

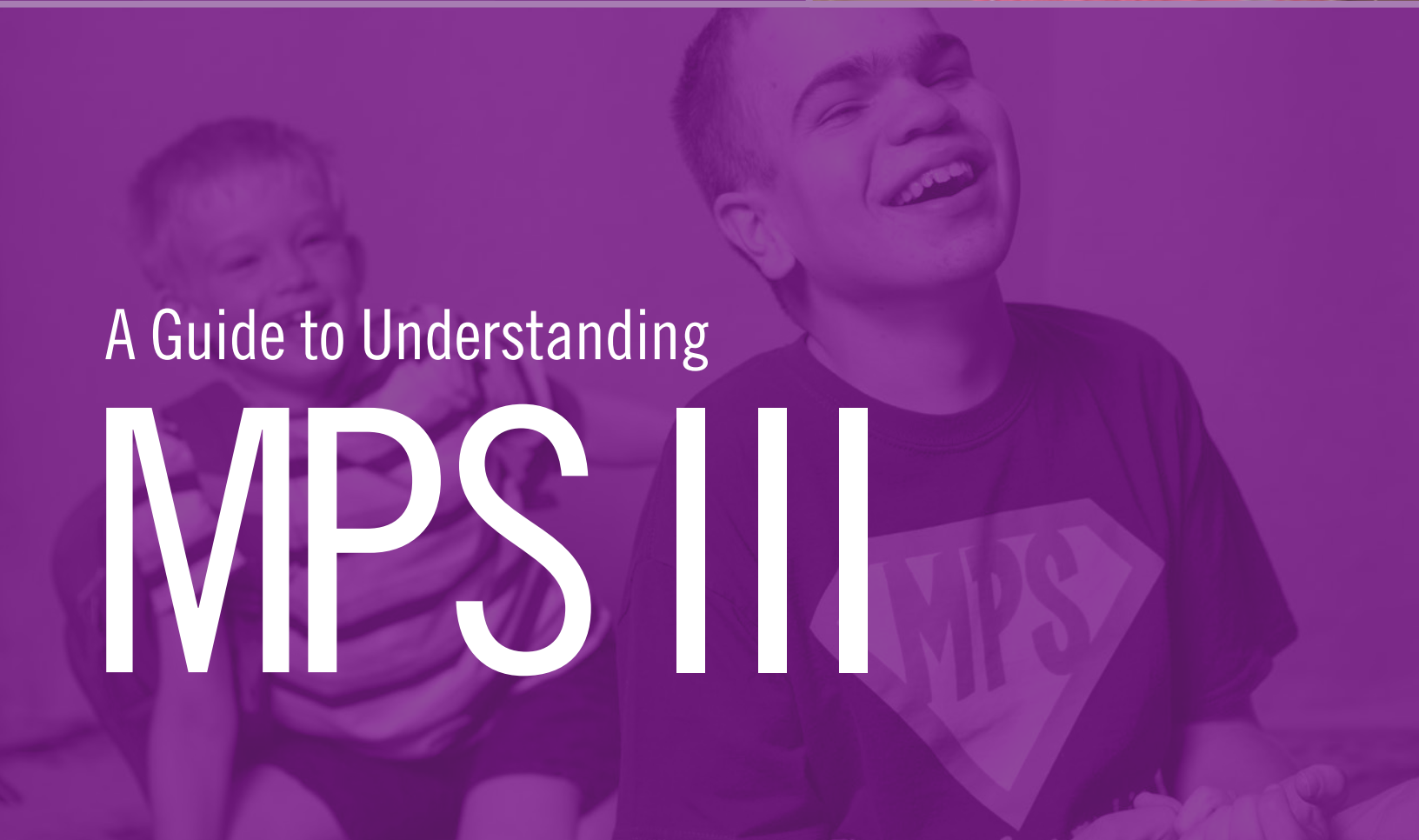


# Sanfilippo Syndrome



A Guide to Understanding

# MPS III



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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) Lulu, Jonah, Levi

**Pictured on right:** (top to bottom) Belle, Cole, Miriam



# What is MPS III?

Mucopolysaccharidosis III (MPS III; pronounced “mew·ko·pol·ee·sak·ah·ri·doh·sis three”) is a rare genetic disorder that affects many organs in the body. It is also known as Sanfilippo syndrome, named after Dr. Sylvester Sanfilippo, who first described it in 1963.

MPS III belongs to a group of inherited metabolic diseases called mucopolysaccharidoses (MPSs), a subgroup of lysosomal storage disorders (LSDs). MPS is a degenerative disease in which at least one long-chain sugar carbohydrate called glycosaminoglycan (GAG; pronounced “gly·cose·a·mee·no·gly·can” and formerly called mucopolysaccharide) accumulate in the lysosome, an organelle within cells. There are seven distinct clinical types of MPS, some of which have several subtypes. Each form of MPS is caused by deficiency of a specific enzyme, which is involved in the breakdown of one or more GAGs.

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

- It can be an **attenuated** (less severe) form that usually manifests later in childhood and progresses slowly.
- It can be a **severe** form that manifests early in childhood and progresses rapidly.

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 III, but there are ways to manage the challenges they will have, and to ensure their 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).



CHARLOTTE

# What causes MPS III?

*Are there different types of MPS III? (see page 9 for more information).*

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 GAG 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 are 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, often permanent, cellular damage that affects the individual's appearance, physical abilities, proper functioning of organs and systems, and, in most cases, mental development.

MPS III is caused by accumulation of a particular GAG called heparan sulfate (HS). HS is everywhere and is found on the cell surface and in the extracellular matrix. HS is also one of the most complex GAGs in the body. When it is not degraded, it remains stored inside the cells in the body. HS is not intrinsically toxic, but when it accumulates in large amounts, the effect of storing it in the body can lead to many physical problems.

HS is broken down sequentially by several enzymes in a pathway described in detail on page 9. Enzymes



EVERETT

are special types of proteins that help build and break down complex molecules inside a cell. Deficiency in any enzyme in the pathway results in accumulation of HS and is the cause of each unique subtype of MPS III.

Usually, babies show no sign of the disease at birth, but as more and more GAGs accumulate, symptoms start to appear as a result of progressive damage. Unlike other MPS diseases, most of the damage in MPS III is to the central nervous system (CNS).

Consuming sugar or foods normally eaten will not affect whether there is more or less buildup of GAG.

**MPS III is caused by accumulation of the GAG, heparin sulfate, that seems to particularly affect the CNS. Consuming sugar or foods normally eaten will not affect the buildup of GAGs in the body.**

# How is MPS III diagnosed?

Doctors may consider testing for MPS III 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.

To diagnose MPS III, the doctor will typically first do a urine test to look for levels of GAGs that are higher than normal. The results are compared to levels of GAGs that are known to be normal for age-matched individuals without MPS III. Most, but not all, individuals with MPS have GAG levels in their urine that are higher than those of individuals without MPS.

A urine test is only one of the first steps in diagnosing MPS III. To confirm the diagnosis, the doctor needs to measure 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 III, the enzyme activity levels are much lower or absent.

Early diagnosis of MPS III is critical. The earlier MPS III is diagnosed, the sooner potential treatment options can be explored.

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.

A clear diagnosis of MPS III requires tests conducted by experts showing enzyme activity much lower than normal or absent.

## Genetic testing

The four subtypes are caused by separate genes that encode the separate enzymes. Each of the four

subtypes of MPS III have a different enzyme deficiency, but they all lack the ability to break down the GAG HS.

Type	Gene	Enzyme
MPS IIIA	<i>SGSH</i>	heparan <i>N</i> -sulfatase
MPS IIIB	<i>NAGLU</i>	<i>N</i> -alpha-acetylglucosaminidase
MPS IIIC	<i>HGSNAT</i>	acetyl-CoA:alpha-glucosaminide <i>N</i> -acetyltransferase
MPS IIID	<i>GNS</i>	<i>N</i> -acetylglucosamine 6-sulfatase

DNA tests can identify the specific changes in the genes that are responsible for making the missing enzyme. There are two major types of gene mutations. Some mutations (missense mutations) encode for an enzyme that is just slightly modified, while other mutations (nonsense mutations) are so severe that

no enzyme is produced at all. While the implications of each of the many possible mutations are not understood at this time, individuals who have mutations where no enzyme is produced are more likely to have the severe form of MPS III.



## ALLIE

Until recently, the common diagnostic genetic test was a chromosomal microarray that could detect approximately 15%-20% of cases with a genetic basis. New technologies are being developed, however, that may allow DNA tests to become a first-line diagnostic tool for MPS diseases. Next-generation sequencing techniques can now quickly, and more cost effectively, analyze the exome through whole exome sequencing (WES) or genome through whole genome sequencing (WGS) of individuals. WES sequences all of the DNA that encode proteins and is about 1.5%-2% of the entire genome.

Multi-gene panels that test specifically for groups of diseases are another approach to offer sequencing of all of the known genes for a particular group of

diseases. Some of these panels are specific for all of the MPS disease-causing genes and are currently being offered free of charge. Please contact the National MPS Society for more details.

It is important to note that different methods of DNA analysis will detect different types of genetic variants. No test will perfectly cover all possible mutations. Many commercial DNA testing sites are now advertising relatively inexpensive DNA tests. Some are of little predictive value to individuals with MPS. Even when the complete genome is sequenced, the quality of testing can vary significantly.

If you want a personal DNA analysis, be sure to pick a clinical-grade laboratory that is Clinical Laboratory Improvement Amendment certified and College of American Pathologist accredited. Additionally, the results should be analyzed by someone familiar with genetics as the implications for disease are very specific, and not all mutations are harmful. Once the genetic mutations in the individual with MPS III have been identified, accurate testing is available for other interested relatives.

Individuals with MPS III should receive DNA testing prior to discussing treatment options.

DNA tests can be diagnostic in many situations when performed by a clinical-grade laboratory, and the results are analyzed by appropriate genetic counselors. Gene panels may offer an initial analysis that is more affordable. Consult your doctor or genetic counselor for more information.

Individuals with MPS III should have DNA testing after the initial diagnosis through analysis of urine or blood. In some cases, severity may be predicted by mutational analysis.

# Specific treatment of MPS III

## Overview

The goals of managing MPS III 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 III; however, early intervention may help prevent some irreversible damage.

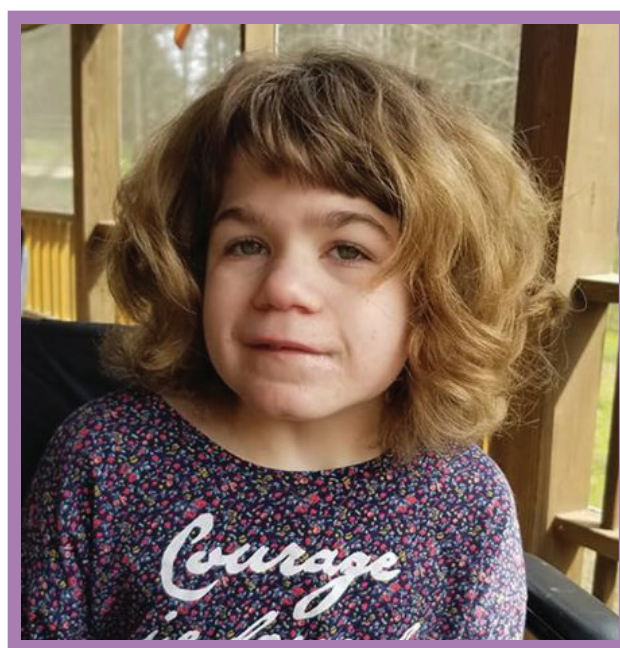
Until recently, the main treatments for MPS III have been symptom management, but newer treatments are entering clinical trials that may significantly improve disease outcomes in the future.

## 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, enzyme replacement therapy (ERT) provides an external source of the deficient enzymes. The enzyme travels through the bloodstream and enters cells in various organs where it helps break down GAG buildup.

Unfortunately MPS III requires that the enzyme enter directly into the brain, and this does not happen in regular ERT. Several new approaches are in development to get ERT successfully into the brain, including intrathecal delivery (into the spinal canal).

There are also approaches that modify the enzymes so that they will be able to cross the blood-brain barrier. Enzymes have been successfully fused to several different molecules that can help transfer the enzyme directly into the brain. Early clinical trials of some of these modified enzymes are underway and have shown



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promise in delivering the enzyme into neurons and associated cells in the brain.

For parents or individuals to fully understand the risks, benefits, and limitations of ERT, it is important to talk with physicians familiar with MPS III 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)

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Like ERT, HSCT is used to restore activity of the deficient enzyme. HSCT has become the treatment of choice for many individuals with MPS I; however, it has rarely been used on individuals with MPS III.

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 reduce 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.

Donor stem cells must be carefully chosen to match the recipient as closely as possible to minimize rejection. Before a transplant, the individual needs a conditioning protocol. Typical protocols include chemotherapy and other medications to prepare the body to accept the transplanted stem cells and to avoid graft-versus-host

disease (GVHD). This process eliminates the individual's immune system that will be "rebuilt" over time as the new donor cells reproduce and repopulate the individual. After a transplant procedure the child will need to repeat all vaccinations received prior to the procedure.

The disadvantages of HSCT include the risk of mortality, the problem of finding a suitable donor, GVHD, and the necessity of a very specialized medical facility. The procedure and guidelines have been improved over time so that experienced centers now report up to 90% survival rates.

Transplants require very specialized medical centers and extended hospitalizations. They will also require frequent follow-ups and regular evaluations. Transplants should be performed at Centers of Excellence familiar with the unique needs of individuals with MPS.

As genetic techniques have improved, new methods of HSCT are being attempted using the individual's own cells. For example, a healthy copy of the *SGSH* gene (MPS IIIA) has been modified and introduced back into an individual's own stem cells that are reintroduced into their body. As the cells belong to the same individual, the possibility for rejection and immune complications are significantly less, and healthy enzyme can be produced. This process is in clinical trial.

**For individuals to fully understand the risks, benefits, and limitations of HSCT, it is important to talk with transplant physicians and families who have had the procedure. The National MPS Society can put you in touch with physicians and families so you can become better informed before reaching a treatment decision.**

For more information, see the Mucopolysaccharide (MPS) Disorders and Hematopoietic Stem Cell Transplantation (HSCT) Fact Sheet <https://mpssociety.org/learn/education/fact-sheets/hsct-facts/>.



## Gene therapy

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Gene therapy is another promising treatment option that is in several clinical trials. There are two approaches to gene therapy. *Ex vivo* therapies attempt to modify an individual's own cells (usually stem or blood) to correct the gene deficiency and then to reintroduce these cells back into the individual.

*In vivo* gene therapy involves inserting a healthy gene into a type of vector (DNA transfer vehicle) that can introduce the gene into a person's body. The vector is usually a type of modified virus. Retroviral vectors insert the healthy gene directly into an individual's genome, but this method can lead to unintended disruption of other genes and is no longer the first choice of treatment.

Adeno-associated viral vectors (AAV) do not integrate into the host genome. They can replicate within cells and are less likely to cause other genetic mutations or damage. This method of gene delivery is currently being

used in multiple clinical trials. It was reported to be well tolerated following a one-time administration, and there were signs of neurocognitive stability in one patient and continued normal cognitive development in a second younger patient. Clinical trials are ongoing.

Genome editing techniques are also under investigation. These techniques can be used to modify an individual's own stem or blood cells by correcting mutated genes. The healthy enzyme-producing cells can then be reintroduced into the body through HSCT.

While there are many promising new techniques and emerging clinical trials, they are mostly in early safety stages and will require further study to determine their long-term safety and efficacy. Be sure to consult with your doctor and genetics specialist to determine the best options to consider.

**Many promising new treatments are currently entering clinical trials. Consult your doctor and genetics specialist to determine which options are the best to consider.**

## Substrate reduction therapy

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Substrate reduction is a potential treatment method that works by slowing down the production of GAGs in order to reduce the rate at which they build up in lysosomes. Research into this treatment has shown promising results in children with MPS IIIA and IIIB,

including lower levels of GAG in the urine, improved cognitive function, reduced hyperactivity and irritability, and improved sleep. Subsequent studies have not been as promising, and more work needs to be done.

## Autophagy Activators

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A new potential treatment area is developing from observations that autophagy (a process used by cells to dispose of their waste) is impaired in at least some forms of MPS. There is hope that enhancing autophagy can help reduce accumulated GAG in individuals with MPS III. Preclinical studies in a mouse model of

MPS IIIB demonstrate that trehalose (a small sugar molecule) can reach the brain when given orally, and can reduce inflammation in the brain and retina, as well as extend the animal's life span. It has been shown to be safe in clinical trials for other diseases, and preparations for clinical trials for MPS III are underway.

Other investigational approaches that may be effective in the future for certain individuals with MPS III include molecular chaperone and small nuclear RNA (snRNA) therapies. A list and description of current clinical trials

can be found at [clinicaltrials.gov](https://clinicaltrials.gov). Contact the National MPS Society for more detailed information about current and emerging treatment options.

Currently, there are no specific treatments to cure the underlying enzyme deficiency for MPS III, but promising therapies are being studied.

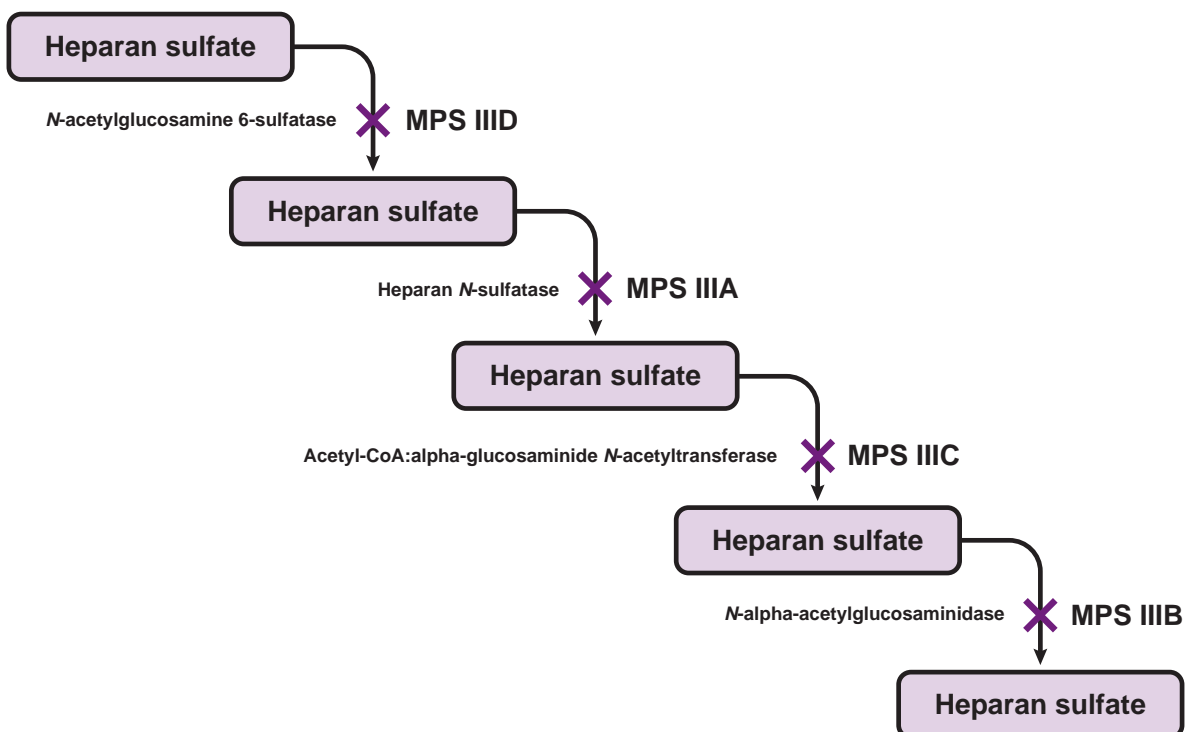
## Are there different types of MPS III?

There are four types of MPS III (A, B, C, and D), each associated with a specific enzyme deficiency (**Figure 1**). Enzymes are special types of proteins 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 in any of these four enzymes results in accumulation of the GAG, heparan sulfate, and this causes MPS III. Individuals with any

form of MPS III experience similar symptoms; however, those with MPS IIIA tend to have symptoms that develop earlier, and the disease progresses more rapidly. Each form of the disease has a wide spectrum of clinical severity. Therefore, it is more appropriate to view MPS III as a continuous spectrum of disease from the most severely affected individuals to the less severely affected (attenuated) individuals.

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

**Figure 1.** HS degradation and types of MPS III.





COLIN

### ***MPS IIIA***

MPS IIIA is the most common and often the most rapidly progressing of the four types of MPS III. The disease usually begins in early childhood with symptoms beginning to appear around 2 years of age. Symptoms include severe neurological manifestations, eg, progressive dementia, aggressive behavior, hyperactivity, seizures, deafness, loss of vision, and sleep disorders. It is caused by a defect in the *SGSH* gene that codes for heparan *N*-sulfatase (also known as *N*-sulfo-glucosamine sulfohydrolase, HS sulfatase, and HS sulfatase sulfamidase), an enzyme involved in the breakdown of HS. Individuals with MPS IIIA do not have a normal, functional form of this enzyme that results in an incomplete breakdown product of this GAG accumulating in the cells. Most individuals with MPS IIIA rarely live beyond their teenage years.

### ***MPS IIIB***

Often symptoms of MPS IIIB also begin in early childhood. Symptoms include severe neurological manifestations, e.g., progressive dementia, aggressive behavior, hyperactivity, seizures, deafness, loss of vision, and sleep disorders. It is caused by a defect in the *NAGLU* gene that codes for *N*-alpha-acetylglucosaminidase, another enzyme involved in the breakdown of HS. Individuals with MPS IIIB do not have a normal, functional form of this enzyme that results in an incomplete breakdown product of this GAG accumulating in the cells. Individuals with MPS IIIB rarely live beyond the second decade, although some live longer.

## MPS IIIC

MPS IIIC, although not as common as MPS IIIA, also manifests in early childhood. Symptoms include severe neurological manifestations, e.g., progressive dementia, aggressive behavior, hyperactivity, seizures, deafness, loss of vision, and sleep disorders. It is caused by a defect in the *HGSNAT* gene that codes for acetyl-CoA:alpha-glucosaminide *N*-acetyltransferase (also known as heparan-alpha-glucosaminide *N*-acetyltransferase), another enzyme involved in the breakdown of HS. Individuals with MPS IIIC do not have a normal, functional form of this enzyme that results in an incomplete breakdown product of this GAG accumulating in the cells. Most individuals with MPS IIIC live well into their teenage years and some live longer.

## MPS IIID

MPS IIID is the most rare form of MPS III, and can also begin to show symptoms in early childhood. Symptoms include severe neurological manifestations, e.g., progressive dementia, aggressive behavior, hyperactivity, seizures, deafness, loss of vision, and sleep disorders. It is caused by a defect in the *GNS* gene that codes for *N*-acetylglucosamine 6-sulfatase (also known as glucosamine-6-sulfatase), another enzyme involved in the breakdown of HS. Individuals with MPS IIID do not have a normal, functional form of this enzyme that results in an incomplete breakdown product of this GAG accumulating in the cells. Most individuals with MPS IIID live well into their teenage years and some live longer.



LUKE

## How common is MPS III?

MPS III is a rare mucopolysaccharide disease. It is the most common of all MPS diseases, with an estimated combined frequency for all four types of 1 in 70,000 live births. MPS IIIA is the most common with an estimated frequency of 1 in 60,000 live births. The next most common is MPS IIIB with an estimated frequency of 1 in 95,000 live births. MPS IIIC, at an estimated

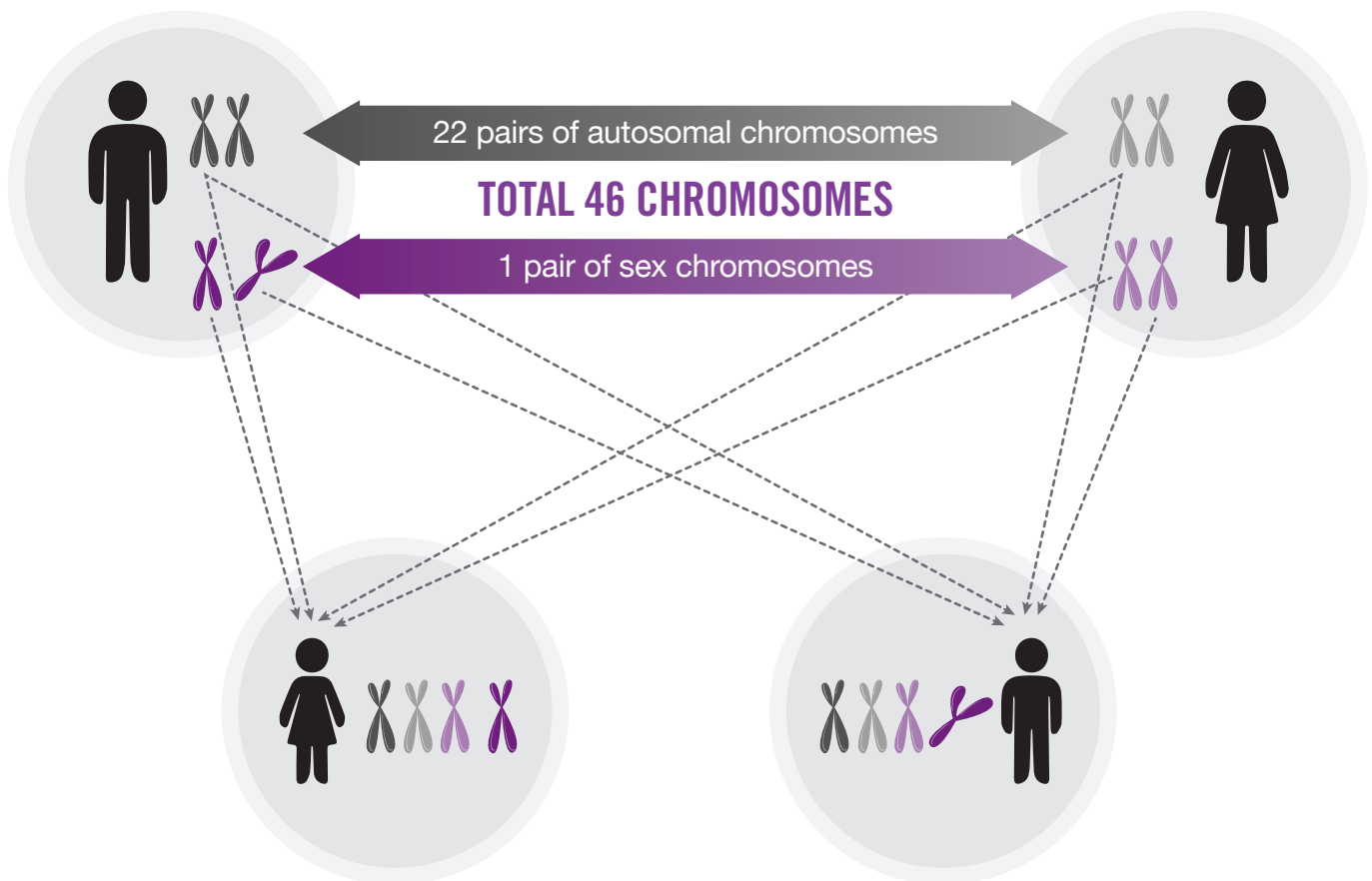
frequency of 1 in 230,000 live births, and MPS IIID, at an estimated frequency of less than 1 in 1,000,000 live births, are much rarer. Although MPS III itself is rare, the cumulative incidence of all MPS diseases is 1 in 25,000 births, and the larger family of LSDs collectively occur in about 1 in every 5,000 to 7,700 births.

# How is MPS III inherited?

To understand inheritance of MPS III, it is important to grasp some basic concepts about genetics and inheritance (**Figure 2**). 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.

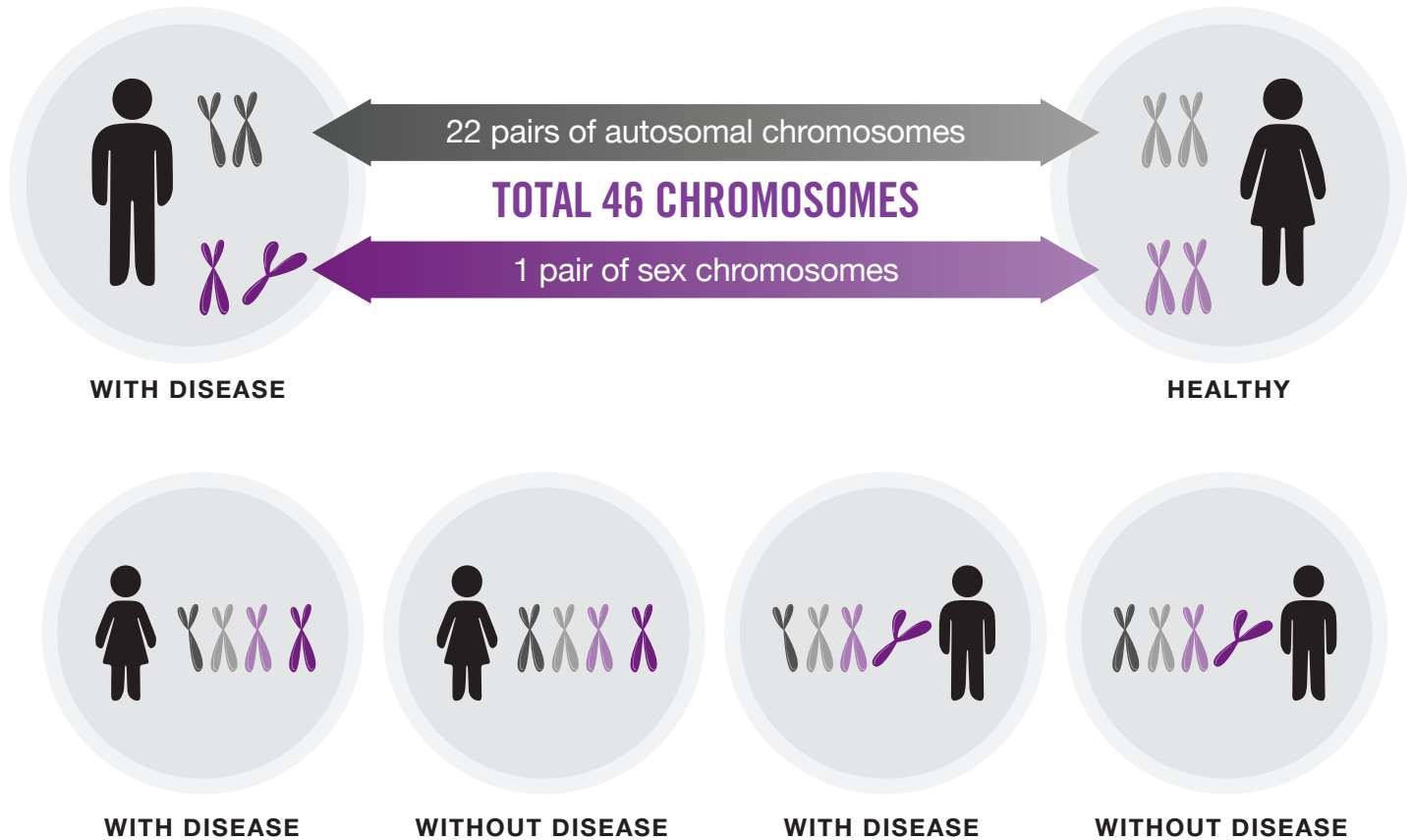
**Figure 2.** Normal inheritance.



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 3**). That is because the

inappropriately functioning gene from the parent that has the disease dominates over the healthy gene of the other parent.

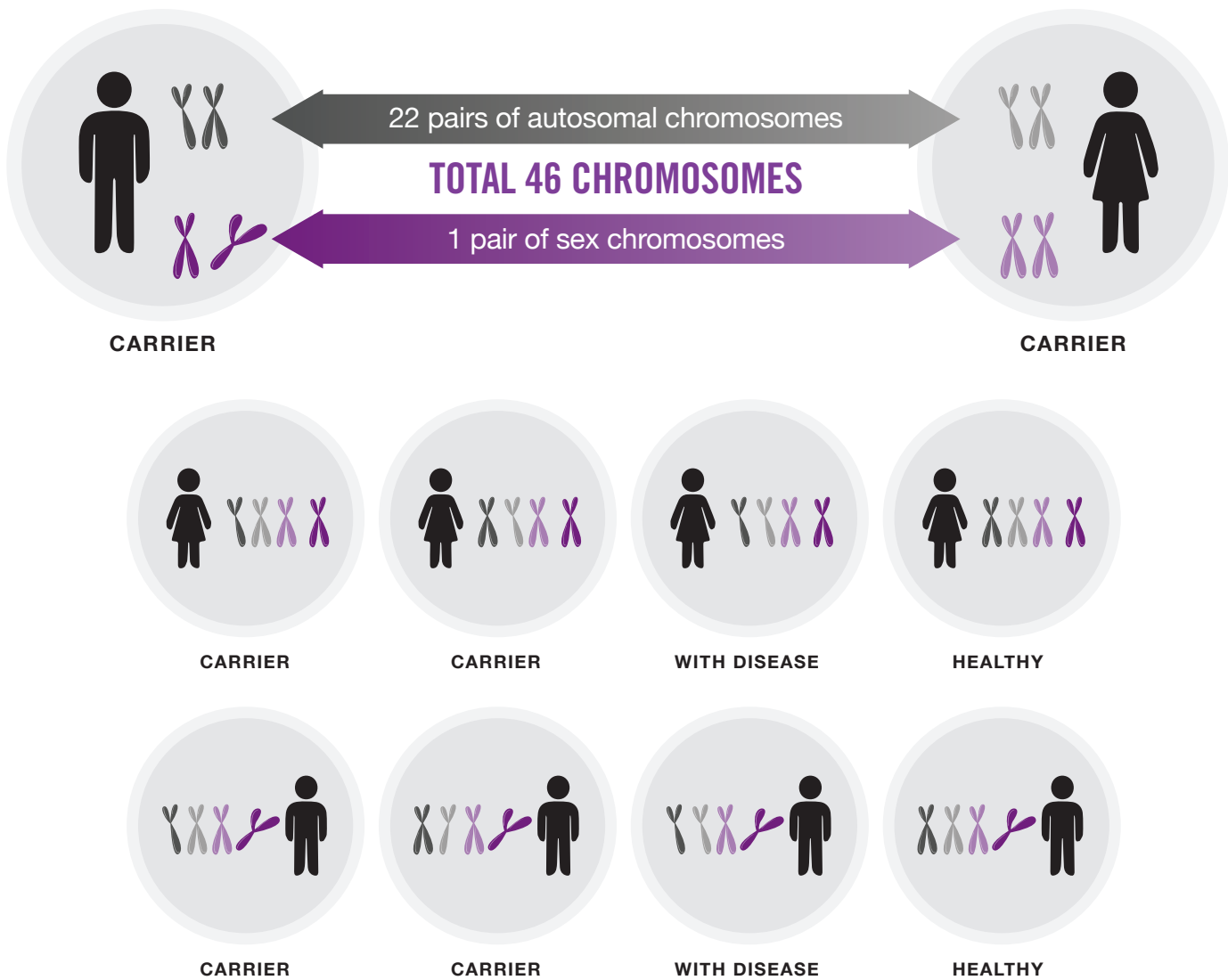
**Figure 3.** Autosomal dominant inheritance with one parent affected.



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. Individuals with these recessive genes appear normal because they have one normally

functioning gene from one of their parents 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 4**).

**Figure 4.** Autosomal recessive inheritance with both parents as carriers.



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.

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 one 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.



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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 and 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.

**MPS III is an autosomal recessive disease caused by deficiency in specific enzymes that all interfere with the breakdown of the GAG, HS.**

**All families of affected individuals 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.**

The probability of related parents having similar recessive gene mutations increases dramatically.

Some genes code for enzymes. Since there are 2 copies of each gene, 1 inherited from the father and the other from the mother, each enzyme is produced from 2 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 1 of the 2 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 III is an autosomal recessive genetic disease; that means that the genes that cause this disease are on the 22 autosomal chromosomes and that it shows up only when both copies of the genes, 1 each inherited from the father and mother, are not functioning properly (**Figure 4**). MPS IIIA is caused by a defect in the *SGSH* gene that is located on chromosome 17. MPS IIIB is caused by a defect in the *NAGLU* gene that is also located on chromosome 17. MPS IIIC is caused by a defect in the *HGSNAT* gene that is located on chromosome 8. MPS IIID is caused by a defect in the *GNS* gene that is located on chromosome 12.



# 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 product 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 excess or a deficiency in the gene production. When the defective gene codes for an enzyme, this could mean too much or too little enzyme activity. In the case of the four MPS III subtypes, each subtype has a different defective gene, resulting in a different defective enzyme. Each subtype results in highly reduced or completely absent activity of that particular enzyme, but all four result in incomplete degradation of the same GAG. Furthermore, the reduction of any of these enzymes can cause variable disease severity due to the nature of the particular mutation an individual may have. For example, there are well over 100 different mutations described that can cause MPS IIIA. Taken together, the complex nature of the disease and the underlying causes result in a disease with a spectrum of severity.

The genes coding for heparan *N*-sulfatase (*SGSH*; MPS IIIA) and *N*-alpha-acetylglucosaminidase (*NAGLU*; MPS IIIB) have been studied extensively, and mutations that cause deficiencies in these two enzymes have been identified. Individuals with mutations that result in absolutely no enzyme being produced have more severe disease. Other mutations result in little or defective enzyme being produced. Still others are not common at all and may occur in only one family. The genes coding for acetyl-CoA:alpha-glucosaminide

*N*-acetyltransferase (*HGSNAT*; MPS IIIC) and *N*-acetylglucosamine 6-sulfatase (*GNS*; MPS IIID) have also been studied, but not as extensively because MPS IIIC and IIID are very rare forms of this disease.

To date, there are only a few correlations between specific gene mutations and enzyme activity, and consequently, little correlation with disease severity. Based on available evidence, there is no definitive process known to predict the severity of the disease. Further, data suggests there are other factors, which are not yet fully understood, involved in determining disease severity. Thus, DNA tests or mutational analysis are not always sufficient to predict disease severity.



NATHAN

All forms of MPS III are complex diseases with widely varying severity that is not always predictable based on DNA testing or enzyme activity alone.

# How long do individuals with MPS III live?

The lifespan of a patient with MPS III depends on many factors including, but not limited to, severity of the disease, specific symptoms, treatment received, when the treatment was started, how long the treatment continued, etc. With our current knowledge of the disease, it is difficult to predict how long individuals with MPS III will live. Typically, individuals with MPS III live into their teens. Individuals with severe disease,

e.g., MPS IIIA, may not even live that long. Some individuals live into their twenties. Other individuals with attenuated phenotypes (milder presentation) have been known to live into their thirties and forties, and rarely into their fifties or sixties. There is always hope for better outcomes for patients with MPS III with ever-improving newer treatments and technology.

The lifespan of patients with MPS III can vary widely depending on severity of disease, treatment received, and how fast the disease progresses.

## Signs and symptoms of MPS III

MPS III affects multiple organ systems and is associated with a wide range of symptoms. The many signs and symptoms of MPS III that are common to all four types are summarized in the Table.

Detailed descriptions are given further below. Please note that not all individuals with MPS III will exhibit all symptoms or to the same degree; the symptoms and their severity can vary widely between individuals.

**Table:** List of symptoms exhibited by individuals with MPS III by organ systems.

General symptoms	Physical appearance
<ul style="list-style-type: none"><li>• Hyperactivity</li><li>• Restlessness</li><li>• Aggressive/destructive behaviors (decline with age)</li><li>• Sleep disorders</li><li>• Autistic-like behaviors</li><li>• Frequent chewing (hyperorality)</li><li>• Difficulty chewing or swallowing (late-stage disease)</li><li>• Delayed language</li></ul>	<ul style="list-style-type: none"><li>• Mild physical abnormalities</li><li>• Abnormal facial features (such as flat face, thick lips with upper lip upturned, fleshy nose tip, slightly bulging eyes, enlarged tongue that may stick out), but much less prevalent and pronounced than other MPS diseases</li><li>• Large head (macrocephaly) in children, but not older individuals</li><li>• Normal or just below normal height</li><li>• Coarse hair and more hair than usual (hirsutism)</li><li>• Dark, bushy eyebrows</li><li>• Protruding stomachs</li></ul>
Eyes	
<ul style="list-style-type: none"><li>• Vision problems due to retinal damage</li><li>• Night blindness</li><li>• Loss of peripheral vision</li></ul>	

<p><b>Mouth and teeth</b></p> <ul style="list-style-type: none"> <li>• Thick lips with upper lip upturned</li> <li>• Enlarged tongue (macroglossia)</li> <li>• Abnormal teeth (widely spaced and very thin enamel)</li> <li>• Broad gum ridges</li> </ul>	<p><b>Heart and blood vessels</b></p> <ul style="list-style-type: none"> <li>• Heart valve problems (usually mild)</li> </ul>
<p><b>Ears, nose, and throat</b></p> <ul style="list-style-type: none"> <li>• Frequent ear infections (otitis media)</li> <li>• Hearing loss</li> <li>• Frequent and recurrent sinus infections (sinusitis)</li> <li>• Enlarged tonsils and adenoids</li> <li>• Narrow, floppy, and soft trachea</li> <li>• Sleep apnea</li> </ul>	<p><b>Brain and nerves</b></p> <ul style="list-style-type: none"> <li>• Behavioral problems</li> <li>• Developmental delays</li> <li>• Altered circadian rhythm (day-night cycle)</li> <li>• Lack of fear and/or irrational anxieties</li> <li>• Cognitive decline</li> <li>• Loss of language</li> <li>• Seizures</li> <li>• Early onset dementia (slowly progressing disease)</li> <li>• Fluid in the brain (hydrocephalus)</li> <li>• Carpal tunnel syndrome (rare)</li> </ul>
<p><b>Gastrointestinal system</b> (abdomen and intestines)</p> <ul style="list-style-type: none"> <li>• Abnormal metabolism of medications (in some cases)</li> <li>• Slightly enlarged liver and spleen (hepatosplenomegaly)</li> <li>• Diarrhea and/or constipation</li> <li>• Umbilical and inguinal hernias</li> </ul>	<p><b>Musculoskeletal system</b> (bones and joints)</p> <ul style="list-style-type: none"> <li>• Minimal problems with bone formation and growth</li> <li>• Joint stiffness</li> <li>• Hip pain</li> <li>• Hip deformities (femoral head osteonecrosis)</li> <li>• Scoliosis (mild-to-moderate)</li> <li>• Osteoporosis at an early age</li> <li>• Increased risk of fractures</li> <li>• Hip dislocation (uncommon)</li> <li>• Bent fingers (occasional)</li> <li>• Difficulty extending arms fully</li> <li>• Knock knees (mild)</li> <li>• Tight Achilles tendon</li> <li>• Broad feet with toes curled under</li> <li>• Carpal tunnel syndrome (rare)</li> </ul>
<p><b>Gastrointestinal system</b> (abdomen and intestines)</p> <ul style="list-style-type: none"> <li>• Lung problems</li> <li>• Reduced lung function</li> <li>• Frequent coughs and colds</li> </ul>	

MPS III affects many areas of the body. Because its signs and symptoms are so variable, it can affect each individual very differently.

## Growth

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Growth is affected in about 50% of individuals with MPS III who are older than 12 years. However, most

individuals with MPS III grow to a reasonably normal height.

## Physical appearance

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Individuals with MPS III usually have very mild abnormalities in their facial features that are often easily missed. In younger individuals, the head tends to be larger than for normal individuals. However, this difference seems to lessen with age as older individuals with MPS III have a normal head circumference. The tip of the nose may appear fleshy and the outer ears may appear thickened. These facial features are due to GAG storage in the soft tissues of the face and abnormal facial bones and cartilage. Occasionally, individuals with MPS III are described as having “coarse facial features,” which is not intended to be insensitive, but rather help with a quick and accurate diagnosis. However, it must be noted that these features are far less pronounced among individuals with MPS III than with other MPS diseases.



SARA

Unlike individuals with other MPS diseases, those with MPS III usually have very mild abnormalities in their facial features, which are often missed.

## Mouth and teeth

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Individuals with MPS III often have a thick lower lip that is turned outwards and an upturned upper lip. They may also have an enlarged tongue (macroglossia). Their gum ridges can be broad. Their teeth are often widely spaced and poorly developed 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 III should be given daily 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 severely affected young child.

If an individual with MPS III 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 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 III 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 III should discuss supplemental fluoride with their dentist. Cleaning inside the mouth with a small sponge on a stick soaked in mouthwash will help keep the mouth fresh and avoid bad breath.

Dental surgery, under anesthesia, including simple extractions, must be done only in a hospital setting with an experienced anesthetist and dentist. Additional precautions must be taken for those with heart conditions.

## Skin

Individuals with MPS III tend to have thickened and tough skin, making it difficult to draw blood or place IV catheters. Some individuals have dark, bushy eyebrows

that meet in the middle. Some individuals have excessive hair on their face and back (hirsutism).

Individuals with MPS III may have thickened and tough skin and extra hair.

## Eyes

Unlike many other MPS diseases, individuals with MPS III do not have corneal clouding. Storage of GAG in the retina can cause changes in the retina, leading to night blindness and the loss of peripheral vision (ability to see things out of the corner of the eyes). Night blindness may hamper a person's ability to go through

dark areas and waking up at night might cause them to be afraid. Adequate, but not too bright, night lighting in the bedroom or hall can help alleviate the last issue. It is important to consult an eye doctor (ophthalmologist) to take corrective action.

Problems with night blindness are common among individuals with MPS III. It is important to consult an eye doctor (ophthalmologist) to determine the cause for vision loss and take corrective action.



### NEVAEH

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

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.

### *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 III.

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.

## *What is otitis media?*

Otitis media (OM) is the medical term for an infection of the middle ear. It is common for healthy children to have OM usually caused by blockage of the Eustachian tubes due to large adenoids or problems with drainage of fluid from the middle ear. In children with MPS III, this is complicated by the buildup of GAG in the middle ear, nose, mouth, and throat resulting in recurrent ear infections which become more stubborn, thereby exacerbating the problems. There are two types of OM, acute and OM with effusion.

***Acute otitis media:*** This occurs when fluid is present in the middle ear, along with signs or symptoms of ear infection such as bulging eardrum often with pain, ear tugging, fever, irritability, decreased appetite, vomiting, and diarrhea. Complications, although rare, can include broken eardrum (tympanic membrane perforation), inflammation in the area surrounding the middle and inner ear (acute mastoiditis), or a serious, potentially life-

threatening inflammation of the membranes covering the brain (meningitis). Language development can also be affected by repeated ear infections.

***OM with effusion (OME):*** OME is diagnosed when there is fluid in the middle ear without signs or symptoms of middle ear infection. OME can lead to conductive deafness, difficulty with learning speech and language (hearing problems interfere with speech and language development), and thickening or scarring of the eardrum.

For some individuals with MPS III, a number of middle ear infections may occur before MPS III is diagnosed. The individual may not have any symptoms, but hearing can be affected. Any individual who has fluid in the middle ears for at least 3 months should have a hearing test. A careful examination of the ear may be difficult for a child with MPS III but is essential for proper diagnosis. Ear, nose, and throat (ENT) specialists, also called otolaryngologists, can help diagnose MPS III by identifying children with recurrent infections and abnormalities seen under examination. Once a diagnosis of MPS III has been made, the ENT specialist can be very helpful with many of the issues regarding managing the symptoms associated with the ears, nose, and throat.



MORGEN

**Medication:** Children with MPS III tend to have many ear infections that can be very difficult to treat. If your child has ear infections that are hard to get rid of, it may be necessary for the doctor to do a “culture” of the fluid in the middle ear. The doctor will take a sample of this fluid and test it to see which bacteria, viruses, or fungi are living in the fluid. Identifying the bacteria, virus, or fungus that may be causing the infection allows the doctor to prescribe the appropriate medication. For example, if the infection is fungal, frequent antibiotic use will only worsen the situation.



SOLOMON

Antibiotics are the usual treatment for OM. There is a wide array of antibiotics available for treatment. Some require refrigeration or frequent dosing. Antibiotic injections can be considered for a child who has difficulty taking medications by mouth. Some common side effects of antibiotics include diarrhea, nausea, and vomiting. They may also cause skin rashes and allergic reactions. Occasionally, older children may have infections caused by other bacteria (such as *Pseudomonas aeruginosa* or *Staphylococcus*

*aureus*) that can be more difficult to treat. If the child has t-tubes, ear drops may be used to treat the infection. Steroid drugs which reduce inflammation (corticosteroids) may also be helpful.

**Use of ear tubes:** In most cases of repeated ear infections, inserting tubes into a hole in the eardrum (tympanostomy) is recommended to allow the fluid to drain. T-tube insertion is a 10–15-minute procedure usually performed under general anesthesia. The tubes help the child by keeping the middle ear ventilated. There are several different types of ear tubes. Ear tubes may become blocked or infected. They may also damage or scar the eardrum. It is important to consult with an ENT specialist experienced with MPS III to determine which tube is best. Please note that this should always be done at a properly equipped hospital and only after consultation with the anesthesiologist, because of anesthesia concerns for children with MPS III (described in a separate section in this resource). After the procedure, a culture should be made from the drained fluid to identify the offending organism.

**Surgery:** Removal of the adenoids (tissues at the back of the nasal cavity) and tonsils might also be recommended for children with MPS III who have recurrent acute OM. If the child is to have general anesthesia for the placement of ear tubes, removal of the adenoids and tonsils should also be considered at the same time. This avoids some of the risk by reducing the number of procedures requiring anesthesia.

**Prevention:** Children can receive a vaccine for *Streptococcus pneumoniae*, which is one of the more common bacteria that cause ear problems. This might help reduce the number of future bacterial infections. Vaccines may cause a mild fever or pain, redness, or swelling at the site of injection. More serious side effects include allergic reactions (these are rare). Some children



may benefit from eliminating common food allergens from the diet. These can include soy, citrus, peanuts, wheat, fish, eggs, corn, and tomatoes. Some parents report positive results from supplementation with cod liver oil or other fish oils. Check with your doctor about adding a multivitamin to the child's diet. Exposure to second-hand cigarette smoke is recognized as a risk factor for OM, and every effort should be made to keep children away from smoke exposure.

Ear infections seem to be a persistent and recurrent problem in children with MPS III, and anything that can help relieve the symptoms may be warranted. Each child may respond differently to various treatments, so every option should be tried if needed. Consult with your doctor before trying a new treatment, including herbal or alternative treatments. MPS III can cause frequent ear infections, hearing loss, an enlarged tongue, decreased mental capacity, and blocked airways. Any of these symptoms may lead to speech and language problems. A speech therapist may help those with MPS III with their speech. Hearing aids and sign language may also be useful for individuals with hearing loss.



ZOE

Object exchange systems have been developed that use technology to help facilitate communication. Augmentative and alternative communication (AAC) applications on tablets and devices can help individuals communicate. A popular example of an AAC is a picture exchange communication system (PECS).

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

It is important to consult with an ENT specialist experienced with MPS III to determine how best to treat ear infections and deafness.

Treatment for otitis media may include medication, ear tubes, or surgery. Surgery should only be performed in a hospital under appropriate anesthesia and under the care of specialists with expertise in treating MPS III or at least MPSs in general.

Prevention of ear infections in individuals with MPS III may be an option. Please consult your doctor about vaccinations.



DANIELLA

## Nose and throat

Nose and throat problems are common among most individuals with MPS disease in general but less common among individuals with MPS III. How severe the problems are seems to depend on the individual.

### Runny nose

The bridge of the nose may be flattened in some individuals, making the passage behind the nose smaller than usually seen in individuals without MPS disease. This is due to the bones in the mid-face not having grown well and the mucosal lining in the nose being thicker. GAG buildup in the soft tissues of the nose and throat, combined with abnormal bones, can cause the

airway to become easily blocked. Some individuals often have a long-term (chronic) discharge of clear mucus from the nose (rhinorrhea) due to abnormal drainage of normal secretions and chronic ear and sinus infections.

### Throat

The adenoids (tissues at the back of the nasal cavity) and tonsils often become enlarged and can partly block the airway. The windpipe (trachea) becomes narrowed by stored GAGs and this can cause problems with anesthesia, swallowing, and sleep apnea than in individuals without MPS disease, due to abnormal cartilage rings in the trachea.

**Nose and throat problems are worse in individuals with more severe MPS III. Please consult an ENT specialist (otolaryngologist) to determine best course of action for nose and throat issues that arise.**

**A speech therapist may be able to help individuals with MPS III with their communication.**

## Respiratory system

Individuals with MPS III tend to suffer from frequent coughs and colds. They may have restless nights, waking up frequently. Some individuals may stop

breathing for short periods during sleep (sleep apnea). However, sleep apnea is uncommon among individuals with MPS III.

## *Infections*

Colds are caused by viral infections and do not require antibiotic treatment. However, many individuals with MPS III develop secondary bacterial infections in addition to colds. These bacterial infections usually occur in the sinuses or middle ear (discussed earlier). In individuals with MPS III, storage of GAGs in the mouth and throat can cause blockage and/or malfunction of the tube that connects the middle ear to the throat to equalize pressure in the middle ear, drain secretions from the ear, and protect the ear from mucus from the nose and throat (Eustachian tube), thereby causing middle ear infections. Storage of GAGs in the nose and throat results in abnormal shapes and blockage of sinus passages that increases the risk for sinus infections. Bacterial infections of the middle ear and sinuses should be treated with antibiotics under the care of a physician knowledgeable about MPS.

There are many different antibiotics available and each one has its own spectrum of side effects. Some common side effects of antibiotics include diarrhea, nausea, vomiting, skin rashes, and allergic reactions. Since the middle ear and sinuses do not drain properly, getting rid of infections can be difficult. It is

common to have infections seem to go away while the individual is taking antibiotics and then come back after the antibiotic course is over. Many individuals with MPS III may become allergic to antibiotics or may develop resistant infections. Your doctor can prescribe other antibiotics to help manage this problem. While overusing antibiotics is never advised, most individuals with MPS III will require multiple treatments for most infections. You will need a doctor knowledgeable in MPS diseases with whom you can develop a good working relationship to manage the frequent infections.

Individuals with MPS III may respond differently to drugs. It is important that you consult your doctor before using any over-the-counter medications. Drugs for controlling mucus production may not help. Drugs such as antihistamines (allergy medications) may dry out the mucus, making it thicker and harder to dislodge. Decongestants usually contain stimulants that can raise blood pressure and narrow blood vessels, both undesirable for individuals with MPS III. Cough suppressants or drugs that have sedatives may cause more problems with sleep apnea by decreasing muscle tone and breathing rates.

**Secondary bacterial infections of the respiratory system are common among individuals with MPS III. Bacterial infections can be treated with antibiotics, but often recur when treatment is stopped. Multiple rounds of treatments may be needed.**

**Please consult a physician knowledgeable in treating MPSs to treat infections. Please be aware that over-the-counter medications can cause more harm than good.**

## Secretions

Some individuals with MPS III often have collections of mucus (secretions) in the lungs. Chest postural drainage is a technique that can help with clearing such secretions. It involves placing the affected person in different positions to help mucus drain from the lungs. It may be used in combination with tapping the chest or back with a cupped hand (chest percussion) to help loosen the mucus. A physical or respiratory therapist will be able to teach the technique to you, your family, and someone at school for children with MPS III. Possible side effects of chest postural drainage include injury to the ribs, lungs, or diaphragm; bleeding in the lungs; vomiting; aspiration (inhaling mucus, saliva, or vomit into the breathing tubes), difficulty getting enough oxygen during treatment; and fainting (certain positions for chest postural drainage can cause the blood to rush from the head, causing the individual to lose consciousness).

There are also some mechanical devices that can help with clearing secretions. Inflatable vests (“shaky vests”) deliver high-frequency oscillations to the chest. The vibrations help to loosen and potentially thin the mucus in the lungs. The individual puts on the vest, connects it to the vest machine and breathes normally as the chest is massaged. After 5 minutes they stop the machine and attempt to cough. This procedure is repeated for about 30 minutes or as directed by the doctor. There are also cough-assist machines that are basically a mask and mouthpiece connected to a machine. The cough-assist device slowly blows air into the lungs through the mouthpiece and then quickly pulls the air out along with any mucus, simulating a cough. A nebulizer can also be used alone or in conjunction with these devices to deliver saline or prescribed medications into the lungs to help thin secretions.

Chest postural drainage, a technique to drain mucus from the lungs, may be required for some individuals with MPS III and must be done with training from a physical therapist. Please be aware of the side effects of this technique and take the appropriate care.

## Sleep apnea

Although rare, sleep apnea can occasionally be caused by enlarged adenoids or tonsils. It can also occur due to other issues within the CNS.

Obstructive sleep apnea, defined as temporary breathing interruptions (usually 10–30 seconds) while asleep, is an uncommon airway problem for individuals with MPS III. When it occurs, it can result in decreased oxygen levels that can cause heart problems. Although individuals with MPS III affected by sleep apnea may breathe like this for years, a sleep specialist should be consulted for an evaluation with a sleep study,



ROBYN AND RACHEL

especially if a parent or bed partner notices significant choking or episodes of interrupted breathing.

Individuals with MPS III may be admitted to the hospital overnight for a sleep study in which monitors are placed on the skin and connected to a computer to measure the levels of oxygen in the blood, breathing effort, brain waves during sleep, and other indicators of the body's function. From this study, sleep experts can assess the possibility of breathing blockage, the difficulty in inhaling (moving air into the lungs) during sleep, and the effect on the body as a whole.

Sleep apnea can be treated in some individuals by removing the tonsils and adenoids (which may regrow) or opening up the airway during sleep with a continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) machines (please see page 57



PAIGE

for more information on these machines). If these do not work or are inappropriate, a hole into the airway can be made in the front of the neck (tracheostomy) to help individuals breathe.

Sleep apnea is rare among individuals with MPS III. Sleep apnea can be treated by removing the tonsils and adenoids or airway pressure machines (CPAP/BiPAP), or a tracheostomy (if other procedures do not work or are inappropriate).

## Heart

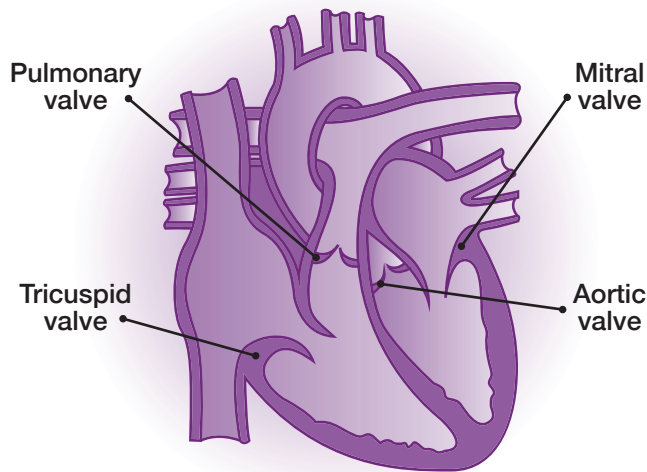
Although heart disease is a major cause of death in many MPS diseases, it is relatively uncommon in individuals with MPS III. Serious heart problems are rare in individuals with MPS III. Heart problems, when they occur, may not develop or cause medical problems until later in life. Heart problems in MPS III usually can be managed with medications.

### *Effects on the heart valves*

Some individuals with MPS III may develop problems, including thickening or stiffening and leakage from their heart valves due to GAG storage. There are four valves in the heart: the tricuspid, the mitral, the pulmonary, and the aortic.

***The tricuspid valve*** is on the right side of the heart between the right atrium (also known as “auricle,” a collecting chamber for blood flowing back from the body) and right ventricle (a muscular pumping chamber that pumps blood to the lungs). The valve prevents blood from flowing backward into the right atrium when the right ventricle of the heart contracts.

***The mitral valve*** is on the left side of the heart between the left atrium (a collecting chamber for blood flowing back from the lungs) and the left ventricle (a muscular pumping chamber that pumps blood to the rest of the body). The valve prevents blood from flowing backward into the left atrium when the left ventricle of the heart contracts.



**The pulmonary valve** sits between the right ventricle and the pulmonary artery (the vessel that transports blood from the heart to the lungs). The valve prevents blood from flowing backward into the heart between its contractions.

**The aortic valve** sits between the left ventricle and the aorta (the vessel that transports blood from the heart to the rest of the body). The valve prevents blood from flowing backward into the heart between its contractions.

The doctor may hear heart murmurs (sounds caused by turbulence in blood flow in the heart) if the valves become damaged by stored GAG. The heart valves are designed to close tightly to prevent blood from flowing back in the wrong direction. Individuals with MPS III with defective valves due to damage by GAG accumulation may experience regurgitation (blood shooting backwards) and/or stenosis (stiffening of the valve).

**Regurgitation:** This occurs when the weakened valve cannot shut firmly enough and a small amount of blood may shoot backwards, causing turbulence and a murmur, e.g., when the mitral valve does not shut firmly causing blood from the left ventricle to flow back into the left atrium (mitral valve regurgitation), or when the aortic valve does not shut firmly causing blood from the aorta to flow back into the left ventricle (aortic valve regurgitation).

**Stenosis:** Stenosis refers to a stiffened heart valve. The valve may not be able to open completely thereby narrowing the opening through which the blood is pumped. When the problem becomes severe, the damaged heart valves may need to be replaced surgically.

Heart valve replacement is not common for individuals with MPS III. There are two types of valves used for valve replacements – tissue or mechanical. Mechanical valves are made of strong durable materials that can last for a patient’s lifetime; however, in order to prevent blood clots from forming, patients are usually treated with blood thinning medication for the rest of their lives.

Tissue valves are created from animal tissue and can last from 10 to 20 years in normal individuals without MPS. They do not usually require the need for blood thinners; however, GAG can still build up on the replacement tissue, possibly limiting their effectiveness. Most published cases used mechanical valves. Please consult with a heart specialist (cardiologist) knowledgeable in MPS diseases for appropriate treatment and care.

Some individuals with MPS III experience heart problems due to abnormal heart valves, which make them susceptible to reverse blood flow (regurgitation) and/or stenosis (stiffened heart valves) that may require surgical intervention. Please consult with a heart specialist (cardiologist) knowledgeable in MPS diseases for appropriate treatment and care.

## *Importance of regular heart checkups*

Although major heart problems are rare in individuals with MPS III, all affected individuals should have regular heart checkups. This includes an annual (or as often as your doctor thinks necessary) echocardiogram to detect any problems as early as possible. The test is painless and similar to the ultrasound screening of babies in the womb. It can detect problems with heart

muscle, heart function, and heart valves. However, like any test, it cannot detect all possible heart problems. It is important to consult a cardiologist knowledgeable in MPS III, or at least MPS diseases. Medications are available to manage heart problems that result from MPS III.

Individuals with MPS III should have regular heart checkups, e.g., echocardiogram, to detect problems early. Please consult with a heart specialist (cardiologist) knowledgeable in MPS diseases for appropriate treatment and care.

## **Gastrointestinal system**

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### *Liver and spleen*

Many individuals with MPS III have mildly enlarged liver (hepatomegaly), or spleen (splenomegaly), or both (hepatosplenomegaly) due to accumulation of GAGs.

The enlargement of these organs does not usually lead to problems, but it can interfere with eating and breathing.

Although enlargement of the liver and spleen themselves may not be problematic, they can interfere with eating and breathing.

### *Abdomen and hernias*

In most individuals with MPS III, the abdomen bulges out due to weakness of the muscles and the enlarged liver and spleen. Part of the abdominal contents will 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 (groin) hernias should be repaired surgically, but they may recur. Umbilical (navel) hernias are not usually treated unless the intestine gets caught in the abdominal opening, which cuts off its blood supply (entrapment) or are very large and are causing problems.

Inguinal (groin) hernias should be repaired surgically but may recur. Umbilical hernias are usually not treated unless they cause other, more serious, problems.

## *Bowel problems*

It is unclear why many individuals with MPS III suffer periodically from loose stools and diarrhea. Sometimes, the problem is caused by severe constipation and leakage of loose stools from behind the solid mass of feces. More often, however, it “comes straight through.” GAG buildup has been found in nerve cells of the intestine which may cause a problem with the autonomic nervous system, the system that controls those bodily functions usually beyond voluntary control, resulting in abnormal bowel movements and diarrhea.

An examination by a physician, supplemented by an X-ray if necessary, may establish the cause of diarrhea. In individuals with MPS III, the problem may disappear as they get older. However, it can be made worse by antibiotics prescribed for other problems. If the diarrhea appears to be affected by diet, it may help to stop eating those foods causing it. If the diarrhea appears to

be caused by antibiotics, eating plain live-culture yogurt may help, especially during episodes. This provides a source of lactobacillus (“friendly” bacteria in the bowel) to help prevent the growth of harmful organisms within the bowel wall, which can cause the diarrhea or make it worse. A diet low in roughage (fiber) may also be helpful. Please consult your doctor before starting live-culture yogurt or a diet low in roughage.

Constipation may become a problem as children with MPS III get older, less active, and the muscles weaken. If an increase in roughage in the diet does not help or is not possible, the doctor may prescribe laxatives or a disposable enema. Depending on the type of laxative used, side effects may include bloating, gas, abdominal cramps, or diarrhea. Side effects of enemas include rectal irritation or damage.

**Most individuals with MPS III experience bowel problems. Please consult a doctor knowledgeable in MPS diseases to determine the cause and receive the optimum treatment.**

## *Dietary considerations*

There is no scientific evidence that any particular diet is helpful for individuals with MPS III. Symptoms such as diarrhea tend to come and go naturally. However, some parents find that a change in their child’s 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. Please consult your doctor or a dietician if you plan major dietary changes to make sure that the proposed diet does not leave out any essential nutrients. If the individual’s problems are eased, foods can be reintroduced one at a time to test whether

any particular item seems to increase symptoms. It is important to note that there is no diet that can prevent the storage of GAGs, as these are naturally synthesized by the body as part of its normal functioning. So, reducing sugar intake or other dietary components cannot reduce GAG storage.



**PENNY**



Although there is no evidence of specific diets being generally helpful for individuals with MPS III, eliminating certain foods may improve symptoms for some individuals. Diets cannot prevent storage of GAGs. Please consult your doctor and/or dietician knowledgeable in MPS diseases to determine optimum nutrition.



LUCAS

### *Swallowing and choking*

There are usually no problems with early feeding in children with MPS III. However, some children may not progress to eating food that needs chewing. Others may learn to chew, but have difficulties eating lumpy food, particularly when it is mixed in with other food with smooth texture. When an individual, especially a child, cannot chew and has difficulty swallowing, there is an increased risk for choking.

As children with MPS III grow and the disease progresses, swallowing becomes more difficult, and some may even lose their ability to swallow. They may splutter and cough during eating which may result in choking. Another hazard is aspiration of food and liquids into the lungs, which may result in recurrent pneumonia. Swallowing can be encouraged by placing your hand under the chin and gently moving it along the curve and down the throat. It may be better to feed them mashed food, which is easier for them to swallow. For example, slow-cooked meat is easier for them to eat than cooked meat cut into small pieces. Even very small pieces of food can be a choking hazard because

of the difficulties with swallowing. Consequently, many children with MPS III become very picky with their diet and reject many foods for apparently no reason obvious to the parent and/or caregiver.

Choking can be very frightening, especially for children. You can reassure the individual by rubbing their back and holding their hands. Choking can also occur with liquids, including secretions made by the body, such as saliva. As swallowing becomes more difficult, the individual may begin drooling and may need to be suctioned.

Even with all precautions, individuals with MPS III may still experience choking. Act quickly to dislodge the food item. If this happens with a child, turn him/her upside down or lay him/her head down over your knee and pound sharply between the shoulders three or four times. If necessary, put your finger down his/her throat to try to dislodge the food item. Pounding on the back while the individual is sitting upright might cause them to breathe in the food rather than coughing it out, making things worse.

If an individual develops a fever within a few days of a choking episode, please consult your doctor as quickly as possible. It could be that some food particles entered the lungs (aspiration) and the individual may need to be treated for pneumonia that may have developed. Catching it early is crucial for preventing a severe infection.

When swallowing becomes increasingly difficult and the risk for choking is high, it may take more time to feed individuals with MPS III and the feeding may be inefficient. As a result, some individuals may lose weight more rapidly than normal. In these situations, families and caregivers often consider alternate means of feeding, such as through a gastrostomy tube (please see below for more details). Please consult with your physician, medical geneticist, and surgeon to determine the best course of action.



HARLEY

As the disease progresses, individuals with MPS III may experience greater difficulty with chewing and swallowing which increases the risk for choking, aspiration, and pneumonia.

If left untreated, aspiration-caused pneumonia can be life-threatening. Please consult your doctor immediately if the individual develops a fever after a choking episode.

If feeding, chewing, and swallowing become very difficult resulting in poor nutrition and loss of weight, a feeding tube (enteral nutrition) may become necessary. Please consult your doctor about this option.

### *Non-feeding chewing*

As individuals with MPS III become increasingly out of touch with their environment, they will entertain themselves by rocking or by chewing on their fingers, clothes, or whatever else they can reach. As there is little caregivers can do to prevent this behavior, it is best to provide them with a wide range of things that

are safe for them to chew, e.g., rubber toys, teething rings, or soft clothes. If the problem becomes severe, and there is risk of injury to fingers, it may become necessary to splint elbows for extended periods during waking hours so that the hands cannot reach the mouth.

As disease progresses, individuals with MPS III may lose touch with the outside world and entertain themselves by chewing on their fingers, clothes, and any other object they can reach. It is important to provide them safe options. In extreme cases, elbow splints may be needed to prevent the hands reaching the mouth.

## *Feeding tubes*

As stated above, individuals with rapidly progressing MPS III may develop problems with chewing and swallowing which increases their risk for choking, aspiration (causing pneumonia, which can be life-threatening), and poor nutrition. In these cases, a feeding tube can be used to help individuals with MPS III receive the nutrition they need without the risk for choking or aspiration. It is also easier for the caregiver to feed the affected individual. Tube feeding is also known as “enteral nutrition.”

Essentially, a feeding tube is a flexible tube that bypasses the mouth and throat and delivers the food directly to the stomach or intestine. Nasogastric tubes that are inserted through the nose to convey the food to the stomach, are usually a temporary measure used for

a few weeks at most. When longer-term or permanent feeding tubes become necessary, they require surgical placement of a G-tube or a J-tube.

The decision to use a feeding tube, i.e., change to enteral nutrition, is a difficult one and should be made in consultation with your healthcare team (the primary physician, geneticist, gastroenterologist, nutritionist, surgeon, nurse, psychosocial specialist, etc.). For your healthcare team to provide you with the best guidance for this decision, you will need to maintain an accurate track of the affected individual’s food intake, time required for feeding, weight (gain or loss), and episodes of choking, gagging, aspirations, and pneumonia. This information will help determine whether a feeding tube/ enteral nutrition is necessary.

The decision to use a feeding tube is difficult and should be made in consultation with your healthcare team and only to ensure proper nutrition for the individual with MPS III.

**G-tubes and J-tubes:** Long-term tube feeding is usually accomplished with a surgically placed gastrostomy tube (G-tube) or a jejunostomy tube (J-tube). A G-tube goes into the stomach through a surgical opening in the abdominal wall. A special kind of G-tube tube, called a percutaneous endoscopic gastrostomy tube, is inserted with the help of an endoscope (a camera on a flexible tube to see inside the body). A J-tube is surgically placed through the



GRACE

abdominal wall into the part of the small intestine called the jejunum. Each tube is a flexible (usually silicone) catheter that remains in place at all times and is clamped between feedings to prevent leakage of contents.

G-tube feeding can be done at regular mealtimes. It can be given at once, called bolus feeding, or it can be given slowly over a period of several hours using the gravity (drip) method or the pump-controlled (continuous) method.

Once a decision to insert a feeding tube is made, the doctor will perform X-rays of the stomach and intestines

(gastrointestinal tract) to help decide which type of tube to use and check for gastroesophageal reflux disease (GERD). Placement of a G-tube may worsen existing GERD, in which case a J-tube may be a better choice. A J-tube may also be an option if there is very poor spontaneous movement (motility) of the stomach that moves the food through the digestive tract.

As with other MPS diseases, there are special concerns regarding anesthesia in individuals with MPS III. Please consult an anesthesiologist knowledgeable in MPS III, or at least MPS diseases, before any surgery is planned.

**Long-term feeding tubes, either G-tube (to the stomach) or J-tube (to the small intestine), need to be surgically placed. Please consult with your healthcare team on the need and placement of feeding tubes.**

***Caring for the tube:*** The surgical opening for the G-tube or J-tube is called a stoma. The stoma can be slow to heal after surgery. Proper care of the stoma site is very important to avoid infection or irritation from stomach and intestinal juices. The area should be kept covered and dry with a dressing and changed as often as needed. The skin around the stoma should remain tight around the tube. The stoma may become infected. Signs of infection include fever, pain, swelling, warmth, or increased redness near the stoma. Please contact your doctor if you notice any of these symptoms. Swimming in lakes or ponds is not recommended because of the high risk of infection at the stoma site due to the bacteria living in these areas.

A G-tube is anchored inside the stomach and a J-tube inside the intestine by a small balloon at the tip of the tube. Over time, the balloon can deteriorate and deflate causing the tube to fall out. If this happens with a G-tube, the doctor will provide a replacement tube and

instructions on how to insert it. However, only a trained doctor can reinsert the J-tube. Please contact the doctor immediately if the J-tube falls out. Feeding tubes can become clogged. Please discuss with the doctor appropriate methods to unclog them.



**EMILY**

The MIC-KEY® low-profile gastrostomy feeding tube/kit is a skin-level device to replace the G-tube. Since this device does not protrude and is level with and flush to the skin, it is less likely to be snagged or pulled out accidentally. It is also easily covered by clothes, making it less obvious. During feedings, an extension tube is attached to the Mic-key opening in the skin and the feed pumped in. After feeding, the extension tube can be removed and cleaned.

Individuals with feeding tubes can still accidentally inhale food or liquid into the lungs (aspiration) that can result in pneumonia. Aspiration can be a common issue for tube fed individuals. If the aspiration is primarily due to reflux, a surgical procedure called a Nissen fundoplication can help to reduce complications. Coughing during or around feeding may indicate possible aspiration. Coughing, difficulty breathing, and fever may be signs of pneumonia. Please contact a physician immediately if you observe any of these signs.

**When and how to feed:** An optimum tube feeding schedule ensures that the individual with MPS III maintains an adequate weight, tolerates the tube feedings comfortably, and can be fed at convenient times for both the individual and the caregiver. Regular consultation with a nutritionist to discuss and modify, if necessary, the individual's feeding needs ensure proper nutrition. For many individuals with MPS III, regular feedings with easily available liquid formulas,

e.g., Pediasure®, Resource®, or Enfamil Kindercal®, supply their dietary needs. These formulas are usually well tolerated by most individuals with MPS III. Fiber can be beneficial for both diarrhea and constipation, but should be given under the guidance of a physician or nutritionist. Individuals who are being tube fed sometimes may experience bloating, diarrhea, or vomiting. These problems may be due to changes in feeding formula, receiving too much formula at a single feeding, problems digesting the formula, or contamination of the formula. Please consult a physician if you notice any of these signs.

Good positioning of the individual being fed through a feeding tube is critical. Improper positioning may result in the individual having trouble receiving food through the tube or being able to breathe properly. It is important that the individual should not be slumped over, as this can put too much pressure on the stomach. If the individual has trouble maintaining an upright position, special equipment and supports are available to help.

Many individuals thrive after the placement of a feeding tube. Refer any difficulties that are encountered to the medical team in charge of the individual's care as they are best equipped to address them. Regular contact and consultation with the medical team is essential for successful enteral feeding (i.e., enteral feeding that meets the individual's nutritional needs).

**It is important to keep the feeding tubes and the stoma clean, dry, and unclogged to prevent potentially life-threatening infections. Please consult with your doctor if you observe any unusual signs or symptoms.**

**Many individuals with MPS III thrive after placement of a feeding tube.**



## MARTIN

### Musculoskeletal system (bones and joints)

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Individuals with MPS III tend to have fewer musculoskeletal problems than those with other MPS diseases who typically have significant problems. The

areas in which individuals with MPS III have problems are detailed below.

#### *Spine*

The bones of the spine (vertebrae) normally line up from the neck to the buttocks. The problems with the spine, e.g., angular curve (kyphosis) or bump in the lower back (gibbus) often reported in individuals with other MPS diseases have not been reported for individuals

with MPS III. Individuals with MPS III tend to have only minimal problems with bone formation and growth, although scoliosis can occur in some individuals and may require corrective methods such as bracing, under the guidance of an orthopedic specialist.

#### *Neck*

Unlike with other MPS diseases, spinal cord compression has not been reported in individual with MPS III. Still, individuals with MPS III can have a lax neck that can cause problems during anesthesia. If

surgery is needed, it is important to consult with an anesthesiologist with experience in dealing with difficult airways, and preferably also with MPS III or MPS diseases.

Although spinal cord compression has not been reported in individuals with MPS III, they can still have a lax neck that may be problematic during anesthesia. If surgery is needed, please consult an anesthesiologist knowledgeable about MPS diseases and dealing with difficult airways.

## Bones and joints

Individuals with MPS III have minimal problems with bone formation and growth. Osteoporosis can develop as early as in the teens, making bones brittle and fragile. This leads to decreased stability and increased risk for falling and fractures. Decreased mobility and prolonged treatments for seizures also contribute to brittle bones and further increase the risk for fractures.

Joint stiffness is common to most MPS diseases, but individuals with MPS III tend to have minimal joint

problems. As the individual ages and the disease progresses, they may experience some joint stiffness. The limited movement in the shoulders and arms may make dressing difficult. Joint stiffness may cause pain that may be relieved with warmth, stretching, and pain medications. Anti-inflammatory drugs, such as ibuprofen, can help with joint pain, but their use should be monitored closely to make sure that irritation and ulcers in the stomach do not occur.

Individuals with MPS III have minimal problems with bone formation and growth. Joint stiffness may occur later in life. Pain can be treated with anti-inflammatory drugs, but their uses should be carefully monitored.

## Hands

The hands of individuals with MPS III are less affected than those seen in individuals with other MPS diseases. Over time, the fingers stiffen and gradually become curved, due to limited joint movement caused by GAG buildup. The tips of the fingers can become permanently bent over, giving rise to the characteristic “claw hand.”

Some individuals with MPS III experience cold hands or feet. This is most often caused by disruption of the normal neurologic regulation of blood flow. It may not bother the individual but using heavy socks and warm gloves may help if it does. As disease progresses, the body’s temperature control mechanism may become

damaged. The individual may sweat at night and have cold hands and feet during the day. Some individuals may experience episodes when their body temperature drops below normal (hypothermia). If this happens, keep the individual warm and consult with your doctor on the best ways to manage the problem.



POL

The hands of individuals with MPS III are less affected than among those with other MPS diseases. As disease progresses, the tips of fingers may become permanently bent and joints locked causing the “claw hand” and trigger finger appearance. Trigger fingers can be treated with heat and massage, or through surgery.

## Hips

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Some individuals experience hip problems due to hip dysplasia or osteonecrosis (loss of bone tissue) of the femoral head (hip joint) that can lead to pain and difficulty

walking. Although rare, some may also experience hip dislocation.

**Hip problems can occur for some individuals with MPS III.**

## Legs and feet

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The feet of individuals with MPS III may be broad and stiff with the toes curled under, similar to fingers. Many individuals with MPS III stand and walk with their knees and hips flexed. Combined with a tight Achilles tendon in the heel and joint stiffness, this stance may cause them to walk on their toes. Several approaches are used to aid in walking and to increase flexibility. Stretching exercises are an important part of physical therapy (below). Special braces can be used to stabilize the feet and ankles. An appropriate orthosis can help to increase mobility and prevent muscle shortening by holding a joint in the proper position.

Ankle foot orthoses (AFOs) are tall braces that stretch almost to the knee. The braces can keep legs in proper alignment and can also address issues of the knee, such as hyperextensions and instability. Supramalleolar orthoses (SMOs) are significantly shorter, typically

stopping just above the ankles. This allows for more freedom of movement and can help control pronation (flat feet) and supination (arches too high).

Achilles tendon lengthening (ATL) is a surgical procedure that aims to stretch the Achilles tendon to allow a person to walk flat-footed. This procedure elongates a contracted Achilles tendon by making small cuts on the tendons at the back of the ankle.

Some individuals with MPS III have knock-knees, a condition in which the knees are bent in so much they touch each other when walking, but rarely requiring treatment. When it is severe, knock-knees can be treated with surgery; however, this is not common among individuals with MPS III.

**Many individuals with MPS III stand and walk on their toes with their knees and hips flexed and have difficulty sitting upright in the tailor position. Individuals with severe knock-knees can be treated with corrective surgery.**

## *Physical therapy*

The goal of physical therapy is to help relieve symptoms and improve the individual's ability to function. A young, mobile child with MPS III may not need physical therapy. However, as the child gets older, the joints of the feet and ankles may become tight and spastic, requiring treatment. Hydrotherapy to keep the joints mobile may help greatly. Range-of-motion physical therapy may

be useful. These exercises need not be intensive and those that cause pain should be avoided. As disease progresses and the individual becomes immobile, it is important to ensure that they have the proper support when sitting to avoid uneven pressure on any joint. Chest physiotherapy may be needed to help clear an infection.



A variety of physical problems have been reported by parents of teenagers with MPS III, including eye fluttering and fast breathing. Some parents report extreme restlessness, which can lead to sweating, jerking of arms and legs, kicking, and dystonia-like

spasms with rigid arms and legs. Some individuals may appear to be in pain, while others may not. Physical therapy, massages, and hydrotherapy have been tried with varied success. Consult your doctor before trying any of these or any over-the-counter medications.

**Physical therapy may help alleviate physical symptoms and improve joint motion which may occur as a result of MPS III progression.**

## Brain and CNS

CNS deterioration is the primary characteristic of MPS III. Compared with other MPS disorders there is relatively little effect on the rest of the body (systemic manifestations). When the brain and CNS are affected, the symptoms for many individuals include language and motor delays, behavior and sleep dysfunctions, as well as cognitive decline, epilepsy and dementia that usually begin later as the disease progresses.

GAG storage in the neurons (nerve cells) in the brain can adversely affect brain function, the extent of which depends on the severity of disease. Developmental

delay, behavioral problems (including hyperactivity), or a combination of both are usually the first overt symptoms of MPS III commonly observed between the ages of 2 and 6 years, although they may occur later in individuals with slower progressing disease. It is often discovered at diagnosis of MPS III that speech development is much more delayed than physical development.

As the child's body initially appears relatively normal, they are often initially misdiagnosed with autism spectrum disorder or attention-deficit/hyperactivity disorder.

## Behavior

Behavioral problems are a common, and often the first symptom of MPS III. As the disease progresses, individuals develop extreme activity and restlessness, unaware of the danger in which such behavior places them. They can be aggressive and often exhibit behavior that is very difficult to control. Unfortunately, language skills and understanding are gradually lost making communicating with them more difficult.

The Sanfilippo Behavior Rating Scale (SBRS) was developed specifically to evaluate individuals with MPS III and as a way to monitor behavioral changes. The SBRS has four abnormality clusters: movement, lack of fear, social/emotional and executive dysfunction.



**AUSTIN**

Autistic-type behaviors are common, and there have been recent suggestions to use some behavioral interventions from autism therapy such as applied behavioral analysis (ABA). The results of behavioral interventions are variable; however, some individuals have been partially managed by combining behavioral therapy with certain drugs such as psychiatric and sleep medications. This must be done with a qualified doctor, and individuals may respond to medications in unexpected ways. A major difficulty with individuals with MPS III is that mental functions tend to decline, and any behavioral gains may be temporary.

When dealing with difficult behaviors it is important to try to determine which behaviors are caused by physical problems like pain or a hearing deficit, which are caused by fatigue, and which are caused by seizures or neurological issues. This should help make any interventions more likely to succeed. Sleep issues (see below) can exacerbate behavioral issues.

Some children never become toilet trained, and those who do may eventually lose this ability. Children with MPS III may have behaviors difficult to manage at home since, unlike those with other MPS diseases, they may have normal physical strength and mobility at the outset. As the child with MPS III ages, the behavioral problems decline as developmental delay progresses.

Medications or behavioral therapy are not usually effective in treating behavior problems of children with MPS III. Limited success has been reported in some cases of enlisting a psychologist. However, the individual's behavior will continue to worsen as the disease progresses and the utility of any particular behavior modification technique may not last. Families and caregivers will need to adapt their lives as much as possible. It is important for parents, other family members, and caregivers to seek regular breaks for their own health.

**Behavioral problems are symptomatic of individuals with MPS III and are not usually treatable. Families and caregivers will need to adapt their lives to accommodate the affected individual.**

## *Sleep*



**JOSHUA**

Sleep disturbances are very common with MPS III. Clinicians have reported that 80%-95% of individuals with MPS III have sleep problems, and that behavioral problems tend to correlate with the sleep issues in many cases. Individuals tend to take longer to fall asleep, and often sleep more in the daytime. Their day/night cycle (circadian rhythm) can be disrupted or even reversed. Many individuals with MPS III of all ages are very restless at night, not sleeping for more than a couple of hours at a time. Some sleep-inducing medications have been helpful for certain individuals, and melatonin has been successful at times as it may



## SADIE RAE

help adjust the circadian rhythms. Sleep disturbances can also be caused by sleep apnea (discussed on page 27).

Medications may help but will need to be tested through trial and error to determine which, if any, will work. Furthermore, any medication may lose its effect after prolonged use. Parents and caregivers may

adapt to the situation choosing either to ration the use of medication to few nights a week or discontinue medication for a while after a few weeks. It is vital for parents and caregivers to get sleep to be able to function properly themselves. Please consult a doctor for options. It is important for parents, other family members, and caregivers to seek regular breaks for their own health.

**Many individuals with MPS III have disturbed sleep. Medications may work but will need to be tested individually in consultation with your doctor.**

### *Seizures*

As disease progresses, individuals with MPS III can have frequent, minor seizures (petit mal), during which they momentarily lose the ability to focus and concentrate. During such times, the individual may seem more out of touch or harder to feed than usual. Some individuals may experience generalized seizures (grand mal), which can be controlled by medications. It is important to place the individual on their side during seizures to prevent inhalation of vomit. The individual

should be left in that position until the seizure is over. Check that the airway is clear and do not put anything in the individual's mouth. Seizures can usually be prevented or reduced in frequency with conventional anti-seizure medications. As with sleep disturbances, you may need to try several medications before finding one that works best for the individual. Some doctors may recommend that the individual wear a helmet to prevent head injury.

**Seizures become more frequent as MPS III disease progresses. Seizures can be treated with anticonvulsant medication. Place the individual on their side to prevent inhalation of vomit. A helmet may be worn to prevent head injury.**

## Hydrocephalus

MPS III can cause hydrocephalus, a condition where fluid accumulates in the brain, causing a pressure buildup that can lead to brain damage. Hydrocephalus was once known as “water on the brain.” The “water” is actually cerebrospinal fluid (CSF), a clear fluid surrounding the brain and spinal cord. The CSF protects the brain and spinal cord from injury by providing a liquid cushion, and is continually being produced, circulated, and absorbed. Communicating hydrocephalus (also known as “non-obstructive hydrocephalus”) is caused when the CSF is not absorbed properly. This causes the CSF to build up, leading to an abnormal enlargement of the spaces in the brain called ventricles. This causes potentially harmful pressure on the tissues of the brain.

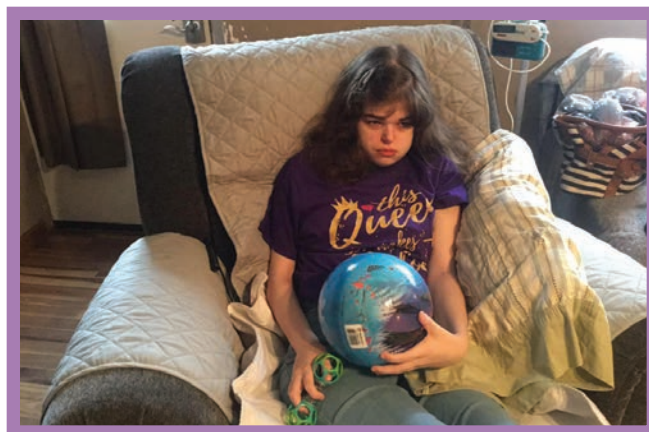
This condition is more common among individuals with severe neurological symptoms associated with the brain and nervous system. Early detection and treatment of hydrocephalus is believed to improve quality of life. However, neurosurgeons are often unfamiliar with the unique aspects of diagnosing communicating hydrocephalus in MPS III, creating a frustrating situation for parents and caregivers.

**Effects of hydrocephalus:** In infants, the most obvious sign of hydrocephalus is often a rapid increase in head circumference or an unusually large head size. In older children and adults, typical symptoms may include headache followed by vomiting, nausea, blurred or double vision, downward deviation of the eyes (called “sunsetting”), problems with balance, poor coordination, abnormal walking patterns, urinary incontinence (difficulty holding urine), slowing or loss of development, lethargy, drowsiness, irritability, memory loss, or other changes in personality or thinking. If hydrocephalus develops slowly, these typical signs and symptoms may not be seen.

**Diagnosing hydrocephalus:** Hydrocephalus is diagnosed through clinical neurological evaluation (where the doctor checks the individual’s brain and nerve function); by using imaging techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI); and through techniques to measure pressure, such as lumbar puncture (spinal tap).

It is recommended that individuals with MPS III have a “baseline” head scan (CT or MRI) at the time of diagnosis with regular follow-up scans (as frequently as the doctor recommends). Measuring intracranial pressure (pressure inside the brain) allows the doctor to diagnose hydrocephalus. Intracranial pressure is measured in millimeters of mercury (mm Hg), and once the pressure is over 180-200 mm Hg, it is considered to be high. Once the fluid buildup is too severe, the doctor may recommend a shunt (see below).

An alternate method of measuring intracranial pressure is by cerebrospinal fluid opening pressure, also called opening pressure at lumbar puncture. A high measure can be an indication of intracranial pressure. A normal measurement is often considered less than 25-28 cm H<sub>2</sub>O (sometimes also written as 250–280 mm H<sub>2</sub>O); however, there are some doctors who report up to 29 cm H<sub>2</sub>O as normal in certain children.



ANNIE

Sometimes lumbar puncture may be necessary for the diagnosis of hydrocephalus, as CT and MRI often do not demonstrate it conclusively for individuals with MPS. Additionally, if elevated pressure on the optic nerve is noticed during eye examinations, assessment should be made for signs of increased intracranial pressure.

**Treatments:** Hydrocephalus is most often treated with acetazolamide (Diamox), which is a diuretic for removing fluid from the brain. Further treatment could require the surgical placement of a shunt. A shunt is a flexible plastic tube (cannula) that diverts the flow of CSF from the brain to another area of the body where it can be absorbed as part of the circulatory process. If a shunt is placed, specialists recommend a high-pressure shunt to prevent rapid decompression (reduction of fluid in the ventricles of the brain). Shunts must be inserted surgically. Before surgery, doctors should check for signs of blockage in the form of spinal cord compression, which is described below.

### ***Spinal cord compression***

Usually, the length of the spinal cord is surrounded by a system of tissue, ligaments, and bones that are intended to protect it from damage when there is movement. In individuals with MPS III, GAG accumulation over time causes these tissues and ligaments to gradually become thicker and start pressing against the spinal cord. This results in a condition called spinal cord compression, particularly in the neck (cervical) region of the spinal column. As a result of this compression, individuals may experience



**OWEN**

a range of symptoms including neck pain, weakness or numbness in the limbs, poor balance, and dizziness. The compression may also obstruct the proper flow of the CSF around the brain and spinal column that can contribute to hydrocephalus (described earlier). Doctors usually can detect spinal cord compression with an X-ray or MRI evaluation. The main method used to relieve this condition is a surgical procedure called a laminectomy.

In this procedure, the joints that surround the spinal cord may be trimmed and/or some of the cervical vertebrae (bones surrounding the spinal cord) are removed or adjusted to make more room for the spinal column and ease the compression. Complications of laminectomy include slowing of heart rate and difficulty breathing. Surgery should only be undertaken with an anesthesiologist and surgical team knowledgeable in the complexities associated with MPS III.

**Individuals with MPS III, especially those with severe disease, can have hydrocephalus. Hydrocephalus is diagnosed through a clinical neurological evaluation and when severe, is treated with a shunt. Individuals should be tested for spinal cord compression via X-ray or MRI, prior to surgical implantation of a shunt.**

## At what age are people usually diagnosed with MPS III?

This varies between individuals depending on the severity of the disease. In general, babies do not show any signs of the disease. Symptoms begin to appear between ages of 2 and 6 years. Change is usually gradual, which may help with adjusting your lifestyle.

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

Early diagnosis of MPS III is critical and allows earlier intervention.



SAWYER

## 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. Each state makes its own decisions about what 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? Is there a current therapy or is bone marrow transplant an option?
- 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?



**MADDISON**

Currently, there is a growing movement promoting newborn screening for MPS disorders such as MPS III. It is now widely recognized that for many families, information about the diagnosis alone is helpful with the opportunity for genetic counseling, education about various and new treatment options, and improved quality of care with early medical help and therapy services.

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 III, 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 III will likely continue to become more involved in the promotion of newborn screening.

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

## **Prenatal diagnosis**

If you have a child with MPS III, it is possible to have tests during a subsequent pregnancy to find out whether the baby you are carrying is affected. It is very important to know which type of MPS III (type A, B, C, or D) your child has as each type requires its own specific test. It is important to consult your doctor early in the pregnancy if you wish to perform these

tests. The decision to have prenatal testing is complex and personal. Talking with your genetic counselor or doctor can help you explore these options and other strategies, such as egg or sperm donation, for having additional children while limiting the probability they will have or be carriers for MPS III.

**Newborn screening and prenatal diagnosis for MPS III may help with early diagnosis in the future. There is still much research to be done and these tests are not offered in all states. Please check with your doctor for the options in your community.**

# Living with MPS III

Living with an individual with MPS III can vary significantly depending on the severity of the disease.

## Keep a journal

A diagnosis of MPS III can be overwhelming with an overload of information. Keep a journal recording all activities, changes, nutrition, medications, doctor visits, etc. This will help you get organized and keep track of the myriad of items and changes that accompany such

a diagnosis. A journal will also help you with providing accurate information to your medical team as they make decisions that are best for the individual with MPS III. Keeping a journal may also help you regain some control over your life.

## Talking with your healthcare providers

Getting involved in treatment means having a good partnership with your medical team. Parents and caregivers of a child with MPS III may feel helpless and uncertain about the child's future. Here are some suggestions for becoming an active participant in the child's care and working with your doctor to make the choices that are right for the child.

- **First visit:** Use your journal to provide your doctor and other members of the medical team with information on all symptoms, when they began, how often they occur, and how they have changed with time, medications that your child takes, child's medical history, other doctors treating your child, previous medical procedures, problems with daily activities, etc.
- **Communication:** Keep an open line of communication with your healthcare providers. Open and honest communication will help create a partnership with your medical team. Be honest about what you are having difficulty with or do not understand. This will allow the healthcare provider better to help your child and you.
- **Plan ahead:** Before every visit, prepare a list of questions and concerns that you want to ask your medical team, including new information on disease, treatments, support, etc.
- **Inform:** Inform the medical team of any changes in symptoms, behavior, etc. from the previous visit.



TRINITY



- **Ask:** When in doubt, ask. Do not be embarrassed to ask questions. It is important that you understand what is best for your child with MPS III. If necessary, ask the healthcare provider to explain it again differently and to define any new words. Repeat in your own words what you understood giving the healthcare provider an opportunity to confirm or correct your understanding.
- **Treatment options:** Currently, there is no cure for MPS III. Treatment options include disease management and supportive or palliative (providing comfort for an incurable disease) care, or evaluation for clinical trials that may be available. Learn about each option and ask your doctor. Examples of questions are listed below
  - What treatment would you recommend for my child?
  - Is the treatment a one-time procedure or will it require repeated procedures on a regular basis?
  - What are the side effects?
  - Will it interact with other medications/treatments?
  - What is the cost? Will insurance cover it? How much?
  - How long will it take before we see the treatment work?



**VICTORIA**

- **Goals:** Ask about next steps and goals to set for your child and yourself.
- **Record:** During the visit, write down the information you receive and request a summary of your visit from the healthcare provider.

Stay informed between visits to the doctor so that you can have a more knowledgeable discussion with your doctor about making the best choices for the individual with MPS III.

## *Emotional support*

Receiving a diagnosis of MPS III can be a life-altering event for families. As a parent or caregiver of an individual with MPS III, you will slowly come to grips with the situation and realize that you need to gain control of how the diagnosis affects your child and the rest of the family. You will devote a substantial amount of time and energy taking care of the individual.

However, you will also need to take care of yourself so that you are healthy enough to continue to take care of your ward.

When a child is first diagnosed with MPS III, you may have a variety of feelings, including fear, grief, uncertainty, and anger that will subside with time.

You may also feel relieved to finally have a diagnosis for their child's problems. You may experience an overload of information on the changes to their daily lives. Over time, parents and caregivers may also feel frustrated, isolated, stressed, and exhausted. It is important

### *Taking care of yourself*

As a caregiver, there are many demands on you. As important as they are, you cannot fulfill them if you do not take care of yourself and your needs. Arrange for others to take care so that you can have some respite.

### *Taking care of others in the family*

Caring for any child is hard work and even more so when the child has special needs. As a parent and caregiver taking care of a child with MPS III, you may need to remind yourself that the other children in the family also need their share of attention and care. They may need to be reassured about parents spending increased time away from home, getting less attention, missing events in their own lives, etc. Plan outings and activities that other siblings need even if they may not be appropriate or feasible for a child with MPS III. Many parents employ some form of respite care or have someone help regularly at busy times to cope with the demands.

Remember, children can be very perceptive about their brother or sister who has MPS III. They will know if their parents are not being completely honest with them. Therefore, it is often best to be as open and honest as possible. Siblings will also need to know what to expect for their brother/sister affected with MPS III. Taking time to provide age-appropriate information about medical procedures that are to be performed on the affected child will help them remain engaged and may reduce their anxieties for their brother/sister. Consider age-appropriate activities in which the healthy sibling(s) can help with taking care of the child with MPS III. This may not only engage and educate the sibling(s) but make

to know that you are not alone. Many services are available to help you cope, including respite care, counseling, funding, and support groups. You can decide which services you need and suit you best.

Continue to participate in activities that you enjoy as they can help you hold on to your sense of self as well as give you the mental and emotional energy ("recharge your batteries") to take care of the individual with MPS III.

them feel important and needed. This can help reduce potential resentment and encourage healthy family dynamics. Parents should make sure their children know that they are available to answer any questions that may result from these discussions. Answers to questions should be honest, straightforward, and age-appropriate.



**FLETCHER**

Asking for help is not easy for many, but help is available for those who request it. Please do not be shy about asking for help. You may be pleasantly surprised.

### *Helping your children deal with MPS III*

Parents and caregivers of children with MPS III have the extremely difficult task of helping those children cope with the physical and emotional aspects of MPS III. Listening and discussing the issues honestly is a good way to provide support. Some children may believe that MPS III is a punishment while others may resist discussing their feelings for a variety of reasons. It is important to reassure children and that you are available to talk with them about any concerns they have without fear of judgment. Always maintain an open line of communication. Remember that children's thoughts and feelings about MPS III and their impact may change with time.

Children need to know what to expect in their lives. Taking time to provide age-appropriate information about medical procedures will help reassure the child and decrease anxiety. Sometimes just the presence of parents and caregivers are sufficient to help the child. Having MPS III may make a child feel like they have no control in their lives. Whenever possible, provide children with MPS III with some choices as this fosters a greater sense of control. For example, let them decide within limits which program to watch or what they want to eat or where they may like to go for an outing. Siblings may also enjoy getting a choice of which caregiver tasks they would like to perform and when.

Help your child with MPS III, and the other children in the family, have as normal a life as possible. Try to treat the child with MPS III like any other child. Although children with MPS III have special needs, it is important to encourage them and their siblings to participate in activities that involve other children of the same

age. Ensure that siblings and playmates understand the limits of the child with MPS III and the activities that are appropriate for them. Do not be afraid to discipline your child with MPS III. Like any child, those with MPS III also need discipline appropriate with their ability and developmental age. Consistent structure and behavior towards all children make them feel safe and secure and helps foster healthy family relationships.

Give your child with MPS III responsibilities and assign tasks at which they can be successful. Remember to maintain daily routines as much as possible; children prefer routines that are predictable and consistent. It is important to acknowledge and praise tasks that have been done well just as would be done for the healthy siblings. It is one way to help all children, especially those with MPS III, feel valued and lead as normal a life as possible.

Please be careful of what you say within earshot of your children, affected and unaffected. It is important that children receive consistent and age-appropriate information. They should not be exposed to conflicts related to MPS III and its management, whether at home or at a healthcare facility. Such interactions can lead to feelings of insecurity and mistrust.

Parents can help prepare their children on what to say to others by providing age-appropriate information on what MPS III is and how it affects people. Teach them how to handle teasing and bullying. Role-playing is a useful tool to help them craft their own responses to such situations.

## *Talking with your family*

Talking about MPS III can help both you and your family. Since MPS III is a genetic disorder, your other family members may be carriers. Making them aware that MPS III may run in your family will give them the opportunity to be tested. Telling your family can help them understand what you are going through. The more they know about MPS III, the more likely they will be able to help.

Telling your family about MPS III may not be easy and you may want to plan it carefully. Some things you may want to consider include:

- When and where to tell them – you may want to take time first to digest the diagnosis and deal with your immediate family before informing others, preferably in person at a time when they are not stressed about issues of their own.
  - Making an outline about what you would like to say – this will help you decide what you want to focus on what you would like to keep private. It is okay not to share everything. The suggestions below are a guideline to help you with developing what you would like to say. You do not have to talk about any of the suggested topics, if you are not comfortable. Each family's situation is unique, and you will need to customize the suggestions to fit your need. Some suggestions on what you may want to tell your extended family include:
    - What MPS III is and some information on variable range of disease symptoms, severity and progression, and where they can find more information.
    - When you noticed symptoms and how they affected your child's life.
    - Where did you go for help and how was your child finally diagnosed.
    - What treatments are available, what your decisions are, and why.
    - The current status of your child's health.
    - How you are maintaining a positive attitude.
    - What will this mean for the family, e.g., should they be tested.
  - How you may deal with their reactions – while it is impossible to predict the reactions that each member of your family will have to your news, there are some reactions that occur often, including:
    - They may want to know how they can help you – be prepared for this and think about what they could do to help, e.g., running errands, preparing meals, etc.
    - They may want to learn more about MPS III – make a list of resources, including this brochure.
    - They may be concerned about whether they or their children are at risk for MPS III – you may want to tell them how MPS III is inherited (see section in this brochure).
    - If others in the family have some of these symptoms, sharing this information may help them to finally have a diagnosis. Family members may choose to be tested.
- Discussing these issues can help you to cope with the diagnosis of MPS III as a family.

## *Talking with peers*

You can talk with other families who are also affected by MPS III. The National MPS Society may be able to match you up with families in your area who have volunteered to share their experiences and offer emotional support to other families affected by MPS III. Some families even have created websites to share their experiences with others.

You may also attend MPS meetings and family events or conferences. Attending these events can help parents connect with other families affected by MPS III and get a new sense of hope from ongoing research. Many people find that talking to someone who understands may help them feel less alone and eases their fears.

Visit [www.mpsociety.org](http://www.mpsociety.org) or contact the National MPS Society (877-MPS-1001) for more information.

## *Talking with your community*

Although they may not have experience with MPS III, these are the people who care about you and would like to help you. They are your regular “support network.” Think of a few specific things they could do to help you, such as just coming over to talk, running some

errands for you, babysitting, or bringing over some food. Getting a break, even on the small things, might really help. They may even be able to provide you some much needed respite.



MEREDITH AND ROSS

## Talking to employers

If your child has MPS III, you may find yourself struggling to meet the demands of the workplace while still giving your child the care and attention they need. You may need time off to take your child for medical appointments or treatment. You may also need to send them to a special daycare or school. Fortunately, there are programs to help working parents cope, including:

- The Family and Medical Leave Act (FMLA) – detailed information is available at: [www.dol.gov/esa/whd/fmla/](http://www.dol.gov/esa/whd/fmla/)
- Employee Assistance Programs – some companies offer these programs to connect employees to qualified professionals who can help families deal with the stresses of having a child who is ill and can direct them to other resources as needed. Please check with your employer.
- Daycare – some companies offer daycare facilities, but these may or may not be equipped to deal with children with special needs. Please check with your employer.
- Health insurance – many employer health insurance plans cover your children as well. Two programs may help protect your child’s access to healthcare through your employer’s plan:
  - COBRA (Consolidated Omnibus Reconciliation Act) – detailed information is available at: [www.dol.gov/dol/topic/health-plans/cobra.htm](http://www.dol.gov/dol/topic/health-plans/cobra.htm).
  - HIPAA (Health Insurance Portability and Accountability Act) – detailed information is available at: [www.dol.gov/dol/topic/health-plans/portability.htm#doltopics](http://www.dol.gov/dol/topic/health-plans/portability.htm#doltopics).
- The National MPS Society – the Society can connect you to other families with similar problems and who can provide helpful peer support and information.

## Talking to educators

Educators can play a critical role in your child’s development. They need to understand your child’s special needs, both physically and emotionally, so that they can help appropriately. Parents of children with MPS III must ask school personnel to do something different from the norm. Give them time to adjust and see how you can support them in the process. Make sure that you compliment them on what they are doing well – a positive approach helps achieve better outcomes. Ensure that the school system becomes your partner in educating your child. Some suggestions on communicating with educators include:



NILS



## CATHERINE

- Sharing information with teachers on MPS III, e.g., this booklet.
- Informing your child's educators of their specific medical care needs, including hearing loss, vision difficulties, speech impairment, behavior problems, etc.
- Your child's strengths, preferences, and triggers for negative behavior.
- Your goals for your child's education.
- Proactively asking the teacher how your child is doing and how you can help them reach their education goals.
- Maintaining a strong relationship with your child's teacher.

There are three major laws that are relevant to the education of your child. These are the Individuals with Disabilities Education Act (IDEA), Section 504 of the Vocational Rehabilitation Act of 1973, and No Child Left Behind. You may want to familiarize yourself with them. Some of the provisions of IDEA require having an individualized education program for children with special needs.

School attendance and socialization should be encouraged and fostered through integrating the child into the classroom and through interventions for specific social skills. Teachers can do much to improve the acceptance of the child through instructional activities such as cooperative learning and encouraging support for all children in the classroom.

**School attendance and socialization should be encouraged and fostered for children with MPS III who may benefit from attending mainstream school but will need a multitude of resources from the school system, especially teachers.**

## Home adaptations

Individuals with MPS III may become increasingly less mobile and more dependent on their parents and/or caregivers to meet their everyday needs. The booklet *Daily Living with MPS and Related Diseases*, published by the National MPS Society has many helpful suggestions for making adaptations in the home. Some suggestions for adaptations include:

- Setting aside a room or part of a room for their child with MPS III.
  - The room should be within a caregiver's hearing distance and be made safe for the child to play without constant supervision. This allows the parent to interact with the other children or deal with household tasks.
  - Furniture that is fragile or has sharp edges should be removed and replaced by large cushions on the floor.
  - Windows may need to be fitted with strengthened glass or Plexiglass, and the floor should be easy to clean.
  - Replacing the door to the room with a Dutch door will allow the child to see the parent, increasing his/her sense of security while keeping him/her safe.
- Making favorite durable toys and playthings accessible to the child.
- Placing the television or stereo speakers high on a shelf or suspended from the ceiling and operated by the parents using remote control.

## 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 which 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. He or she should be able to locate additional information and/or resources for your family.



AAYAN

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



# General Management of MPS III

The primary goals of treatment and management of MPS III are to improve quality of life, slow disease progression, and prevent permanent tissue and organ damage. At present, there is no cure for MPS III. Early diagnosis and intervention may prevent irreversible damage in some individuals. Treatment options for MPS III comprise those aimed at disease management (including treating underlying enzyme deficiency), and

supportive or palliative care (care that focuses on comfort for an individual with an incurable disease).

This section only briefly describes some management and treatment options. However, the decisions of which interventions and treatments are best for the individual is an important and complex one that cannot be summarized here. These are best discussed with medical professionals with expertise in treating MPS III.

## Importance of multidisciplinary care

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As described earlier in this resource, individuals with MPS III usually have a wide range of signs and symptoms. As a result, they often need to be managed by a many different medical specialists, including cardiologists, neurologists, pulmonologists, otolaryngologists, ophthalmologists, orthopedic surgeons, physical therapists, speech therapists, occupational therapists, and others. All healthcare professionals involved in the care of an individual with MPS III should have a basic understanding of the disease and how the condition may affect treatment decisions.

Dealing with so many specialists can be overwhelming for individuals with MPS III and their caregivers. It can be very helpful to have a single physician with experience in MPS III, either as a primary care physician (who might be a pediatrician) or a geneticist, who takes responsibility for overseeing the overall care across medical specialties, and who will keep track of the “big picture.” This physician can then refer the individual to other specialists as needed and help make sure they are receiving the best possible care.

**A multidisciplinary approach to treatment and management coordinated by a single healthcare professional experienced in MPS III is recommended.**

## Diet

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There is no scientific evidence that a particular diet has any helpful effect on individuals with MPS III, and symptoms such as diarrhea tend to come and go naturally. However, some caregivers find that a change in the individual’s 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 leave out essential nutrients. If the individual’s problems are eased, you could try reintroducing foods one at a time to test whether any particular item seems to increase their symptoms.

*Some medications being investigated for use in MPS III, such as trehalose, are sugar compounds used as a drug. Please note that this statement is about general diet and that reducing sugar intake or other dietary components do not reduce GAG storage.*

There is no scientific evidence that diet has an effect on disease. However, it may help with some individuals. Please consult your doctor or dietician when making dietary decisions.

## Feeding tubes

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As the disease progresses, individuals with MPS III, especially those with severe disease, may have problems chewing and swallowing. If so, they are at risk for poor nutrition, choking, and aspiration (inhaling food or other substances into the lungs), which can lead to respiratory infections and pneumonia. During these episodes, the individual may need increasingly more time to be fed and may lose weight. Choking

can also occur with liquids, including those made by the body, e.g., saliva. With swallowing becoming more difficult with disease progression, the individual often drools, which will need to be suctioned. Please refer to the section earlier in this brochure in which the use of feeding tubes has been discussed in detail.

## Physical therapy/sports

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Joint stiffness is a common feature of MPS III. Limitation of motion and joint stiffness can cause significant loss of abilities. Range-of-motion exercises (passive stretching and bending of the limbs) may offer some benefits in preserving joint function and should be started early. Exercises that cause pain should

be avoided. Once significant limitation has occurred, increased range-of-motion may not be achieved, although further limitation may be minimized. Please refer to the section earlier in this brochure in which physical therapy has been discussed in detail.

## CPAP and BiPAP

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Sleep apnea can be improved in some individuals with MPS III by opening the airway using CPAP or BiPAP machines during sleep. These machines distribute oxygen to a patient if needed, using a mask covering the face or nose. Both CPAP and BiPAP are noninvasive (no surgery, breaking the skin, or inserting a device into a body cavity). Both require the individual to wear a mask covering the nose, and sometimes the mouth, when sleeping. While both CPAP and BiPAP

are very effective in managing sleep apnea, they do not treat the underlying problem of GAG accumulation. Occasionally, CPAP can increase the work involved in natural breathing. In these cases, it may be advisable to switch to a BiPAP machine. Individuals will need to get acclimated to using these devices. In cases where CPAP or BiPAP are not effective or are not appropriate, a tracheostomy (a surgical procedure to insert a breathing tube in the throat) may be used.

CPAP and BiPAP are noninvasive options usually sufficient to address sleep apnea, although they do not address the underlying GAG accumulation.

## Tracheostomy (very rare)

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A tracheostomy (tray-kee-ossta-mee; also called an artificial airway or “trach,” pronounced “trake”) is a surgically created opening through the neck into the trachea (or the windpipe). It is very rarely required for individuals with MPS III.

A tube is usually placed through the opening into the trachea. This tube is referred to as a tracheostomy tube or a “trach” tube. The function of the tube is to open an airway and to remove secretions from the lungs. A tracheostomy is usually performed under general anesthesia (please see below). After the area is cleaned, incisions are made to expose the outer wall of the trachea, which is made up of tough cartilage rings. A surgeon inserts the tracheostomy tube into the trachea after creating an opening through the cartilage rings.

It is important to discuss trach care in detail with the doctors. The surgical incision needs to be cleaned frequently as it heals, perhaps as many as four to five times per day. Once the skin heals, it should be kept clean and dry. Most people use soap and water to clean the skin. Some people use a small amount of water-soluble antibiotic ointment around the skin incision. Mucus secretions or blood can block the tracheostomy tube and interfere with breathing. The tube may be blocked if you notice bubbles in the trach tube, if you hear loud gurgles coming from the trach tube, or if the individual with the tube seems to be having difficulty breathing (for babies, the signs may include agitation, flared nostrils, increased heart rate, or pale or blue-colored skin). If this occurs, the tube should be suctioned.

From time to time, the tracheostomy tube will need to be changed. Changing an old tube for a new, fresh tube can be challenging but often becomes easier with time. Shortly after surgery, if the entry site has not healed

properly, it may cave in when the tube is removed and block the trachea. There is also a risk of the new tube being inserted incorrectly. As the wound heals, the chance that either situation will occur will decrease.

One of the biggest challenges that people face following the insertion of the trach is adjusting to new breathing patterns and changes to the vocal cords. Communication is perhaps the biggest adjustment because it may be difficult for the individual to talk or make sounds. However, with proper training, many individuals can learn to speak with a tracheostomy tube.

Water-related activities can be hazardous to the person with a trach because there is not an easy way to hold their breath underwater, and water could enter their lungs. Special care needs to be taken during bathing to shield the tracheostomy tube opening from the water. A person with a trach also may benefit from using a cotton cover or scarf to protect from inhaling dust and other particles.

With proper planning, discussion with doctors, and after-surgery care, a tracheostomy may significantly help individuals with MPS III whose upper airway is blocked.

A tracheostomy is generally a routine procedure, but as with any other surgical procedure, there are risks. With the anesthesia, there is a risk of adverse reactions to medications and problems with breathing. Because individuals with MPS III are at a higher risk for problems with anesthesia, the tracheostomy should be done in a hospital that is fully equipped to deal with these issues. Make sure that the anesthesiologist for the procedure has experience with MPS III.

Tracheostomy is an option to help with breathing when other methods have failed. It must be done in a hospital under anesthesia and the care of a surgeon who is knowledgeable in treating MPS.

Tracheostomies require a life-long and specialized care of the tubes. This gets easier over time.

## Anesthetics

Giving an anesthetic to an individual with MPS III requires skill and should always be undertaken by an experienced anesthesiologist. Inform your child's school or any other caregivers of this in case you cannot be contacted in the event of an emergency. If you must go to a different hospital in an emergency, be sure to tell the anesthesiologist there might be problems 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 advanced intubation techniques, such as a flexible bronchoscope, laryngeal mask airway or fiber optics. 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 due to excessive swelling. It is important to advise physicians of the critical nature of these problems, and that many problems have occurred during anesthesia of MPS individuals.

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 instead of a local hospital. See additional information on anesthesia in the booklet titled *Is Your Child Having an Anesthetic?*, published by the National MPS Society.

For any elective surgery in an individual with MPS, especially a child, it is important to choose an anesthesiologist/pediatric anesthesiologist who has experience with difficult airways.



FIONA

# Research for the future

The mission of the National MPS Society is to find cures for MPS and mucopolidosis (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 living with MPS III and what they can do to manage it. This booklet was updated by the National MPS Society in 2021.



## Updates

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Medical professionals and researchers are constantly learning new things about MPS III 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 III and its management, visit [www.mpssociety.org](http://www.mpssociety.org).

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

<b>Update:</b> <b>Date:</b> <b>Link to more information:</b>	
<b>Update:</b> <b>Date:</b> <b>Link to more information:</b>	
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<b>Update:</b> <b>Date:</b> <b>Link to more information:</b>	

# 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 genetic 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:

- *eCourage*, 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
<b>Aspiration</b>	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.
<b>Attenuated</b>	Weakened, reduced, or diminished in size. Attenuated MPS means a less severe form of the disease.
<b>Bronchoscopy</b>	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.
<b>Carpal Tunnel Syndrome</b>	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, carpal tunnel syndrome occurs because of the accumulation of GAG deposits.
<b>Carrier</b>	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.
<b>Cerebrospinal Fluid (CSF)</b>	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.
<b>Chromosomes</b>	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.
<b>Echocardiogram</b>	Ultrasound of the heart to evaluate heart valve and heart muscle function.



<b>Enzyme</b>	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).
<b>Enzyme Replacement Therapy (ERT)</b>	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.
<b>Gastrostomy Tube (G-Tube)</b>	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.
<b>Gene</b>	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.
<b>Gene Therapy</b>	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.
<b>Glycosaminoglycans (GAGs)</b>	Complex linear sugar molecules that are widely found throughout the body in connective tissue, the area between cells, and secretions on the surfaces of many cell types. GAGs were previously called mucopolysaccharides.
<b>Hernia</b>	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.
<b>Hematopoietic Stem Cell Transplantation (HSCT)</b>	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.

<b>Hydrocephalus</b>	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.
<b>Individualized Education Program (IEP)</b>	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.
<b>Kyphosis</b>	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.)
<b>Lumbar Puncture</b>	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.
<b>Lysosomal Storage Disorder (LSD)</b>	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 GAGs, 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).
<b>Lysosome</b>	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.
<b>Mitral Valve Prolapse</b>	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.

<b>Mucopolipidosis (ML)</b>	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).
<b>Mucopolysaccharidosis (MPS)</b>	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.
<b>Mutation</b>	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.
<b>Otitis Media</b>	Inflammation of the middle ear occurring commonly in children as a result of an infection, causing pain and temporary hearing loss.
<b>Port-a-cath</b>	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.
<b>Scoliosis</b>	A sideways curve of the spine.
<b>Shunt</b>	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.
<b>Sleep Apnea</b>	A sleep disorder where breathing stops repeatedly during sleep. It is frequently caused by an obstruction of the airway.
<b>Tracheostomy</b>	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.
<b>Vocational Rehabilitation</b>	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](http://mpssociety.org/fact-sheet-glossary).



## For more information or to join the National MPS Society:

Visit [www.mpssociety.org](http://www.mpssociety.org)

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