National MPS Society

Support for Families. Research for a Cure.

Morquio Syndrome

A Guide to Understanding

MPS IV

Table of Contents

The National MPS Society exists to find cures for MPS and related diseases. We provide hope and support for affected individuals and their families through research, advocacy, and awareness of these diseases.

Pictured on cover: (top) Keller, (bottom) Sherri, Melissa, Fanny
Pictured on right: (top to bottom) Dawn, Jayce, Annabelle

What is MPS IV?

Mucopolysaccharidosis IV (MPS IV; pronounced "mew·ko·pol·ee·sak·ah·ri·doh·sis four") is a rare genetic disorder characterized by short stature and severe bone disease. It is also known as Morquio syndrome, named after Dr. Morquio, a pediatrician in Montevideo, Uruguay. In 1929, Dr. Morquio described a family of four children affected by this condition. The same year, Dr. Brailsford from Birmingham, England, also described the same characteristics. Consequently, it is sometimes known as Morquio-Brailsford syndrome.

KIMBREL

MPS IV belongs to a group of inherited metabolic diseases called mucopolysaccharidoses (MPSs), a subgroup of lysosomal storage disorders (LSDs). MPS is a disorder in which at least one long-chain sugar carbohydrate called glycosaminoglycan (GAG; pronounced "gly·cose·a·mee·no·gly·can" and formerly called mucopolysaccharide) accumulates in the lysosome, an organelle within cells. There are seven distinct clinical types of MPS, some of which have several subtypes.

If you are a parent of a newly diagnosed child, or someone who has been diagnosed with MPS IV yourself, it is important to remember that there is a wide spectrum of severity in how MPS IV shows up and progresses:

- It can be a severe, rapidly progressing form that manifests between 1 and 3 years of age and typically presents with knock-knees and prominent breastbone; OR
- It can be a slow progressing (attenuated) form that usually manifests in adolescence and typically presents with hip pain and stiffness.

Even children from the same family may be affected differently. A range of possible problems is described in this booklet; however, this does not mean that you or your child will experience all of the symptoms described. Some complications arise early in childhood, while others present much later or may never occur. As yet, there is no cure for individuals affected by MPS IV, but there are ways to manage the challenges they will have and to ensure the best quality of life.

> The word "mucopolysaccharide" can be broken down into its parts: "Muco" refers to the thick, jelly-like consistency of the molecules; "poly" means many; and "saccharide" is a general term for a sugar molecule (think of saccharin).

What causes MPS IV?

In healthy individuals, GAGs are used in the building of bones, cartilage, skin, tendons, and many other tissues in the body. For instance, the slippery synovial fluid that lubricates your joints contains GAGs, as does the rubbery cartilage in your joints. All tissues have some of this substance as a normal part of their structure. As more GAGs are produced, older GAGs get broken down; this is the normal cycle of events that maintains a healthy balance in the body. However, when this cycle does not function properly and GAGs are not broken down, they accumulate within the cells. This malfunction results in progressive, sometimes permanent, cellular damage that affects the individual's physical abilities, proper functioning of organs and systems, appearance, and, in some cases, cognitive development.

MPS IV is caused by accumulation of a particular GAG called keratan sulfate (KS), which is primarily found in the bones and connective tissue. The KS remains stored inside cells in the body. The GAG itself is not toxic, but the amount of it and the effect of storing it in the body lead to many physical problems. Babies may show little sign of the disease, but as more and more GAGs accumulate, symptoms start to appear as a result of progressive damage.

> MPS IV is caused by accumulation of the GAG keratan sulfate (KS). Consuming sugar or foods normally eaten will not affect GAG accumulation.

KIANNA

How is MPS IV diagnosed?

As stated previously, MPS IV is one type of MPS, which are a subgroup of LSDs. As such, although each MPS type has its own specific combination of symptoms, there are many symptoms common to all MPS types. In addition, since MPS IV has a range of disease severity, the symptoms of the disease also vary in severity. These issues make it complicated to diagnose the disease.

KAYLA

Doctors often consider testing for MPS IV when signs and symptoms of the disease are present and are not explained by other causes. All diagnostic tests should be overseen by a doctor with expertise in LSDs, as the tests are complicated, and results may be difficult to interpret.

In some cases, doctors may diagnose MPS IV based on the symptoms alone, e.g., skeletal dysplasia early in childhood. However, in many cases, the symptoms by themselves are not definitive enough for a positive diagnosis. To diagnose MPS IV, the doctor typically first tests whether the individual has higher than normal levels of the GAG KS in his/her urine compared with people of the same age who do not have MPS IV. Most, but not all, individuals with MPS IV have higher urine KS levels than those individuals without MPS IV. However, a urine test to diagnose MPS IV is not always accurate, especially in young children. Testing for elevated levels of both KS and chondroitin-6-sulfate may be more diagnostic than levels of either alone. Next, the doctor typically measures the levels of enzyme activity in the blood and/or skin cells. In healthy individuals, normal levels of enzyme activity are seen in the serum, white blood cells, and skin cells. In individuals with MPS IV, the enzyme activity levels are much lower or absent.

After deficient enzyme activity is established, the individual's cells are tested to identify the specific genetic mutation(s) to confirm the diagnosis. This 3-level testing is now the standard of diagnosis for MPS IV.

Once a diagnosis of MPS IV is confirmed, it is important that siblings of the individual, if any, also be tested. Since MPS IV has a wide spectrum of presentation and severity, the siblings may not appear to have MPS IV. Knowledge of their disease status may help them make informed decisions about their own healthcare and personal lives.

Early diagnosis of MPS IV is critical. The earlier MPS IV is diagnosed, the sooner potential treatment options can be explored and supportive care may be started to help you or your loved one and potentially prevent some of the permanent damage that may be caused by the disease.

> Doctors may consider testing for MPS IV when signs and symptoms of the disease are present and cannot be explained by other causes.

Prenatal diagnosis

If you have a child with MPS IV, it is possible to have tests during a subsequent pregnancy to find out whether the baby you are carrying is affected. It is important to consult your doctor early in the pregnancy if you wish to perform these tests. You may also want to consult with your doctor if one of your brothers or sisters had a child with MPS IV, as this may mean that you are also a carrier. The decision to have prenatal testing is complex and personal. Some prenatal genetic tests are listed below. The specific test(s) used will be a decision you make together with your doctor and genetic counselor. Knowing the exact mutation that your child has will allow the laboratories to test specifically for the same or similar mutations in your subsequent pregnancy.

Chorionic villus sampling

Chorionic villus sampling (CVS) is a procedure in which a small sample of cells (chorionic villi) is taken from the placenta where it attaches to the wall of the uterus. Chorionic villi have the same cells as the fetus and are therefore genetically identical to the fetus. CVS is performed much earlier than amniocentesis (see below). The risk of miscarriage is slightly greater with CVS than with amniocentesis mainly because it is performed earlier during pregnancy. Other risks include infection and defects in fingers and toes, especially if the procedure is performed before 9 weeks' gestation. Consequently, it is recommended that CVS be performed at the earliest at 10 weeks. The test is more than 98% accurate. Since CVS can be done much earlier than amniocentesis, the results will be known much earlier in the pregnancy. Please consult a genetic counselor on the interpretation of the results.

Amniocentesis

Amniocentesis is a procedure performed between the 15th and 18th week of pregnancy in which a small sample of the amniotic fluid (the liquid that envelops and protects a developing fetus in the womb) is taken with a fine, long, hollow needle inserted into the uterus through the abdomen with ultrasound guidance. The amniotic fluid contains cells and proteins from the developing fetus. The proteins can be tested for abnormal levels or activities that could help identify potential developmental abnormalities in the fetus. The cells can be tested for genetic abnormalities specific to MPS IV. Amniocentesis is more than 99% accurate. Please consult a genetic counselor on the interpretation of the results. The most important risk involved with amniocentesis is miscarriage (<0.1%) with others, e.g., injury to the baby or mother, infection, and preterm labor, occurring at a lower frequency.

Percutaneous umbilical blood sampling

Percutaneous umbilical blood sampling (PUBS; also known as cordocentesis, fetal blood sampling, or umbilical vein sampling) is a procedure in which a small sample of fetal blood is collected from the umbilical cord with a fine, long, hollow needle inserted through the abdomen. PUBS is usually performed after the 18th week of pregnancy. It is done only when a diagnosis cannot be made with amniocentesis. The use of PUBS is becoming rare since the risks of fetal death are much lower with CVS or amniocentesis. Serious risks with PUBS include fetal death (1%–2%), fetal bleeding, cord hematoma, slowing of the fetal heart rate, infection, fetal-maternal bleeding, and transfer of maternal infections to the fetus. Please consult a genetic counselor and/or doctor to discuss both the risks of testing and the interpretation of the results.

Other options

Consulting your genetic counselor and/or doctor can help you explore other strategies for having additional children. One option is in vitro fertilization (IVF) with preimplantation genetic diagnosis (PGD). In IVF, eggs are harvested from the mother and fertilized in the laboratory with sperm from the father. When the embryo reaches a certain stage called blastocyst, a few cells from the outside can be taken for genetic analysis. These cells are part of what will eventually develop into the placenta and not directly part of the fetus. So, taking these cells will not harm the development of the fetus. Since the genetic diagnosis is performed prior to implantation of the embryo into the uterus, this process is called PGD. Only healthy embryos are implanted into the uterus. Any remaining healthy embryos can be frozen in case additional children are desired at a later date. Preimplantation genetic screening can also be performed at the same time as PGD. Other options include egg or sperm donation from unrelated donors that could increase the probability that the children will not have MPS IV. However, there is a risk that the children may not look like you. Please consult your genetic counselor, psychologist, social worker, and doctor in making these decisions.

Neonatal (newborn) screening

Newborn screening is the testing of newborn babies to see whether they have specific genetic disorders. The goal is to help with early diagnosis and treatment. In the US, each state makes its own decisions about which health conditions should be included in their newborn screening programs. The factors that are considered when deciding on newborn testing include:

- Is the disorder clearly defined?
- What is the incidence rate of the disorder?
- Does early diagnosis help?
- Are tests available to diagnose the disorder accurately and cost-effectively?
- Can the tests be done quickly or is there a long waiting time for results?
- Is there a current therapy? Is bone marrow transplant an option?

JULIE

Currently, there is a growing movement promoting newborn screening for MPS disorders such as MPS IV. It is now more widely recognized that for many families, just knowing about the diagnosis is helpful, along with the opportunity for genetic counseling and education about additional medical help and management options. Considering the potential benefits of early diagnosis, the current aim is to develop a test that would allow children with LSDs to take advantage of these options.

Overall, research into newborn screening for LSDs is still in early stages. The National MPS Society has worked expeditiously in these efforts. MPS I was approved for screening in January of 2016 by the federal government. States have 3 years to implement the screening process, though there have been financial struggles state-to-state. In 2019, MPS II Newborn Screening language was presented through the Recommended Uniform Screening Panel, the mechanism to present a disorder screening. The Society will continue efforts in MPS IV, and the remainder of the disorders next. The process is lengthy, but essential.

Important questions remain about the screening process and testing methods. There will likely continue to be debate over the appropriateness of screening. There also may be concern about the effect on the parent–child relationship when a newborn is identified with a condition before symptoms appear. The test may also not be able to tell how severe the child's symptoms may become. This will leave many questions for families and healthcare professionals who want to choose the best treatment. As a community, those whose lives have been touched by MPS IV will likely continue to become more involved in the promotion of newborn screening.

> There is a growing movement promoting newborn screening for MPS.

Specific treatment of MPS IV

Overview

The goals of managing MPS IV are to improve quality of life, slow down the progression of the disease, and prevent permanent tissue and organ damage. Currently, there is no cure for MPS IV; however, early intervention may help prevent irreversible damage.

Treatment options for MPS IV include those aimed at disease management and supportive or palliative care (care focused on increasing comfort for a person with a disease that cannot be cured), as well as those aimed at treating the underlying enzyme deficiency.

BROOKS FAMILY

Enzyme replacement therapy (ERT)

Individuals with MPS have a deficiency in certain enzymes that break down GAGs, leading to their buildup in the cells of various organs. Given by intravenous (IV) infusion, ERT provides an external source of the deficient enzyme. The enzyme travels through the bloodstream and enters cells in various organs, where it helps break down GAG buildup.

The first ERT for MPS IVA was approved by the US Food and Drug Administration and European Medicines Agency in 2014. In June 2019, it was also approved for use in China. VIMIZIM® (elosulfase alfa) provides the enzyme galactose 6-sulfatase given via IV infusions. Once in the bloodstream, it is taken up into lysosomes where it breaks down KS—the GAG that accumulates in patients with MPS IVA.

> For parents or individuals to fully understand the risks, benefits, and limitations of ERT, it is important to talk with physicians familiar with MPS IV ERT and families undergoing this treatment. The National MPS Society can put you in touch with physicians and families so you can become better informed before reaching a decision.

Treatment is generally well tolerated but must be delivered weekly for continued effectiveness. Clinical trials demonstrated reduced levels of KS in the urine, which is a biomarker for MPS IVA. Individuals receiving ERT report increased endurance and exercise capacity (measured by the 6-Minute Walk Test) and reduced respiratory decline. Some individuals report decreased pain, and there appears to be a trend toward improvement in daily activities. Safety and effectiveness in pediatric patients younger than 5 years of age have not been established.

Unfortunately, elosulfase alfa does not penetrate into bone tissue, leaving skeletal issues relatively unresolved. At times, hypersensitivity (allergic) reactions have been observed from as early as 30 minutes to up to 6 days after infusion. Initial treatments should be in an appropriate medical setting where such reactions can be monitored and treated with the appropriate medications.

Anecdotal side effects noted by some families include flushing/redness on face and/or body, increased heart rate, and nausea/vomiting/abdominal discomfort; often these begin between infusions 6 and 8 and may require treatment with premedications (such as antihistamines, steroids, and antiemetics).

Some European countries (the Netherlands and Belgium) and Australia will not pay for the high cost of treatment. Currently, ERT is available only for MPS IVA and not available for MPS IVB.

To fully understand the risks, benefits, and limitations of ERT, it is important to talk with physicians familiar with MPS IV ERT and families undergoing this treatment. The National MPS Society can put you in touch with physicians and families so you can become better informed before reaching a decision.

Hematopoietic stem cell transplant (HSCT)

Like ERT, the goal of hematopoietic stem cell transplantation (HSCT), an option for individuals with some other MPS diseases, is to restore activity of the deficient enzyme.

MICHAEL

Stem cells (cells that are capable of differentiating into a wide variety of specific cell types) are harvested from the bone marrow, peripheral blood, or umbilical cord blood of a healthy donor. They are typed in advance to avoid rejection by the recipient. The stem cells are infused into the bloodstream of the recipient, where they migrate into the bone marrow and multiply into new, healthy, enzyme-producing blood cells. These healthy cells migrate back to many parts of the body where they produce properly functioning enzyme. Some of these new cells will migrate into the brain to produce enzyme, thereby preventing further neurological and cognitive damage.

When successful, this treatment only needs to be performed one time. It will provide a continuous source of healthy enzyme as the body is now creating the enzyme on its own in many parts of the body.

HSCT has been successful in very few individuals with MPS IV. In these individuals, there was significant galactose 6-sulfatase enzyme activity up to 10 years after the transplant with concomitant improvements in pulmonary, cardiovascular, and joint function. They also reported a reduction in the number of surgical interventions and improvements in activities. However, HSCT does not have a significant impact on skeletal abnormalities, so it is not generally recommended for patients with MPS IV at this time.

The disadvantages of HSCT include the risk of mortality, the problem of finding a suitable donor, graft-versus-host disease, and the necessity of a very specialized medical facility. Improvements in transplantation methods have dramatically reduced mortality rates, and since 2009 the survival rate has climbed to 95.7%. HSCT, in combination with advances in gene therapy, may still be an option to deliver a targeted enzyme that will be more effective with skeletal manifestations of MPS IV.

> For parents or individuals to fully understand the risks, benefits, and limitations of HSCT, it is important to talk with physicians familiar with MPS IV HSCT and families undergoing this treatment. The National MPS Society can put you in touch with physicians and families so you can become better informed before reaching a decision.

Are there different forms of MPS IV?

There are two different types of MPS IV, A and B, each associated with a specific enzyme deficiency. Enzymes are special types of protein that help build and break down complex molecules inside a cell. Each form of the disease is caused by a deficiency in a specific enzyme. Deficiency of either enzyme results in accumulation of KS and causes MPS IV. Individuals with either form of MPS IV experience similar symptoms; however, those with MPS IVA tend to have more severe symptoms than those with MPS IVB. Each form has a wide spectrum of clinical severity. It is more appropriate to view MPS IV as a continuous spectrum of disease from the more severely affected individuals to the less severely affected (attenuated) individuals.

> MPS IV is a spectrum with a variety of symptoms, and the disease is extremely varied in its effects.

MPS IVA

MPS IVA is the more common form of the disease, affecting about 95% of individuals. MPS IVA is caused by a deficiency in *N*-acetylgalactosamine 6-sulfatase (also called galactose 6-sulfatase), resulting in accumulation of KS and usually manifests as a more severe disease early in infancy. Deficiency in galactose 6-sulfatase also results in increased levels of chondroitin-6-sulfate, another GAG. MPS IVA is a metabolic disease that primarily affects the skeleton but also has effects on other organ systems (see Signs and symptoms of MPS IV on page 11). Although there can be compression of nerves and brain, there is generally little or no effect on cognitive involvement.

> MPS IVA is primarily a skeletal disease that also affects other organ systems. It is the predominant form of MPS IV, affecting 95% of individuals.

MPS IVB

Individuals diagnosed with MPS IVB have a deficiency in beta-galactosidase, which also causes accumulation of KS. MPS IVB occurs in only 5% of individuals and was previously considered to be a less severe, attenuated, or late-onset form of the disease. MPS IVB primarily affects the skeleton. Mutations in the gene coding for beta-galactosidase can also cause GM1 gangliosidosis. However, individuals with MPS IVB do not have degeneration of the nerves or intellectual disabilities as do those individuals with GM1 gangliosidosis.

> MPS IVB is primarily a skeletal disease. It is very rare, affecting only 5% of all individuals with MPS IV. Although MPS IVB and GM1 gangliosidosis are caused by mutations on the same gene, the two diseases are very different. Individuals with MPS IVB have normal intelligence, while individuals with GM1 gangliosidosis have intellectual disabilities.

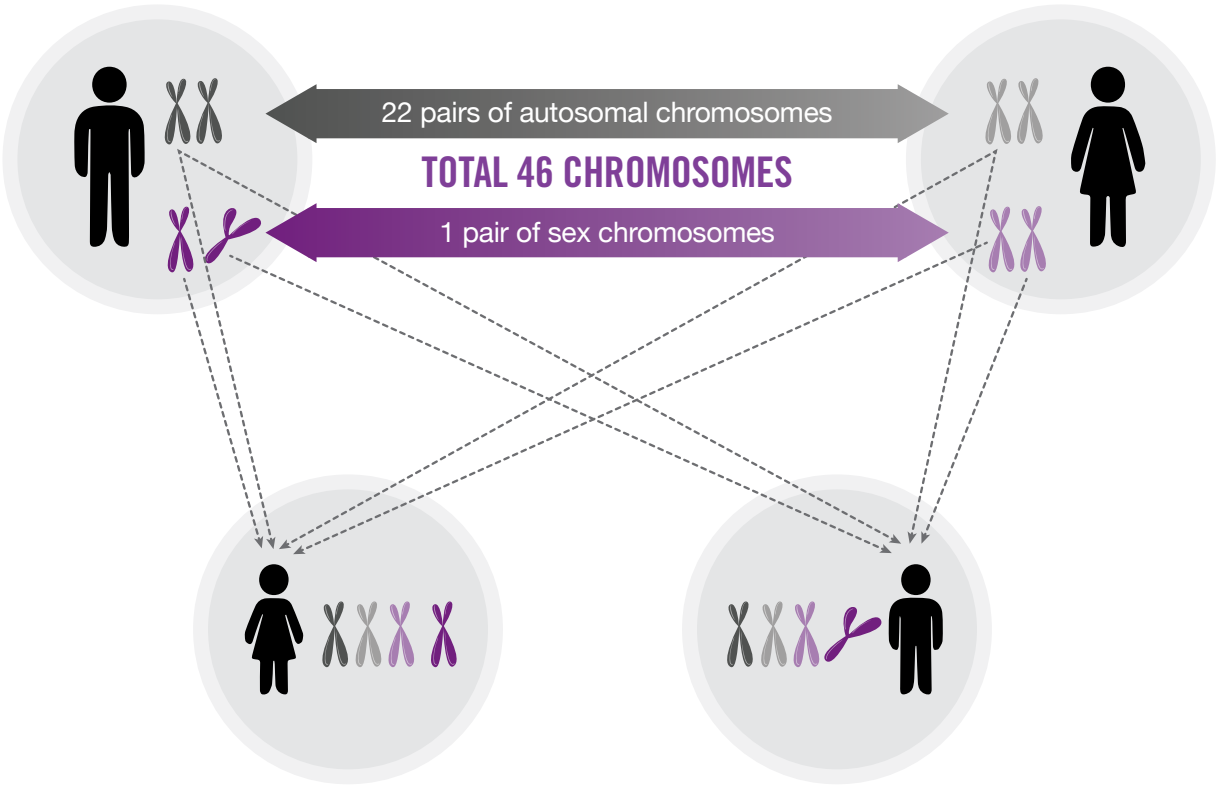
How common is MPS IV?

MPS IV is one of the rarest mucopolysaccharide diseases in the United States. Reliable incidence figures are not available, but estimates vary between 1 in 200,000 to 1 in 300,000 live births. Although MPS IV is rare, the cumulative incidence of all MPS diseases is 1 in 25,000 births, and the larger family of LSDs collectively occur in about 1 in every 5,000 to 7,000 births.

How is MPS IV inherited?

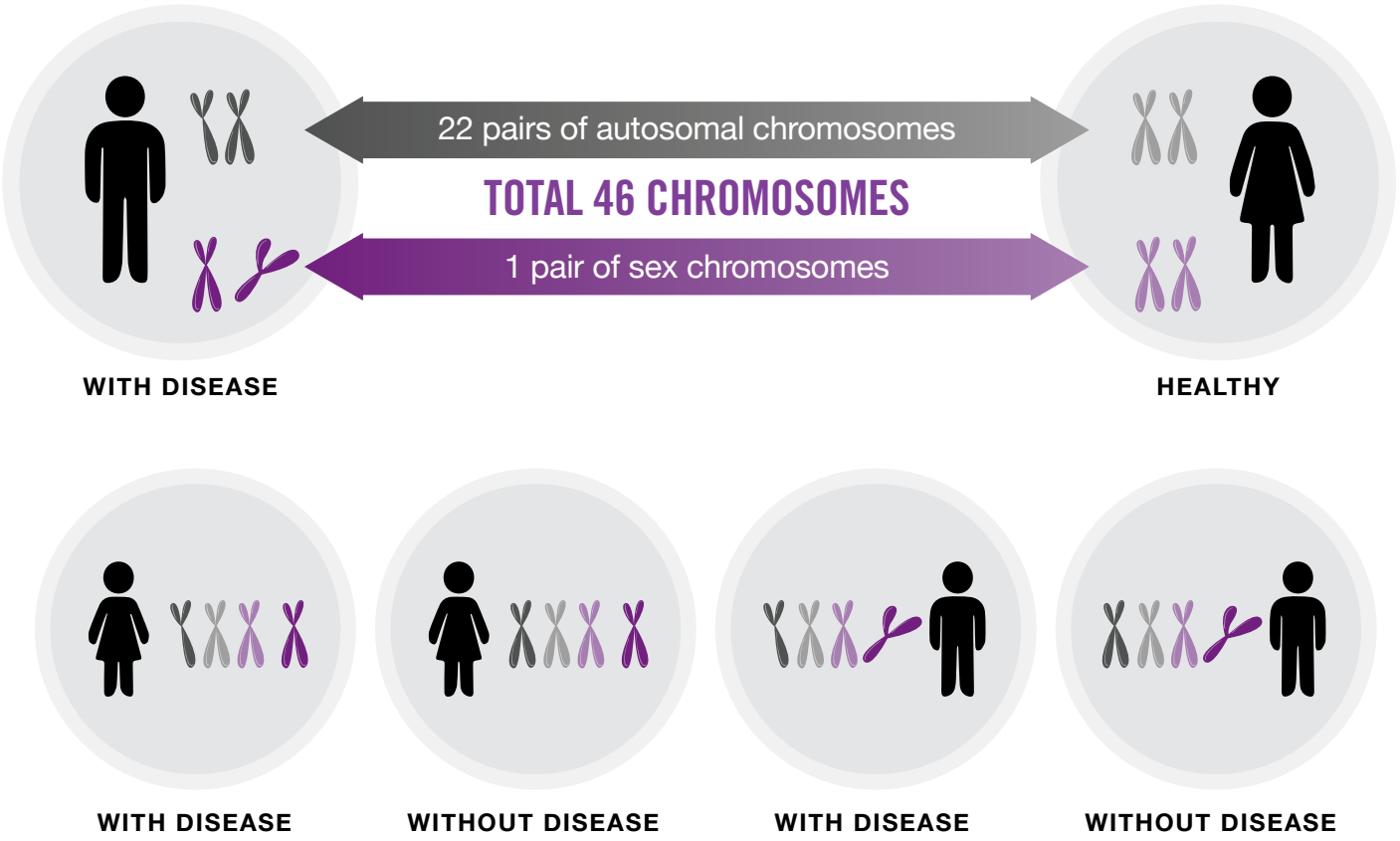
To understand inheritance of MPS IV better, it is important to grasp some basic concepts about genetics and inheritance **(Figure 1)**. All humans have 2 complete sets of chromosomes—1 set of 23 from each parent for a total of 46 chromosomes. Each chromosome is a string of many genes. Twenty-two of the 23 chromosomes are matched and are termed "autosomal" and contain genes that are needed for all individuals regardless of gender. The remaining pair are the sex chromosomes that determine gender of the individual (XX for female and XY for male; the Y chromosome comes from the father). Each of the matched autosomal chromosomes contain the same genes; i.e., chromosome 1 from the father has the same set of genes as does chromosome 1 from the mother, chromosome 2 from the father has the same set of genes as does chromosome 2 from the mother, and so on. Thus, every individual has 2 copies of each gene, 1 copy from each parent, located on the autosomal chromosomes. Consequently, every individual, other than those with certain chromosomal abnormalities, has 22 matched sets of autosomal chromosomes and 1 mismatched set of sex chromosomes, totaling 46 chromosomes.

Figure 1. Normal inheritance.



Most people consider a genetic disease to be one that gets passed down from father or mother to child; in other words, at least one parent clearly has the disorder and so does the child. When only one parent is affected and so is the child, the disease is considered "dominant" **(Figure 2)**. That is because the inappropriately functioning gene from the parent who has the disease dominates over the healthy gene of the other parent.

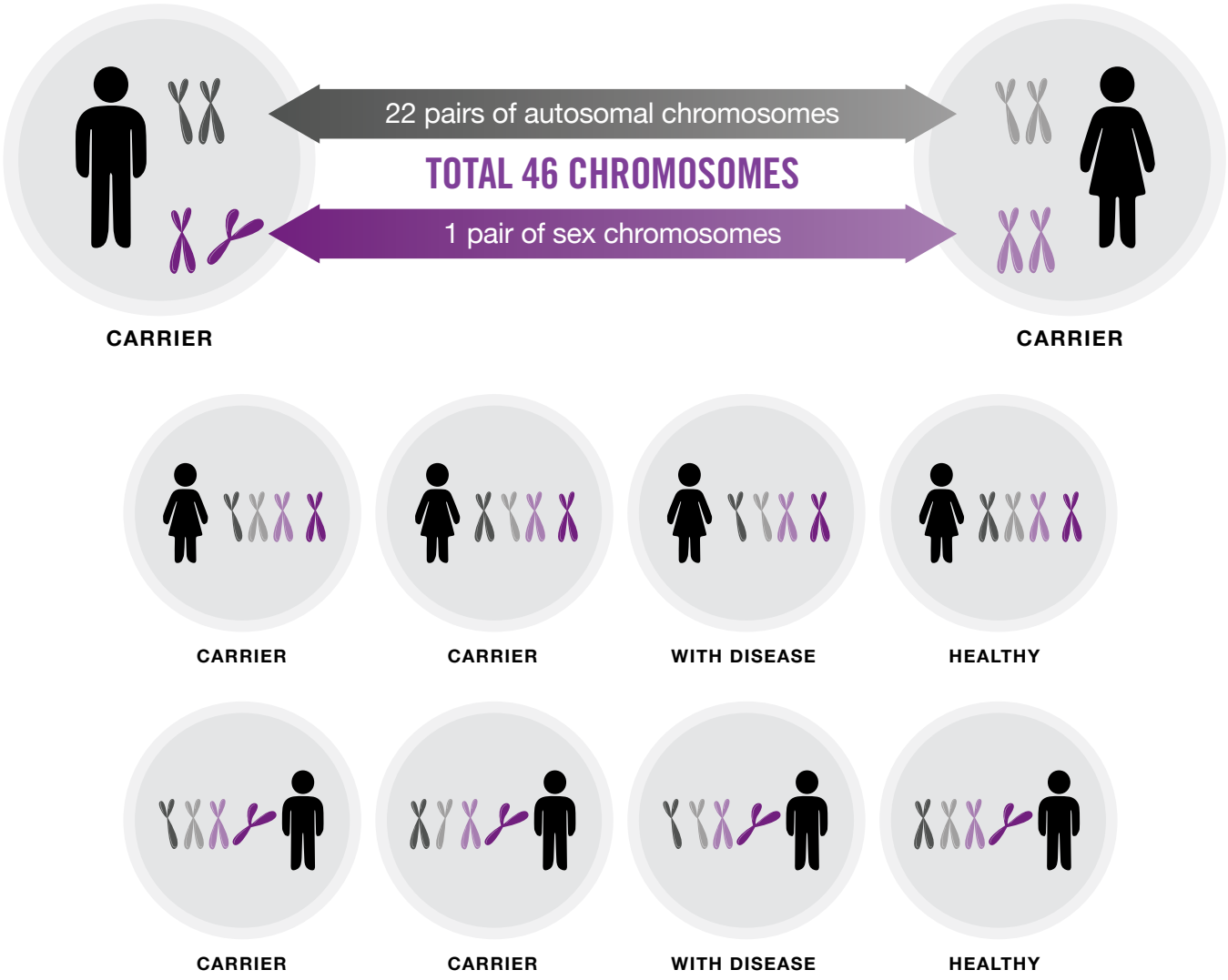
Figure 2. Autosomal dominant inheritance with one parent affected.



However, there are some genetic disorders that appear to show up suddenly without any strong indication that either parent has the disease. These genetic diseases are termed "recessive" or "hidden" because they show up only when genes inherited from both parents are not functioning correctly. People with these recessive genes appear normal because they have one normally functioning gene from one parent that "hides" or overcomes the improperly functioning gene inherited from the other parent. Such individuals are termed "carriers" because although they themselves do not exhibit the disease, they carry the defective gene that can be passed on to their children **(Figure 3)**.

Genetic testing can trace the defective gene back up the family tree for several generations, even if none of the ancestors showed signs of the disease. Depending on whether the affected gene is on 1 of the 22 autosomal chromosomes or on the sex chromosomes, the disease is described as autosomal, X-linked, or Y-linked.

Figure 3. Autosomal recessive inheritance with both parents as carriers.



Females have 2 X chromosomes, 1 each inherited from the father and the mother. Corresponding genes on both X chromosomes need to be mutated for the female to exhibit a recessive disorder. Males have 1 X chromosome inherited from the mother and 1 Y chromosome inherited from the father. Mutations in genes on either chromosome will result in the disease becoming manifest even in the case of rare disorders since there is no corresponding healthy counterpart to overcome the defective gene.

Any child born of carrier parents (those couples in which both have a recessive gene on an autosomal chromosome) has a:

- 50% chance of inheriting 1 normal gene and 1 diseased gene and be a carrier without evident disease, just like the parents;
- 25% chance of inheriting the defective gene from both parents and thus having the disease;
- 25% chance of inheriting the normal gene from both parents, thus being healthy and also not being a carrier.

Therefore, any child has a 75% chance of inheriting at least one normal gene and will not manifest disease.

Furthermore, there is a 67% chance that unaffected brothers and sisters of individuals with the disease will be carriers of the defective gene. This is why individuals who are related to each other should not conceive children. The probability of related parents having similar recessive gene mutations increases dramatically.

Some genes code for enzymes. Since there are two copies of each gene, one inherited from the father and the other from the mother, each enzyme is produced from two genes. A defective gene produces a defective enzyme, i.e., an enzyme that does not have full function or may even be completely inactive. If one of the two genes is defective (as is the case for carriers) the functional enzyme produced by the good gene helps the body compensate for the defective enzyme produced by the defective gene. This prevents the carrier from having symptoms of the disease. Only when genes inherited from both the father and the mother are defective and producing very little or inactive enzyme does the individual exhibit symptoms.

MPS IV is an autosomal recessive genetic disease; that means that the genes that cause this disease are on 2 of the 22 autosomal chromosomes (galactose 6-sulfatase on chromosome 16 and beta-galactosidase on chromosome 3), and that it shows up only when both copies of the gene, one each inherited from the father and mother, are not functioning properly **(Figure 3)**.

> MPS IV is a genetic recessive disease caused by deficiency in specific enzymes.

> All families of individuals with MPS IV should seek further information from their medical genetics doctor or from a genetic counselor if they have questions about the risk for recurrence of the disease in their family or other questions related to inheritance of MPS diseases.

HANNAH

Why does disease severity vary so much?

Any change in a gene is called a mutation. Many mutations do not have any effect on the gene function; in other words, the fundamental gene structure does not change. These are called “silent” mutations. However, other mutations trigger changes in the gene structure that cause them to behave abnormally i.e., a defective gene could result in either an overproduction or a deficiency in the gene product. When the gene codes for an enzyme, this could mean too much or too little enzyme activity. In the case of MPS IV, the genes coding for either galactose 6-sulfatase or beta-galactosidase are defective, resulting in highly reduced or completely absent enzyme activity of at least one of these enzymes.

The genes coding for galactose 6-sulfatase (*GALNS*) and beta-galactosidase (*GLB1*) have been studied extensively, and many mutations that cause enzyme deficiency have been identified. Some common mutations result in absolutely no enzyme being produced. If both copies of the defective gene inherited by an individual are of this kind, evidence suggests that this individual’s symptoms will likely be at the severe end of the spectrum. Other common mutations cause very small amounts of defective enzyme to be produced. Still, other mutations are not common at all and may only occur in a single known family. However, other than absence of enzyme activity being associated with manifestation of severe disease, there is no clear correlation between gene mutations, enzyme activity, and disease severity. These data suggest that there are other, not yet fully understood, factors involved in determining disease severity. Thus, DNA tests or mutational analysis are not always sufficient to predict disease severity.

As MPS IV is a condition that gets worse with time, all individuals will experience progression of symptoms no matter where they are on the spectrum of disease severity when first diagnosed. However, it is important to understand that although symptoms worsen and become more pronounced with time, individuals do not progress from one type of MPS IV to another, i.e., from type A to type B or vice versa. MPS IV type is determined by which enzyme is deficient in the individual.

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> MPS IV is a complex disease with widely varying severity not always predictable based on DNA testing.

How long do individuals with MPS IV live?

The lifespan of an individual with MPS IV depends on many factors including, but not limited to, severity of the disease, specific symptoms, what treatment is given, when the treatment was started, and how long the treatment continued. Individuals with less severe symptoms and slowly progressing disease may have an almost normal lifespan; some individuals are known to live well into their 60s. However, individuals with more severe symptoms, fast-progressing disease, and lack of access to treatment options usually do not live beyond their teens or early 20s. There is always hope for better outcomes for individuals with MPS IV with ever-improving newer treatments, surgical procedures, and technology.

> The lifespan of individuals with MPS IV can vary widely depending on severity of disease and treatment received.

Signs and symptoms of MPS IV

With tips for care and management

MPS IV affects multiple organ systems and is associated with a wide range of symptoms. Signs and symptoms of MPS IV are summarized in the table below with detailed descriptions following. Please note that not all individuals with MPS IV will exhibit all symptoms or to the same degree; the symptoms and their severity can vary widely among individuals.

Table: List of symptoms exhibited by individuals with MPS IV by organ systems (those of particular significance to MPS IVA are shown in italics).

General symptoms	Heart and blood vessels
Reduced endurance	*Heart valve problems*
Physical appearance	**Gastrointestinal system** (abdomen and intestines)
• Coarse facial features (such as a flat-bridged nose or square jaw) • Very short neck • Large head (macrocephaly) • *Severely short stature* • Uneven, swaying gait	• Enlarged liver and spleen (hepatosplenomegaly) • Umbilical and inguinal hernias

Mouth and teeth	Musculoskeletal system (bones and joints)
• Prominent chin, wide mouth, and enlarged tongue • Abnormal teeth (widely spaced with small, sharp-pointed cusps and very thin enamel)	• *Skeletal abnormalities (dysostosis multiplex with odontoid hypoplasia)* • Abnormal hip formation (hip dysplasia) • Lax joints and loose ligaments • Bone deformities in the spine (scoliosis, gibbus, kyphosis), knees (knock-knees or genu valgum), and ankles (valgus deformity)
Ears, nose, and throat	**Brain and nerves**
• *Hearing loss* • Frequent ear infections (otitis media) • Frequent upper respiratory tract infections (e.g., tonsillitis)	• Pressure on the neck area of the spinal cord from abnormal tissue growth nearby (*cervical spinal cord compression*) • Intelligence not affected in most cases
Respiratory system (lungs and breathing)	**Eyes**
• *Lung problems and reduced lung function* • *Sleep apnea* • Frequent lung infections • *Upper airway obstruction*	• *Vision problems, such as corneal clouding*

Growth

CASEY

Children with MPS IV usually grow normally at first, but growth often slows down around age 18 months. Those who are severely affected usually stop growing around 8 years of age, reaching a final height between 3 and 4 feet. Less severely affected individuals continue growing into their teens and can reach 5 feet; however, the trunk may be disproportionately short compared with limbs.

Physical appearance

Facial features of individuals with MPS IV are usually altered to some extent. They are often described as having “coarse facial features,” which is not intended to be insensitive but rather help with quick and accurate diagnosis. The mouth tends to be wide, the jaw square, the bridge of the nose flattened, and the neck very short. However, the texture of the hair is not affected as it is in other MPS diseases. Individuals with MPS IV may develop rounded and prominent abdominal regions due to organ enlargement and a characteristic way of walking and holding their arms due to joint contractures at their shoulders, elbows, hips, knees, and ankles.

Mouth and teeth

Individuals with MPS IV may have a prominent chin, wide mouth, and enlarged tongue. The teeth can be widely spaced and poorly formed with a fragile outer layer (enamel). It is important that the teeth are well cared for, as tooth decay can be a cause of pain. Teeth should be cleaned regularly. If the water in your area has not been treated with fluoride, individuals with MPS IV should be given fluoride tablets or drops. Cleaning inside the mouth with a small sponge on a stick soaked in mouthwash will help keep the mouth fresh and help avoid bad breath. However, even with the best dental care, an infection (abscess) around a tooth can develop due to its abnormal formation. Irritability, crying, and restlessness can sometimes be the only signs of an infected tooth in a young child.

If an individual with MPS IV has a heart problem, it is advised that antibiotics be given before and sometimes after any dental treatment. This is because certain bacteria in the mouth may get into the bloodstream and cause an infection in the abnormal heart valve, potentially damaging it further. Depending on the antibiotic used, side effects could differ. Some common side effects of antibiotics include diarrhea, nausea, and vomiting. Antibiotics may also cause skin rashes and allergic reactions.

If teeth need to be removed while an individual is under an anesthetic, this should be done in the hospital under the care of both an experienced anesthetist and a dentist, but never in the dentist’s office. Dentists should be informed of the diagnosis of MPS IV and provided contact information for other medical providers working with the individual.

> Teeth should be cleaned regularly, and if the water in your area has not been treated with fluoride, individuals with MPS IV should be given fluoride tablets or drops. Cleaning inside the mouth with a small sponge on a stick soaked in mouthwash will help keep the mouth fresh and avoid bad breath. For individuals with MPS IV, dental surgery must be done only in a hospital setting with appropriate anesthesia. Additional precautions must be taken for those with heart conditions.

Eyes

The circular window at the front of the eye (cornea) can become cloudy due to storage of GAGs. Corneal clouding tends to be mild and not particularly noticeable in most individuals with MPS IV and rarely interferes with vision. If corneal clouding is severe, it may reduce sight, especially in dim light. Some individuals cannot tolerate bright light, as the clouding causes uneven refraction of light. Wearing caps with visors or sunglasses can help. Surgical correction may be required for those with severe corneal clouding.

ERIN

Ears

With normal hearing, sound waves cause the eardrum (a thin membrane between the outer and middle ear) to vibrate. Three small bones in the middle ear amplify these vibrations. The middle ear needs to be at the same pressure as the outside air in order to work properly. The Eustachian tube, which reaches from the middle ear to the back of the throat, is used to regulate the pressure in the middle ear. The vibrations of the middle ear bones are picked up by the inner ear. Tiny hair cells in the inner ear sense these vibrations and send a message through the auditory nerve to the brain, which then interprets them as sound.

Some degree of deafness is common in MPS IV. It may be conductive, sensorineural deafness, or both (mixed deafness) and may be made worse by frequent ear infections. It is important that individuals with MPS IV have their hearing monitored regularly so that problems can be treated early to maximize their ability to learn and communicate.

Conductive deafness

Conductive deafness occurs when something prevents the eardrum or middle ear bones from vibrating properly. Correct functioning of the middle ear depends on the pressure behind the eardrum being the same as that in the outer ear canal and the atmosphere. This pressure is equalized by the Eustachian tube, which runs to the middle ear from the back of the throat. If the tube is blocked, the pressure behind the eardrum will drop and the drum will be drawn in. If this negative pressure persists, fluid from the lining of the middle ear will build up and in time become thick like glue (middle ear effusion). This can prevent the eardrum or middle ear bones from vibrating properly, resulting in conductive deafness because of a blocked Eustachian tube. This is an important factor contributing to hearing loss in individuals with MPS IV.

If it is possible for the child to have a light general anesthetic, a small incision through the eardrum can be made (myringotomy) to remove the fluid by suction. A small ventilation tube may then be inserted to keep the hole open and allow air to enter from the outer ear canal until the Eustachian tube starts to work properly again. The tubes placed in the eardrum may quickly fall out. If this happens, the surgeon may decide to use tympanostomy tubes (T-tubes), which usually stay in place much longer. It is expected that, once a ventilation tube is in place, fluid should drain out and hearing should improve.

Sensorineural (nerve) deafness

In most cases, nerve deafness is caused by damage to the tiny hair cells in the inner ear. Unlike conductive deafness, sensorineural deafness cannot be managed by inserting ear tubes. The hair cells are small, delicate, and difficult to repair. For this reason, sensorineural deafness is often not reversible. Nerve or sensorineural deafness can be managed by the fitting of a hearing aid or aids in most individuals. In general, it is felt that hearing aids are underutilized in MPS diseases.

Mixed deafness

When individuals experience both conductive and nerve deafness, it is referred to as mixed deafness. Managing mixed deafness involves treating both types of deafness as described above.

> It is important that individuals with MPS IV have their hearing monitored regularly.

Chest

Normally, the breastbone (sternum) is joined to the spine by the ribs. In individuals with MPS IV, the growth of the spine is affected. The breastbone continues to grow more normally, but as it is joined to the spine, it is forced to buckle outward in a rounded curve or sometimes in a prominent beak shape. The chest is bell-shaped, and the ribs are held fixed in a horizontal position, causing restriction of efficient breathing. Individuals with MPS IV can develop respiratory failure secondary to reduced chest volume and airway collapse due to tracheomalacia, a condition characterized by structural abnormality in the cartilage of the windpipe (trachea), making it excessively collapsible. A breathing test, called a pulmonary function test, can be used by a lung specialist to assess the amount of breathing restriction caused by abnormal bone growth and an unstable trachea.

TRACY

Breathing difficulties

The trachea continues to grow while, in some cases, the cervical spine does not. This, along with deposition of GAG in the trachea, can lead to tracheomalacia. Individuals with MPS IVA commonly experience progressive tracheal blockage (obstruction), leading to moderate to severe laryngotracheobronchial disease caused exclusively by major tracheal deformity without laryngeal disease. Obstruction could be in the upper or lower airway. Older teenagers and adults may need to tip their heads back to keep the trachea extended and prevent it from kinking and blocking the airway.

In addition, in older teenagers and adults, the heart and lungs are compressed within a small thorax (area of the body between the neck and the diaphragm). This leads to difficulties in efficiently exchanging gases in the lungs, and restrictive respiratory failure can occur in adults. Individuals with severe tracheal obstruction are at increased risk for dying of sleep apnea and other related complications. This is a difficult complication to treat, so it is important to treat additional chest problems, such as infections, very seriously.

FANNY

Treatment of tracheal obstruction

Obstruction of the upper portion of the trachea (upper airway obstruction), even when severe, can be treated with tracheostomy. This is a temporary or permanent procedure that involves making an opening in the neck below the vocal cords and placing a tube into the trachea, allowing air to enter the lungs. However, performing this procedure in an individual with MPS IVA is challenging due to the extremely short neck, fixed cervical vertebrae, and tracheomalacia. Furthermore, tracheostomy does not address or prevent lower airway obstruction caused by a collapsed or kinked trachea.

Currently, tracheal obstruction and tracheomalacia can only be treated with a surgical procedure called tracheal reconstruction, which is usually accompanied by vascular reconstruction to provide appropriate blood flow to the affected organs. Tracheal reconstruction, as its name suggests, involves making an incision in the trachea, removing the section that has closed or collapsed, and reconnecting the trachea. The trachea is shortened to match the length of the spine to minimize the risk for further blockage through kinking or collapse.

It is important to recognize that this procedure is associated with some severe complications in about 1 in 5 individuals and includes separation of the reconnected (anastomosed) trachea, granulation tissue formation, re-blockage (restenosis) of the trachea, wound infection, and respiratory infections (see below). Separation of the reconnected trachea (anastomotic separation) is the most-feared complication and can present very subtly and can quickly lead to death if not diagnosed and treated swiftly. Prompt treatment and aggressive management of anastomotic separation usually yield good results.

Many people with MPS IV, especially type A, experience tracheomalacia which can lead to other respiratory problems, including tracheal obstruction. Upper airway obstruction can be treated with tracheostomy. Lower airway obstruction and tracheomalacia can be treated with tracheal reconstruction surgery. However, this procedure can result in other dangerous complications. Please consult your doctor for more advice. It is important to work with anesthesiologists and surgeons knowledgeable about MPS diseases to minimize complications.

Respiratory infections

Although children with MPS IV are not necessarily more prone to respiratory infections than children without the disease, their restricted chests mean they are less able to cope with an infection if it involves the lungs. Common symptoms include fever, coughing, trouble breathing, wheezing, and sleep apnea. You may be advised to contact your doctor immediately if you suspect an infection might be starting so that an antibiotic can be prescribed, if necessary. It is common for individuals with MPS IV to require additional diagnostic testing to determine the type and source of infections for the most rapid and effective treatment, frequently through specimen culture.

Cases have been reported of individuals with MPS IV experiencing severe breathing problems after spending several days at high altitude. Please consult your doctor if you are planning a long airplane flight or a vacation in the mountains.

Treatment of respiratory infections

Although most individuals with colds do not require antibiotics, individuals with MPS IV have an increased risk for developing secondary bacterial infections of the sinuses or middle ear. These infections should be treated with antibiotics. Poor drainage of the sinuses and middle ear worsens the problem of overcoming infections. Therefore, it is common for infections to recur promptly after the antibiotic course is completed. Chronic antibiotic therapy may be used to help some individuals with recurring ear infections. Ventilation tubes can be used to improve drainage from the ear and speed resolution of infections. It is important to consult an otolaryngologist (ear, nose, and throat specialist) experienced with MPS diseases to determine which tube is best.

Many people with MPS IV become allergic to antibiotics or may acquire resistant infections. Your doctor can prescribe different antibiotics to help manage this problem. While overusing antibiotics is not advised, most people with MPS will require some treatment for infections. You will need a doctor with whom you can develop a good working relationship to manage frequent infections.

Heart

Heart disease can occur in people with MPS IV but may not develop or cause any real problems until later in life. The heart consists of four chambers separated by valves. Heart valves are designed to close tightly as blood passes from one chamber of the heart to another to stop blood from flowing back in the wrong direction.

There are four valves in the heart: the tricuspid (between the right atrium and right ventricle), the mitral (between the left atrium and left ventricle), the pulmonary (between the right ventricle and pulmonary artery), and the aortic (between the left ventricle and aorta). Your doctor may hear heart murmurs (sounds caused by turbulence in blood flow in the heart) if the valves become damaged by stored GAGs. If a valve is weakened, it may not shut firmly enough and a small amount of blood may shoot backward, leading to turbulence and a murmur. Many individuals with MPS IV have some degree of heart valve leakage or blockage. Some individuals with MPS IV may develop problems with the aortic or mitral valves. They may have slowly progressive valvular heart disease for years without any apparent clinical symptoms.

Medications are available to help manage the heart problems that occur in MPS. If the condition worsens, an operation may be needed to replace the damaged valves. If there is continued accumulation of GAGs on the replaced valves, the cardiologist may consider replacing them with mechanical valves that can last longer. Furthermore, there may be a need for follow-up surgeries.

As heart problems occur in MPS IV, individuals should have a test known as an echocardiogram annually (or as often as your doctor thinks necessary) to catch signs of problems as early as possible. The test is painless and similar to the ultrasound screening of babies in the womb. It can identify problems with the heart muscle, heart function, and heart valves, but like many tests it cannot detect all possible problems.

Because of the unusual special problems that can occur in the MPS group of diseases, you should select a cardiologist with specific knowledge of MPS IV. At a minimum, you should inform the doctor about heart problems commonly experienced by individuals with MPS IV.

TINSLEY

> Heart disease can occur in people with MPS IV but may not develop or cause any real problems until later in life.

Abdomen and hernias

Individuals with MPS IV develop an enlarged liver and spleen (hepatosplenomegaly) due to the storage of GAG. The enlarged liver does not cause problems or lead to liver failure, but its volume can interfere with eating and breathing.

Occasionally part of the abdominal contents may push out behind a weak spot in the wall of the abdomen. This is called a hernia. The hernia can come from behind the navel (umbilical hernia) or in the groin (inguinal hernia). Inguinal hernias should be repaired by an operation, but hernias will sometimes recur. Umbilical hernias are not usually treated unless they are small and cause entrapment of the intestine or are very large and are causing problems. It is very common to have a reoccurrence of an umbilical hernia after a repair has been made. Any hernia that becomes painful, turns red or purple, or does not retract is considered a medical emergency and will require immediate treatment.

Bones and joints

People with MPS IV tend to have significant problems with bone formation and growth. The bone disease in MPS IV is different from that seen in other MPS diseases. The major clinical features of MPS IV are those related to the bones and their effect on the nervous system if nerves are compressed by abnormal bone movement.

Spine

The bones of the spine (vertebrae) normally line up from the neck to the buttocks. In individuals with MPS IV, the spine tends to be severely affected and its bones or vertebrae are abnormally flattened (platyspondyly). The vertebrae are often poorly formed and may not stably interact with each other. If this happens, the vertebrae can compress and injure the spinal cord. One or two of the vertebrae in the lower back are sometimes slightly smaller than the rest and set back out of alignment. This backward slippage of the vertebrae can cause an angular curve (kyphosis or gibbus) to develop, but it usually does not need surgical treatment. If curvature is not severe, bracing may be suggested. There are different opinions on whether surgery is needed or whether a brace can be used either to correct a curve or to support the back. If a brace is used, it should not be the kind that restricts the movement of the chest even further. If surgery is recommended, it is critical that individuals with MPS IV undergo careful monitoring of the spine while under anesthesia.

> The vertebrae are often poorly formed and may not stably interact with each other.

Neck (cervical spine)

Problems with the neck are perhaps the most serious concern for individuals with MPS IV. Discuss potential neck difficulties with the doctor at the time of diagnosis, as serious problems can occur before 5 to 6 years of age. The difficulties arise from a structural defect in the upper vertebrae of the spine, which is worsened

by very loose ligaments. The bones that stabilize the connection between the head and neck usually are malformed (odontoid dysplasia) in people with MPS IV. There should be a piece of bone called the odontoid process sticking up between the first and second vertebrae that gives support as the head moves backward and forward. With odontoid dysplasia, the neck can become unstable, which places the spinal cord at risk for life-threatening injury. The spinal cord is a big bundle of nerves that carries messages between the brain and the rest of the body. If the cord is compressed or squeezed (cervical myelopathy), there will be gradual worsening effects on the individual, with paralysis or death occurring if left untreated.

Children with MPS IV should be referred to an orthopedic surgeon from an early age to monitor the condition of the cervical spine. MRI studies or X-rays will be performed with the head bent forward and with the neck straight (flexion and extension view) and will be repeated from year to year to monitor the situation. A baseline study of the neck is recommended at the time of diagnosis. If severe pain or pain associated with weakness or tremors in the lower legs occur, the individual should have studies of the neck (MRI and flexion-extension X-rays) to evaluate for slippage of the neck vertebrae.

Parents may be alarmed that their child may have weakness in such a vital place and may be harmed by a severe fall. The surgeon will be able to advise you on the risks. It is important to keep a balance between avoiding risks and letting the child lead as normal a life as possible. However, activities such as somersaults, headstands, or diving should be avoided completely. The problem with the cervical spine can be corrected by an operation called a cervical fusion. Small pieces of bone are taken from the legs and fixed into the neck where they eventually grow to form a firm support, joining the top two vertebrae to the base of the skull.

Fusion operations are often carried out on individuals with other conditions, but there are special problems with individuals with MPS IV and common methods may fail. Most orthopedic surgeons have minimal or no experience with individuals with MPS IV. One or two hospitals have taken a particular interest in individuals with MPS IV and have performed a number of fusion operations. The National MPS Society has information about orthopedic surgeons and hospitals where successful cervical fusions have been performed.

After cervical fusion, it is essential to immobilize the neck in the correct position for more than 4 months while the grafted bone grows up to join the base of the skull. One method of achieving this successfully is known as the “halo” method. A metal halo ring is attached to the skull, and bars leading from it are fixed to the body by a plaster cast. The operation involves a hospital stay of usually no more than 1 week. The halo is typically required for 3 to 4 months to allow healing and fusion of the spine. Although caring for an individual in a halo is hard work, individuals adjust remarkably well.

Children with MPS IV should be referred to an orthopedic surgeon at an early age to monitor the condition of the cervical spine.

The National MPS Society has information about orthopedic surgeons and hospitals where successful cervical fusions have been performed.

Scoliosis

Abnormal curvature of the spine, or scoliosis, also can occur. Curvature is measured in degrees and may be monitored for some time. It is important to note that scoliosis may progress quickly. When it is severe, it may require intervention. In general, fusion with bone is the best alternative and surgically implanted spinal rods are not well tolerated. In any case, the soft bone makes the surgery and recovery difficult. Many individuals need multiple procedures.

Kyphosis

The backward slippage of the vertebrae can cause an angular curve, called kyphosis (forward bend) or gibbus (bump in the lower back), to develop. Kyphosis occurs in about 70% of children with severe MPS IVA. Gibbus (also called thoracolumbar kyphosis) develops from poor bone growth in the upper front part of the vertebrae and is often one of the earliest signs noted in MPS IVA. This causes a wedging of the vertebrae because the bones are smaller in the front than in the back.

Some individuals with thoracolumbar kyphosis have been stabilized with spinal surgery. Individuals should be assessed early in life to determine a baseline value of the spinal curve so they can be monitored for changes over time. Although rare, there can be serious neurological consequences if the spinal cord compression is left untreated. Surgery might be recommended if there is increased progression of the curve or in cases of severe pain or spinal cord disease (myelopathy). Some surgeons only advocate surgery if the curve progresses beyond 70 degrees. All surgeries should be monitored by anesthesiologists familiar with Morquio syndrome, and specific precautions are required.

Joints

Joint stiffness is common in MPS IV. All joints become stiff and their movement may become limited. Later in life, this can cause pain that may be relieved by heat and prescribed analgesics. Limited movement in the shoulders and arms may make dressing difficult. Aches and pains may commonly occur in various joints due to the abnormal anatomy of individuals with MPS IV. Some individuals also may develop osteoarthritis.

COOPER

Hips

It is common for the hips to become dislocated, but this is often not a major problem and treatment may not be advisable or necessary. If the individual continues to be able to walk and pain occurs later in life, surgery may be considered.

Knock-knees

As a child with MPS IV grows older, the knees gradually become more “knocked” (genu valgum). It is sometimes possible for the legs to be straightened by an operation, but it is usually considered best to wait until the child has stopped growing. Joints are held in place by strong bands of protein fiber called ligaments. Individuals with MPS IV have ligaments that are often very lax. If this is the case, surgery may not achieve any noticeable improvement.

Ankles and feet

The ankles may be weak and turn inward as a result of ligaments being lax. Occasionally boots and splints are worn, but firm supportive shoes may be equally adequate. The bones composing the arches in the feet are held in position by ligaments and tendons. These are likely to be weakened, resulting in flat feet. The toes may be misshapen.

Shoulders

The shoulders often are partially dislocated downward (subluxed) so the arms cannot be raised straight above the head. This does not usually cause discomfort to the individual; however, it can create difficulty in activities of daily living and personal care, such as washing hair and dressing, and may cause pain if the shoulders are overextended.

Wrists

The wrists are enlarged and curved. They may become very loose and floppy as the tiny carpal bones fail to develop properly, and the ligaments are lax. This can mean considerable loss of strength in the hands. Attempts have been made to correct this problem surgically by grafting bone from another part of the body to the wrists, but unfortunately, the technique has not yet been successful. Small plastic splints with wristbands may be helpful in some cases. Writing may be difficult, and some individuals may find it easier to use a computer.

Carpal tunnel syndrome is common in most forms of MPS diseases but has not been a frequently reported problem in MPS IV. If pain or numbness in the hands, particularly at night, is a problem, it would make sense to have an electrical test called a nerve conduction study performed. This test will show whether carpal tunnel syndrome is the cause. If there is any weakness at all in the hand or decreased muscle mass at the base of the thumb, ask for the test from a neurologist. Be persistent, as many physicians may not believe that carpal tunnel syndrome is present without the classic symptoms. Most individuals affected by MPS do not have the classic symptoms of carpal tunnel syndrome, even with severe nerve entrapment and damage.

> Carpal tunnel syndrome is common in most forms of MPS diseases but has not been a frequently reported problem in MPS IV. Nevertheless, individuals are encouraged to seek professional diagnosis when they experience difficulties, numbness, or persistent pain in their wrists and hands.

Intelligence

There is no storage of GAGs in the brain of individuals with MPS IV; therefore, intelligence is not usually affected. If developmental delays or cognitive impairment are observed in individuals diagnosed with MPS IVB, they should have additional tests done to confirm the diagnosis since these are usually symptoms associated with GM1 gangliosidosis, another disease that is caused by mutations in the *GLB1* gene, the same gene responsible for MPS IVB.

Living with MPS IV

Education

The majority of children and adolescents with MPS IV will attend mainstream school and should be able to maintain academic achievement. Obtaining a college education is not unusual. For individuals with MPS IV to reach their full academic potential, it is important to ensure that the school is aware of the resources required. It is important for parents or caregivers to work with the school system and develop the best Individualized Education Program, Section 504 Plan, or medical plan for your child. For more information on education, see the booklet titled *A Guide for Parents: Education Strategies and Resources*, published by the National MPS Society.

Puberty

Adolescents with MPS IV will go through normal developments of puberty, although the onset of menstruation in girls may be delayed. Normally, puberty is the time for a growth spurt, which includes rapid growth and elongation of bones. However, since individuals with MPS IV have several skeletal (bones and joints) abnormalities, as discussed earlier, the growth spurt during puberty can pose additional skeletal problems.

Reproduction

Individuals with MPS IV are fertile. Fertility studies in humans with any MPS type are rare. Spermatogenesis may be reduced among males with MPS IV. Individuals with MPS IV who have received an allogeneic (from a donor with a different genetic background) HSCT (see more on page 4) often experience an adverse impact on fertility due to the chemotherapy and radiotherapy associated with HSCT. Irradiation can also have adverse effects on the uterus including poor implantation, and poor fetal growth. Premature termination or birth may occur. Women whose stature is significantly restricted may be advised not to become pregnant because of risks to their health. It is important to remember that all children born to a parent with MPS IV are automatically carriers, but none will have the disease unless the other parent also is a carrier or has MPS IV too. It is advisable for individuals with MPS IV to take the following points into account when considering having a child:

- Preconception genetic counseling
- Preconception medical evaluation
- Preconception discussion of risks during pregnancy and delivery, e.g., high probability of a caesarian delivery
- Health risks during pregnancy, e.g., difficulty with respiration due to the uterus pushing up, fluid overload, cardiopulmonary complications
- Health risks during delivery, e.g., premature delivery due to skeletal limitations, anatomical differences making diagnosis of delivery process difficult, problems with administering and managing anesthesia
- Newborns with skeletal problems will need immediate specialized medical care

All children born to a parent with MPS IV are automatically carriers, but none will have the disease unless the other parent also is a carrier or has MPS IV. There are considerable risks associated with pregnancy for individuals with MPS IV. Please consult your doctor when making these decisions.

Independence

Individuals with MPS IV should be encouraged to be as independent as possible to lead full and enjoyable lives. The teenage years may be difficult if they have restrictions imposed by their disease. This may be helped by meeting or contacting other teenagers and adults who also have MPS IV. Individuals with short stature may find additional support and helpful information through Little People of America, www.lpaonline.org.

KHUNSHA AND TAYYAB

Employment

The physical disabilities of those with MPS IV should not prevent people from accessing meaningful employment. The Americans with Disabilities Act helps both employees and employers. Individuals with MPS IV may find it helpful to contact their local Vocational Rehabilitation office. These are in every state, usually with multiple offices in each state, and help provide information about and access to employment.

Adaptations

Appropriately adapted living accommodations will greatly enhance the ability of an individual with MPS IV to develop independent living skills. Where stature is severely restricted, kitchen and bathroom facilities set at a lower height will be required. If mobility is restricted to such an extent that a wheelchair is used, plans for any home adaptations will need to allow adequate space to accommodate this. Additional information about home adaptations can be found in the booklet titled *Daily Living with MPS and Related Diseases,* published by the National MPS Society.

Some individuals with MPS IV may require vehicle modifications to safely operate a vehicle. Vehicles may be customized with assistive devices such as additional mirrors or hand controls or modified to have extended foot pedals or lifts. Children with MPS IV may need to be secured in car seats beyond an expected age due to smaller stature to increase safety while in a vehicle.

Psychosocial issues

Those with genetic conditions such as MPS IV may find it beneficial to receive some counseling or psychological support beginning at the time of diagnosis and periodically thereafter around processing the diagnosis and incorporating this into daily life. It is expected that as individuals with MPS IV meet developmental milestones for social and emotional skills, they will need opportunities to engage with others and participate in activities. Limitations that may be in place (such as not being able to participate in group sports) can be challenging for children and teenagers. Caregivers should consider other activities for social engagement.

As a caregiver of a child or young person with MPS IV, it is important to consider how their disability may cause them to experience additional challenges in life. Some children and young adults with MPS IV may adapt socially and emotionally by becoming socially inhibited or by internalizing problems or developing an aggressive, outgoing personality. Adolescence may be more of a challenge as they experience all of the normal physiological and psychosocial changes as well as any disease-related changes or limitations. Developing the necessary skills to lead independent adult lives can be challenging, although important, to achieving social maturity. Referral for counseling is recommended, particularly if there are symptoms of depression, anxiety, or other mental health challenges present.

> Individuals with MPS IV should experience the same expected developmental milestones and may require some accommodations or adaptations to be able to engage socially with peers.

Healthcare information

Assistance may be available from specialized agencies for individuals with disabilities and from genetics clinics. Explore Social Services, Social Security, Medicaid Waivers, and the Katie Beckett Law. Investigate these options and others that may be available for you on federal, state, and local levels. In most states, it is beneficial to start with the Department of Social Services or Department of Health and Human Services for additional information. If you already have Medicaid, calling the phone number on the card will help to get you connected with a social worker or case manager who will serve as a “point person” to help you get set up with things for which you qualify. If you do not have Medicaid or an established social worker, you can ask to speak with one through your healthcare provider. Many physicians have access to social workers, as do most hospitals. Your social worker should be able to locate additional information and/or resources for your family.

> Assistance may be available from specialized agencies for individuals with disabilities and from genetic clinics.

Lifespan

Disease severity varies significantly for individuals with MPS IV, and it is not possible to predict the expected lifespan for a given individual. Those on the more slowly progressing end of the disease spectrum may have a reasonably normal lifespan. The availability of new and ever-improving treatments as well as surgical procedures provides hope for better future outcomes for individuals affected by MPS IV.

Taking a break

Mildly affected individuals may need help to become more independent from their families and may benefit from a vacation, perhaps with others who have disabilities. Caring for a severely affected individual is hard work. Parents and caregivers need a break to rest and enjoy activities, and this may not be possible when their child or ward with MPS IV is with them. Brothers and sisters need their share of attention and need to be taken on outings that may not be feasible with a sibling with MPS. Many parents use some form of respite care or have someone come to help at busy times.

> Taking care of yourself and others in the family is important and should not be sidelined.

General management of MPS IV

Diet

There is no scientific evidence that any symptoms of MPS IV can be managed with a particular diet. Digestive system problems, such as diarrhea, tend to come and go naturally. Some individuals and parents, however, find that a change in diet can ease problems such as excessive mucus, diarrhea, or hyperactivity. Reducing intake of milk, dairy products, and sugar, as well as avoiding foods with too many additives and coloring, have helped some individuals. It would be advisable to consult your doctor or a dietician if you plan major dietary changes to make sure the proposed diet does not omit essential nutrients. If your problems or your child's problems are eased, you could try reintroducing foods one at a time to test whether any particular item appears to increase symptoms. It is important to remember that GAGs are synthesized by cells as part of their natural process. This is not a disease caused by overproduction of GAGs, but rather the failure to break down GAGs. As such, there is no diet that can prevent GAG accumulation.

Please note:

Consuming sugar or foods normally eaten will not affect the buildup of GAGs in the body.

JOCELYN

Physical therapy

Loose joints, rather than joint stiffness, are a common feature of MPS IV and can be a problem. Intensive physical therapy will be needed to help an individual with MPS IV start walking again after neck, spine, or knee surgery. Individuals with MPS IV should be as active as possible to maintain muscle strength and general health. Your doctor or physical therapist may be able to suggest ways of achieving this. It is important for children and adults to keep a balance between avoiding risks and leading as normal a life as possible. Activities such as somersaults, headstands, or diving should be avoided completely because of risk to the neck.

Occupational therapy

While physical therapy targets gross motor or "large" movements of the body (such as walking), occupational therapy focuses on fine motor movements and targets activities of daily living. It is important to consider occupational therapy following surgery or if there are difficulties with dressing, toileting, transitioning, and other motions that involve the use of the hands. Occupational therapy may be helpful for young children with MPS IV to help them and their families to learn strategies for making adaptations early on, so that these become more natural.

Mobility

Many individuals with MPS IV remain ambulatory into their teens and adult life. Others may need to use a wheelchair from an early age for longer periods of activity. An electric wheelchair is vital to encourage independence. Many hospitals offer wheelchair clinics to help with fit and customization for an individual's needs. Consult your physical therapist or occupational therapist for advice.

> Individuals with MPS IV should be as active as possible to maintain muscle strength and general health.

Vomiting

Many of those with MPS IV have a tendency to vomit easily, especially first thing in the morning, perhaps because mucus has built up overnight. Restricted space for internal organs in small bodies can mean the stomach may be constricted and discomfort could be experienced after a large meal, resulting in vomiting. Sometimes there is a feeling of finding it hard to breathe as the lungs also are constricted. A few children have had episodes of vomiting to such an extent that they become dehydrated. Consult your doctor if vomiting continues over several hours.

Drugs and medications

Individuals, especially children, with MPS may be affected differently by drugs. Hence, it is essential to consult your doctor rather than using over-the-counter medications. Drugs may be tried for controlling mucus production, but some may make the mucus thicker and harder to dislodge or they may make the individual more irritable. Decongestants usually contain stimulants that can raise blood pressure and narrow blood vessels, both undesirable for people with MPS IV. Cough suppressants or drugs that are too sedating may cause more problems with sleep apnea by depressing muscle tone and respiration.

Individuals, especially children, with MPS may be affected differently by drugs, so it is essential to consult your doctor rather than using over-the-counter medications.

Anesthetics

Giving an anesthetic to an individual with MPS IV requires skill and should always be undertaken by an experienced anesthetist. If the cervical spine is unstable, the individual with MPS IV is at risk if the neck is flexed while unconscious, and special precautions must be taken. Individuals with MPS IV should have careful monitoring of the spine when sedated. Inform your child's school or any other caregivers of this in case you cannot be contacted in the event of an emergency. Adults and children with MPS IV may wish to wear a medical identifier, e.g., bracelet or necklace, with this information. If you have to go to an unfamiliar hospital in an emergency, tell the anesthetist there may be problems with the neck and possibly with intubation (placement of the breathing tube).

The airway can be very small and may require a very small endotracheal tube. Placing the tube may be difficult and require the use of a flexible bronchoscope to place it gently. In addition, the neck may be somewhat lax and repositioning the neck during anesthesia or intubation could cause injury to the spinal cord. For some individuals, it is difficult to remove the breathing tube after surgery is completed. Advise physicians of the critical nature of these problems and that many problems have occurred during anesthesia of individuals with MPS. For any elective surgery in a child with MPS, it is important to choose a pediatric anesthesiologist who has experience with difficult airways. This may require that the surgery be performed at a regional medical center, not at a local hospital. See additional information on anesthesia in the booklet titled *Is Your Child Having an Anesthetic?* published by the National MPS Society.

Giving an anesthetic to an individual with MPS IV requires skill and should always be undertaken by an experienced anesthetist.

MORQUIO CONFERENCE, NEMOURS/ALFRED I DUPONT HOSPITAL FOR CHILDREN

Research for the future

The mission of the National MPS Society is to find cures for MPS and mucolipidosis (ML). As part of that mission, the Society funds research grants. The Society recognizes the need for targeted research for treatment of bone and joint problems and for treating the brain, and Society research funding has focused on those areas. Information about Society-funded research and promising new areas of research can be obtained by contacting the Society's office.

> This booklet is intended as an introduction into the nature of the disease as well as to help individuals and families understand more about what is happening to those with MPS IV and what they can do to manage it. This booklet was updated by the National MPS Society in 2020.

Updates

Medical professionals and researchers are constantly learning new things about MPS IV disease and treatments. Some of the information provided in this booklet may change over time. To keep up to date on the latest information on MPS IV and its management, visit www.mpssociety.org.

We have reserved the space below to call out new developments or updates we think deserve your attention.

Update: **Date:** **Link to more information:**	
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Benefits of the National MPS Society

Common bonds unite the lives of those with MPS and ML—the need for support and the hope for a cure.

The National MPS Society is committed to making a difference in the lives of MPS families through support, research, education, and advocacy. Families from around the world gain a better understanding of these rare genetically determined diseases through the Society's assistance in linking them with healthcare professionals, researchers, and, perhaps most importantly, each other.

Benefits of membership in the National MPS Society:

- *E-Courage*, our monthly newsletter containing stories and information about individuals with MPS and ML
- Educational materials such as syndrome booklets, fact sheets and an MPS glossary
- Conference and education scholarships
- The Family Assistance Program, which provides financial support for durable medical goods
- News about various Society-sponsored conferences and gatherings, where families and leading MPS scientists, physicians, and researchers join together for a common cause
- Information on local events, such as regional social events and fundraisers. These events create opportunities for families to meet each other and help raise community awareness of these rare genetic diseases
- A listing in our membership directory that assists families with connecting with one another

Glossary

Term	Definition
Aspiration	To draw in or out by suction. For individuals with MPS, it most commonly means the accidental inhaling of a fluid or solid like saliva or food into the windpipe or lungs where it can lead to coughing, difficulty breathing, choking, or aspiration pneumonia.
Attenuated	Weakened, reduced, or diminished in size. Attenuated MPS means a mild form of the disease.
Bronchoscopy	A medical procedure that lets a doctor look into the lungs and airways. The doctor inserts a thin tube with a light and camera through the nose or mouth down the throat and into the lungs.
Carpal Tunnel Syndrome	Thickening of the ligaments in the carpal tunnel (space in the wrist where the nerves pass between the carpal bones and the connective tissue) that causes pressure on the nerves. This can cause irreversible nerve damage if not surgically corrected. In children with MPS, carpel tunnel syndrome occurs because of the accumulation of GAG deposits.
Carrier	An individual who has a recessive, disease-causing version of a gene on 1 chromosome of a pair and a normal version of that same gene on the other chromosome. By definition, carriers of a recessive condition do not have clinical signs and symptoms of the condition.
Cerebrospinal Fluid (CSF)	The fluid that surrounds the brain and spinal cord which cushions them from shock, brings nutrients to the brain, and carries waste away. It is produced in the ventricles (cavities) of the brain and is reabsorbed into bloodstream.
Chromosomes	Linear, double-stranded structural units of genetic material consisting of DNA and supporting proteins called chromatin. Human cells contain 46 chromosomes identified as 23 pairs; 22 pairs are autosomes (the same from each parent) and 1 pair are the sex chromosomes.
Echocardiogram	Ultrasound of the heart to evaluate heart valve and heart muscle function.

Enzyme	A protein that facilitates a biological reaction without itself being used up in the reaction (i.e. it acts as a catalyst). An enzyme acts by binding with the substance involved in the reaction (the substrate) and converting it into another substance (the product of the reaction).
Enzyme Replacement Therapy (ERT)	A medical treatment for a genetic disease whereby the missing protein (enzyme) is manufactured separately and given intravenously to the patient on a regular basis.
Gastrostomy Tube (G-Tube)	A tube surgically inserted through the abdomen into the stomach. It is used to deliver nutrition and/or medications directly into the stomach when swallowing is difficult because of disease or obstruction of the esophagus.
Gene	The basic unit of heredity. Genes are made up of sequences of DNA that code for specific proteins or other functional units. Hundreds of genes are arranged together in strings to form a chromosome.
Gene Therapy	A medical treatment for a genetic disease whereby normal genes are inserted into a patient's cells to replace or correct the effects of mutated or disease-causing genes.
Glycosaminoglycans (GAGs)	Complex linear sugar molecules that are widely found throughout the body in connective tissue, the area between cells, secretions, and on the surfaces of many cell types. GAGs were previously called mucopolysaccharides.
Hernia	The bulging of an organ or tissue through some part of the body that should be containing it. Common examples are bulges in the umbilical (belly button) or inguinal (inner groin) regions of the body.
Hematopoietic Stem Cell Transplantation (HSCT)	A medical procedure that replaces enzyme-deficient cells with healthy enzyme-producing cells. Hematopoietic (blood) stem cells are capable of differentiating into a variety of specific cell types. The patient's bone marrow cells must first be eliminated by chemotherapy and/or radiation therapy. Then the healthy donor stem cells are infused into the bloodstream where they migrate into the bone marrow and multiply into new, healthy, enzyme-producing blood cells. These healthy cells migrate back to many parts of the body and brain where they produce properly functioning enzyme and "reboot" the immune system.

Hydrocephalus	A buildup of cerebrospinal fluid (CSF) in the cavities (ventricles) of the brain. This can put pressure on the brain and is sometimes characterized by an enlarged head in infants. Older children and adults can experience symptoms like headache, impaired vision, and cognitive difficulties. Communicating hydrocephalus can occur when the normal outflow of the fluid is blocked. It can be treated surgically by inserting a shunt into a ventricle to drain the excess fluid.
Individualized Education Program (IEP)	A specifically designed program for each child in the public school system who receives special educational services. The aim is to improve teaching, learning, and appropriate goal setting for each individual. A team including members from the school system and the family are generally involved in designing the IEP. Federal legislation is in place to guide the development of appropriate IEPs.
Kyphosis	An exaggerated, forward curve of the spine that causes a hunching of the back. (Similarly, a gibbus deformity is a type of kyphosis that involves a shorter section of the spine with a more angular curve.)
Lumbar Puncture	A lumbar puncture (also known as a spinal tap) is a procedure in which a needle is inserted into the space surrounding the spinal column in the lower back to withdraw cerebrospinal fluid (CSF) or to deliver medicine. This procedure may be performed to diagnose or treat a condition, but it is also used as a measure of intracranial pressure to aid in diagnosing hydrocephalus.
Lysosomal Storage Disorder (LSD)	An inborn error of metabolism, resulting in a particular lysosomal dysfunction. In the case of MPS disease, it is an inherited enzyme deficiency that blocks the natural breakdown of GAG, causing a buildup of waste products in the lysosomes (specialized compartments within cells that contain the enzymes responsible for breaking down substances into smaller molecules so that they can be used again in various bodily processes).
Lysosome	Specialized compartments within cells that contain the enzymes responsible for breaking down substances into smaller molecules so that they can be either eliminated or used again in various bodily processes.
Mitral Valve Prolapse	When the flaps between the left atrium and the left ventricle of the heart don't close evenly or smoothly, the mitral valve that connects the two chambers forms a bulge (prolapse) into the left upper chamber (left atrium) as the heart contracts. This can lead to blood leaking backward into the left atrium, causing mitral valve regurgitation.

Mucolipidosis (ML)	An inherited metabolic disease that affects the body's ability to break down various materials within cells. Patients with ML do not produce enough of one of the many enzymes required for a properly functioning lysosome. The name ML is used to classify all of the diseases with the clinical features common to both the mucopolysaccharidoses and the sphingolipidoses (diseases characterized by abnormal lipid or fat metabolism, affecting nerve tissue).
Mucopolysaccharidosis (MPS)	An inherited condition in which the body is unable to properly break down glycosaminoglycans (GAGs; formerly known as mucopolysaccharides). All of the various MPS diseases are characterized by defective lysosomal enzymes.
Mutation	Any change to the DNA sequence of a gene. Mutations are permanent alterations in the genetic code that can be passed down to future generations.
Otitis Media	Inflammation of the middle ear occurring commonly in children as a result of an infection, causing pain and temporary hearing loss.
Port-a-cath	A small medical device that allows easy access to a patient's veins. The port is installed beneath the skin and is connected to a catheter (a thin, flexible tube) that connects the port to a vein. A needle can be inserted through the skin into the port in order to draw blood or to give treatments, including drugs and blood transfusions. It can stay in place for many weeks or months.
Scoliosis	A sideways curve of the spine.
Shunt	A passage that will allow fluids to move from one part of the body to another. It is often used to treat hydrocephalus, where a tube is surgically placed into the brain to help drain cerebrospinal fluid (CSF) and redirect it to another part of the body where it can be reabsorbed.
Sleep Apnea	A sleep disorder where breathing stops repeatedly during sleep. It is frequently caused by an obstruction of the airway.
Tracheostomy	A surgical procedure in which a hole is made into the trachea (windpipe) through the front of the neck and a tube is inserted to help a person breathe.
Vocational Rehabilitation	A series of services that are designed to help individuals with disabilities get or keep a job, or to return to work or other useful occupation. These services are often provided by federal- or state-run programs.

You can find a complete list of terms in our online glossary at mpssociety.org/fact-sheet-glossary.

National MPS Society

Support for Families. Research for a Cure.

For more information or to join the National MPS Society:

Visit www.mpssociety.org

Contact us at 877.MPS.1001

Or email us at info@mpssociety.org

ACKNOWLEDGEMENT

The National MPS Society would like to thank BioMarin for their resources.