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Mucopolysaccharidosis Type II

Synonyms: Hunter Syndrome, Iduronate-2-Sulfatase Deficiency, MPS II

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Summary

Clinical characteristics

Mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) is an X-linked multisystem disorder characterized by glycosaminoglycan (GAG) accumulation. The vast majority of affected individuals are male; on rare occasion heterozygous females manifest findings. Age of onset, disease severity, and rate of progression vary significantly among affected males. In those with the neuronopathic phenotype, central nervous system (CNS) involvement (manifesting primarily as progressive cognitive deterioration), progressive airway disease, and cardiac disease usually results in death in the first or second decade of life. In those with the non-neuronopathic phenotype, the CNS is minimally or not affected. However, the effect of GAG accumulation on other organ systems can be severe. Survival into the early adult years with normal intelligence is common in the non-neuronopathic phenotype. Additional findings in neuronopathic and non-neuronopathic MPS II include: short stature, macrocephaly with or without communicating hydrocephalus, macroglossia, hoarse voice, conductive and sensorineural hearing loss, dysostosis multiplex, spinal stenosis, carpal tunnel syndrome, and hepatosplenomegaly.

Diagnosis/testing

The diagnosis of MPS II is established in a male proband by identification of absent or reduced iduronate 2-sulfatase (I2S) enzyme activity in leukocytes, fibroblasts, or plasma in the presence of normal activity of at least one other sulfatase; or of a hemizygous pathogenic variant in *IDS* by molecular genetic testing. The diagnosis of MPS II is usually established in a female proband with suggestive clinical features by identification of a heterozygous *IDS* pathogenic variant by molecular genetic testing.

Management

Targeted therapies: Weekly enzyme replacement therapy (ERT) with infusions of idursulfase (Elaprase®), a recombinant form of human I2S, is approved to treat somatic manifestations and prolong survival. Pretreatment

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with anti-inflammatory drugs or antihistamines may be needed for mild or moderate infusion reactions. Hematopoietic stem cell transplantation (HSCT) could provide sufficient enzyme activity to slow or stop the progression of the disease; however, no controlled clinical studies have been conducted in individuals with MPS II.

Supportive care: Treatment of ocular manifestations by ophthalmologist with experience in MPS; tonsillectomy and adenoidectomy as needed; early and aggressive treatment of ear infections including pressure-equalizing tubes; hearing aids may be helpful; hip replacement as needed; physiotherapy; positive pressure ventilation (CPAP) as needed; CT examination of the trachea to assess airway issues; tracheostomy only as needed; anesthesia is best administered in centers familiar with the potential complications in persons with MPS II; umbilical and inguinal hernia repair as needed; treatment of cardiovascular manifestations per cardiologist with medications and/or cardiac valve replacement; developmental and educational support; occupational and physical therapy; shunting for hydrocephalus as needed; carpal tunnel release as needed; treatment of spinal stenosis per neurosurgeon/orthopedist; standard management of behavioral problems and seizures; melatonin may be beneficial for sleep problems; transitional care plan; family and social work support.

Surveillance: Assess growth every six to 12 months throughout childhood; ophthalmology examination annually or as needed; assess feeding and swallowing at each visit or at least every six to 12 months in those with neuronopathic MPS II; assess for adenoid and tonsil hypertrophy at least annually; dental evaluation every six months; audiogram at least annually; annual orthopedic evaluation; annual pulmonology evaluation including pulmonary function testing; sleep study as needed and prior to surgery; assess for umbilical and inguinal hernia, chronic diarrhea, and liver and spleen size annually or as needed; cardiology assessment with echocardiogram annually or per cardiologist; EKG annually in adults or more frequently as needed; annual developmental, cognitive, behavioral, and neurologic assessment including assessment for seizures and manifestations of spinal stenosis; head and neck MRI to assess ventricular size and for cervical medullary narrowing as needed; assess opening pressure on lumbar puncture as needed; nerve conduction study for carpal tunnel syndrome annually; assess family needs at each visit.

Evaluation of relatives at risk: I2S biochemical testing and/or *IDS* molecular genetic testing of at-risk male family members allows early diagnosis and prompt initiation of treatment; the importance of prompt initiation of treatment has been demonstrated in studies involving affected sibs who were diagnosed and treated at different ages.

Genetic counseling

MPS II is inherited in an X-linked manner. The risk to sibs depends on the genetic status of the mother. If the mother of the proband has an *IDS* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be carriers and will typically be asymptomatic. Affected males transmit the pathogenic variant to all of their daughters and none of their sons. Once the *IDS* pathogenic variant has been identified in an affected family member, molecular genetic carrier testing for at-risk female relatives and prenatal/preimplantation genetic testing for pregnancies at increased risk are possible.

Diagnosis

The diagnosis of mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) cannot be established on clinical findings alone. Clinical and radiographic findings vary widely, and the evolution of manifestations is often a better indicator of the diagnosis of MPS II. Recommendations for establishing the diagnosis have been developed by the Hunter Syndrome European Expert Council (HSEEC) using an evidence-based approach [Scarpa et al 2011].

Suggestive Findings

Scenario 1: Abnormal Newborn Screening (NBS) Result

NBS for MPS II is primarily based on quantification of iduronate 2-sulfatase (I2S) enzyme activity on dried blood spots.

I2S enzyme activity below the cutoff reported by the screening laboratory is considered positive and requires follow-up biochemical and/or molecular testing to establish the diagnosis.

Note: To date, NBS for MPS II is performed in the United States and Taiwan.

Scenario 2: Symptomatic Individual

MPS II **should be considered** in probands with the following supportive – but nonspecific – clinical, radiographic, and laboratory findings and family history.

Clinical findings (common at age 18 months to four years)

- Short stature
- Hepatosplenomegaly
- Joint contractures
- Coarse facies
- Frequent ear/airway infections
- Umbilical hernia

Radiographic findings. Skeletal survey reveals dysostosis multiplex (i.e., generalized thickening of long bones, particularly the ribs; irregular epiphyseal ossification centers in many areas; notching of the vertebral bodies; and hip dysplasia).

Note: These clinical and radiographic findings may not be present in early life and are not specific to MPS II.

Laboratory findings. Urine glycosaminoglycan (GAG) analysis shows large concentrations of the GAGs dermatan sulfate and heparan sulfate.

Note: These laboratory findings are not specific to MPS II; the profile is similar to that seen in MPS I.

Family history is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

Analyte Diagnosis

The diagnosis of MPS II **is established** in a male proband by identification of absent or reduced I2S enzyme activity in leukocytes, fibroblasts, or plasma. Most affected males have no detectable activity using the artificial substrate. Detailed analytic protocols for measurement of I2S enzyme activity have been published [Johnson et al 2013]. Note: Documentation of normal enzymatic activity of at least one other sulfatase is required for diagnosis of MPS II, as low levels of I2S enzyme activity are also present in multiple sulfatase deficiency (see Differential Diagnosis), which can share some clinical features with MPS II.

Molecular Diagnosis

Male proband. Identification of a hemizygous *IDS* pathogenic (or likely pathogenic) variant by molecular genetic testing (see Table 1) **confirms** the diagnosis of MPS II in a male proband and may be useful in persons with an unusual phenotype or a phenotype that does not match the results of GAG analysis.

Female proband. Although the disease is almost exclusively reported in males, rarely females have clinical manifestations. The diagnosis of MPS II **is usually established** in a female proband presenting with suggestive clinical features by identification of a heterozygous *IDS* pathogenic (or likely pathogenic) variant on molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMG variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a hemizygous or heterozygous *IDS* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of MPS II, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *IDS* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

  Note: A 178-bp deletion in the promoter region was identified in two affected individuals with low I2S enzyme activity [Brusius-Facchin et al 2013]. Alteration of the promoter region may explain low enzyme activity in some affected individuals in whom no *IDS* pathogenic variant was detected.

- **A multigene panel** that includes *IDS* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of MPS II has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Mucopolysaccharidosis Type II

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
IDS	Sequence analysis [3]	82% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	9%
	Analysis for complex rearrangements [7]	9%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Single-nucleotide changes and splicing variants account for 65% of all pathogenic variants; small (i.e., intraexon) deletions and insertions account for 17% of all pathogenic variants [Froissart et al 2007].
5. Sequence analysis may not detect complex rearrangements in males or females that result from a common pathogenic inversion between *IDS* and its pseudogene (*IDSP1*).
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
7. Complex rearrangements result from recombination with the *IDSP1* pseudogene or from other types of processes. Testing may require multiple molecular methods (e.g., sequencing, SNP analysis, gene-targeted deletion/duplication analysis, chromosomal microarray) to confirm and map rearrangement breakpoints [Lualdi et al 2005, Froissart et al 2007, Oshima et al 2011].

Clinical Characteristics

Clinical Description

Mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) has multisystem involvement with significant variability in both age of onset and rate of progression. Two phenotypes have been described based on severity of neurologic disease and rate of progression. In those with neuronopathic MPS II, neurologic involvement (manifesting primarily as cognitive deterioration) and progressive airway and cardiac disease usually result in death in the first or second decade of life. In those with non-neuronopathic MPS II, the central nervous system (CNS) is minimally or not affected, although glycosaminoglycan (GAG) accumulation affects other organ systems; survival into the early adult years with normal intelligence is common. Additional findings in both forms of MPS II include: short stature, macrocephaly with or without communicating hydrocephalus, macroglossia, hoarse voice, conductive and sensorineural hearing loss, hepatosplenomegaly, dysostosis multiplex, spinal stenosis, and carpal tunnel syndrome.

Table 2. Mucopolysaccharidosis type II: Frequency of Select Features

Feature		% of Persons w/Feature by Phenotype		Comment [1]
		Neuronopathic	Non-neuronopathic	
Characteristic facial features		91%	82%	
Ear, nose, throat	**Macroglossia**	72%	41%	In those age <10 yrs
	Swallowing difficulties	22%	6%	
	Abnormal dentition	41%	24%	
	Rhinorrhea	48%	33%	
	Nasal congestion/obstruction	46%	28%	
	Purulent ear discharge	28%	57%	

Table 2. continued from previous page.

Feature		% of Persons w/Feature by Phenotype		Comment [1]
		Neuronopathic	Non-neuronopathic	
Joints/skeletal	**Joint stiffness & limited function**	85%	88%	
	Gait abnormalities	60%	26%	In those age <10 yrs
	Phalangeal contractures	77%	67%	
	Kyphosis/gibbus	49%	28%	
	Musculoskeletal pain	37%	47%	
Respiratory	**Lower airway infection / pneumonia**	39%	26%	In those age <10 yrs
	Dyspnea	24%	8%	
Gastrointestinal	**Hepatomegaly**	87%	80%	
	Hernias	78%	75%	
Cardiac valve disease		75%	78%	

Adapted from Lau et al [2023]

1. The percentages for some features were specifically reported for individuals younger than age ten years.

Infants with MPS II identified by newborn screening and follow-up enzymatic and/or molecular genetic testing are asymptomatic and have no clinical or radiographic manifestations of MPS II in infancy.

Craniofacial features. Macrocephaly is universal. Coarsening of facial features – the result of macroglossia, prominent supraorbital ridges, a broad nose, a broad nasal bridge, and deposition of glycosaminoglycan (GAG) in the soft tissues of the face resulting in large-rounded cheeks and thick lips – generally manifests between ages 18 months and four years in the neuronopathic form of MPS II and about two years later for those with the non-neuronopathic form.

Dermatologic findings. Some individuals develop ivory-colored skin lesions on the upper back and sides of the upper arms, which are pathognomonic of MPS II [Tylki-Szymańska 2014].

Growth. Infants with MPS II have normal growth parameters at birth. In the first years of life the height of most children with MPS II is above the 50th centile and in some it is above the 97th centile [Różdżyńska-Świątkowska et al 2022]. However, growth velocity decreases with age. In the first 36 months of life, the average z score for body height ranges from 0.24 to 1.92; for body weight the z score range is 0.34 to 4.80; and for head circumference the z score range is 0.71 to 4.17 [Rozdzynska et al 2011]. By age eight years, height is below the third centile, and nearly all children exhibit growth deficiency before puberty [Schulze-Frenking et al 2011]. The cause of short stature is unknown; it may be related to osseous growth plate disturbances. Although no statistical difference is observed between height in the neuronopathic and non-neuronopathic phenotypes, the growth pattern can help in monitoring disease progression and assessing therapeutic efficacy [Patel et al 2014].

Eye. In contrast to MPS I, corneal clouding occurs occasionally and is not a typical feature of MPS II. However, discrete corneal lesions that do not affect vision may be discovered by slit lamp examination [McGrath et al 2023].

Optic nerve head swelling (papilledema) in the absence of increased intracranial pressure is present in approximately 20% of affected individuals and subsequent optic atrophy in approximately 11% [Collins et al 1990, Ashworth et al 2006], mainly as a result of scleral thickening due to GAG deposition.

Retinopathy has been reported most commonly in individuals with neuronopathic MPS II, although it can also be present in individuals with non-neuronopathic MPS II. Progressive reduction in electroretinography (ERG) amplitude suggests deterioration in retinal function [Leung et al 1971]. Retinal degeneration leads to poor

peripheral vision and night blindness, which occur frequently in individuals with MPS II, while central visual impairment due to retinal degeneration is rare [Suppiej et al 2013]. Such retinal dysfunction can be revealed by ERG. Visual field loss can also occur; initially, rod-mediated responses are more affected by early progression than cone-mediated responses [Caruso et al 1986]. However, signs and symptoms do not necessarily correlate with ERG change, as often only minimal changes are observed in the retinal pigment epithelium despite significant ERG changes [Ashworth et al 2006].

Although glaucoma is not commonly reported in individuals with MPS II, there are instances of increased intraocular pressure due to GAG deposition, which can lead to chronic disc elevation without increased intracranial pressure [Kong et al 2021].

Other ocular findings include bilateral uveal effusions, peripheral pigment epithelial changes, and radial parafoveal folds [Ashworth et al 2006].

Enzyme replacement therapy does not halt the eventual progression of the ocular involvement [McGrath et al 2023].

Ear, nose, throat. Common oral findings in boys with MPS II include macroglossia, diastema, hypertrophic adenoids and tonsils, and ankylosis of the temporomandibular joint, which limits opening of the mouth. These changes may be responsible for progressive swallowing impairment and/or breathing difficulties. GAG deposition in the larynx typically results in a characteristic hoarse voice.

Teeth are often irregularly shaped and gingival tissue is overgrown. Anterior open bite and ectopic and/or unerupted teeth can be present. Dentigenous cysts can also occur, often causing pain and discomfort. Dentigenous cysts can be difficult to diagnose particularly in males with CNS involvement. Painful dental caries and cysts can cause hyperactivity and aggression in individuals with neuronopathic MPS II [de Bode et al 2022].

Conductive and sensorineural hearing loss, complicated by recurrent ear infections, occurs in most affected individuals. Otosclerosis can contribute to the conductive hearing loss. Neurosensory hearing loss can be attributed to compression of the cochlear nerve resulting from arachnoid hyperplasia, reduction in the number of spiral ganglion cells, and degeneration of hair cells.

Joints/skeletal. Joint contractures, particularly of the phalangeal joints, are universal. The contractures cause significant loss of joint mobility and are one of the earliest manifestations of MPS II. Upper body stiffness is reported in 78% and lower body stiffness in 61%. The majority of individuals with MPS II have at least three joint manifestations; the most affected joints are the shoulders.

The skeletal abnormalities in MPS II are similar in neuronopathic and non-neuropathic phenotypes but are not specific to MPS II. Termed "dysostosis multiplex," these radiographic findings are found in all MPS disorders and manifest as a generalized thickening of most long bones, particularly the ribs, with irregular epiphyseal ossification centers in many areas. Notching of the vertebral bodies is common.

Hip dysplasia is the most common long-term orthopedic problem and can become a significant disability with early-onset arthritis if not treated. Gait abnormalities in individuals with MPS II are common and arise from a complex interplay of skeletal deformities, joint stiffness, and muscle weakness. Approximately 25% of individuals with non-neuropathic MPS II exhibit abnormal gait, with a median age of onset of 5.4 years. Gait issues can develop relatively early in the disease progression, often following initial skeletal manifestations that typically appear by age 3.5 years [Link et al 2010].

Kyphosis/scoliosis occurs in approximately 33.8% of all individuals with MPS II, with a median age of onset of 6.4 years [Link et al 2010]. A recent analysis from the Hunter Outcome Survey reports the presence of kyphosis in 49% of individuals with neuronopathic and 28% of individuals with non-neuronopathic MPS II under age 10 years [Lau et al 2023].

Musculoskeletal pain is more common in individuals with non-neuronopathic MPS II than in individuals with neuronopathic MPS II.

Respiratory. Frequent upper-respiratory infections are one of the earliest findings in MPS II. The airway progressively narrows as GAGs accumulate in the tongue, soft tissue of the oropharynx, and the trachea, eventually leading to airway obstruction. Complicating this obstruction are thickening of respiratory secretions, stiffness of the chest wall, and hepatosplenomegaly, which can reduce thoracic volume. The progression of airway obstruction is relentless and usually results in sleep apnea and the need for positive pressure assistance and eventually tracheostomy. Recurrent pneumonia/bronchopneumonia also occurs in individuals with MPS II.

Gastrointestinal. Hepatomegaly and/or splenomegaly occur in most affected individuals. Umbilical/inguinal hernia is also a frequent finding. In persons with early progressive MPS II, chronic diarrhea is common.

Cardiovascular. The heart is abnormal in the majority of boys with MPS II and is a major cause of morbidity and mortality; 82% of individuals have cardiovascular signs/symptoms, and 62% have a murmur that can be related to valvular disease, including (in order of frequency) the mitral, aortic, tricuspid, and pulmonary valves. Cardiomyopathy, hypertension, rhythm disorder, and peripheral vascular disease are seen occasionally (<10%) [Wraith et al 2008, Dehghan et al 2024].

Nervous system. Infants with MPS II appear normal at birth; early developmental milestones may also be within the normal range. Delay in global developmental milestones is typically the first indication of brain involvement in children with neuronopathic MPS II. The characteristic signs and symptoms of neuronopathic MPS II can vary and may include the following.

- Cognitive impairment/decline. Individuals may experience developmental delays or cognitive impairment. This can range from mild learning difficulties to significant intellectual disability.
- Behavioral issues. Individuals may exhibit behavioral problems such as aggression, hyperactivity, and social withdrawal.
- Neurologic manifestations. Individuals can show signs of neurologic involvement, including seizures, ataxia, gait disturbances.

Presence of sleep disturbance, behavior difficulties, increased activity, seizure-like behavior, perseverative chewing behavior, and inability to achieve bowel and bladder training may be strongly correlated with subsequent cognitive dysfunction [Holt et al 2011]. Progression of the CNS manifestations is inexorable, usually resulting in developmental regression between ages six and eight years.

Behavioral problems occur in individuals with neuronopathic and non-neuronopathic MPS II [Wraith et al 2008] but are more common and more severe in the neuronopathic phenotype. Sleep problems are common in individuals with neuronopathic MSP II.

Chronic communicating hydrocephalus may complicate the clinical picture, especially in those with neuronopathic MPS II and deteriorating cognitive ability and seizures. Males with non-neuronopathic MPS II have normal or near-normal intelligence and seizures are uncommon; however, chronic communicating hydrocephalus may still occur.

Carpal tunnel syndrome (CTS) is an often-overlooked complication of MPS II. Unlike adults with CTS, most children with MPS II do not report the typical symptoms of CTS. Nonetheless, nerve conduction studies are abnormal. Hand function improves after surgical correction.

Spinal stenosis can occur, particularly in the cervical region, with spinal cord compression. Spinal stenosis might occur less frequently in individuals with MPS II than in other mucopolysaccharidoses [Pantel et al 2022]. In a cohort of 32 individuals with MPS II, 80% had a normal space available for cord (SAC; 10.4-2.5 mm) or mild stenosis (SAC 2.5-1 mm), while 20% had a severe stenosis (SAC <1 mm) or mild cord compression (spinal cord

diameter >5 mm) [Manara et al 2011]. These findings usually appear in the first decade of life, particularly in individuals with neuronopathic MPS II [Żuber et al 2015].

Table 3. Mucopolysaccharidosis Type II: Frequency of Neurobehavioral/Psychiatric and Neurologic Features by Phenotype and Age

Feature		% of Persons w/Feature by Phenotype & Age			
		Neuronopathic		Non-neuronopathic	
		Age <10 yrs	Age >10 yrs	Age <10 yrs	Age >10 yrs
Neurobehavioral/ psychiatric	**Behavioral problems**	82%		28%	
	Hyperactivity	66%		12%	
	Frequent chewing	21%	15%	4%	2%
	Aggression	18%	17%	8%	6%
Neurologic	**Cognitive impairment**	82%		10%	
	Bowel incontinence	27%		2%	
	Bladder incontinence	27%		6%	
	Seizure disorders	22%	37%	4%	10%
	Hydrocephalus	21%		4%	
	Abnormal reflexes	18%	30%	8%	12%
	Carpal tunnel syndrome		10%		33%

Adapted from Lau et al [2023]

Prognosis. In individuals with neuronopathic MPS II, the decline of cognitive function, combined with progression of early progressive pulmonary and cardiac disease, generally heralds the terminal phase of the disease, with death in the first or second decade of life. In individuals with non-neuronopathic MPS II, survival into the early adult years with normal intelligence is common. Respiratory failure (56%) and cardiac failure (18%) are the predominant causes of death in individuals with non-neuronopathic MPS II, alongside severe infections (3%) and post-traumatic organ failure (3%) [Lin et al 2016].

Genotype-Phenotype Correlations

Limited information is available regarding genotype-phenotype correlations:

- The pathogenic variant c.1122C>T (which creates a new donor splice site at exon 8 with the loss of 20 amino acids) is primarily associated with non-neuronopathic MPS II [Muenzer et al 2009].
- Males with complete absence of functional enzyme as a result of gene deletion or complex gene rearrangements (~17% of affected individuals) invariably manifest the neuronopathic phenotype of MPS II [Wraith et al 2008].
- Data from a cohort study of Dutch individuals with MPS II suggest that very low or cell-type-specific iduronate 2-sulfatase residual activity is sufficient to prevent the neuronal phenotype of MPS II. While the molecular effects of *IDS* pathogenic variants do not discriminate between MPS II phenotypes, the *IDS* genotype is indicated as a strong predictor [Vollebregt et al 2017].

Penetrance

Penetrance of MPS II in males is complete.

Nomenclature

Other terms used to describe the phenotypic variability of MPS II include:

- Mild/attenuated MPS II and severe MPS II; and
- Slowly progressive MPS II and early progressive MPS II.

Prevalence

Several surveys suggest an incidence between 1:100,000 and 1:170,000 male births [Nelson et al 2003, Baehner et al 2005]. The neuronopathic phenotype may be more than twice as prevalent as the non-neuronopathic phenotype in individuals with MPS II; however, accurate prevalence rates are not available.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *IDS*.

Contiguous gene deletions. Deletions in the Xq28 region involving *IDS* and adjacent genes are typically associated with severe phenotypes and features that are atypical of MPS II. These deletions cause an earlier progressive central nervous system phenotype and may be associated with other atypical features such as ptosis and seizures [Probst et al 2007]. Neurodevelopmental features may be more pronounced in individuals with contiguous gene deletions involving *IDS* than features suggestive of MPS II [Jezela-Stanek et al 2021].

Differential Diagnosis

The differential diagnosis for mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) includes multiple sulfatase deficiency, mucolipidosis type II and type III alpha/beta, mucolipidosis type III gamma, and essentially all the other MPS disorders (given the significant overlap of clinical presentation and radiologic findings).

Selected disorders of interest in the differential diagnosis of MPS II are listed in Table 4.

Table 4. Genes and Disorders of Interest in the Differential Diagnosis of Mucopolysaccharidosis Type II

Gene [1]	Disorder	MOI	Biochemical Findings	Other Findings / Comment
ARSB	MPS VI (OMIM 253200)	AR	Galactosamine-4-sulfatase deficiency	
FUCA1	Fucosidosis (OMIM 230000)	AR	Alpha-fucosidase deficiency	
GALNS	MPS IVA	AR	N-acetylgalactosamine-6-sulfatase deficiency	
GLB1	MPS IVB (See *GLB1*-Related Disorders.)	AR	Beta-galactosidase deficiency	
GNPTAB	ML II & ML IIIα/β (See *GNPTAB*-Related Disorders.)	AR	Activity of nearly all lysosomal hydrolases is 5- to 20-fold higher in plasma & other body fluids compared to normal controls.	• Dysostosis multiplex (multiple skeletal abnormalities visible on imaging) • Coarse facial features such as thickened lips & macroglossia • Joint stiffness & contractures that can significantly impact mobility
GNPTG	ML IIIγ	AR	Activity of nearly all lysosomal hydrolases is up to tenfold higher in serum dried blood & other body fluids (e.g., media from cultured fibroblasts or amniocytes) compared to normal controls.	
GUSB	MPS VII	AR	Beta-glucuronidase deficiency	
IDUA	MPS I	AR	Alpha-L-iduronidase deficiency	

Table 4. continued from previous page.

Gene [1]	Disorder	MOI	Biochemical Findings	Other Findings / Comment
MAN2B1	Alpha-mannosidosis	AR	Alpha-mannosidase deficiency	
NEU1	ML I (sialidosis type II) (OMIM 256550)	AR	Neuraminidase deficiency	
SUMF1	Multiple sulfatase deficiency	AR	Low activity levels in at least 2 sulfatase enzymes	• Coarse facial features, hepatosplenomegaly, joint stiffness, skeletal abnormalities • Multiple sulfatase deficiency & MPS II differ significantly in their neurologic manifestations, skin manifestations, & age of onset. MPS II typically presents with more pronounced skeletal issues & organ involvement without the severe neurologic decline seen in multiple sulfatase deficiency, particularly in its neonatal form.

AR = autosomal recessive; ML = mucolipidosis; MOI = mode of inheritance; MPS = mucopolysaccharidosis

Management

Management guidelines for individuals with mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) have been published [Scarpa et al 2011].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with MPS II, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Mucopolysaccharidosis Type II: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Growth	Assess linear growth, weight, & head circumference.	
Eye	Ophthalmologic eval	To assess for glaucoma, papilledema, & retinopathy [Kong et al 2021]
ENT	• Assessment of feeding/swallowing issues (incl macroglossia, limited mouth opening) • Assessment for adenoid & tonsil hypertrophy • Dental assessment for abnormal teeth & dentigenous cysts • Audiologic eval	
Joints/Skeletal	Assess for joint contractures, mobility issues, ADL, & skeletal deformities [Link et al 2023].	

Table 5. continued from previous page.

System/Concern	Evaluation	Comment
Respiratory	Pulmonary function testing (PFT)	Preferably in persons age ≥6 years; PFT (e.g., spirometry) can be challenging in younger persons & may be impossible for those w/significant CNS involvement since it requires full cooperation & is effort dependent.
	Sleep study if sleep apnea is a potential concern & prior to surgery	Also consider for sleep disturbances not related to upper-airway obstruction or impairment of ventilatory control (e.g., difficulty initiating or maintaining sleep, awakening several times per night, decreased REM sleep, atypical sleep stage distribution, & restless legs), which might start to manifest at median age of 4-5 yrs [1]
Gastrointestinal	• Assess for umbilical/inguinal hernia & for chronic diarrhea. • Assess liver & spleen size.	
Cardiovascular	• Echocardiogram to assess for valvular disease & cardiomyopathy • EKG to assess arrhythmias	
Neurologic	• Developmental & cognitive assessment • Behavioral assessment by neurodevelopment specialist &/or psychiatrist	Given complexity of cognitive & behavioral manifestations, eval should be done by experts in the field.
	• Neurologic eval incl assessment for seizures • Assessment for spinal stenosis	At diagnosis
	Head/cervical MRI &/or opening pressure on lumbar puncture to assess for hydrocephalus & spinal cord compression	Because MRI needs to be performed under sedation &/or intubation in persons w/neuronopathic MPS II, there is ↑ risk of compromising upper airway.
	Nerve conduction velocity & nerve ultrasound exam to assess for carpal tunnel syndrome [2]	At approximately age 2 yrs
Genetic counseling	By genetics professionals [3]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of MPS II to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

ADL = activities of daily living; CNS = central nervous system; MOI = mode of inheritance; MPS II = mucopolysaccharidosis type II
1. Rapoport & Mitchell [2017]
2. Dabaj et al [2019], Muenzer et al [2023]
3. Clinical geneticist, certified genetic counselor, certified genetic nurse, genetics advanced practice provider (nurse practitioner or physician assistant)

Treatment of Manifestations

Targeted Therapies

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition);

would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Enzyme replacement therapy (ERT). Intravenous idursulfase (Elaprase®), a recombinant form of human iduronate 2-sulfatase (I2S), is approved in the United States and the European Union at a weekly dose of 0.5 mg/kg for the treatment of MPS II. Idursulfase has positive effects on functional capacity (distance walked in 6 minutes and forced vital capacity), liver and spleen volumes, and urine glycosaminoglycan (GAG) excretion [da Silva et al 2016]. A 3.5-year independent study determined that long-term use of ERT is similarly effective in young (age 1.6 to 12 years at the start of ERT) and older individuals (age 12 to 27 years at the start of ERT) [Tomanin et al 2014, Muenzer et al 2017]. In addition, two studies have confirmed ERT efficacy in improving somatic signs and symptoms of the disease in all individuals, including infants younger than age one year and individuals with neuronopathic MPS II [Lampe et al 2014a, Lampe et al 2014b].

Analysis of data from the Hunter Outcome Survey (HOS) showed that survival in idursulfase-treated individuals was longer than in those who were untreated [Burton et al 2017]. An additional report from the analysis of the HOS data, investigating clinical outcomes after up to three years of idursulfase treatment in a broad population of individuals with MPS II, suggests that the treatment improves GAG storage (as evidenced by decreases in urinary GAG levels and hepatosplenomegaly) as well as results on the six-minute walk test, left ventricular mass index, absolute forced vital capacity, and absolute forced expiratory volume in one second [Muenzer et al 2017].

Earlier introduction of ERT was associated with improved respiratory outcome in individuals with MPS II at age 16 years. The median predicted forced vital capacity in those who started ERT at younger than age eight years was 69% (range: 34%-86%) and in those who started ERT at older than age eight years was 48% (range: 25%-108%) (P=0.045) [Broomfield et al 2020].

Since Elaprase® does not cross the blood-brain barrier, no effect on central nervous system (CNS) disease is anticipated; however, there is reason to believe that somatic manifestations of those with severe CNS involvement would benefit from ERT. There are no additional safety concerns for younger individuals, and individuals have significant amelioration of somatic symptoms [Lampe et al 2014a].

Infusion-related reactions that may occur with use of Elaprase® ERT are comparable to similar reactions seen with other ERT products used in treatment of lysosomal storage diseases and with other infused proteins such as monoclonal antibodies (e.g., infliximab). The etiology of the more severe forms of these non-allergic reactions, referred to as anaphylactoid, is unknown. Current evidence suggests that anaphylactoid (as opposed to anaphylactic) reactions are not immune mediated [Mayer & Young 2006].

Infusion reactions are generally mild and include brief, insignificant decreases or increases in heart rate, blood pressure, or respiratory rate; itching; rash; flushing; and headache. Mild reactions can usually be managed by slowing the infusion rate for several treatments and then slowly returning to the prior rate.

Pretreatment with anti-inflammatory drugs or antihistamines, as is often done for ERT in other conditions, is not suggested on the label for Elaprase®; however, if mild or moderate infusion reactions (e.g., dyspnea, urticaria, or systolic blood pressure changes of ≤20 mm Hg) cannot be ameliorated by slowing the infusion rate, the addition of treatment one hour before infusion with diphenhydramine and acetaminophen (or ibuprofen) to the regimen usually resolves the problem. Pretreatment can typically be discontinued after six to ten weeks.

Severe non-allergic anaphylactoid reactions such as major changes in blood pressure, wheezing, stridor, rigors, or drop in oxygen saturations should be immediately addressed by stopping the infusion and giving appropriate doses of subcutaneous epinephrine, intravenous (IV) diphenhydramine, and hydrocortisone or methylprednisolone. Subsequent infusions should then be given at a significantly reduced rate with pretreatment with prednisone 24 hours and eight hours before the infusion, diphenhydramine and acetaminophen or ibuprofen orally one hour before the infusion, and IV methylprednisolone just before beginning the infusion.

Current data are insufficient to indicate whether the incidence or severity of infusion-related reactions is different for individuals younger than age five years with severe respiratory compromise or with severe CNS disease. Further studies and longer follow up are needed to better understand the effects of ERT. A recent attempt to assess the impact of anti-idursulfase antibodies during long-term idursulfase ERT did not establish a clear association between infusion-related adverse events and antibody levels [Giugliani et al 2017].

Hematopoietic stem cell transplantation (HSCT) using umbilical cord blood or bone marrow is a potential way of providing sufficient enzyme to slow or stop disease progression [Guffon et al 2009, Annibali et al 2013]. However, the use of HSCT is controversial because of the associated high risk of morbidity and mortality. Furthermore, it remains unclear if treatment early in life significantly reduces the progression of neurologic disease [Mullen et al 2000], and results from anecdotal case reports have been disappointing. Overall, the efficacy of HSCT for MPS II demonstrated improvement in biochemical disease markers and somatic manifestations [Kubaski et al 2017, Barth & Horovitz 2018]. It has been shown that HSCT and ERT have equal efficacy in restoring growth in children with MPS II; both treatments are limited by age of the affected individual and disease progression (e.g., neurologic and heart impairment) at the start of treatment [Patel et al 2014].

Until two decades ago, HSCT had high mortality rates because of (1) the preconditioning regimen prior to HSCT, which caused severe side effects including increased susceptibility to infection and (2) poor donor selection, which resulted in a high risk of graft-vs-host disease [Stapleton et al 2017]. With the development of new conditioning protocols and the creation of bone marrow donor registries and umbilical cord banks, HSCT has become more accessible [Barth et al 2017]. Although further studies are required, HSCT should continue to be considered as a treatment option particularly because of its lower cost (compared to lifelong ERT treatment) and potential for improving quality of life for affected individuals and their families [Barth et al 2017]. HSCT is used as the primary treatment for neuronopathic MPS II in China due to limited ERT access and in Japan [Barth & Horovitz 2018], and it is a therapy option if it is performed early in the disease course [Selvanathan et al 2018].

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 6).

Table 6. Mucopolysaccharidosis Type II: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Eye	Treatment per ophthalmologist w/experience in MPS	
ENT	• Tonsillectomy & adenoidectomy as needed for airway obstruction • Early & aggressive treatment of ear infections • Pressure-equalizing tubes for recurrent ear infections	
	Hearing aids may be helpful per otolaryngologist.	Community hearing services through early intervention or school district
Joints/Skeletal	• Hip replacement as needed • PT	

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Respiratory	• Positive pressure ventilation (CPAP) as needed • CT scan of trachea to identify anatomic alterations that may modify trachea structure, ↓ benefit from CPAP, & complicate tracheostomy procedure • Tracheostomy should be last option to manage respiratory problems. [1]	
Anesthesia issues	• Anesthesia should be administered in centers familiar w/MPS II given risks assoc w/sedation w/& w/o intubation. • Nasopharyngeal intubation is often necessary. When endotracheal intubation is difficult or when sedation is required for brief procedures, laryngeal mask airway may be indicated. • CT scan of trachea is always recommended due to anatomic alterations that may modify trachea structure & impair anesthesia procedure. [1]	Risks assoc w/general anesthesia incl: [2] • Ankylosis of temporomandibular joint that can restrict oral access to airway; • Visualization of vocal cords compromised by macroglossia, GAG-infiltrated soft tissues, & large tonsils & adenoids; • Hyperextension of neck secondary to atlantoaxial instability & cervicomedullary compression.
Gastrointestinal	Umbilical & inguinal hernia repair as needed	
Cardiovascular	Treatment per cardiologist w/medication or cardiac valve replacement as needed	
Neurologic	• Developmental & educational support (See Developmental Delay / Intellectual Disability Management Issues.) • OT & PT • Shunting for hydrocephalus as needed • Carpal tunnel release as needed • Treatment of spinal stenosis per neurosurgeon/orthopedist	
Behavioral problems	Mgmt is similar to those in general population [3]	Before starting treatment for behavioral problems, it is important to exclude any issues that could cause or exacerbate behavior problems (e.g., hydrocephalus, pain, seizures, or sleep problems). [3]
Sleep problems	Sleep problems might be ameliorated w/high doses of melatonin (5-10 mg) 30 min before sleeping in the dark [M Scarpa, personal observation].	Sleep problems might be due to frontal nonconvulsive status epilepticus that may be detected via polysomnography w/EEG. [4]
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [5]
Transition from pediatric to adult-centered multidisciplinary care	As a lifelong disorder w/varying implications according to age, a smooth transition of care from the pediatric setting to an adult setting for long-term mgmt is ideal [Lampe et al 2019]. [6, 7]	Unfortunately, standardized procedures for transitional care do not exist for MPS II due to the absence of multidisciplinary outpatient departments.

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; CPAP = continuous positive airway pressure; ENT = ear, nose, throat; GAG = glycosaminoglycan; MPS = mucopolysaccharidosis; OT = occupational therapy; PT = physical therapy

1. Lee et al [2023]

2. The risk of airway complications may continue following successful surgery. Extubation may be difficult because laryngeal edema, which has been reported up to 27 hours post surgery, may prevent maintenance of a proper airway [Hopkins et al 1973]. Breathing a helium-oxygen mixture during extubation has been reported to relieve obstruction and improve outcome [McGarvey & Pollack 2008].

3. Escolar et al [2017]

4. Bonanni et al [2012], Cannizzaro et al [2024]

5. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

6. Transitional care concepts have been developed in which adult internal medicine specialists initially see individuals with MPS II together with pediatric metabolic experts, dietitians, psychologists, and social workers.

7. As the long-term course of pediatric metabolic diseases in this age group is not yet fully characterized, continuous supervision by a center of expertise with metabolic diseases with sufficient resources is essential.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected

individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Guidelines for surveillance have been developed [Scarpa et al 2011]. Because all persons with MPS II face the same organ failure issues, with the time of failure being dependent on severity, when and how often to monitor for change cannot be generalized. However, the studies/evaluations summarized in Table 7 are likely indicated on at least a yearly basis beginning in early to mid-childhood.

Table 7. Mucopolysaccharidosis Type II: Recommended Surveillance

System/Concern	Evaluation	Frequency
Growth	Assess linear growth, weight, & head circumference.	At each visit or at least every 6-12 mos throughout childhood
Eye	Ophthalmology exam, incl exam through dilated pupil to view optic disc	Annually or as needed
ENT	Assess for feeding/swallowing issues.	At each visit & at least every 6-12 mos in those w/neuronopathic MPS II
	Assess for adenoid & tonsil hypertrophy.	At least annually
	Dental assessment for abnormal teeth & dentigenous cysts	Every 6 mos
	Audiogram	At least annually
Joints/Skeletal	Orthopedic eval to assess joint contractures, mobility issues, ADL, & skeletal deformities (incl hip dysplasia)	Annually
Respiratory	Eval w/pulmonologist incl pulmonary function testing	
	Sleep study for obstructive sleep apnea	As needed & prior to surgery
Gastrointestinal	• Assess for umbilical/inguinal hernia. • Assess for chronic diarrhea. • Assess liver & spleen size.	Annually or as needed
Cardiovascular	Cardiology assessment w/echocardiogram to assess for valvular disease & cardiomyopathy	Annually or per cardiologist
	EKG	Annually or more frequently in those w/cardiac insufficiency [1]
Neurologic	• Developmental & cognitive assessment • Behavioral assessment by neurodevelopment specialist &/or psychiatrist • Neurologic exam • Assessment for seizures • Assessment for manifestations of spinal stenosis	Annually
	• Head/neck MRI to document ventricular size & cervicomedullary narrowing • Assessment of opening pressure on lumbar puncture	As needed
	Nerve conduction velocity study for evidence of carpal tunnel syndrome	Annually

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

ADL = activities of daily living; MPS II = mucopolysaccharidosis type II
1. Braunlin et al [2011]

Evaluation of Relatives at Risk

Iduronate 2-sulfatase (I2S) biochemical testing and/or *IDS* molecular genetic testing of at-risk male family members allows early diagnosis and prompt initiation of treatment (see Targeted Therapies). The importance of prompt initiation of treatment has been demonstrated in studies involving affected sibs who were diagnosed and treated at different ages [Tajima et al 2013, Grant et al 2022].

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

A number of interventions are being evaluated for potential use in individuals with MPS II.

A Phase II/III open-label, multicenter study (NCT02055118) investigated the effects of intrathecally administered idursulfase-IT on cognitive function in individuals with MPS II. Preliminary results showed no toxicity of the protein injected intrathecally at the dosages used (10 mg and 30 mg). The glycosaminoglycan (GAG) concentration in the cerebrospinal fluid (CSF) was significantly reduced [Muenzer et al 2014]; however, the primary endpoint (change from baseline in Differential Ability Scales™-II general conceptual ability [DAS-II GCA] score at week 52 in a linear mixed-effects model for repeated measures analysis) was not met. A smaller decrease in DAS-II GCA scores was observed in the individuals treated with idursulfase-IT at week 52 compared to those not receiving idursulfase-IT. There were no changes from baseline in Vineland Adaptive Behavioral Scales-II adaptive behavior composite scores at week 52 (the secondary endpoint). There were trends toward a potential positive effect of treatment with idursulfase-IT across DAS-II composite, cluster, and subtest scores, notably in individuals younger than age six years at baseline (P=0.0174). Idursulfase-IT reduced CSF GAG levels from baseline by 72% at week 52. Idursulfase-IT was generally well tolerated [Muenzer et al 2022].

Other therapies under preclinical investigation include more direct delivery of enzyme into the CNS. Tissue uptake (including the brain and spinal cord) via the transferrin receptor of a fusion protein between iduronate 2-sulfatase (I2S) and a monoclonal antibody against the transferrin receptor are being studied [Boado 2022, Imakiire et al 2023].

Gene editing has been attempted in nine individuals with MPS II, and in one individual a transient increase in plasma I2S approaching normal levels was detected; however, there was no evidence of genome editing [Harmatz et al 2022].

Table 8. Mucopolysaccharidosis Type II: Selected Therapies Under Investigation

Treatment Class	Treatment Objective	Specific Therapy	Clinical Trials ID / Reference
ERT	More direct delivery of enzyme into CNS	Tividenofusp alfa (DNL310): CNS-penetrant ERT	NCT04251026
		I2S: intrathecal delivery	NCT00920647 & others
		Idursulfase beta: intracerebroventricular delivery	Seo et al [2023]
		Pabinafusp alfa (JR-141); idursulfase fused w/anti-human transferrin receptor antibody	NCT05594992
	Fetal treatment using in utero ERT	I2S	NCT04532047
Gene therapy	Transduce cells w/wild type *IDS* to provide expression of functional I2S	RGX-121: adeno-associated viral vector administered by intracisternal injection	NCT04571970 NCT03566043 NCT04597385
		Retroviral-mediated transfer of *IDS* into lymphocytes	NCT00004454
	In vivo gene editing to insert corrective *IDS* transgene	SB-913: zinc finger nuclease-mediated genome editing	NCT03041324 NCT04628871

CNS = central nervous system; ERT = enzyme replacement therapy; I2S = iduronate 2-sulfatase

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) is inherited in an X-linked manner. Hemizygous males are affected; heterozygous females are typically asymptomatic.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *IDS* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the *IDS* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has gonadal mosaicism. Somatic/gonadal mosaicism has been observed in MPS II [Froissart et al 2007, Oliveira Netto et al 2021].
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier), the affected male may have a *de novo IDS* pathogenic variant (in which case the mother is not a carrier), or the mother may have somatic/gonadal mosaicism.

- Molecular genetic testing of the mother is recommended to evaluate her genetic status and inform recurrence risk assessment. (Note: Testing of maternal leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ [gonadal] cells only.) If the proband has a complex chromosomal rearrangement involving *IDS*, testing for a chromosome rearrangement in the mother is also recommended.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an *IDS* pathogenic variant, the chance of transmitting it in each pregnancy is 50%:
  - Males who inherit the *IDS* pathogenic variant will be affected;
  - Females who inherit the *IDS* pathogenic variant will be carriers. On rare occasion, heterozygous females manifest findings of MPS II. This is thought to result from skewed inactivation of the normal paternally inherited X chromosome and expression of the maternally inherited *IDS* pathogenic variant [Jurecka et al 2012, Guillén-Navarro et al 2013].
- If the mother of the proband has a chromosome rearrangement, the risk to sibs is increased and depends on the specific chromosome rearrangement.
- If the proband represents a simplex case and if the *IDS* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population because of the possibility of maternal gonadal mosaicism [Froissart et al 2007, Oliveira Netto et al 2021].

Offspring of a male proband. Affected males transmit the pathogenic variant to:

- All of their daughters, who will be heterozygotes (carriers) and will usually not be affected;
- None of their sons.

Other family members. The maternal aunts and maternal cousins of a male proband may be at risk of having an *IDS* pathogenic variant.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Carrier Detection

Molecular genetic testing. Carrier testing for at-risk female relatives requires **one** of the following:

- Identification of the *IDS* pathogenic variant in an affected male relative, OR
- If an affected male is not available for testing, *IDS* molecular genetic testing:
  1. First by sequence analysis;
  2. If no *IDS* pathogenic variant is identified, use of gene-targeted deletion/duplication analysis;
  3. If no *IDS* pathogenic variant is identified, use of appropriate molecular methods to detect complex rearrangements.

Biochemical genetic testing. Measurement of iduronate 2-sulfatase (I2S) enzyme activity is not reliable for detection of heterozygous females, as a carrier may have normal I2S enzyme activity resulting from X-chromosome inactivation that may be non-random.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *IDS* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Canadian Society for Mucopolysaccharide and Related Diseases**
  Canada
  Phone: 800-667-1846
  Email: info@mpssociety.ca
  mpssociety.ca
- **MedlinePlus**
  Mucopolysaccharidosis type II
- **MPS Society**
  United Kingdom
  Phone: 0345 389 9901
  Email: mps@mpssociety.org.uk
  mpssociety.org.uk
- **National MPS Society**
  Phone: 877-MPS-1001
  mpssociety.org
- **National Organization for Rare Disorders (NORD)**
  Phone: 800-999-6673
  RareCare® Patient Assistance Programs
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  newbornscreening.hrsa.gov/your-state

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Mucopolysaccharidosis Type II: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
IDS	Xq28	Iduronate 2-sulfatase	IDS @ LOVD	IDS	IDS

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Mucopolysaccharidosis Type II (View All in OMIM)

300823	IDURONATE 2-SULFATASE; IDS
309900	MUCOPOLYSACCHARIDOSIS, TYPE II; MPS2

Molecular Pathogenesis

IDS encodes iduronate 2-sulfatase (I2S), a protein that catalyzes the release of sulfate from the iduronate sulfate residues of heparan sulfate and dermatan sulfate [Neufeld & Muenzer 2015]. Pathogenic variants in *IDS* result in absent or reduced I2S enzyme activity, which decreases the amount of sulfate moiety released from glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate during their degradation, disrupting cellular function and causing disease.

Mechanism of disease causation. Loss of function

***IDS*-specific laboratory technical considerations.** An *IDS* pseudogene, *IDSP1*, is located about 25 kb telomeric to *IDS*. Homologous regions shared by *IDS* and *IDSP1* predispose to unequal recombination events, leading to complex rearrangements and sometimes large deletions.

Table 9. *IDS* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000202.5 NP_000193.1	c.1122C>T	--	See Genotype Phenotype Correlations.

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Maurizio Scarpa, MD, PhD, pediatrician, is the Director of the Regional Coordinating Centre for Rare Diseases at the University Hospital of Udine, Italy. He is Professor of Paediatrics at the Department for Woman and Child Health, University of Padova, Italy, and the Co-Founder of the Brains for Brain Foundation (www.brains4brain.eu) together with Prof David Begley, Kings College of London, London, UK. Prof Scarpa has extensive expertise as a basic scientist in genetics and biotechnology, as well as a clinician in the diagnosis and treatment of pediatric rare disorders, neurometabolic diseases in particular. Together with Dr Christina Lampe he founded the Center for Rare Diseases at the Helios Dr Horst Schmidt Kliniken in Wiesbaden, Germany. He is especially interested in developing innovative health approaches for the diagnosis and treatment of metabolic

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Christina Lampe, MD, is the Director of the Center for Rare Diseases within the Department of Pediatric Neurology, Muscle Diseases, and Social Pediatrics at the University of Giessen, Germany. She pursued her medical degree at the Humboldt-University of Berlin (Charité) and completed her internship at the same university's Surgical Department. Since 2007, Dr Lampe has served as a consultant in surgery. In 2008 she joined Villa Metabolica at the Department of Pediatric and Adolescent Medicine at the Johannes Gutenberg-University of Mainz, Germany, where she managed individuals with lysosomal disorders. In January 2014, in collaboration with Professor Maurizio Scarpa, Dr Lampe established the Center for Rare Diseases at the Dr Horst Schmidt Clinics in Wiesbaden, with a primary focus on mucopolysaccharidoses and other lysosomal diseases. In 2017, Dr Lampe collaborated on the foundation of MetabERN, the European Reference Network for Hereditary Metabolic Disorders. In October 2018, Dr Lampe extended her efforts by establishing a Center for Rare Diseases at the University Hospital in Giessen (ZSEGI), Germany. She oversees the care of a substantial number of pediatric and adult individuals with MPS and other lysosomal diseases. Dr Lampe actively participates as an investigator and co-investigator in several clinical trials related to lysosomal diseases.

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