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Evidence and recommendation for mucopolysaccharidosis type II newborn screening in the United States

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Abstract

Mucopolysaccharidosis type II (MPS II), also known as Hunter syndrome, is an X-linked condition caused by pathogenic variants in the iduronate-2-sulfatase gene. The resulting reduced activity of the enzyme iduronate-2-sulfatase leads to accumulation of glycosaminoglycans that can progressively affect multiple organ systems and impair neurologic development. In 2006, the US Food and Drug Administration approved idursulfase for intravenous enzyme replacement therapy for MPS II. After the data suggesting that early treatment is beneficial became available, 2 states, Illinois and Missouri, implemented MPS II newborn screening. Following a recommendation of

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Conflict of Interest

The authors declare no conflicts of interest.

the Advisory Committee on Heritable Disorders in Newborns and Children in February 2022, in August 2022, the US Secretary of Health and Human Services added MPS II to the Recommended Uniform Screening Panel, a list of conditions recommended for newborn screening. MPS II was added to the Recommended Uniform Screening Panel after a systematic evidence review reported the accuracy of screening, the benefit of presymptomatic treatment compared with usual case detection, and the feasibility of implementing MPS II newborn screening. This manuscript summarizes the findings of the evidence review that informed the Advisory Committee's decision.

Keywords

ACHDNC; Evidence review; Hunter syndrome; Mucopolysaccharidosis type II; Newborn screening

Introduction

In the United States, individual state public health programs determine how newborn screening (NBS) programs operate, including which conditions are included. To help standardize screening across the country, the US Secretary of Health and Human Services maintains a list of conditions recommended for inclusion in NBS, referred to as the Recommended Uniform Screening Panel (RUSP). Decisions about which conditions to include on the RUSP are based on recommendations from the US Secretary of Health and the Human Services Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC). The ACHDNC uses an evidence-based approach to evaluate the potential benefits and harms of NBS for a particular condition and the ability of NBS programs to implement the proposed screening.

In August 2022, mucopolysaccharidosis type II (MPS II; also known as Hunter syndrome) was added to the RUSP based on a recommendation from the ACHDNC in February 2022. This article summarizes the key elements leading to this recommendation, which are fully documented in the MPS II evidence review that was commissioned for the ACHDNC. The evidence review, the letter from the ACHDNC to the Secretary of Health and Human Services, and the Secretary's final response regarding the committee's recommendation to add MPS II to the RUSP are available at the ACHDNC's website.[1]

Overview of MPS II

MPS II is an X-linked recessive lysosomal storage disorder (LSD) caused by pathogenic variants in the iduronate-2-sulfatase (*IDS*) gene leading to reduced activity of the enzyme iduronate-2-sulfatase (I2S; OMIM 309900). This results in the accumulation of the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate, which can cause a broad range of health problems among affected males, including cognitive and behavioral impairment; progressive hepatomegaly, splenomegaly, and cardiac valve thickening; restrictive lung disease; and skeletal abnormalities that impair mobility. Females rarely develop clinical signs of MPS II unless there is abnormal X-chromosome inactivation.[2] Published estimates of the birth prevalence of MPS II based on clinically diagnosed cases in various countries, excluding outliers, range from 0.26 cases to 1.07 cases per 100,000

newborns, with the vast majority of these cases being males.[1,3] The lower estimate comes from a voluntary US registry maintained by the National MPS Society.[4] NBS programs in Illinois and Missouri published preliminary, incomplete estimates of 0.9 and 1.3 diagnosed MPS II cases per 100,000 newborns screened.[5,6]

MPS II has variable phenotypic expression, with several different classification schemes: severe or attenuated, neuronopathic or non-neuronopathic, and early progressive or slowly progressive. In general, earlier-onset disease is more rapidly progressive and more likely to cause significant neurologic impairment, including cognitive disability and behavioral problems.[7] Approximately 60% of people with MPS II have the severe or neuronopathic form of the disease. Although it is difficult to predict the phenotype when MPS II is identified presymptomatically based on genotype and biochemical findings, affected individuals within a family generally have a similar phenotype.[8]

MPS II Treatment

The 2 available targeted treatment strategies are enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT). In 2006, the US Food and Drug Administration approved idursulfase (Elaprase; Takeda Pharmaceutical Company Limited), an ERT administered through weekly intravenous infusions. Idursulfase is associated with improved ambulation, pulmonary function, and survival.[9–11] However, it does not cross the blood-brain barrier; therefore it cannot treat central nervous system (CNS) involvement. Idursulfase infusion reactions occur in some patients. Symptoms are generally mild and can be minimized with premedication with antihistamines and/or corticosteroids. Although antibodies to idursulfase can develop, they do not appear to decrease treatment effectiveness nor increase the risk of infusion reactions.[12,13]

A 2020 expert consensus practice resource from the American College of Medical Genetics and Genomics recommended starting idursulfase at the time of diagnosis and before the onset of symptoms for individuals predicted to have severe MPS II by genotype, or in anyone with symptoms due to MPS II, regardless of predicted severity.[14] This expert group also recommended against presymptomatic treatment with ERT for those expected to have attenuated MPS II based on genotype, which is challenging because of the high proportion with private variants that limit the ability to make predictions about phenotype.[15] Although traditional intravenous idursulfase does not cross the blood-brain barrier and hence cannot protect against CNS complications, alternative forms of ERT are being tested. One is intrathecal delivery of idursulfase, which gets around the need to cross the blood-brain barrier. The other is a molecularly modified idursulfase that is delivered intravenously and able to penetrate the blood-brain barrier by binding to receptors. In addition to studies evaluating those 2 approaches, studies are underway to assess the effectiveness of gene therapy in MPS II.[16]

HSCT is an alternative treatment for MPS II that provides cells producing functional I2S enzyme that can migrate to end organs, including the brain.[17] HSCT has the advantage of being a one-time treatment and less costly compared with long-term treatment with ERT.[18,19] However, experts are cautious about HSCT because of early reports of high mortality (up to 8%)[20] and reported lack of efficacy for CNS symptoms, even though the

same limitation regarding CNS symptoms applies to ERT.[21–23] More recent data suggest that HSCT can be effective in relation to CNS symptoms, organ function, and activities of daily living in selected patients.[19,20,24,25] One study reported a nonsignificant trend toward improved activities of daily living in subjects with severe MPS II, defined as having cognitive impairment, who underwent HSCT (n = 18) compared with those who received ERT (n = 29).[25] This study assessed activities of daily life with a standardized scale and categorized early HSCT as that implemented before 5 years of age. Although outcomes appear to be improved when transplant occurs early in the course of disease before significant CNS involvement, the optimal timing of HSCT is unknown. Because of the lack of HSCT clinical trials and insufficient data on long-term follow-up outside of Japan, the US expert group did not come to a consensus regarding the use of HSCT in children with MPS II and instead called for additional research.[14]

MPS II NBS

MPS II NBS is based on measuring I2S enzyme activity in dried blood spots using tandem mass spectrometry or fluorometry.[26,27] Testing can be multiplexed with other LSDs. If I2S enzyme activity is low on the initial screen, GAG levels in dried blood spots can be measured through a second-tier biochemical screen. Infants with low I2S activity and elevated GAGs on in newborn blood spots require referral for clinical evaluation and diagnostic confirmation. The diagnosis of MPS II after a positive newborn screen is based on confirming low I2S enzyme activity in plasma and elevated urine GAG concentration. Measuring at least one other sulfatase can exclude the diagnosis of multiple sulfatase deficiency. Molecular genetic findings can be supportive but are not necessary for the diagnosis given the large number of variants: more than 700 pathogenic variants in the *IDS* gene have been described, and approximately 60% of individuals carry a private pathogenic variant.[15] However, large deletions and complex rearrangements are more likely to be associated with severe disease.[8] When diagnosis is unclear, clinical follow-up is required to monitor for signs associated with MPS II. NBS for MPS II began in Taiwan in 2015, in Illinois in 2017, and in Missouri in 2018.

MPS II NBS Population-Level Projections

Modeling was used to predict screening outcomes and the number of cases detected at the US population level through NBS of MPS II compared with clinical identification. Assumptions about case detection after MPS II NBS compared with usual clinical case detection were based on published and unpublished data, with feedback from MPS II experts, as described in the full evidence review report.[1] For purposes of population modeling in the evidence review, the incidence of clinically detected MPS II (either attenuated or severe) was assumed to be 0.67 per 100,000 births and the incidence after NBS was assumed to be 1.6 per 100,000 births. Additional assumptions regarding cases lost to follow-up and the time to establish diagnosis were based on the experience of US NBS programs currently screening for MPS II.

The modeling predicted that if all 3.6 million newborns in the United States were screened for MPS II, there would be 480 positive screens (range: 346–523), 59 cases of MPS II of any severity identified (range: 44–61), 59 still undergoing diagnostic follow-up within a year

who did not have a diagnosis of MPS II but who were also not clearly unaffected (range: 34–218), 322 false positives (range: 131–352), and 41 lost to follow-up (range: 34–87). Although all cases identified through NBS are likely to be males, there is a small possibility of identifying females with MPS II. In comparison, based on the case detection rate through usual clinical care of 0.67 per 100,000 live births, only 24 cases of MPS II of any phenotype (range: 5–78) would be identified.

Outcomes After Presymptomatic Diagnosis versus Usual Clinical Case Detection

The benefit of early detection in children identified through usual clinical care, because of symptoms or family history, was evaluated through 2 sources of data: reports involving subjects identified early, usually because of a family history of MPS II, and case reports of sibling pairs with MPS II in which the younger sibling was treated at a younger age than the older sibling.

These reports demonstrate that outcomes with early treatment are often better than expected based on clinically identified and later-treated children. A series of 8 children who were diagnosed between the fetal period and 5 months of age, and who initiated ERT between 10 days of life and 6 months of age, were followed for up to 5.5 years.[28] Two of these patients received HSCT as infants and discontinued ERT; their outcomes were not described in this report. All 6 patients who continued with ERT had normal cognitive development, 1 had significantly impaired cardiac function, and all had mild skeletal involvement. Reported outcomes were not standardized across subjects in the study.

Four peer-reviewed case reports comparing outcomes of symptomatically diagnosed older siblings with pre-symptomatically diagnosed younger siblings are summarized in Table 1. Outcome measures were not standardized, but these data support a possible benefit of presymptomatic diagnosis and early treatment. Whether treatment is with ERT or HSCT, early initiation of treatment has been reported to be associated with better outcomes compared with later initiation in relation to activities of daily living.[25] Data from the Hunter Outcome Survey (an international voluntary patient registry), when stratified by age of ERT initiation (<18 months vs ≥18 months to <5 years vs ≥5 years), suggest that earlier treatment may be associated with greater improvement in the 6-minute walk test, which is a measure of walking endurance, and faster improvement in organomegaly.[33] These reports suggest that early treatment, which is aided by early diagnosis, such as through NBS, may improve outcomes.

Comparing outcomes of cases detected through NBS with usual clinical care is challenging. Systematically applied outcome measures at standardized early ages after identification through NBS compared with clinically detected cases, whether due to symptoms or family history, are not available.

Implementation of MPS II NBS

A survey was developed and distributed to NBS programs across the United States to determine their readiness to implement comprehensive screening for MPS II. Among the 37 NBS programs that were included in the survey analysis, 8% reported they could implement MPS II NBS in less than 1 year, 24% reported that they could implement in 1 to 2 years,

38% reported that it would take 2 to 3 years, and 30% reported that it would take more than 3 years to implement. These estimates do not take into account that a state may have other priorities to address before they can screen for MPSII, such as adding other RUSP conditions to their NBS panel or upgrading their laboratory information management systems.

Barriers to MPS II screening reported by NBS programs in the survey included hiring and staffing issues, competing NBS interests, lack of funding, and administrative approval barriers. The additional cost of adding MPS II NBS from the program perspective, above and beyond the costs of operating the NBS program, was estimated to be between $2 and $6 per newborn.

Despite these challenges, NBS programs continue to add new conditions to their panels. Facilitators of MPS II NBS implementation, according to the survey results and interviews with NBS programs, included the addition of the condition on the RUSP, funding and fee increases, the ability to multiplex screening with other LSDs, advocacy, and having a US Food and Drug Administration–approved laboratory kit.

Long-Term Follow-Up After MPS II Diagnosis Through Newborn Screening

The ACHDNC recognizes the importance of long-term follow-up for individuals with conditions identified through NBS.[34,35] Optimization of health outcomes for those individuals requires timely access to high-quality and well-coordinated health care services, which may be difficult to achieve given fragmented systems of care and payment for services. Organizations have proposed data standards for the voluntary reporting of outcomes data by clinical centers, but states lack resources for the implementation of population-based data systems for NBS longterm follow-up. Administrative health care databases can be used to monitor utilization of services, including pharmacologic treatments but not clinical outcomes.[36] Novel approaches, such as real-time data linkages with interoperability could potentially facilitate tracking of outcomes, but doing so could require dedicated resources.[37]

Final Recommendation

In February 2022, considering the accuracy of screening, the likely benefit of presymptomatic treatment, and the feasibility of implementing MPS II NBS, the ACHDNC recommended the addition of MPS II to the RUSP. In August 2022, the Secretary of Health and Human Services accepted this recommendation, thereby adding MPS II to the RUSP. Early detection could lead to early treatment, which has clinical benefit for somatic non-CNS complications, including musculoskeletal progression and organ involvement. Additionally, the Secretary of Health and Human Services requested a follow-up report in 5 years describing the status of state implementation of MPS II screening, access, and cost of treatment for infants diagnosed with MPS II and the impacts on families.

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Table 1

Sibling case reports, with clinical findings at follow-up after treatment[a]

	Tajima et al[29]		Tylki-Szymanska et al[30]		Tomita et al[31]		Grant et al[32]	
Clinical Characteristics	**Older Sib**	**Younger Sib**	**Older Sib**	**Younger Sib**	**Older Sib**	**Younger Sib[b]**	**Older Sib**	**Younger Sib**
Age at diagnosis	2.6 y	<1 mo	5 y	14 d	2 y	1 mo	3.7 y	1 y
Age at ERT initiation	3 y	4 mo	7.5 y	3 mo	2 y	1 mo	3.8 y	1.1 y
Age at follow-up	6 y	3 y	10 y	3 y	9 y	4 y	5 y	5 y
Course facial features	Present	Absent	Present	Absent	NR	NR	NR	NR
Skin abnormalities	Present	Absent	NR	NR	NR	NR	NR	NR
Organomegaly	Present	Absent	Present	Absent	Present	Absent	Absent	Absent
Cardiac disease[c]	Present	Absent	Present	Absent	NR	NR	Present	Present
Musculoskeletal abnormalities[d]	Present	Present	Present	Absent	Present	Present	Present	Present
Developmental score[e]	42	74	24	98	53	104	46	91

ERT, enzyme replacement therapy; *NR*, not reported.

[a]Presence or absence of the finding was not reported.

[b]Tomita et al[31] younger sib switched to CNS-penetrant ERT, pabinafusp alfa, at 1 year 11 months.

[c]Cardiac disease included decreased function, dilated cardiomyopathy, and/or valve thickening.

[d]Musculoskeletal abnormalities included joint limitations, dysostosis multiplex, and/or contractures.

[e]Specific developmental test used varied by study, but all studies used tests standardized to a mean of 100 and SD of 15 points.

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