductive system.

Anoscopy: A medical procedure used to identify abnormalities inside the anus and the rectum.

Anovulatory cycles: Menstrual cycles without ovulation.

Antegrade continence enema: A procedure that empties the bowel.

Antibodies: Proteins produced by the blood that attack foreign substances, such as bacteria, viruses, and foreign tissue that the body does not recognize as part of itself.

Aphthae: Ulcers of the oral mucosa.

Aphthous stomatitis: Recurrent aphthous ulcers or canker sores that occur in the oral mucosa.

Aseptic necrosis of bone: The loss of bone primarily in the hip, knee, and shoulder joints.

AST: *Aspartate aminotransferase*. An enzyme measured to detect liver damage.

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 a transplant. ATG is also used as a therapy for aplastic anemia.

ATR: *Ataxia telangiectasia and Rad3-related protein*. A serine-threonine protein kinase that responds to DNA damage and phosphorylates multiple Fanconi anemia proteins.

Audiometric threshold: The softest level of sound a person can detect.

Autosomal dominant condition: A genetic inheritance pattern in which an affected individual has one copy of a mutant gene and one normal gene on a pair of autosomal chromosomes.

Autosomal recessive condition: A genetic inheritance pattern in which an affected individual has two copies of a mutant gene on a pair of autosomal chromosomes.

B cells: A type of white blood cell that is responsible for antibody production.

BA: *Bone age*. A test used to assess the degree of bone maturation in children.

Basophil: A type of white blood cell that is involved in allergic reactions.

BCC: *Basal cell carcinoma*. The most common type of skin cancer in the general public.

Beta-thalassemia minor: An inherited blood disorder that affects the beta chain of hemoglobin. The minor indication reflects mild signs and symptoms.

Biallelic variants: Genetic variants that are found in both copies (alleles) of the same gene.

Binucleated erythroid cells: Erythrocytes (red blood cells) that contain two nuclei.

Biopsy: A medical procedure in which a small piece of tissue is removed surgically, which is then examined under a microscope to determine whether dysplasia (pre-cancer) or cancer is present.

BMD: *Bone mineral density*. A measurement of the mineral content of bones.

BMF: *Bone marrow failure*. A condition that occurs when bone marrow fails to produce an adequate number of blood cells.

BMI: *Body mass index*. A measure of physical fitness that accounts for height and body weight.

Bone marrow: The spongy tissue inside bones that produces blood cells.

Bronchoscopy: An endoscopic procedure that allows internal visualization of the lungs.

BU: *Busulfan*. An alkylating agent used to treat chronic myelocytic leukemia.

Café au lait macules: 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 on a copy of the abnormal gene to their offspring.

Carrier frequency: The proportion of carriers in a population.

CBC: *Complete blood count*. A laboratory test that provides the number, and/or percentage, and/or characteristics of certain blood cells, primarily white cells, red cells, and platelets.

Centralization: A surgical procedure that moves and centers the wrist over the end of the ulna.

Cetuximab: An epidermal growth factor receptor inhibitor used to treat some cancers.

Cholestasis: Any condition in which the flow of bile from the liver is reduced or blocked.

Cholestatic jaundice: Yellowing of the skin and eyes due to obstructed bile flow in the liver.

Cholesterol: A sterol compound found in most tissues of the human body that is necessary for cell membranes and precursors of other steroid compounds.

Chromosome: The structure of nucleic acids and proteins that carries genetic information that is found in the nucleus of most living cells. 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 test: The gold standard test for diagnosing Fanconi anemia. This test measures the types and rates of breakages and rearrangements found in the chromosomes of cells after treatment with DNA damaging agents. It also reveals how well the chromosomes can repair themselves after injury.

Cirrhosis: Abnormal liver function resulting from long-term damage.

Cisplatin: An alkylating agent used to treat many cancers.

Clastogen: An agent that induces breaks in chromosomes.

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.

Clone: A population of cells.

CMC: *Carpometacarpal joints*. Five joints in the wrist that articulate the distal row of carpal bones and the proximal bases of the five metacarpal bones.

CMM: *Congenital mirror movements*. Intentional movements of one side of the body are mirrored by involuntary movements of the other side.

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.

CNA: *Copy number aberrations*. Deletions or amplifications in chromosomes that occur in cancer cells.

Colposcopy: A medical procedure that examines the vulva, vagina, and cervix.

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 Fanconi anemia (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 hormone produced in the adrenal glands that plays important roles in the body's stress response, immunity, metabolism of nutrients, and other processes.

C-reactive protein test: A liver function test that measures C-reactive protein, a protein produced by the liver.

CRISPR/Cas9: *Clustered regularly interspaced palindromic repeats/Cas9*. CRISPR is a gene editing technique based on the bacterial CRISPR-Cas9 antiviral defense system that can be used to edit the genomes of living organisms.

Cryopreservation: The use of very low temperatures to preserve living cells and tissues.

CsA: *Cyclosporine A*. A drug that suppresses the immune system and is used to prevent transplant rejection.

CVS: *Chorionic villus sampling*. A prenatal procedure in which a sample of the chorionic villus from the placenta is removed and tested.

CY: *Cyclophosphamide*. A drug that is used to suppress the immune system and 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 DNA damaging agent used in the chromosome breakage test.

Diabetes mellitus: A metabolic disease in which the body's ability to produce or respond to the hormone insulin is impaired.

DNA ICLs: *DNA interstrand crosslinks*. Crosslinked DNA that occurs when exogenous or endogenous agents react with two nucleotides of DNA, forming a covalent linkage between them.

Duodenal atresia: A condition in which 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.

Dysmorphology: The study of human congenital malformations and syndromes.

Dyspareunia: Pain during sexual intercourse or other sexual activity that involves vaginal penetration.

Dysphagia: Difficulty swallowing.

Dysuria: Painful urination.

EA: *Esophageal atresia*. A congenital medical condition in which the esophagus does not develop properly; frequently, the lower end of the esophagus is incomplete or blocked and does not allow food to pass 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 or lymphoma.

Echocardiogram: A non-invasive imaging procedure used to assess heart function.

EGFR: *Epidermal growth factor receptor*. A protein that is a receptor for members of the epidermal growth factor family of ligands.

Electrocardiogram: A test that records the electrical signals of the heart.

Encopresis: Involuntary leakage of stool.

Endocarditis: Infection of the endocardium, which is the inner lining of the heart chambers and valves.

Endocrine: Relating to the body system that produces hormones.

Endoscopy: Insertion of a long, thin tube that is used to observe an internal organ.

Enteral supplementation: Supplemental feeding via feeding tube.

Erythrocytes: Red blood cells that carry oxygen to the body's tissues.

Erythroplakia: Also known as *erythroplasia*. A reddened patch in the oral or genital mucosa that is considered a precancerous lesion.

Erythropoietin: A hormone that plays a key role in the production of red blood cells.

Esophageal stenosis: Narrowing of the esophagus.

Esophagitis: Inflammation or irritation of the esophagus.

Esophagoscopy: Examination of the esophagus by means of a flexible endoscope.

Estrogens: Steroid hormones that promote the development and maintenance of female characteristics of the body.

Exons: Segments of DNA that contain information needed to make proteins.

Extracorporeal photopheresis: A procedure used to treat chronic graft-versus-host disease 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 ability of cells in the body to repair DNA. Fanconi anemia can lead to bone marrow failure and cancer.

FAAP: *Fanconi anemia core complex associated proteins*. Proteins that play a role in the FA pathway that have not been ascribed to an FA disease phenotype.

Ferritin: A blood 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 to separate, count, and evaluate cells with distinct characteristics; used to diagnose blood cancers and other conditions.

FLU: *Fludarabine*. A drug used to suppress the immune system before hematopoietic cell transplant and for treating some cancers.

Fluoroscopy: A type of medical imaging that uses continuous X-ray images.

Fructosamine test: A laboratory test that measures the total amount of fructosamine, a glycated protein, in the blood.

FSH: *Follicle stimulating hormone*. A hormone produced by the pituitary gland that stimulates the growth of ovarian follicles in females and sperm-producing cells in males.

FT4: *Free thyroxine*, also called *Free T4*. Thyroxine is a hormone produced by the thyroid that plays a role in several bodily functions, including growth and metabolism. It exists in two forms in the blood: T4 that is bonded to protein in the blood and free T4. Free T4 is the type available for use by the body's tissues.

Gastric accommodation: The gastric accommodation reflex allows the proximal stomach to have an appropriate gastric volume to accommodate an ingested meal.

Gastrojejunostomy: A surgical procedure to create an anastomosis from the stomach to the middle part of the intestine.

Gastrostomy tubes: A feeding tube inserted through the abdomen that delivers nutrition directly to the stomach.

G-Banding: A laboratory technique used to stain and visualize chromosomes for analysis.

G-CSF: *Granulocyte colony-stimulating factor*. A growth factor drug that stimulates the bone marrow to release stem cells.

GERD: *Gastroesophageal reflux disease*. A chronic digestive disorder of persistent acid reflux that occurs when the lower esophageal sphincter is weak or relaxes inappropriately, allowing stomach acid to flow up into the esophagus.

GGT: *Gamma-glutamyl transpeptidase*. An enzyme that is found in many organs throughout the body. A GGT blood test can indicate liver damage.

GHD: *Growth hormone deficiency*. A metabolic condition caused by insufficient levels of growth hormone in the body.

Gingivitis: Inflammation of the gums, or gingiva.

Glucose: A sugar that provides fuel for human cells to function.

GM-CSF: *Granulocyte-macrophage colony-stimulating factor*. A hematopoietic growth factor and immune modulator that has profound effects on the functional activities of circulating leukocytes and stimulates multipotent progenitor cells. It is used clinically to treat neutropenia in patients undergoing chemotherapy as well as after bone marrow transplant

GnRH: *Gonadotropin releasing hormone*. A hormone regulator of the secretion of follicle stimulating hormone (FSH) and luteinizing hormone from the anterior pituitary.

Gonadotoxic therapy: Treatments, such as chemotherapy and radiation, that impair reproductive function.

Granulocyte: White blood cell (neutrophil, basophil, or eosinophil).

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

GvHD: *Graft-versus-host disease*. Complication of allogeneic stem cell transplantation where donated bone marrow or peripheral blood stem cells interpret the recipient's body as foreign and attack the body.

Halitosis: Unpleasant breath odor.

Haploidentical transplant: A half matched transplant from a biological parent or sibling donor.

HAT: *Hearing assistive technology*. Technology systems and/or devices (frequently digital or wireless) that help people with hearing, voice, speech, or language disorders to communicate more effectively in their daily lives.

HbA1c: *Glycosylated hemoglobin*. Hemoglobin bound glucose that is measured to monitor control of diabetes over time.

HbF: *Fetal hemoglobin*. The main blood protein that carries oxygen in the fetus.

HCC: *Hepatocellular carcinoma*. Liver cancer.

HCT: *Hematopoietic cell transplantation*. An allogeneic HCT is a procedure in which a donor's bone marrow stem cells or umbilical cord blood are used to replace diseased bone marrow stem cells of a recipient.

HDL: *High-density lipoprotein*. A lipoprotein that removes cholesterol from the blood and carries it back to the liver to be flushed from the body. Commonly known as the "good" cholesterol because higher levels of HDL are associated with reduced risk of atherosclerosis and heart disease.

Hemizygous variant: Having only one copy of a gene present in diploid cells.

Hepatic fibrosis: Imbalance between production and dissolution of extracellular matrix in the liver caused by injury that leads to build up of scar tissue.

Hepatic transaminases: Enzymes measured on a liver function test. Elevated levels may indicate liver damage.

Hepatitis: Inflammation of the liver.

Hepatocellular adenoma: Benign liver tumor.

Heterozygous: Having two different alleles of a particular gene or genes.

HgB: *Hemoglobin*. A red blood cell protein that transports oxygen throughout the body via the bloodstream.

HLA: *Human leukocyte antigen*. A protein on the surface of cells that helps the body to 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."

HNSCC: *Head and neck squamous cell carcinoma*. Cancers that develop in the mucous membranes of the oral cavity, oropharynx, hypopharynx, and larynx.

Homozygous: Having two identical alleles in a particular gene or genes. 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*. A virus that can cause warts and cancer.

HR: *Homologous recombination proteins*. Proteins that participate in homologous repair of DNA.

HSC: *Hematopoietic stem cells*. Rare blood cells in bone marrow that give rise to all other blood cells during a process called hematopoiesis.

Hydronephrosis: Swelling of the kidneys; occurs when urine accumulates and is unable to make its way out of the kidneys.

Hyperestrogenism: Higher than normal levels of estrogen.

Hypergonadotropic hypogonadism: Failure of the testes to produce sufficient quantities of testosterone.

Hyperpigmentation: A condition in which patches of skin are darker in color than normal surrounding skin.

Hypertransaminasemia: Elevated levels of the liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST).

Hypoestrogenism: Lower than normal levels of estrogen.

Hypogenitalism: Diminished functional activity of the genitals.

Hypomagnesemia: Lower than normal blood magnesium levels.

Hypoparathyroidism: A state of decreased secretion or activity of parathyroid hormone.

Hypopharyngeal cancer: Disease in which malignant cells form in the tissues of the hypopharynx.

Hypopigmentation: A condition in which patches of skin are lighter in color than normal surrounding skin.

Hypopituitarism: Diminished hormone secretion by the pituitary gland.

Hypoplasia: Under- or incomplete development of an organ or tissue in the body.

Hypothyroidism: A condition caused by low levels of the thyroid hormone.

IFAR: *International Fanconi Anemia Registry*. A registry that serves as the central repository for clinical, hematologic, and genetic information on patients with Fanconi Anemia, and cellular material from patients and their families. This growing clinical database supports the study of the full spectrum of the diverse features of the disease. Established at The Rockefeller University in 1982.

IGF-1: *Insulin-like growth factor 1*. The hormone that mediates the growth promoting effect of growth hormone (GH). Elevated levels indicate sustained production of GH.

IGFBP-3. *IGF-binding protein* 3. The protein that binds IGF-1. Elevated levels indicate high levels of growth hormone.

Impaired glucose tolerance: An abnormal state when blood glucose is raised beyond normal levels, but not high enough to warrant a diabetes diagnosis.

Imperforate anus: A physical defect in which the opening to the anus is missing or blocked.

In cis variant: Variants located together on the same copy of a given gene.

In trans variant: Variants situated on opposite copies of the same gene.

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.

Jejunal feeds: Feeding directly into the small intestine.

Jejunostomy: An operative procedure in which a feeding tube is placed into the proximal jejunum.

Laryngeal cancer: Disease in which malignant cells form in the tissues of the larynx.

Laryngeal edema: Swelling of the larynx.

LDL: *Low-density lipoprotein*. A lipoprotein that delivers fat molecules to cells throughout the body. Commonly known as the "bad" cholesterol because higher levels of LDL have been associated with the progression of atherosclerosis and blockage of the arteries.

Leukemia: A bone marrow cancer characterized by an uncontrolled increase in white blood cells (leukocytes).

Leukoplakia: White patches of epithelium in the oral cavity.

LFT: *Liver function tests*. A set of blood tests used to help diagnose and monitor liver function, infection, damage, or disease by measuring the levels of certain enzymes and proteins in the blood. Common LFTs include: alanine transaminase (ALT); aspartate transaminase (AST); alkaline phosphatase (ALP); albumin and total protein; bilirubin; gamma-glutamyltransferase (GGT); L-lactate dehydrogenase (LD); and prothrombin time (PT).

Lichen planus: A chronic inflammatory skin condition affecting the skin and mucosal surfaces.

Lichen sclerosis: A chronic condition that affects the skin of the genital and anal areas. May increase the risk of cancer.

Lymphocyte: A type of white blood cell that fights infection by producing antibodies and other protective substances. There are two types of lymphocytes: B-cells and T-cells.

Macrocytosis: Term used to describe red blood cells that are larger than normal.

Macrophage: A type of white blood cell that helps to destroy invading micro-organisms.

MDS: *Myelodysplastic syndrome*. The presentation of a set of health conditions that develop when the myeloid class of blood cells are not present in sufficient numbers in the bone marrow.

Megaduodenum: Congenital or acquired dilation and elongation of the duodenum.

Melanocytic nevi: Moles.

Melanoma: An aggressive form of skin cancer.

Menarche: The first occurrence of menstruation.

Menopause: The time that marks the end of menstrual cycles; diagnosed after 12 months without a menstrual period.

Menorrhagia: Heavy menstrual bleeding.

Metabolic syndrome: A cluster of conditions, including high blood pressure, high blood sugar, high triglycerides, and low HDL cholesterol, that occur together and increase the risk of heart disease, stroke, and diabetes.

Microcephaly: Smaller than normal head circumference.

Microdentia: Small teeth.

Micrognathia: Undersized lower jaw.

MLPA: *Multiplex ligation-dependent probe amplification*. An efficient and sensitive genomic testing technique for identifying large deletions of DNA sequence as part of the FA testing algorithm.

MMC: *Mitomycin C*. A chemotherapy agent used in the chromosome breakage test.

MMF: *Mycophenolate mofetil*. A drug used to suppress the immune system in patients who receive transplants.

MRI: *Magnetic resonance imaging*. An imaging technique used for visualizing internal organs.

MTX: *Methotrexate*. A chemotherapy drug used to treat leukemia and certain types of cancer of the breast, skin, head and neck, or lungs.

Mucositis: A condition that causes pain and inflammation on the surface of the mucous membrane.

Myocardium: The muscular middle layer of the wall of the heart.

Nasogastric tube: A flexible tube that is passed through the nose and down through the nasopharynx and esophagus into the stomach.

Nasojejunal tube: A flexible tube that is passed through the nose and into the jejunum.

Nasopharyngeal carcinoma: Disease in which malignant cells develop in the tissue of the nasopharynx.

Neutropenia: A health condition characterized by abnormally low levels of neutrophils in the blood.

Neutropenic ulcers: Lesions of the oral mucosa commonly encountered in patients receiving intensive myelosuppressive chemotherapy for diseases such as acute leukemia.

Neutrophils: A type of white blood cell that fights infection and helps heal damaged tissue.

Odynophagia: Painful swallowing.

OGTT: *Oral glucose tolerance test*. A blood test that measures the body's response to sugar. Variations of the test are commonly used to screen for type 2 diabetes and gestational diabetes.

Oligomenorrhea: Infrequent menstrual periods.

Opportunistic infection: A type of infection common in immune-compromised patients who are unable to fight off microbes that do not normally cause disease in humans.

Oropharyngeal cancer: Disease in which malignant cells develop in the tissues of the oropharynx.

Osteopenia: Lower-than-normal bone density. Often a precursor to osteoporosis.

Osteoporosis: A disease characterized by mineral and protein depletion in bones that leads to thinning and brittle bones that break easily.

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, also known as cervical cytology testing, used to detect cervical cancer and precancerous lesions.

Parenteral nutrition: Supplemental feeding via intravenous infusion.

PDT: *Photodynamic therapy*. Treatment that combines light and a photosensitizing drug to destroy precancerous and cancerous cells.

Periodontitis: A severe gum infection (gum disease) that can lead to tooth loss and other serious health conditions.

Petechiae: Small areas of bruising.

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.

PHENOS: The acronym for the grouping of major phenotypic features common to individuals with FA, including skin Pigmentation, small Head, small Eyes, central Nervous system, Otology, and Short stature.

PLT: *Platelets*. Disc-shaped fragments of cells that circulate in the bloodstream and help promote clotting to stop or prevent bleeding.

POI: *Primary ovarian insufficiency*. Premature ovarian failure.

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 of a single disease.

Pouce flottant: A so-called "floating" thumb or residual digit 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 may be separate digits.

Progesterone: A female sex hormone.

PSIS: *Pituitary stalk interruption syndrome*. A rare congenital anatomical defect of the pituitary gland characterized by a very thin or "interrupted" pituitary stalk; an ectopic or absent posterior pituitary; and aplasia or hypoplasia anterior pituitary, with permanent deficit of growth hormone (GH).

PT-Cy: *Post-transplant cyclophosphamide*. A treatment strategy following hematopoietic cell transplantation to reduce the occurrence of complications, such as graft-versus-host-disease and graft rejection, particularly in patients whose donors are not fully HLA-matched.

Purpura: Large areas of bruising.

Radialization: A surgical procedure to realign the bones of the wrist.

Radiosensitivity: Relative susceptibility of cells, tissues, organs, and organisms to ionizing radiation.

Radius: One of the two long bones in the forearm. The radial bone lies laterally and parallel to the ulna; extends from the lateral side of the elbow to the thumb side of the wrist; and pivots around the ulna to produce movement at the proximal and distal radio-ulnar joints.

RB: *Retinoblastoma gene*. The gene that encodes for the tumor suppressor protein, pRB.

Recessive: A genetic mutation is recessive if an individual must inherit two copies of the mutant gene to express the disease. Individuals with one mutant and one normal gene appear normal. They are called "heterozygotes" or "carriers."

Recto-perineal fistula: A type of anorectal malformation in which the anus is not present and the rectum, instead, connects to the perineum.

Renal dysplasia: Abnormal formation of the kidney, along with irregular cysts.

ROS: *Reactive oxygen species*. Oxygen containing radicals that can cause tissue damage.

SCC: *Squamous cell carcinoma*. A type of cancer that is derived from squamous cells. Commonly found on the skin, oral cavity, and the anogenital region.

Serostatus: The presence or absence of a serological marker in the blood.

SGA: *Small for gestational age*. A term used to describe babies who measure smaller than usual in weight for the number of weeks of pregnancy, typically with birthweights below the 10th percentile for infants of the same gestational age.

Short bowel syndrome: A condition that occurs when a large segment of the small intestine is non-functional or has been surgically removed causing malabsorption of nutrients.

SIL: *Squamous intraepithelial lesion*. Abnormal growth of squamous cells on the cervix.

SNP arrays: *Single nucleotide polymorphism arrays*. A type of DNA microarray used to detect polymorphisms within a population.

Somatic stem cell mosaicism: Spontaneous correction or reversion of an inherited variant to a normal genetic status in a stem cell that then repopulates the bone marrow with unaffected cells.

SS: *Sweet's syndrome*; also called *acute neutrophilic dermatosis*. A rare skin condition which presents as painful red plaques or nodules.

Stadiometer: A piece of medical equipment used for measuring human height.

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 uses gene therapy 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.

STI: *Sexually transmitted infection*. An infection transmitted predominantly through intimate skin-to-skin or sexual contact, though some also can be spread through non-sexual means such as via blood or blood products, or from mother to child during pregnancy and childbirth. More than 30 different bacteria, viruses, and parasites are known to be transmitted through sexual contact. Some can be treated and/or cured, some cannot.

Supernumerary teeth: Teeth that appear in addition to the normal number of teeth. Children typically have a full set of 20 baby teeth by three years of age. Most adults have a full set of 32 adult teeth by age 21.

T4: *Thyroxine*. A hormone secreted by the thyroid gland.

T cells: White blood cells that play a key role in the immune response by searching out and destroying material that is considered "foreign."

TALENs: *Transcription activator-like effector nucleases*. Restriction enzymes engineered to cleave specific regions of DNA.

TAR: *Thrombocytopenia absent radius syndrome*. A disorder characterized by absence of a radius in each forearm, short stature, and thrombocytopenia.

Tardive dyskinesia: A neurological disorder characterized by involuntary and abnormal movements of the jaw, lips and tongue, including facial grimacing, sticking out the tongue, and sucking or fish-like movements of the mouth.

TBG: *Thyroid hormone binding globulin*. A binding protein that transports thyroid hormones.

TBI: *Total body irradiation*: Radiation therapy to the entire body used in some hematopoietic cell transplant procedures.

TEF: *Tracheoesophageal fistula.* An abnormal passage between the esophagus and the trachea that may result in food from the esophagus crossing into the airways or air entering the esophagus.

Thrombocytopenia: Low platelet count.

Transaminitis: Also called *hypertransaminasemia.* A condition characterized by high levels of liver enzymes called transaminases.

Transferrin: A binding protein that transports iron in the blood.

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.

Trismus: Reduced opening of the mouth due to spasm of the jaw muscles.

TSH: *Thyroid stimulating hormone*. A hormone produced by the anterior pituitary and primary stimulus for thyroid hormone production.

UCB: *Umbilical 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.

UCL: *Ulnar collateral ligament*. A ligament on the inside of the elbow.

USP1: *Ubiquitin specific peptidase 1*. A protein that regulates proteins by removing ubiquitin substrates.

UV: *Ultraviolet light*. A type of electromagnetic radiation that covers the wavelength range 100-400 nm, which is a higher frequency and lower wavelength than visible light. Ultraviolet light is divided into three bands: UVA (315-400 nm), UVB (280-315 nm), and UVC (100-280 nm). In humans, increased exposure, particularly to high-frequency UVA, can damage living tissue and cause skin cancers, cataracts, and immune system damage.

UVA: *Ultraviolet A*. A subtype of ultraviolet radiation that causes premature aging and wrinkling of the skin.

UVB: *Ultraviolet B*. A subtype of ultraviolet radiation that induces DNA damage and is the major cause of skin cancer.

VACTERL: The acronym for 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.

VACTERL-H: The acronym for a group of classical congenital abnormalities including Vertebral, Anal, Cardiac, Tracheo-esophageal fistula, Esophageal atresia, Renal defects, upper Limb defects, and Hydrocephalus.

Vaginal stenosis: Narrowing and shortening of the vagina.

Venous thromboembolism: A condition in which a blood clot forms in the leg, groin or arm.

Verruca vulgaris: Warts.

VUS: *Variants of unknown significance*. A form of a gene identified through sequencing in which the significance on health and function is not known.

WES: *Whole exome sequencing*. A genome sequencing technique that analyzes all protein-coding regions of the genome.

WGS: *Whole genome sequencing*. A genome sequencing technique that analyzes the entire genome.

WRN: *Werner syndrome ATP-dependent helicase complex*. Helicase involved in DNA repair that also has exonuclease activity.

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.

Xerostomia: Dry mouth syndrome.

ZFN: *Zinc finger nucleases*. Restriction enzymes used in targeted gene editing of DNA.

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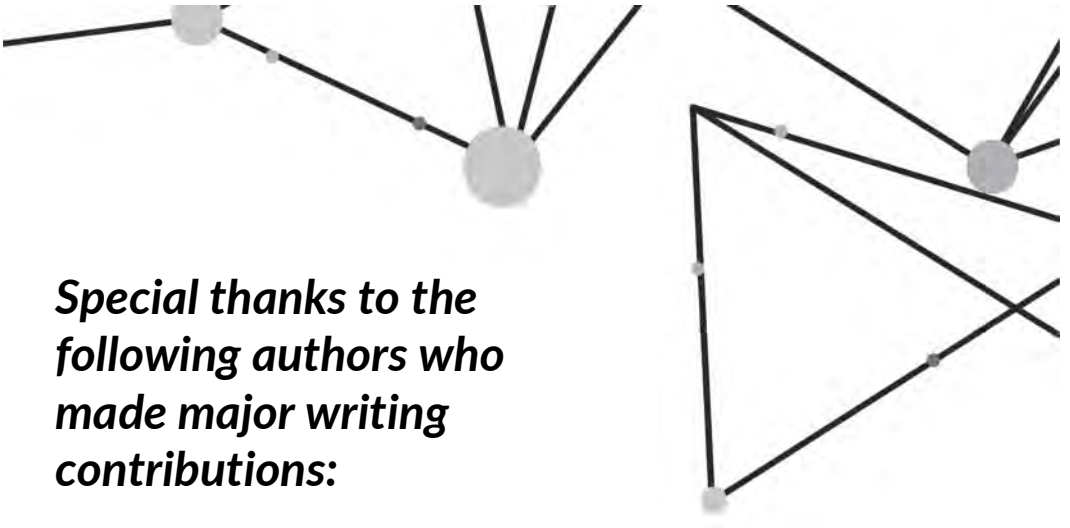


Special thanks to the following authors who made major writing contributions:

Kalejaiye Adedoyin, MD
Howard University Hospital
2041 Georgia Avenue, NW
Towers Suite 4200
Washington, DC 20060
United States
202-865-1432
adedoyin.kalejaiye@howard.edu

Blanche P. Alter, MD, MPH, FAAP
Clinical Genetics Branch
Division of Cancer Epidemiology and Genetics National Cancer Institute
9609 Medical Center Drive
Room 6E452
Rockville, MD 20850
United States
alterb@mail.nih.gov

Farid Boulad, MD
MSK Kids
Memorial Sloan Kettering
1275 York Avenue
New York, NY 10065
United States
212-639-6684
bouladf@MSKCC.ORG

Lesley Breech, MD
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, OH 45229
United States
513-636-4200
gynecology@cchmc.org

Carmen C. Brewer, PhD
Otolaryngology Branch
National Institute on Deafness and Other Communication Disorders
10 Center Drive, Room 5C422
Bethesda, MD 20782
United States
301-496-5294
brewerc@nidcd.nih.gov

Maria Cancio, MD
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10065
United States
212-639-2446
canciom@mskcc.org

Mercedes Castiel, MD
University of Chicago Medicine
5841 S. Maryland Avenue
Chicago, IL 60637
United States
773-834-0742
Mercedes.castiel@uchospitals.edu

Stephanie Cizek, MD
Pediatric and Adolescent Gynecology
Stanford Children's Health
Lucile Packard Children's Hospital
300 Pasteur Drive, Dept of OB/GYN
Stanford, CA 93405
United States
408-426-5590
scizek@stanford.edu

Roger Cornwall, MD
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, OH 45229
United States
513-636-7319
roger.cornwall@cchmc.org

Stella Davies, MBBS, PhD, MCRP
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, OH 45229
United States
513-636-1371
stella.davies@cchmc.org

Christen L. Ebens, MD, MPH
University of Minnesota
Pediatric BMT Mayo A528
420 Delaware Street SE
Minneapolis, MN 55455
United States
612-626-2961
ebens012@umn.edu

David K. Fiaschetti, DDS
Oral Surgery & Dental Implant Center, Inc.
65 W Main Road
Middletown, RI 02842
United States
401-848-0070
dmjfiaschetti@juno.com

Moisés Ó. Fiesco-Roa, MD, MSc
Clinical Genetics Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
Laboratorio de Citogenética
Instituto Nacional de Pediatría
Programa de Maestría y Doctorado en Ciencias Médicas
Universidad Nacional Autónoma de Mexico
Insurgentes Sur 3700 Letra C, Insurgentes Cuicuilco
Coyoacán, Mexico City 04530
Mexico
+52 5522631758
fiescoroa@facmed.unam.mx

Lynn Frohnmayer, MSW
Co-founder, board member
Fanconi Anemia Research Fund
545 Spyglass Drive
Eugene, OR 97401
United States
541-556-4321
lfrohn@gmail.com

Neelam Giri, MD
National Cancer Institute
9609 Medical Center Drive
MSC 9772
Rockville, MD 20850
United States
240-276-7256
girin@mail.nih.gov

Joel Greenberger, MD
University of Pittsburgh School of Medicine
5117 Centre Avenue
Pittsburgh, PA 15213
United States
412-624-0253
greenbergerjs@upmc.edu

Eva Guinan, MD
Dana-Farber Cancer Institute
Pediatric and Radiation Oncology
450 Brookline Avenue
Boston, MA 02215
United States
617-632-4932
eva_guinan@dfci.harvard.edu

Betsy Hirsch, PhD, FACMG
University of Minnesota
MMC 609 Mayo 8609
420 Delaware Street SE
Minneapolis, MN 55455
United States
612-273-4952
hirsc003@umn.edu

Jennifer Huang, MD
Oregon Health & Science University
700 S.W. Campus Drive
Portland, OR 97239
United States
503-346-0640
jennifer.huang@childrens.harvard.edu

Krystal M. Jones, MD
Boston's Children's Hospital
300 Longwood Avenue, Fegan, 6th Floor
Boston, MA 02115
United States
617-355-6117
Krystal.Jones@childrens.harvard.edu

Roopa Kanakatti Shankar, MD, MS
Assistant Professor of Pediatrics
Children's National Hospital, The George Washington University School of Medicine
111 Michigan Avenue NW
Washington, DC 20012
United States
202-476-2121
Roopa.shankar@childrensnational.org

Jennifer A. Kennedy, MS, CGC
Memorial Sloan Kettering Cancer Center
222 East 70th Street
New York, NY 10021
United States
646-888-4102
kennedj1@mskcc.org

Bradley Kesser, MD
UVA Health
ENT Clinic - 2nd Floor, Suite 2200
415 Ray C Hunt Drive
Charlottesville, VA 22903
United States
434-924-5700
BWK2N@hscmail.mcc.virginia.edu

H. Jeffrey Kim, MD
Georgetown University Hospital
Gorman Building, 1st Floor
3800 Reservoir Road NW
Washington, DC 20007
United States
202-444-7035
HK7@gunet.georgetown.edu

Kelly King, PhD, ABPP-CN
University of Minnesota
Clinical Behavioral Neuroscience
Voyager Pediatric Specialty Clinic
2512 S. 7th Street, First Floor, Suite R103
Minneapolis, MN 55454
United States
kingx780@umn.edu

Scott H. Kozin, MD
Shriners Hospital for Children
Lewis Katz School of Medicine at
Temple University
Sidney Kimmel Medical College at
Thomas Jefferson University
3551 N Broad Street
Philadelphia, PA 19140
United States
215-430-4000
SKOZIN@shrinenet.org

David Kutler, MD
Weill Cornell Medicine
1305 York Avenue
New York, NY 10021
United States
646-962-4323
dik2002@med.cornell.edu

Jeffrey M. Lipton, MD, PhD
Feinstein Institutes for Medical Research
Steven and Alexandra Cohen
Children's Medical Center of New
York
269-01 76th Avenue, Suite 255
New York, NY 11040
United States
718-470-3460
jlipton@northwell.edu

Margaret L. MacMillan, MD, MSc, FRCPC
Division of Blood and Marrow
Transplantation
University of Minnesota Medical School
420 Delaware Street SE
Minneapolis, MN 55455
United States
612-626-2961
macmi002@umn.edu

Kelsey McIntyre, PhD, FACMG
University of Minnesota
MMC 609 Mayo
420 Delaware Street SE
Minneapolis, MN 55455
United States
612-625-5468
mcintyrk@umn.edu

Melissa Merideth, MD
National Institutes of Health
10 Center Drive, Building 10, 10c103
MSC 1851
Bethesda, MD 20892
United States
301-496-9101
mmeridet@mail.nih.gov

Vinod Nambudiri, MD, MBA
Dana-Farber Cancer Institute
Brigham and Women's Hospital
211 Longwood Avenue
Boston, MA 02115
United States
617-632-6171
vnambudiri@bwh.harvard.edu

Susan Olson, PhD, FACMG
Oregon Health & Science University
3181 SW Sam Jackson Park Road
Portland, OR 97239
United States
855-535-1522
olsonsu@ohsu.edu

Mark Osborn, PhD
University of Minnesota
Pediatric BMT Masonic Cancer Research Building
MCRB 460E
425 East River Parkway
Minneapolis, MN 55455
United States
612-626-2961
osbor026@umn.edu

Zora R. Rogers, MD
University of Texas Southwestern
Children's Health, Dallas
5323 Harry Hines Boulevard
Dallas, TX 75390
United States
214-648-3896
zora.rogers@utsouthwestern.edu

Susan R. Rose, MD
Cincinnati Children's Hospital Medical Center
3333 Burnet Avenue
Cincinnati, OH 45229
United States
513-636-4744
mslrose4@gmail.com

Philip S. Rosenberg, PhD
National Cancer Institute
9609 Medical Center Drive
Room 7E130
Rockville, MD 20850
United States
240-276-7312
rosenbep@mail.nih.gov

Arturo Saavedra, MD, PhD, MBA
UVA Health
Dermatology - Third Floor
1221 Lee Street
Charlottesville, MD 22903
United States
434-924-5115
AS4DA@hscmail.mcc.virginia.edu

Sarah Jane Schwarzenberg, MD
University of Minnesota
Pediatric Gastroenterology, Hepatology, & Nutrition
6th Floor East Building MB616
2450 Riverside Avenue
Minneapolis, MN 55454
United States
612-624-1133
schwa005@umn.edu

Bhuvanesh Singh, MD, PhD
Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, NY 10065
United States
212-639-2024
singhb@mskcc.org

Agata Smogorzewska, MD, PhD
The Rockefeller University
1230 York Avenue
New York, NY 10065
United States
212-327-7850
asmogorzewska@rockefeller.edu

Isis Sroka, PhD
Fanconi Anemia Research Fund
360 E 10th Avenue, Suite 201
Eugene, OR 94401
United States
541-687-4658
isis@fanconi.org

Constantine A. Stratakis, MD, D(med)Sci, PhD(hc)
Section on Genetics & Endocrinology
Eunice Kennedy Shriver National Institutes of Child Health & Human Development (NICHD)
National Institutes of Health (NIH)
10 Center Drive, NIH Clinical Research Center,
Room 1-3330 (Lab 1-3216), East Laboratories
Bethesda, MD 20892
United States
301-4962315
stratakc@mail.nih.gov

Pamela Stratton, MD
Office of the Clinical Director
Intramural Research Program
National Institute of Neurological Disorders and Stroke (NINDS)
10 Center Drive
Building 10, Room 7-4647
Bethesda, MD 20892
United States
301-435-4068
strattop@mail.nih.gov

Rebecca Tryon, MS, MA, CGC
M Health Fairview
321 Church Street
6-160 Jackson Hall
Minneapolis, MN 55455
United States
612-624-1510
rtryon1@fairview.org

Ann Van Heest, MD
University of Minnesota
2450 Riverside Avenue S, Suite R200
Minneapolis, MN 55455
United States
612-273-1290
aprahl@umn.edu

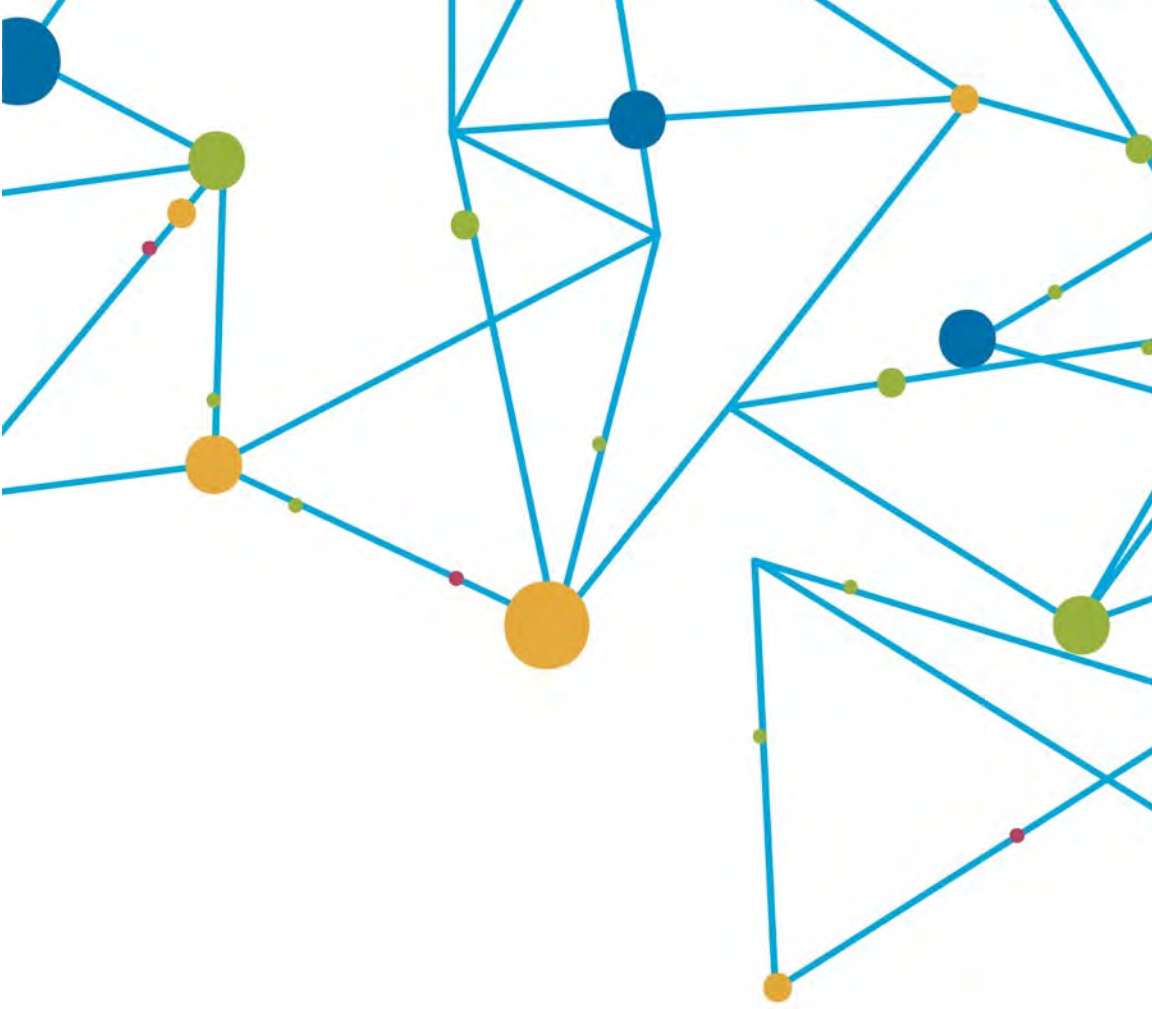
Carter Van Waes, MD
National Institutes of Health
Division of Intramural Research
Building 10, Room 7N240D
10 Center Drive
Bethesda, MD 20814
United States
301-402-4216
vanwaesc@nidcd.nih.gov

John Wagner, MD
University of Minnesota
Pediatric BMT 660 MCRB
425 East River Road
Minneapolis, MN 55455
United States
612-626-2961
wagne002@umn.edu

Karen L. Wilber, AuD
Boston's Children's Hospital
Department of Otolaryngology and
Communicative Enhancement
333 Longwood Avenue
Boston, MA 02115
United States
781-216-2999
karen.wilber@childrens.harvard.edu

William William, MD
Hospital BP, a Beneficencia Portuguesa
de Sao Paulo
Rua Martiniano de Carvalho, 965
Sao Paulo, Sao Paulo 01323-001
Brazil
+55-11-35056302
williamwilliamjr@gmail.com

Christopher Zalewski, PhD
National Institutes of Health
Otolaryngology Branch
Building 10, Room 5c422a
10 Center Drive
Bethesda, MD 20814
United States
301-596-5145
zalewski@nidcd.nih.go



Fanconi Anemia Clinical Care Guidelines, Fifth Edition, is a publication of the Fanconi Anemia Research Fund. The fifth edition is a revision of the fourth edition published in 2014. The contributing authors are physicians or clinical care providers with expertise in treating patients with Fanconi anemia (FA). The fifth edition provides evidence-based recommendations from published peer-reviewed medical literature and is geared toward clinical providers as the primary intended audience. Patients and families who wish to secure optimal treatment by improving their understanding of FA may also benefit from this edition.

The fifth edition starts with a brief summary of the molecular mechanisms of the FA DNA repair pathway and the diagnostic testing process for FA. Subsequent chapters examine more specific health issues faced by people with FA, including hematologic issues, squamous cell carcinoma, oral and dental care, gynecologic care, dermatologic care, gastrointestinal issues, endocrine disorders, hearing and ear issues, and skeletal abnormalities. The guidelines conclude with a summary of clinical care recommendations for patients with FA.

About the Fanconi Anemia Research Fund

The Fanconi Anemia Research Fund (FARF) is the world leader in advancing research for better treatments and a cure for Fanconi anemia (FA). Founded in 1989 by parents Lynn and David Frohnmayer, FARF's mission is to find better treatments and a cure for Fanconi anemia and to provide education and support services to affected families worldwide.

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FANCONI ANEMIA
RESEARCH FUND
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