

**Evidence-Based Review of Newborn Screening for Mucopolysaccharidosis  
Type II: Final Report (02/20/2022)**

**Prepared for:  
MATERNAL AND CHILD HEALTH BUREAU**

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## EXECUTIVE SUMMARY

### Overview

This report summarizes the evidence regarding the benefits and harms of newborn screening for Mucopolysaccharidosis Type II (MPS II) and the capability of state newborn screening programs to offer comprehensive testing and follow up for the condition.

This executive summary highlights key findings from the final version of the complete report developed for the United States Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) regarding newborn screening for MPS II. This summary is not intended to replace the complete report, which describes the methods for evidence identification and synthesis, and a full discussion of findings. This summary instead provides a high-level review of findings from the complete report.

### MPS II: Epidemiology and Clinical Course

MPS II, also referred to as Hunter syndrome, is an X-linked lysosomal storage disorder due to mutations in the iduronate-2-sulfatase (*IDS*) gene leading to dysfunction of the enzyme iduronate-2-sulfatase (I2S). This leads to impaired hydrolysis and accumulation of two glycosaminoglycans (GAGs). The prevalence in Japan and Taiwan based on clinical identification has been reported to be 0.84-1.07 per 100,000 births and, excluding outlier estimates, 0.26-0.64 per 100,000 births elsewhere.

MPS II is commonly classified as severe or attenuated. MPS II has a highly variable spectrum of signs and symptoms. Individuals with the severe form have more significant intellectual disability than those with the attenuated form. Assigning phenotype, especially in infancy and early childhood can be difficult and is often dependent on the presence of age-related clinical findings. Based on the Hunter Outcome Survey, a voluntary registry restricted to data on individuals with MPS II who are either untreated, treated with the enzyme replacement therapy (ERT) idursulfase, or received a hematopoietic stem cell transplant (HSCT), the median age at symptom onset is about 1.5 years and a median age at diagnosis about 3.2 years. Untreated, common health problems include facial dysmorphism, hepatomegaly, splenomegaly, cardiac involvement including valvular thickening, enlarged tonsils and adenoids that can lead to obstructive sleep apnea, lung involvement with reduced pulmonary function, skeletal disease including dysostosis multiplex, and progressive joint stiffness that can significantly impair mobility. Individuals with the severe phenotype develop significant behavior problems and progressive intellectual impairment. In the United States, ERT is the FDA-approved targeted treatment for MPS II.

### Newborn Screening for MPS II

Newborn screening is based on measuring I2S enzyme activity in dried-blood spots using tandem mass-spectrometry (MS/MS), as used by the Illinois newborn screening program, by two pilot newborn screening programs in Taiwan, and in a research project in New York, or using fluorometric enzymatic assay, as used by the Missouri newborn screening program. Dried-blood spot GAG levels can be used as a second-tier test. The diagnosis is established by confirming low I2S enzyme activity in the presence of elevated urine GAG levels. Molecular analysis can be helpful. Although the Illinois and Missouri newborn screening programs use different

approaches to MPS II newborn screening, their results are similar, with 12-13 newborns per 100,000 screened referred for diagnostic follow-up and 1.5-1.6 cases of MPS II diagnosed per 100,000 newborns screened. Screening also identifies individuals who require monitoring because of diagnostic uncertainty (e.g., low I2S enzyme activity with borderline urinary GAG levels). Although complete data are not available regarding the duration of follow-up when there is diagnostic uncertainty, experts report that follow-up with specialists includes repeat laboratory testing and occurs every 6-12 months for around 2 years. From the Illinois newborn screening program, 0.9 cases per 100,000 newborns screened have diagnostic uncertainty. In contrast, in Missouri, there have been 2.1 cases with diagnostic uncertainty per 100,000 newborns screened since the start of screening in 2018. In Taiwan, the number referred for diagnostic follow-up in the two screening programs has been 44-61 per 100,000 newborns screened, which is substantially higher than the referral rate in Illinois or Missouri. In one pilot program in Taiwan, at least 4.5 per 100,000 newborns required diagnostic follow-up because they had likely pathogenic variants or variants of unknown significance. None of the screening programs evaluated has reported a missed case of MPS II. However, surveillance systems may be inadequate to identify missed cases.

The case detection rate through newborn screening is higher than the estimated range of clinically detected cases. Insufficient information is available to describe the phenotypic distribution of newborn screening-detected cases compared with clinically detected cases.

## **Treatment for MPS II**

The current targeted therapy for MPS II in the United States is idursulfase (Elaprase; Takeda Pharmaceutical Company Limited). This ERT is provided as a weekly intravenous infusion over several hours. However, intravenous ERT does not significantly cross the blood-brain barrier. HSCT is not often used because it might not be an effective strategy for treating the central nervous system (CNS) aspects of MPS II and because of the risk of mortality. A novel therapy in which the ERT has been modified to readily cross the blood-brain barrier (pabinafusp alfa; JCR Pharmaceuticals) is available in Japan but not the United States. Trials are ongoing in the United States for the delivery of ERT intrathecally or intraventricularly. Hunterase, developed by GC Pharma, is a form of ERT for intrathecal delivery and is approved in Japan and other countries in Asia. A trial is also underway to evaluate another novel ERT (DNL310; Denali Therapeutics inc.) designed to cross the blood-brain barrier. Gene therapy is also in development.

Idursulfase is effective in treating the somatic aspects of MPS II but does not directly treat the CNS aspects for those with MPS II. Idursulfase is generally well tolerated. Some require premedication with antihistamines or corticosteroids. Although some develop antibodies to the ERT, small studies suggest that the ERT is still effective when such antibodies are present.

Because ERT can stabilize somatic aspects of MPS II, earlier treatment might lead to better long-term outcomes even if there is no reversal of existing involvement. The evidence review did not identify clinical studies (e.g., clinical trials, cohort studies) directly comparing presymptomatic ERT to later treatment. However, the evidence review identified published and unpublished reports of sibling pairs, in which the younger sibling began treatment early due to the diagnosis in the older sibling. These reports suggest benefit of early intervention for the somatic manifestations of MPS II. Such reports are at risk of bias (e.g., use of non-standardized

measures, selective reporting of cases). However, the rarity of MPS II makes controlled prospective studies challenging.

### **Impact on the Health of the Population**

MPS II newborn screening is expected to identify a greater number of cases of MPS II compared with clinical identification. However, screening will also identify a similar number of cases that require follow-up because of diagnostic uncertainty. Insufficient evidence is available to model outcomes following identification through newborn screening.

### **Impact on Public Health Systems**

The estimated additional cost of adding MPS II from the program perspective, above and beyond the fixed costs of an existing NBS program, varied between \$2 and \$6 per infant in 2022. The bulk of the estimated costs reflected the costs of equipment, reagents, and added laboratory technician and laboratory scientist time for first-tier screening.

Most newborn screening programs (62%) believed that selecting and validating the MPS II newborn screening test, purchasing equipment, hiring the additional staff, and developing the follow-up protocol would take 1 to 3 years. Challenges include issues of funding, staffing, and competing priorities.



## LIST OF ABBREVIATIONS

Abbreviation	Definition
ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children
APHL	Association of Public Health Laboratories
ERG	Evidence-based Review Group
ERT	Enzyme Replacement Therapy
FDA	United States Food and Drug Administration
FTE	Full-time equivalent
GAG	Glycosaminoglycan
HSCT	Hematopoietic Stem Cell Transplantation
<i>IDS</i>	Iduronate-2-sulfatase gene
I2S	Iduronate-2-sulfatase
IT	Intrathecal
LC-MS/MS	Liquid chromatography tandem mass-spectrometry
LIMS	Laboratory Information Management System
LSD	Lysosomal storage disorder
MS/MS	Tandem mass spectrometry
NBS	Newborn Screening
RUSP	Recommended Uniform Screening Panel
TEP	Technical Expert Panel
VUS	Variant of Uncertain Significance

## 1 SCOPE AND METHODS OF THE REVIEW

### Scope of Review

This report was developed to support the Secretary of Health and Human Services' (HHS) Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) in making recommendations to the Secretary, HHS, about whether newborn screening for Mucopolysaccharidosis Type II (MPS II) should be added to the Recommended Uniform Screening Panel (RUSP).

### Nomination and Request for Review

On May 13, 2021, the ACHDNC voted to consider MPS II for the RUSP. This was based on a nomination from Terri L. Klein, NPGC, MPA, President of the National MPS Society, and N. Matthew Ellinwood, DVM, PhD, Chief Scientific Officer of the National MPS Society, that was co-sponsored by Barbara K. Burton, MD, Department of Pediatrics, Northwestern University, Michael H. Gelb, PhD, Department of Chemistry, University of Washington, Priya Kishnani, MD, Department of Pediatrics, Duke University, Joseph Muenzer, MD, PhD, University of North Carolina at Chapel Hill, C. Ronald Scott, MD, Department of Pediatrics, University of Washington, and Bradford Therrell, PhD, National Newborn Screening and Global Resource Center.

### Purpose of the Condition Review of Evidence

The condition review will present the evidence regarding the likely benefits and harms of expanding newborn screening to include MPS II, estimated health impacts of population-based screening in the United States, and potential impact on state newborn screening programs. The review focuses on the decision-making criteria considered by the ACHDNC. The Evidence-based Review Group (ERG) does not make specific recommendations to the ACHDNC about addition of a condition to the RUSP.

### Case Definition

MPS II, also referred to as Hunter syndrome, is an X-linked lysosomal storage disorder (LSD) due to dysfunction of the enzyme iduronate-2-sulfatase (I2S) caused by mutations in the iduronate-2-sulfatase (*IDS*) gene. This leads to impaired hydrolysis of two glycosaminoglycans (GAGs), dermatan sulphate and heparan sulphate, and their accumulation leading to multi-organ involvement.

There is a wide spectrum of phenotypic expression of MPS II, characterized by a variable age of onset and the degree of neurologic involvement. MPS II is typically classified as severe or attenuated or, alternatively, as neuronopathic or non-neuronopathic. For this report, we will classify cases as severe or attenuated since that is the classification system used by most of the published articles and by the newborn screening programs that currently screen for MPS II.

The case definition following newborn screening used in this report will be the presence of elevated urinary GAGs, low I2S enzyme activity in leukocytes, fibroblasts, or dried-blood spots, and normal enzyme activity in at least one other sulfatase. Molecular testing (i.e., sequencing of the *IDS* gene) can support the diagnosis but is not necessary. Identifying elevated urinary GAGs rules out I2S biochemical pseudodeficiency. Ensuring normal activity of at least one other sulfatase rules out multiple sulfatase deficiency. Early classification of phenotype following

newborn screening is possible if there is a variant in the *IDS* gene expected to lead to the absence of I2S enzyme activity or if there is an affected sibling. For this report, the phenotype is not a component of the case definition.

## **Methods – Systematic Evidence Review**

The methods guiding this systematic evidence review (SER) followed approaches outlined in the Condition Review Workgroup – Manual of Procedures (2012, 2014) and revised in 2016 to address requirements in the 2014 Reauthorization of the Newborn Screening Saves Lives Act (Public Law No: 113-240, 12/18/2014). These methods address the limited evidence that is typically available for rare conditions and the recognition that the evidence base for conditions considered for newborn screening is often rapidly changing. These methods were also developed to be completed within the timeline required for the ACHDNC. This section describes specific procedures that guided this Condition Review of newborn screening for MPS II.

### **Literature Search**

#### ***Published Literature Search***

An experienced medical librarian in partnership with the ERG conducted the initial literature search regarding newborn screening and treatment of MPS II. We identified published research articles from MEDLINE, EMBASE, CINAHL, and the Cochrane library using the MeSH terms and key words for each database, as outlined in Appendix A. Published articles could be included if the full text was written in English and included human subjects and they met the criteria for at least one key question.

Appendix A lists the specific search criteria for each database and process leading to article inclusion. As described in the manual of procedures, each database was searched and identified articles were placed into an electronic database. Two reviewers independently evaluated the titles and abstracts for potential inclusion. If either reviewer thought that the article was potentially relevant, then the full text of the article was reviewed. For excluded articles, both reviewers had to agree on the reason for exclusion based on a hierarchical list.

## **Key Questions for Evidence Review: MPS II**

### **Key Questions and Inclusion/Exclusion Criteria**

The following describes the key questions for the systematic evidence review and the inclusion/exclusion criteria for published articles to provide evidence for each of the key questions.

1. What is the natural history and epidemiology of MPS II?

Relevant studies could be cross-sectional, case-control, longitudinal (retrospective or prospective), or randomized. Outcomes could include the incidence or prevalence, timing of the development of signs or symptoms of MPS II, age of diagnosis, age at treatment initiation, quality of life, or mortality. Included studies must include at least 10 subjects with MPS II identified without screening.

The term “natural history” is complex. Traditionally it refers to disease outcomes in the absence of targeted interventions. However, with the availability of ERT, most affected individuals in the United States and many other countries will be offered therapy. Some consider the natural

history to reflect what happens following clinical identification, which now includes targeted treatment. Although the term “natural history” is used throughout this report, information is provided to clarify its use and the implications of the findings.

2. What is the analytic or clinical validity of newborn screening for MPS II?

Relevant studies could be cross-sectional, case-control, longitudinal (retrospective or prospective), or randomized. The studies should include at least 5,000 infants at average risk (e.g., not known to have MPS II), be screened for MPS II in the first month of life, and those with a positive screen should have diagnostic confirmation. Outcomes include sensitivity, specificity, positive predictive value, negative predictive value, reliability, diagnostic yield, or the cost of screening.

3. What are the harms associated with newborn screening for MPS II?

Relevant studies could be cross-sectional, case-control, longitudinal (retrospective or prospective), randomized, case reports, or case series. Studies should include at least one average-risk newborn screened in the first month of life for MPS II. Outcomes include any reported adverse event related to newborn screening for MPS II, including the harms related to false-positive or false-negative screening, or identification of biochemical pseudodeficiency.

4. What are the benefits and harms of MPS II presymptomatic or early treatment compared to when MPS II is usually identified?

Relevant studies had to be longitudinal (prospective or retrospective observational or interventional) with at least 6 months of follow-up after diagnosis or until death if that occurred before 6 months of follow-up after treatment. Studies should include at least one subject diagnosed with MPS II before 12 months of age. Such diagnosis could be based on newborn screening, prenatal diagnosis, or diagnosis based on having an affected family member. Outcomes could include mortality, organ involvement (e.g., cardiac, liver, lung, spleen), development (e.g., cognitive, gross motor, fine motor), ability to ambulate, endurance, joint mobility, sleep apnea, growth (e.g., height, weight, head circumference), quality of life, physical features, urinary GAG level, or harms related to early treatment, including any adverse event or development of antibodies to I2S.

In addition to these key questions, we also considered contextual questions that provide important background information. These included:

1. What is the distribution of MPS II phenotypes and *IDS* biochemical pseudodeficiency? What is the relationship between *IDS* genotype and phenotypic expression? What other factors predict phenotypic expression?
2. What clinical practice guidelines are available for the diagnosis and treatment of MPS II? What is the availability of specialists to provide care for newborns identified with MPS II? How accessible is treatment for MPS II?
3. What is the impact of MPS II newborn screening on newborn screening programs, public health programs, or the population? How feasible is MPS II newborn screening in the United States? To what degree are newborn screening programs ready to screen for MPS II?

## Technical Expert Panel

A panel of Technical Experts was convened to advise the development of this review. Members of this Technical Expert Panel (TEP) are listed in Table 1. The first meeting (July 30, 2021) reviewed the scope of the review and methods, outlined the process of MPS II diagnosis and treatment, and identified current issues in research and health care delivery for children suspected or known to be affected with MPS II. The second TEP meeting (September 13, 2021) focused on the availability of evidence regarding treatment outcomes for presymptomatic or early treatment of MPS II. The third TEP meeting (January 7, 2022) focused on assessing the potential population health impact of newborn screening for MPS II.

**Table 1. List of Technical Expert Panel Members**

Name	Role
Laura Ashbaugh, RN	Nursing Supervisor, Illinois Newborn Screening Program
Khaja Basheeruddin, PhD	Administrator, Illinois Newborn Screening Program
Barbara Burton, MD*	Professor of Pediatrics, Northwestern University Feinberg School of Medicine
Julie Eisengart, PhD, LP	Associate Professor of Pediatrics, University of Minnesota
Matthew Ellinwood, DVM, PhD*	Chief Scientific Officer, National MPS Society
Joan Ehrhardt, MS	Genetic Counselor, Illinois Newborn Screening Program
Nathan Grant	Sibling advocate; Research Associate, Neurodevelopmental Program in Rare Disease, Department of Pediatrics, University of Minnesota
Zhanzhi (Mike) Hu, PhD	Parent Advocate; Cofounder of Project GUARDIAN
Terri L. Klein, NPGC, MPA*	President, National MPS Society
Tracy Klug, BS	Chief, Newborn Screening Laboratory, Missouri Newborn Screening Program
Joseph Muenzer, MD, PhD*	Professor of Pediatrics, University of North Carolina

\* Also a nominator of MPS II to the recommended uniform screening panel.

## 2 REVIEW OF EVIDENCE: NEWBORN SCREENING FOR MUCOPOLYSACCHARIDOSIS TYPE II

### Epidemiology and Natural History of MPS II with Usual Clinical Detection

MPS II (OMIM: #309900), also referred to as Hunter syndrome, is an X-linked (Xq28) lysosomal storage disorder due to dysfunction of the enzyme I2S caused by mutations in the *IDS* gene. This leads to impaired hydrolysis of two GAGs, dermatan sulphate and heparan sulphate. Accumulation of these GAGs leads to the disorder. As an X-linked disorder, MPS II primarily affects males, however, on rare occasion, females have been diagnosed with MPS II, primarily due to abnormalities in the structure of the X-linked chromosome or the inactivation process of the X-chromosome.<sup>1-3</sup>

According to the Human Gene Mutation Database (<http://www.hgmd.cf.ac.uk/ac/gene.php?gene=IDS>), more than 700 variants of the *IDS* gene have been described. One study from 2013 described 218 subjects of whom about 39% had novel large deletions (n=15) or other novel sequence changes (n=69, including a sibling pair).<sup>4</sup> Complete deletion of the *IDS* gene consistently has been associated with the severe phenotype, and some mutations are associated with specific phenotypes, however, many mutations were private or novel.<sup>5,6</sup> Affected family members with the same mutation are expected to have similar phenotypes.

#### Estimated Birth Prevalence Based on Clinically Detected Cases

The evidence review identified reports of birth prevalence estimates of MPS II from clinically detected cases in Europe, Australia, Asia, South America, and the United States, published since 2003, summarized in Table 2. Data come from multiple sources, including a review of hospital medical records, reports from laboratory centers, and patient and family surveys. A recent study based on an international assessment of all MPS disorders estimated the birth prevalence of MPS II to be 0.13 to 2.16 cases per 100,000.<sup>7</sup> In this report, Estonia was an outlier for having a high rate (2.16 cases per 100,000) and Norway was an outlier for having a low rate (0.13 cases per 100,000). Excluding outliers, Japan and Taiwan reported the highest rates, 0.84-1.07 per 100,000, and other places reported rates of 0.26-0.64 per 100,000. The study from the United States with an estimated birth prevalence of 0.26 per 100,000 births is likely an underestimate because it is based on a voluntary registry.

**Table 2. Estimated Birth Prevalence of MPS II based on Clinically Identified Cases**

Pub Year	First Author	Study Region	Time Period	Est. Birth Prevalence per 100,000
2021*	Josahkian <sup>8</sup>	Brazil	1982-2019	0.48
2021	Puckett <sup>9</sup>	United States	1995-2015	0.26
2017	Khan <sup>10</sup>	Japan	1982-2009	0.84
2017	Khan <sup>10</sup>	Switzerland	1975-2008	0.46
2015	Federhen <sup>11</sup>	Brazil	1994-2012	0.38
2020	Federhen <sup>12</sup>	Brazil	1994-2015	0.37
2014	Jurecka <sup>13</sup>	Poland	1970-2010	0.45
2012	Krabbi <sup>14</sup>	Estonia	1985-2006	2.16
2009	Lin <sup>15</sup>	Taiwan	1984-2004	1.07

2008	Malm <sup>16</sup>	Sweden Norway Denmark	1975-2004	0.27 0.13 0.27
2005	Bachner <sup>17</sup>	Germany	1980-1995	0.64
2003	Nelson <sup>18</sup>	Western Australia	1969-1996	0.31
<i>*Update of Brazil MPS II birth prevalence estimate from national reference laboratory.</i>				

## Natural History of MPS II

The Hunter Outcome Survey (HOS) is an important source of data about disease course and the effectiveness of treatment. This is a voluntary registry that collects data regarding patients with MPS II in 29 countries, including retrospective data on patients who died prior to study entry. The registry collects data on those who are untreated or have received either idursulfase or a hematopoietic stem cell transplant (HSCT). Subjects receiving other forms of enzyme replacement therapy (ERT) are not eligible to participate in the HOS. HOS is a component of the required post-marketing long-term safety and effectiveness evaluation required for idursulfase.<sup>19</sup>

An analysis of ERT-treated (n=800) and untreated (n=95) patients from the HOS<sup>20</sup> excluded individuals who died prior to study entry, had received HSCT, or had participated in a clinical trial. The investigators reported that the median ages of symptom onset in the two groups were 1.6 years and 1.5 years, respectively, and the median ages at diagnosis were 3.3 years and 3.2 years, respectively. In both groups, 58% of patients had cognitive impairment (assessed dichotomously, based on provider report) at any time. Among the ERT-treated patients, the median age of treatment initiation was 6.9 years (10<sup>th</sup>-90<sup>th</sup> percentile: 2.1-19.8 years).

An initial report of the first 263 MPS II patients registered in the HOS describes the prevalence of initial symptom characteristics, with age of onset. Of these patients, 24% were receiving ERT at the time of enrollment in the HOS and had a median age of 12.2 years. Table 3 summarizes those features reported by at least 30% of patients in this HOS report, in order of median age of onset. Over 80% of patients registered in the Hunter Outcome Survey (HOS) reported at least one neurological (84%) or cardiovascular (82%) symptom, as well as involvement in the abdomen, head and neck, skeletal, ear, mouth, and chest and lungs, and at least 60% of patients additionally reported throat, skin, nose and gastrointestinal symptoms.<sup>21</sup>

**Table 3. Features of individuals with MPS II registered in the HOS (n=263)**

Clinical Finding	Prevalence (%)	Median age of onset in years
Otitis media	74	1.2
Abdominal hernia	78	1.3
Nasal obstruction	34	2.0
Facial dysmorphism	95	2.8
Enlarged liver or spleen	89	2.8
Enlarged tonsils or adenoids	68	2.9
Cognitive problems	37	3.2
Enlarged tongue	70	3.4
Hyperactivity	31	3.5
Joint stiffness/musculoskeletal	84	3.6
Behavior problems	36	3.7
Fine motor skill impairment	33	4.0
Gait problems	33	5.5
Heart murmur	62	5.8
Cardiac valve disease	57	6.1

Among 20 patients in Minnesota with attenuated MPS II and no cognitive decline, presentation of symptoms was highly variable. In general, with initial symptom onset ranging from infancy (<1 year) to about 8 years, and diagnosis reported across childhood, from 1 to 18 years.<sup>22</sup>

The developmental trajectories of children with severe MPS II are variable. One report describes normal development among 13 Japanese patients with neuronopathic MPS II until about 2 to 4 years of age after which cognitive growth slowed or plateaued for months or years before declining.<sup>6</sup> Recent evidence about the trajectories of symptoms has observed a potential third group of individuals with non-progressive cognitive impairment that appears to stabilize after the periods of growth and developmental slowing and arrest.<sup>23</sup> More research would be needed to better understand the trajectory and this potential intermediate phenotype.<sup>6,24</sup>

A study in England reported long-term outcomes of 110 pediatric patients with MPS II in England assessed between 2006 and 2016, with a median of about 10 years (range: 1 year-18.5 years) of follow-up prior to transition to adult care.<sup>23</sup> ERT was approved in the United Kingdom in 2007. The predicted survival rate at 21 years was 52% for 78 who received ERT vs. 9% in 18 who were never treated ( $p < 0.001$ ). Initiation of ERT before 8 years of age was associated with improved respiratory outcomes at 16 years. However, hearing, carpal tunnel syndrome, and progression of cardiac valve disease were not significantly different compared to initiation of ERT after 8 years of age.

### **Screening, Short-Term Follow-Up, and Diagnostic Confirmation**

There are two general approaches to measuring I2S enzyme activity in newborn screening: liquid chromatography tandem mass-spectrometry (LC-MS/MS), which is currently used by the Illinois newborn screening program, and fluorometric enzymatic assay, which is used by the Missouri newborn screening program. Second-tier GAG testing in dried-blood spots can decrease the number of positive screens from biochemical pseudodeficiency.<sup>25</sup> The Missouri newborn screening program does this as a send-out laboratory test. Additional testing following a positive



screen include measuring urinary GAG levels to rule out biochemical pseudodeficiency and measurement of another sulfatase to rule out multiple sulfatase deficiency. Molecular analysis can be helpful if there is a complete deletion or complex rearrangement.

In some cases, establishing the diagnosis can be challenging. Examples that can raise clinical concern include when there is a very low I2S enzyme activity, normal GAG levels, and a variant of uncertain significance (VUS) or low I2S enzyme activity levels, elevation of one of the GAGs, and a VUS. Individuals with an indeterminate diagnosis are typically followed every 6 to 12 months depending on the degree of clinical concern, until a diagnosis can be established.

### Studies of Anonymized Dried-Blood Spots

A report in 2015 describes the development of an approach to newborn screening for MPS II, MPS IVA, and MPS VI using MS/MS.<sup>26</sup> This was followed by a report describing the use of LC-MS/MS to screen for MPS I, MPS II, MPS IIB, MPS IVA, MPS VI, MPS VII, and type 2 neuronal ceroid lipofuscinosis.<sup>27</sup> These laboratory developments were followed by an analysis of >100,000 anonymous dried-blood spots for several different mucopolysaccharidoses (MPS II, MPS IIIB, MPS IVA, MPS VI, and MPS VII) using LC-MS/MS.<sup>28</sup> Of the 105,214 samples, 18 had an enzyme activity <10% of the daily mean, of which 7 were <5% of the daily mean. The study does describe the *IDS* genotype for those with low enzyme activity, but no additional laboratory or clinical correlation was possible. Based on genotype alone, the study estimates a clinical frequency “between 1 in 53,000 to 1 in 18,000 male samples.” Another report from 2020 described the analysis of >18,000 dried-blood spots for I2S enzyme activity and GAG concentration, concluding that two-tier screening decreases the risk of false positives.<sup>29</sup>

### MPS II Newborn Screening in Illinois

Illinois began screening for MPS II and Krabbe disease in December 2017 with MS/MS. MPS II screening requires a separate punch and a separate extraction process before the screening test is multiplexed with Krabbe disease screening. The incubation time in the Illinois workflow is 17 hours because of the requirements for Krabbe disease newborn screening. Without Krabbe disease newborn screening, the incubation time would be 3 hours.

Two published reports describe MPS II newborn screening in Illinois.<sup>30,31</sup> A positive screening result was an I2S enzyme activity  $\leq 10\%$  of the daily median, and those  $>10\%$  to  $\leq 13\%$  of the daily median were considered borderline with a request for a second dried-blood spot sample. Of the 339,269 screened between December 17, 2017, and February 29, 2020, there were 28 infants with a positive screen and 4 infants with borderline results, of whom 3 continued to have I2S activity  $\leq 13\%$  on retesting.<sup>30</sup> From the 31 who were referred for diagnostic testing, 3 were diagnosed with MPS II, 25 were diagnosed with biochemical pseudodeficiency, and 3 were normal. Based on these findings, the overall referral rate for diagnostic follow-up was 9.1 per 100,000 screened, with a positive predictive value of 9.7% (0.8 cases detected per 100,000). Of these, 2 were started on ERT and one family declined therapy at the time of the report. The age of the infant was not specified.

The Illinois newborn screening program provided an update for this report. From December 13, 2017, to December 31, 2021, Illinois screened approximately 652,000 specimens, representing approximately 546,000 newborns. Of these, 71 infants were referred for clinical follow-up based on an initial positive screen or at least one borderline result. Of these 71 infants, 9 were diagnosed with MPS II, 43 had biochemical pseudodeficiency, 9 were normal, 9 are still being

followed up without the diagnosis of MPS II confirmed (i.e., 0.9 per 100,000 newborns screened), and 5 were lost to follow-up. Based on the number diagnosed with MPS II, the case detection rate was 1.6 per 100,000 newborns screened.

Although systematic information is not available for this report regarding the number of family members incidentally identified with MPS II following diagnosis through newborn screening in Illinois, there was one maternal great uncle diagnosed in one family and another in which a 2-year-old brother was diagnosed. There was also a case of pseudodeficiency diagnosed in a maternal grandfather.

#### MPS II Newborn Screening in Missouri

Missouri received a legislative mandate to screen for MPS II in 2017 and began screening in 2018. The Missouri newborn screening program uses a fluorometric process for MPS II newborn screening. The laboratory time for screening is 3-4 hours. Specimens with I2S enzyme activity below a provisional cut-off are then retested. If the enzyme activity level is still low, then second-tier GAG testing is done as a send-out laboratory test. A notification is sent to the newborn's primary care provider and to the referral center if the GAG levels are abnormal or if the GAG levels are not elevated, but the enzyme activity is below a failsafe cut-off. This screening process and the experience through 2019 is described in a published report.<sup>32</sup> In an update provided by the Missouri newborn screening program for this review, in 2020, there were 86,022 newborn screens from 68,640 unique newborns. Among the newborn screens, 48 were below the provisional cut-off, of which 32 were ultimately sent for second-tier GAG testing. Of these, 10 had elevated GAG levels (including 2 from the same individual) and 2 had non-elevated GAG levels but I2S levels below the failsafe level, leading to 11 referrals (16 referrals per 100,000 newborns). Among these 11, one was diagnosed with severe MPS II and began ERT <30 days after birth (1.5 per 100,000 newborns), 5 with no diagnosis but still being followed including 4 with a VUS (i.e., 7.3 per 100,000 newborns), 2 with biochemical pseudodeficiency, 1 died prior to confirmatory testing, 1 normal, and 1 that declined further testing. From November 2018 through June 2021, in Missouri, there were approximately 233,000 MPS II newborn screening tests from approximately 186,000 unique newborns, which identified 3 with MPS II, a birth prevalence of 1.6 per 100,000 newborns.

#### MPS II Screening in New York As Part of Ongoing Research

Screen Plus is a research project in New York that will include MPS II newborn screening using a MS/MS platform with second-tier GAG testing as a send-out laboratory test. Too few samples have been tested to assess performance.

#### MPS II Pilot Newborn Screening in Taiwan

Newborn screening in Taiwan is conducted through two or three national centers (Liao et al. 2014). The Newborn Screening Center at the National Taiwan University Hospital performs routine screening for approximately 35% of newborns.<sup>33</sup> In 2018, that program piloted adding MPS II, MPS IIIB, MPS IVA, and MPS VI to a multiplex MS/MS screen that included Pompe disease, Fabry disease, Gaucher disease, and MPS I. From March 2018 through April 2019, 73,743 newborns were tested for all 8 disorders. For MPS II, 56 required repeat testing and 32 screened positive. Three (4.07 per 100,000) were diagnosed with MPS II and the remaining 29 had benign variants.

The Neonatal Screening Center of the Chinese Foundation of Health, Taipei, Taiwan, began screening for MPS II in 2015 as a research project with informed parental consent, based at MacKay Memorial Hospital. The proportion consenting was not reported, but roughly half as many infants were screened for MPS II as for MPS I.<sup>34</sup> Results from the pilot screening during August 2015 to August 2017 were reported in 2019, during which 130,175 infants were screened and 3 were diagnosed with MPS II (1.96 per 100,000).<sup>35</sup> A total of 307,731 infants were screened for MPS II through April 2021 in this program.<sup>34</sup> Of 186 referred for diagnostic evaluation after two positive dried-blood spots (61 per 100,000), 9 newborns were diagnosed with MPS II (4.8% positive predictive value). Among 52 other infants with suspected MPS II, 10 were classified as having likely pathogenic variants, 4 with a VUS, 28 with benign variants, and 10 were unclassified. Based on the protocol in the 2019 article, infants with suspected variants are followed up on every three to six years. The cumulative birth prevalence was 2.92 per 100,000 newborns screened.<sup>35</sup>

Another report from MacKay Memorial Hospital described 175 patients diagnosed with MPS disorders from 1985 to 2019, including 78 diagnosed with MPS II.<sup>36</sup> Six infants were identified with MPS II during 2016-2019, all of whom were reported to have been identified through newborn screening, presumably at MacKay Memorial Hospital. Four newborns started ERT at the time of diagnosis (0.1 to 0.2 years). Three of these infants also received HSCT between 0.9 and 1.6 years of age due to definite family history, with 2 infants having good outcomes (normal IDS 2 levels 6 to 14 months post HSCT), and 1 infant dying within 3 months due to infection and sepsis. Two other infants did not receive treatment and remained under regular 6 month follow up.<sup>36</sup> Median age of diagnosis for newborns with MPS II was 0.2 years (range 0.1 to 0.5) with newborn screening (since 2016), compared with 3.8 years across all MPS II patients diagnosed from 1985 to 2019).<sup>36</sup>

**Table 4. Summary of Population-Based MPS II Newborn Screening Studies**

Location	Time Period	Newborns Screened	Diagnostic Follow-up Referral Rate per 100,000 Screened	MPS II Cases Detected per 100,000 Screened	Infants in Diagnostic Follow-up Without Diagnosis per 100,000 Screened
Illinois	2017-2021	546,000	13	1.6	0.9
Missouri	2020	68,640	16	1.5	7.3
Missouri	2018-2021	186,000	15	1.6	2.1
Taiwan	2015-2021	307,731	61	2.9	4.5
Taiwan	2018-2019	73,743	44	4.1	None

### Screening Summary

- Illinois and Missouri have adopted MPS II screening, one with MS/MS and the other with a fluorometric process. MPS II screening in New York with MS/MS is occurring on a limited scale as part of a research project. Taiwan is also screening for MPS II on a pilot basis.

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- Although there is some variation, screening is based on identification of low I2S enzyme activity. Second-tier dried-blood GAG testing, which can be a send-out test, decreases referral rates due to biochemical pseudodeficiency. Variation in approaches to screening, including enzyme activity thresholds and second-tier testing, might alter referral rates and impact the number of infants requiring monitoring to establish a diagnosis.
- Diagnosis following newborn screening is based on low enzyme activity level and elevated urine GAG levels. Although there are many private mutations, in some cases, genotyping can be helpful in predicting the phenotype. When there is diagnostic uncertainty, referral centers continue to follow infants. Experts state that this follow-up is every 6-12 months for up to 2 years.
- The rate of referral for diagnostic evaluation was similar for Illinois and Missouri and much lower than in Taiwan. The case detection rate was substantially higher in Taiwan.
- The case detection rate through screening is higher than the range of expected clinical case detection. Insufficient information is available to describe the phenotypic distribution of newborn screening-detected cases compared with clinically detected cases.
- Neither Illinois nor the Missouri newborn screening program has reported a missed case (i.e., false negative screen) of MPS II.

### Treatment Guideline

We identified only one formal treatment guideline for MPS II published within the last decade. In 2020, the American College of Medical Genetics and Genomics Therapeutics Committee published a practice resource for MPS II based on the results of a Delphi panel (ten specialty experts, no public member) and a prior SER of treatment.<sup>37</sup> This treatment guideline focused on ERT, which is the only specific FDA-approved treatment for MPS II. The final recommendations are:

1. All individuals with severe MPS II or predicted to have severe MPS II based on genotype warrant starting ERT, prior to showing signs or symptoms.
2. Individuals with signs or symptoms with either attenuated or severe MPS II warrant ERT.
3. Individuals with attenuated MPS II who are not showing signs or symptoms of disease do not warrant ERT.
4. Home infusions may be considered for those with early disease, easily managed ERT infusion reactions, and a stable home environment.
5. Individuals receiving ERT who have developed allergic reactions that cannot be controlled by standard therapies or immunomodulation should have ERT discontinued.
6. Pressure equalizing (PE) tubes and hearing aids are useful therapies.
7. Clinical evaluation of liver and spleen size are recommended for judging clinical effectiveness of treatment, with optional use of imaging modalities (ultrasound or MRI of the abdomen) to follow organ size. Pulmonary function tests (PFTs) are recommended if the individual can reliably perform them, but there are concerns on the utility of the 6-minute walk test (6MWT). Lab studies of GAGs are recommended, as well as antibodies

to ERT to assess infusion reactions. Finally, neuropsychology testing is recommended for following disease progress.”<sup>37</sup>

Although the guideline does not recommend beginning ERT for attenuated MPS II in the absence of signs or symptoms, there was debate. For example, in the first round of the Delphi panel, some members felt that starting early therapy was important and “the right thing to do.”<sup>37</sup> The guideline is not specific about the signs or symptoms that should lead to ERT. The signs and symptoms discussed by the Delphi panel might not be identifiable in infancy without newborn screening (e.g., “mild hepatomegaly;” skeletal, cardiac, or neurologic findings).

In contrast to this guideline, the TEP recommended that all infants diagnosed with newborn screening should be offered ERT after diagnosis regardless of the expected phenotype based on the following statements endorsed by the TEP:

- There is greater accumulation of GAGs when MPS II is untreated. This accumulation leads to more significant and progressive somatic involvement regardless of phenotype.
- ERT will not reverse the damage caused by the accumulation of GAGs. Early initiation of ERT can decrease this accumulation and therefore prevent or at least slow irreversible damage.
- Although a significant amount of ERT does not cross the blood-brain barrier, all individuals, regardless of phenotype, benefit from preventing the somatic manifestations of MPS II. Preventing these somatic manifestations could also lead to better developmental outcomes, regardless of phenotype, by preventing sensory deficits (e.g., hearing impairment), preventing spine involvement, decreasing sleep apnea, and through improved mobility.

In summary, the TEP strongly endorsed offering ERT for all infants with MPS II regardless of expected phenotype or whether the phenotype at diagnosis is unknown because of the somatic benefits of treatment. Because ERT as currently approved treats somatic disease that develops in both attenuated and severe MPS II, the evidence review does not stratify by phenotype in evaluating these outcomes unless the report stratified by phenotype. Note that the identified reports often did not provide phenotype information when describing outcomes. The evidence review did consider outcomes specifically related to the neurologic impact of severe disease when such evidence was provided.

The TEP also highlighted the importance of impact of decreased daily functioning on individuals with MPS II, regardless of phenotype, and their caregivers. One example provided was toileting ability.

## **MPS II Treatment**

### *Enzyme Replacement Therapy with Idursulfase*

ERT is the current mainstay of treatment for MPS II. Idursulfase, under the brand name Elaprase (Takeda Pharmaceutical Company Limited) is provided as a weekly intravenous infusion over several hours. Idursulfase does not significantly cross the blood-brain barrier and therefore cannot impact GAG accumulation in the central nervous system. Novel mechanisms to introduce idursulfase in the central nervous system have been explored, including direct delivery of idursulfase into the central nervous system through intraventricular or intrathecal infusions or

modification of the idursulfase molecule with allows it to cross the blood-brain barrier. A form of ERT designed specifically for intrathecal delivery (Hunterase, GC Pharma) has been approved in Japan and other countries in Asia but not by the FDA. A novel version of idursulfase, in which it has been fused with a specific antibody that allows it to actively cross the blood-brain barrier (pabinafusp alfa, brand name Izargo, previously JR-141, JCR Pharmaceuticals), has been approved in Japan but is not currently FDA approved.<sup>38</sup>

#### *Overview of Idursulfase Safety and Effectiveness*

The potential safety and efficacy of idursulfase was explored in a 24-week randomized trial with a 1-year open-label extension.<sup>39</sup> This study enrolled 12 subjects, ages 9 to 20 years of age and found a decrease in urine GAG levels, reduced liver and spleen size, and an overall improvement on the 6MWT from  $398 \pm 117$  meters to  $445 \pm 124$  meters after 12 months of therapy. There was no improvement in joint mobility. Infusion reactions occurred in 6 of the 8 subjects receiving a dose  $> 0.15$  mg/kg, which could be treated with slowing the infusions from 1 to 3 hours and in some cases premedication with antihistamines and/or corticosteroids. Among this group with infusion reactions, one 20 years old subject had potentially life-threatening episode of respiratory distress. Six subjects also developed idursulfase IgG antibodies that did not appear to interfere with the treatment effectiveness. One of these subjects reverted to being antibody negative. Because this study did not include subjects beginning treatment in the first year of life, no inference can be made about early treatment. However, the lack of improvement in joint mobility implies the need for earlier treatment.

The pivotal trial for idursulfase was a phase II/III trial that included 96 subjects with MPS II between ages 5 and 31 years of age randomized to placebo, weekly idursulfase or every-other-week idursulfase with a composite outcome of the 6MWT and change in pulmonary function (forced vital capacity).<sup>40</sup> The group that received weekly ERT had a increase in the 6MWT of 37 meters, a 2.7% increase in the percentage of predicted forced vital capacity that did not meet statistical significance, and a 160 mL increase in absolute forced vital capacity compared to placebo. Although not a primary outcome, elbow mobility also increased. Overall, 46.9% in the treated group developed idursulfase IgG antibodies. Those with antibodies had a lower reduction of urine GAGs but according to the report, it was not associated with changes in clinical findings or increased risk of adverse events. A two-year open-label follow-up of 94 subjects found improvement of the shoulder range of motion but no changes in other joints.<sup>41</sup> Although there was also improvement in the Child Health Assessment Questionnaire Disability Index (parent- and child-reported), these studies cannot directly predict the impact of presymptomatic or early intervention.

A study in England reported outcomes of 110 patients seen since ERT was approved in the United Kingdom in 2007.<sup>23</sup> After a median of about 10 years (range: 1 year 2 months to 18 years 6 months) follow-up after starting ERT treatment, treated patients had higher rates of survival, with median age of death for treated patients (n=16 of 78) at 15 years (range: 9.53 - 20.58 years), compared with median age of death for untreated patients (n=17 of 18) at 11.43 years (range: 0.5-19.13 years;  $p < 0.001$ ). Earlier ERT ( $< 8$  years) was associated with improved respiratory outcomes at 16 years. However, impact on hearing, carpal tunnel syndrome, or progression of cardiac valve disease was not significant relative to initiation of ERT after 8 years of age.

#### **ERT for Patients $> 1$ Year of Age**

Several studies reported retrospective outcomes for subjects 1 year of age and older. For example, a recent retrospective observational study from the Philippines<sup>42</sup> described 40 subjects with a mean age of symptom onset of 2.28 years and an average age of diagnosis of 6.99 years. Of the 8 subjects that received weekly ERT for at least 6 months, there were improved growth parameters (height and weight), improved left ventricular mass index, reduced liver and spleen sizes, and improved joint mobility. Interpreting the joint mobility data is challenging because only 13 of the 40 subjects had baseline data and only 7 had complete data through the 2-year follow-up period. Aortic root dilation improved in 4 of 5 subjects treated with ERT at a mean age of initiation of 15.8 years with a mean duration of treatment of 8.8 years.<sup>43</sup> In 46 patients in Russia (mean age 84 months) with cardiac disease treated with ERT, pre-existing cardiac damage was not reversed but heart failure stabilized.<sup>44</sup> A study of 45 subjects treated in Poland between 2009 and 2017 reported that 25 discontinued because of lack of effectiveness (no additional data provided) and another 3 died due to disease progression while still receiving ERT and two discontinued treatment due to anaphylaxis.<sup>45</sup> This study included subjects 5 years and older and most seemed to be significantly impacted by the condition. Although the report states that 8 had no more than moderate impairment, no quantitative measure was used to categorize degree of impairment. Furthermore, two had not been followed long enough for repeat neurodevelopmental testing on therapy. Eight subjects had no more than moderate impairment. Although these studies provide evidence regarding the overall effectiveness of ERT, they do not provide evidence regarding the potential impact of earlier treatment before significant GAG accumulation.

### **ERT Initiation in the First Year of Life**

The evidence review identified the following reports that provide evidence regarding early MPS II treatment.

A multicenter international 52-week open-label study included 27 out of 28 initial subjects with a mean age of diagnosis of 3.5 years (range: 0.2-6.5 years).<sup>46</sup> More than half (57.1%) had at least one infusion-related adverse event that were managed clinically without the need to end ERT therapy. Nineteen subjects developed anti-idursulfase antibodies. Insufficient evidence was provided to evaluate safety or effectiveness by age of diagnosis or treatment.

Another 52-week open-label study in Korea enrolled 6 subjects diagnosed before 4 years of age, including one diagnosed < 1 year (around 2 months) who began treatment around 4 months, one diagnosed at 1.2 years who began treatment at 1.3 years, and one diagnosed at 1.7 years who began treatment at 2.4 years.<sup>47</sup> One subject had infusion-related reactions that were treated with antihistamines and four subjects had antidrug antibodies at least once. All subjects had lowered urine GAG levels throughout the treatment period. All subjects had an increase in height and weight, although the sample size is insufficient to evaluate differences. Four of the subjects had severe MPS II. The report states that there was no change in developmental milestones over the study period.

One retrospective study of cardiovascular outcomes evaluated 48 subjects in Taiwan with MPS II, including 7 subjects referred from newborn screening.<sup>48</sup> None of the subjects identified through newborn screening had abnormal echocardiographic findings at baseline compared to abnormal findings in the rest of the cohort. Insufficient evidence was provided in this report to directly compare echocardiographic findings at age-matched points for those identified through newborn screening.

One case series describes a convenience sample of 8 infants diagnosed with MPS II based on family history of MPS II (n=7) or MPS I (n=1) and who received ERT from 10 days to 6.5 months of age.<sup>49</sup> Two of the eight infants discontinued ERT after 6 and 10 weeks after receiving a HSCT. Post-treatment outcomes are described for the six infants who continued ERT, with follow-up ranging from 20 months to 5.5 years at the last visit, and all were noted to be continuing ERT at the time of the report. These cases are summarized in the following table:

**Table 5. Summary of 8 Subjects Receiving ERT <1 year of age.**

Factor Leading to Diagnosis	Age at MPS II Diagnosis	Clinical assessment at TX baseline	Age at Treatment Treatment follow up
Family history	Prenatal	<ul style="list-style-type: none"> <li>- Subtle lumbar gibbus</li> <li>- Lumbar x-ray (L3-L5) abnormality</li> <li>- Echocardiogram - normal</li> </ul>	<p><b>ERT Initiation at 10 days of age</b> ERT for 6 weeks, then HSCT at 70 days (no more ERT)</p> <ul style="list-style-type: none"> <li>- Development has progressed</li> <li>- Maternal report doing much better than older brother at same age.</li> </ul>
Sibling diagnosed during pregnancy	1 week	<ul style="list-style-type: none"> <li>- Ultrasound - Ventriculomegaly in the fetus</li> <li>- At 6 hours old, respiratory distress</li> <li>- Hepatomegaly</li> <li>- Lumbar kyphosis</li> </ul>	<p><b>ERT initiation at 6 weeks</b> ERT duration at follow up – 2 years</p> <ul style="list-style-type: none"> <li>- Physical exam completely normal except somewhat broad forehead with mild frontal bossing</li> <li>- Development – normal, age appropriate</li> </ul>
Family history	6 weeks	<ul style="list-style-type: none"> <li>- Cognitive function (Bayley’s scale) – normal</li> <li>- Echocardiogram – normal</li> <li>- Diastasis recti abdominis</li> <li>- Hepatosplenomegaly</li> <li>- Umbilical hernia</li> </ul>	<p><b>ERT initiation at 8 weeks of age</b> ERT duration 10 weeks, then received HSCT</p> <p><u>Follow up at 18 weeks:</u></p> <ul style="list-style-type: none"> <li>- Liver palpable</li> <li>- No developmental delays</li> <li>- Mild left convex scoliosis but no dysostosis multiplex.</li> <li>- No hearing loss.</li> </ul>
Family history	Birth	<ul style="list-style-type: none"> <li>- Failed routine hearing test</li> <li>- Mild frontal bossing</li> <li>- Slightly coarse facial features at 2 weeks</li> <li>- Hepatosplenomegaly</li> <li>- Mild lumbar kyphosis at L2 (imaging only, not clinically)</li> </ul>	<p><b>ERT initiated at 10 weeks</b> <u>At 7 months of age:</u></p> <ul style="list-style-type: none"> <li>- hearing loss treated with tubes and aids</li> </ul> <p><u>At 18 mos of age:</u></p> <ul style="list-style-type: none"> <li>- Mild coarse facial features</li> <li>- Mild joint stiffness</li> <li>- Exam otherwise unremarkable</li> <li>- Parents report development much better than affected brother</li> <li>- Bayley’s scale – gross motor and expressive language age appropriate, self-help, fine motor, receptive language at 6-9-month delay.</li> </ul>
Family history	4 weeks	<ul style="list-style-type: none"> <li>- Hypotonic at birth</li> <li>- pneumonia in first 13 days</li> <li>- Exam at 11 weeks:</li> <li>- Mild coarse facies</li> <li>- Diastasis recti abdominis</li> <li>- Hepatomegaly</li> <li>- Umbilical hernia</li> </ul>	<p><b>ERT initiated at 11 weeks</b> <u>At 5.5 years:</u></p> <ul style="list-style-type: none"> <li>- Normal growth</li> <li>- Very minor joint range of motion restrictions</li> <li>- Echocardiogram – mild aortic valve stenosis, valve insufficiency, normal left ventricular function</li> </ul>



Family History of MPS I (but not MPS II)	11 weeks	<ul style="list-style-type: none"> <li>- Hydrocele</li> <li>- Inguinal hernia</li> <li>- Hepatomegaly</li> <li>- Congestive heart failure</li> </ul>	<p><b>ERT initiation at 12 weeks of age</b> ERT duration at last follow up– 30 months</p> <ul style="list-style-type: none"> <li>- Cardiac symptoms worsening</li> </ul> <p><u>At 1 year:</u></p> <ul style="list-style-type: none"> <li>- Above average growth (height, weight, head)</li> <li>- Normal motor development</li> <li>- Absence of hepatosplenomegaly</li> <li>- Normal joint range of motion</li> </ul> <p><u>At 16 months:</u></p> <ul style="list-style-type: none"> <li>- Echocardiogram showed sustained dilated cardiomyopathy</li> </ul>
Family history	1 week	<ul style="list-style-type: none"> <li>- Mild frontal bossing</li> <li>- Chronic otitis media with effusion</li> <li>- scapular flaring with shoulder abduction</li> </ul>	<p><b>ERT initiated at 6 months of age</b></p> <ul style="list-style-type: none"> <li>- Development average-above average on Mullen Scales at 6 months and 2 years</li> </ul> <p><u>At 4 years:</u></p> <ul style="list-style-type: none"> <li>- Growth parameters normal</li> <li>- Slightly coarse facies, with frontal bossing, receding anterior hairline, eyelid puffiness</li> <li>- Tapering fingers, reduced extension of the digits at the joint</li> <li>- No evidence of macroglossia, organomegaly, spine deformities, hearing loss, or hernias.</li> <li>- Reports he is developing normally and keeping up with peers.</li> </ul>
Family history	5 months	<ul style="list-style-type: none"> <li>- Mild coarse facies</li> <li>- Small, thickened ears</li> <li>- hepatomegaly</li> <li>- Gibbus</li> <li>- Bilateral foot adduction</li> <li>- Frequent upper respiratory infections</li> <li>- Recurrent otitis media</li> </ul>	<p><b>ERT initiated at 6.5 months of age</b></p> <p><u>At 3.5 years:</u></p> <ul style="list-style-type: none"> <li>- Liver size normalized</li> <li>- Echocardiogram remains normal</li> <li>- Gibbus deformity progressed at age 2, stabilized since age 3 years.</li> <li>- Slight contractures of the joints in upper extremities by 3.5 years. Carpal tunnel surgery at 3.5 years.</li> <li>- Neurodevelopmental evaluation at 3 years 8 months – (Cognitive Adaptive Test) Age Equivalent 30 months, visual-motor skills and language quotient of 68 and 75.</li> </ul>

### Early vs. Later ERT Initiation

No prospective studies were identified that directly compare early (i.e., <1 year) vs. later ERT. However, retrospective studies stratified by age and descriptions of siblings with MPS II were identified.

A recent analysis of the HOS compared outcomes based on age group at the start of ERT stratified by age, categorized as <18 months, 18 months to <5 years, and ≥5 years.<sup>50</sup> This analysis was restricted to those subjects who had received ERT for at least 5 years and excluded those who received HSCT or had been in a previous clinical trial for idursulfase. The analysis was based on a regression analysis with age group at start as a fixed effect. Overall, there were 481 subjects included in the model for at least one outcome measure. However, there was significant variation in the completeness of data and length of follow-up time. In addition, the key outcome was time from ERT start not absolute age of the subjects. As a result, the findings

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could not compare younger to older subjects. Insufficient data were provided to evaluate the degree to which age at treatment initiation as a fixed effects variable in the model addressed this potential limitation. Key findings from this study included:

- The urine GAG levels decreased similarly for all subjects (n=180).
- The left ventricular mass index remained stable (n=250).
- Among those without cognitive impairment and  $\geq 5$  years of age, pulmonary function decreased slightly for all groups (n=83 and 84 for FVC and FEV1, respectively).
- Among those without cognitive impairment, the 6MWT increased to over 50 meters at 8 years following the start of ERT (n=76). According to the report, those who started ERT before 18 months “had the highest predicted mean walking distance at post-ERT start.” The 6MWT predicted at 8 years after ERT start by age group was: 507.3 meters (95% CI:344.5-670.1) for 0 to <18 months, 494.7 meters (95% CI: 434.1-555.2) for 18 months to <5 years, and 473.9 meters (95% CI: 439.4-508.4) for  $\geq 5$  years.
- Liver size by palpation decreased for all subjects (n=413) with faster resolution for those who started earlier (by 4.4 years for those who started 0 to <18 months, by 7.4 years for those who started 18 months to <5 years, and by 8.2 years for those who started  $\geq 5$  years).

The following summarizes evidence regarding early treatment from sibling case reports.

In one sibling pair, the older brother started ERT at 3 years old and his younger sibling started ERT at 4 months old.<sup>51</sup> After about 34 months of ERT, the older brother had stabilization of somatic disease without a change in development (baseline developmental quotient 49; after treatment 42). The younger brother had not developed coarse facial features, hepatosplenomegaly, cardiac dysfunction, or joint abnormalities, and his development was closer to the normal range [baseline developmental quotient (DQ) 89; after treatment 74].

One report describes a subject with a twin brother that was diagnosed at 14 days because he had a sister with MPS II.<sup>52</sup> This subject began ERT at 3 months of age. By three years of age, he did not have coarse facial features, echocardiography was normal, he had a normal liver and spleen size, normal joint range of motion, and normal intelligence [Intelligence Quotient (IQ) 98 vs. 118 for his twin brother]. At 3 years of age, the sister, who did not begin ERT until 7 years of age, had mild coarse features, decreased joint range of motion, and an IQ of 50. At 10 years of age, the sister’s MPS II has progressed, with significant joint contractures and an IQ of 24.

Another report describes a sibling pair, one of whom began ERT from the time of diagnosis at 2 years of age. The younger sibling was diagnosed prenatally and started ERT at 1 month of age and then was switched to pabinafusp alfa at 1 year 11 months. The older sibling had a developmental quotient of 53 at 4 years old while the younger had a developmental quotient of 104 at 3 years 11 months.<sup>53</sup> According to the report, “both siblings had histories of inguinal hernia and adenoid vegetation, but only...[the older sibling]...developed hepatomegaly, joint stiffness, and skeletal deformity...[The younger sibling shows]...no somatic symptoms of MPS-II.”

An abstract describes a sibling pair with attenuated MPS II, one of whom began ERT at 4 years of age, about a year after diagnosis.<sup>44</sup> His younger brother began ERT at 5 months of age and at 5 years of age was reported to have “slight coarsening face, mild splenomegaly, [and] slight

thickening of the mitral valve. In contrast, the older brother at 15 years had significant somatic involvement with normal intelligence.

An abstract accepted to the 2022 *WORLD Symposium* describes 3 sibling pairs who started ERT at 1-2 months of age versus 21-36 months for their siblings.<sup>54</sup> According to this report, after 2-3 years of treatment, none of the younger siblings had coarse facial features, joint stiffness, hepatosplenomegaly, or an abnormal echocardiogram. However, two had mild speech delay. In contrast, the older siblings had persistent coarse facial features and generalized stiffness and two had cardiac involvement (aortic root dilataion and thickened mitral and aortic valves).

An abstract accepted for presentation describes two siblings with attenuated MPS II, one who began ERT at 1.7 years and the other at 5.2 years.<sup>55</sup> According to the abstract, after ten years of ERT, both siblings had above-average IQ and communication skills. However, there was a difference in a measure of adaptive skills attributable to disease-related physical limitations, with the younger sibling in the normal range and the older sibling below normal. The report also states that “other findings, without age-match data, such as measures of scoliosis, shoulder and elbow range of motion, and hip disease, indicate early intitation of therapy is associated with residual but less severe disease.”

A recently published article describes two siblings with neuronopathic MPS II, one diagnosed at 3 years 8 months and the other at 12 months, with ERT beginning the month following diagnosis.<sup>56</sup> The older sibling was also in a clinical trial of intrathecal ERT from 6 years to 10 years of age and the younger sibling was in a trial of intrathecal ERT from 5 years to 9 years and then another trial of investigational CNS-penetrant ERT. Because of progression of disease, the older sibling stopped ERT at 11 years of age and is receiving palliative care. When each subject was five years of age, they had significant differences on the Differential Ability Scales (DAS), Second Edition (46 for the older, 91 for the younger). The older sibling has been minimally verbal since 6 years of age compared to the younger sibling who is reported to communicate at the three-year-old level. The older sibling also developed significant behavior problems, including aggression, which improved with medication. Both siblings are hyperactive, for which they are treated with medication. Both siblings have some degree of hearing loss. Only the older sibling has developed thickened mitral and aortic valves. Only the older sibling has organomegaly. The older sibling has developed significant contractures and at 13 years has limited mobility, with a walking distance of less than one mile. The younger sibling does not have these limitations. The older sibling requires significant support from the family. The younger sibling is more independent, including indepedence in the following skills: bathing, dressing and toileting.

The following tables summarize these sibling reports, stratified by the age of the younger sibling at ERT initiation (<7 months vs. ≥7 months).

**Table 6. Sibling Case Reports with ERT Initiation < 7 Months of Age in the Younger Sibling**

Reference	Older sibling (O)	Younger sibling (Y)
Publication: Tajima et al. (2013) <sup>51</sup>	O (M) MPS II dia gnosis at 2 years 7 months <b>ERT initiation at 3 years</b> ERT dura tion 34 months <u>Symptoms Pre- / Post-ERT (34 months)</u>	Y (M) MPS II dia gnosis <1 month (just after O’s dia gnosis) <u>No clinical symptoms</u> <b>ERT initiation at 4 months</b> <u>After 32 months of ERT</u>

Reference	Older sibling (O)	Younger sibling (Y)
	<ul style="list-style-type: none"> <li>- Coarse facial features – yes / stable</li> <li>- Thick and coarse skin – yes / improved</li> <li>- Hepatosplenomegaly – yes/improved</li> <li>- Cardiac dysfunction – yes/stable</li> <li>- Problems in joints – yes/stable</li> <li>- Dysostosis multiplex -yes/slowly progressive</li> <li>- Exudative otitis media -yes/persistent</li> <li>- DQ 49/42</li> </ul>	<ul style="list-style-type: none"> <li>- Course facial features – none</li> <li>- Thick, coarse skin – no/no</li> <li>- Hepatosplenomegaly - none</li> <li>- Cardiac dysfunction – none</li> <li>- Problems in joints – yes/stable</li> <li>- Dysostosis multiplex -yes/slowly progressive</li> <li>- Exudative otitis media – no/yes</li> <li>- DQ Baseline 89, Post ERT 74 – some decline</li> </ul>
Publication: Tyłki-Szymanska et al. (2012) <sup>52</sup>	O (F) MPS II Diagnosis at 5 years <u>Clinical symptoms</u> <ul style="list-style-type: none"> <li>- Coarse facial features - mild</li> <li>- Joint range of motion – decreased (especially elbow, hip and ankle joints)</li> <li>- Slight hepatomegaly and a mild umbilical hernia</li> <li>- Cognitive retardation, IQ of 50</li> </ul> <b>ERT initiated at 7.5 years</b> <u>Post 3 years ERT (10 years of age):</u> <ul style="list-style-type: none"> <li>- MPS II disease progression</li> <li>- Significant joint contractures</li> <li>- Cardiac disease – worsened</li> <li>- Hepatomegaly and short stature</li> <li>- Cognitive decline, IQ of 24</li> </ul>	Y (M) MPS II diagnosis at 14 days (twin brother was healthy) <u>No clinical symptoms</u> <b>ERT initiated at 3 months</b> <u>After 3 years ERT:</u> <ul style="list-style-type: none"> <li>- Coarse facial features - none</li> <li>- Echocardiography -normal</li> <li>- Liver and spleen size – normal</li> <li>- Cardiac function – normal</li> <li>- Joint range of motion – normal</li> <li>- Dysostosis multiplex - none Intelligence – normal (IQ 98 vs. 118 for his twin brother).</li> </ul>
Publication: Tomita et al. (2021) <sup>57</sup>	O (M) MPS II diagnosis at 2 years <b>ERT initiated at 2 years</b> <ul style="list-style-type: none"> <li>- Post ERT follow up of 5 years:</li> <li>- Inguinal hernia and adenoid vegetation</li> <li>- Hepatomegaly</li> <li>- Joint stiffness</li> <li>- Skeletal deformity</li> <li>- Language acquisition – delayed, worsens</li> <li>- Mild ventriculomegaly and brain atrophy</li> <li>- Attention and behavioral problems</li> <li>- Cognitive and motor function - impaired</li> <li>- Ambulation impaired, worsens (Able to go up and down stairs with a handrail, later unable to use stairs)</li> <li>- Cognitive impairment, DQ 53 at 4 years</li> </ul>	Y (M) MPS II diagnosed prenatally <b>ERT initiated at 1 month</b> (switched to pabinafusp alfa at 1 year 11 months) <u>After ERT follow up 5 years:</u> <ul style="list-style-type: none"> <li>- Inguinal hernia</li> <li>- Slight hepatomegaly</li> <li>- Atrial septal defect detected on echocardiography</li> <li>- No somatic symptoms</li> <li>- Cognitive function – normal (DQ of 104 at 3 years, 11 months)</li> </ul>
Abstract: Quadri et al. (2022) <sup>54</sup>  (3 sibling pairs)	3 Os – <b>ERT after diagnosis at 21-36 months</b> <ul style="list-style-type: none"> <li>- Post ERT 2-3 years</li> <li>- Persistent coarse facial features</li> <li>- Persistent generalized stiffness</li> <li>- Cardiac involvement (aortic root dilatation, thickened mitral &amp; aortic valves) in 2 of 3 Os</li> <li>- Hepatosplenomegaly, resolved post ERT</li> <li>- Persistent middle ear effusions or PE tubes</li> <li>- Persistent developmental or speech delays</li> </ul>	3 Ys- <b>ERT at 1-2 months</b> <u>After ERT 2-3 years</u> <ul style="list-style-type: none"> <li>- Coarse facial features – none</li> <li>- Joint stiffness - none</li> <li>- Hepatosplenomegally – none</li> <li>- Echocardiogram – normal</li> <li>- Physical exam - normal</li> <li>- Speech – mild delay in 2 of 3</li> </ul>
Abstract: Vashakmadze et al. (2021) <sup>44</sup>	O – Attenuated MPS II diagnosed at 2.9 years Presenting symptoms: <ul style="list-style-type: none"> <li>- Coarse –facial features</li> <li>- Dystosis multiplex – mild</li> </ul>	Y – Attenuated MPS II diagnosed at 1 mo Presenting symptom: <ul style="list-style-type: none"> <li>- Mild muscle dystony</li> </ul> <b>ERT initiated at 5 months</b>

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Reference	Older sibling (O)	Younger sibling (Y)
	<ul style="list-style-type: none"><li>- Cardiac dysfunction (mitral and aortal incompetence)</li><li>- Hepatomegaly and splenomegaly</li><li>- Otitis adenoid hypertrophy</li></ul> <p><b>ERT initiated at 4 years</b></p> <p><u>After ERT at 11 years</u></p> <ul style="list-style-type: none"><li>- Claw-hand deformity – mild</li><li>- Persistent multiplex dystosis</li><li>- Cardiac dysfunction (mitral and aortal incompetence)</li><li>- Carpal tunnel syndrome</li><li>- Cardiomyopathy</li><li>- Cognitive function - normal</li></ul>	<p><u>After ERT at 5 years:</u></p> <ul style="list-style-type: none"><li>- Slight coarsening face</li><li>- Mild splenomegaly</li><li>- Slight thickening of the mitral valve</li></ul>

**Table 7. Sibling Case Reports with ERT Initiation  $\geq$ 7 Months of Age in the Younger Sibling**

Reference	Older sibling (O)	Younger sibling (Y)
Abstract: Polgreen et al. (2022) <sup>55</sup>	<p>O - <i>Attenuated</i> MPS II diagnosis – age not reported</p> <p><b>ERT initiation at 5.2 years</b></p> <p>Post ERT 10 years</p> <ul style="list-style-type: none"> <li>– Cognitive function– Above average, communication skills 105</li> <li>– Adaptive/daily living skills – 79 (below normal)</li> <li>– Scoliosis, shoulder and elbow range of motion, hip disease– developing post ERT</li> </ul>	<p>Y - <i>Attenuated</i> MPS II diagnosis – age not reported</p> <p><b>ERT initiation at 1.7 years</b></p> <ul style="list-style-type: none"> <li>– Cognitive function – above average</li> <li>– Adaptive/daily living skills – average (106)</li> <li>– Scoliosis, shoulder and elbow range of motion, and hip disease - residual but less severe disease</li> </ul>
Publication: Grant et al. (2022) <sup>56</sup>	<p>O - neuronopathic MPS II diagnosed at 3 years 8 months</p> <p><b>ERT initiated 3 years 9 months</b></p> <ul style="list-style-type: none"> <li>– Intra thecal ERT (clinical trial) from 6 years to 10 years of age</li> <li>– Stopped ERT at 11 years due to disease progression, receiving palliative care.</li> </ul> <p>Other clinical symptoms:</p> <ul style="list-style-type: none"> <li>– 5 years – DAS score – 46 (significantly below average)</li> <li>– Significant speech delays - minimally verbal since 6 years</li> <li>– Significant behavior problems - aggression, improved with medication.</li> <li>– Hyperactivity – treated with medication</li> <li>– Normal hearing at age 8 years</li> <li>– Cardiac dysfunction - thickened mitral and aortic valves</li> <li>– Organomegaly</li> <li>– Significant contractures, at 13 years has limited mobility, with a walking distance of less than one mile.</li> <li>– Requires significant daily living support from family.</li> </ul>	<p>Y - MPS II diagnosis at 12 months</p> <p><b>ERT initiated at 13 months</b></p> <p>Intra thecal ERT (clinical trial) from 5 years to 9 years</p> <p>Investigational CNS-penetrant ERT since 9 years</p> <p><u>Clinical symptoms:</u></p> <ul style="list-style-type: none"> <li>– Hyperactivity – treated with medication</li> <li>– Hearing loss – mild at age 4</li> <li>– Cardiac abnormalities - none</li> <li>– 5 years – DAS score – 91 (average)</li> <li>– Communication – delayed, three-year-old level</li> <li>– Contractures – none</li> <li>– No walking difficulties.</li> <li>– Independent daily living skills (bathing, dressing and toileting).</li> </ul>

### *Hematopoietic Stem Cell Transplantation*

Hematopoietic stem cell transplantation (HSCT) can lead to increased I2S enzyme activity, obviating the need for ERT. However, experts do not typically recommend HSCT as the first line of treatment because of lack of clear benefit on neurological outcomes and the risk of mortality. A recently published abstract describes 36 subjects in the HOS from 2018 who received HSCT, of whom 13 died.<sup>58</sup>

One study in Japan described 26 subjects with MPS II who underwent HSCT, with a five-year survival rate from 1990-2003 of 12.5%.<sup>59</sup> Although there was a decrease in urinary GAGs, the heterogeneity of the study population, treatment, and timing of outcomes precludes further analysis. A subsequent report suggested that there was a delayed decrease in the ability of

individuals to complete activities of daily life for subjects receiving early HSCT versus early ERT or later ERT.<sup>57</sup> However, there are many confounders that limit this analysis. Another report from Japan with overlapping subjects found that growth was similar for 18 subjects who received HSCT, 6 of whom also received ERT, compared to those who were treated with ERT alone.<sup>60</sup> Insufficient information is available to further explore the potential benefits of HSCT or HSCT and ERT by age.

A case series of three subjects describes a subject diagnosed at 16 months of age who received ERT and then HSCT at 22 months. At nearly 6 years of age, the report states, “His regular yearly check-ups...have shown unrefined and immature, nonetheless qualitatively normal motor skills. There is still a developmental cognitive and speech delay; he is hyperactive and has a short attention span.”<sup>61</sup> The somatic manifestations were not described. Another case report describes a subject diagnosed prenatally and transplanted at 70 days of age who demonstrated normal growth, mild dysostosis multiplex, and hearing loss with an IQ of 47.<sup>62</sup>

#### *Intrathecal and Intraventricular Idursulfase*

Because idursulfase does not significantly cross the blood-brain barrier, the role of delivery of ERT directly to the CNS, either intrathecally or intraventricularly, for individuals with severe MPS II is an active area of investigation. It is currently not the standard of care. A 100-week open-label study of intraventricular idursulfase enrolled 6 subjects with a mean age of diagnosis of 28 months already treated with intravenous idursulfase and compared outcomes to 13 who received only intravenous idursulfase (using idursulfase beta, brand name Hunterase, GC Pharma).<sup>63</sup> The primary outcome was reduction of cerebral spinal fluid (CSF) heparan sulfate concentration. Five subjects had >50% reduction. By the end of the study, there was an average 5.1 month difference in the developmental assessment of those in the study compared to the control population; however, there was significant heterogeneity.

Another report described 34 subjects treated with intrathecal and intravenous idursulfase for 52 weeks who had a 74% reduction from baseline in CSF GAG levels but similar improvement in scores on measures of cognitive and behavioral assessments compared to 14 subjects receiving intravenous idursulfase only.<sup>64</sup> In contrast, another study found that among 32 patients with neuronopathic MPS II who received intrathecal (IT) and intravenous idursulfase, 61% achieved independent toileting compared with 22% of 54 intravenous-only subjects.<sup>65</sup> Another recent abstract describes 6 sibling pairs and one set of three siblings in which the younger siblings received ERT before 1 year of age and some of the subjects were also treated with ERT intrathecally.<sup>66</sup> The abstract states, “Overall, idursulfase-IT treatment was generally associated with stabilization of cognitive function, and in some individuals, earlier idursulfase-IT treatment was associated with better cognitive outcomes.” Insufficient information was provided to further explore the potential benefits of early vs. later treatment.

#### *Pabinafusp Alfa*

A phase I/II study in Japan,<sup>67</sup> phase II study in Brazil,<sup>68</sup> Phase II/III study in Japan,<sup>69</sup> and follow-up in one subject up to 104 weeks<sup>70</sup> have found that pabinafusp reduces CSF GAG levels. A 26-week phase 2 trial of pabinafusp alfa in 19 subjects with a mean age of 13.3 years, of whom 14 had the severe phenotype, focused on establishing dose.<sup>68</sup> No serious adverse events were reported. Hepatosplenomegaly improved in all patients who had not previously received ERT (n=8) and remained stable in most who had. Cardiac function and structure was stable over the

study period. The study was too brief to establish impact on neurological outcomes but the study noted that receptive language and play and leisure time improved for more than half of the subjects. Another study of 28 subjects with a mean age of 8.6 years treated for 52 weeks found that among 20 with severe MPS II, 11 maintained similar age-equivalent scores (e.g., within 3 months of their age equivalence, and 2 improved).<sup>71</sup> Studies are needed to determine whether early treatment reduces long-term intellectual disability.

### *Gene Therapy*

Gene therapy is under investigation. RGX-121, developed by RegenXBio, uses an AAV9 vector to deliver the *IDS* gene. Preliminary results presented in abstract form from the first study of RGX-121 gene therapy describes 8 subjects 4 months to 5 years of age with a severe MPS II phenotype who received a one-time infusion into the cisterna magna or intraventricular infusion of RGX-121 and were followed for between 24 and 104 weeks.<sup>72</sup> Three subjects continue with weekly ERT, 2 have discontinued, and 1 subject has not received ERT. Although the CSF heparan sulfate has decreased, it is too early to make conclusions regarding neurodevelopmental outcomes. No adverse drug events were reported.

### **Treatment Summary**

- Idursulfase treats the somatic component of MPS II (e.g., heart, liver, and spleen involvement, joint mobility) and is associated with decreased risk of mortality by adulthood. Idursulfase does not directly treat the CNS aspects of the disease.
- Idursulfase is generally well tolerated. Some subjects require premedication. There is a risk of developing antibodies, but the evidence does not suggest that this significantly impairs the effectiveness of treatment.
- No prospective studies were identified comparing ERT in the first year of life to later. Sibling studies provide indirect evidence of treatment benefit.
- Novel approaches (e.g., intraventricular or IT) of ERT delivery and newer therapies (e.g., pabinafusp alfa) may target the neurological aspects of severe MPS II.
- HSCT is associated with a significant risk of mortality and does not seem to be superior to idursulfase. However, individuals treated with HSCT might be able to avoid the need for ERT infusions.
- Insufficient evidence is available regarding gene therapy.



### **3 ESTIMATED POPULATION IMPACT OF NEWBORN SCREENING FOR MUCOPOLYSACCHARIDOSIS TYPE II**

This aspect of the review answers the question “What would be the impact of newborn screening at the population level if MPS II newborn screening were adopted by all newborn screening programs in the United States compared to clinical case detection in the absence of MPS II newborn screening?”

#### **Overview of Process**

##### **Evidence Evaluation and Methods Workgroup**

In April 2011, an Evidence Evaluation and Methods Workgroup met to consider the methods and used by the external ERG for the Secretary of Health and Human Services’ ACHDNC. One of the recommendations from this group was to incorporate the application of decision analysis into the evidence review process. An April 2012 publication<sup>73</sup> coauthored by some of the workgroup members noted that a decision analytic model “could provide an estimate of the range of cases prevented, deaths prevented, and/or number of children requiring treatment, as well as other health outcomes, for universal screening compared to clinical ascertainment.” Since the recommendations were made, decision analytic modeling has been used as part of the evidence review process for hyperbilirubinemia, Pompe disease, mucopolysaccharidosis type I disease (MPS I), X-linked adrenoleukodystrophy (X-ALD) and spinal muscular atrophy (SMA). MPS II is the sixth condition to incorporate decision analytic modeling into the evidence review process.

##### **Objectives of Decision Analysis**

Decision analysis is a systematic approach to decision making under conditions of uncertainty that has been applied to clinical and public health problems.<sup>74</sup> Decision analytic models can be used to simulate randomized clinical trials for new health interventions, to project beyond the clinical trial time frame, or to compare treatment protocols not directly compared in head-to-head trials. The decision analytic approach allows the decision maker to identify which alternative is expected to yield the most health benefit. It can also allow researchers to characterize the uncertainty associated with projections of clinical and economic outcomes over the long-term,<sup>75</sup> which is important given the lack of long-term outcomes data for most conditions considered for newborn screening.

A decision analytic model (or decision tree) defines the set of alternatives and short- and long-term outcomes associated with each alternative. In the application to screening for MPS II, this approach was anticipated to aid in the estimation of the range of screening outcomes that could be expected for universal newborn screening of MPS II compared with clinical identification.

##### **Applying Decision Analysis to Screening for MPS II**

Published literature for rare disorders such as MPS II is very limited with respect to data for prevalence, natural history, and response to treatment. For this review, we used data from Missouri and Illinois newborn screening programs and additional published and unpublished data. Through modeling, we aim to supplement the evidence base identified through the systematic review by providing projections of key screening outcomes at the population level for newborn screening compared with clinical identification. This process also highlights evidence gaps and areas with the most uncertainty.

### **Expert Panel Meeting Process**

Clinical and scientific experts in the screening and treatment of MPS II were identified and invited to serve on the TEP (see Table 1). TEP members were asked to provide input on the design and assumptions of the decision analysis model. A series of three TEP meetings (see Table 8) were conducted to identify sources for input probabilities for each outcome in the model; to provide feedback on the structure of the initial and revised decision analytic models, including the relevant timeframe for key outcomes; and to develop assumptions where little or no data were available. All meetings were conducted via webinar. TEP participants received a discussion guide that included background information, a schematic of the model structure, proposed data inputs, and proposed modeling inputs for discussion by the group. The identification of data sources and the development of a decision analytic model is typically an iterative process.

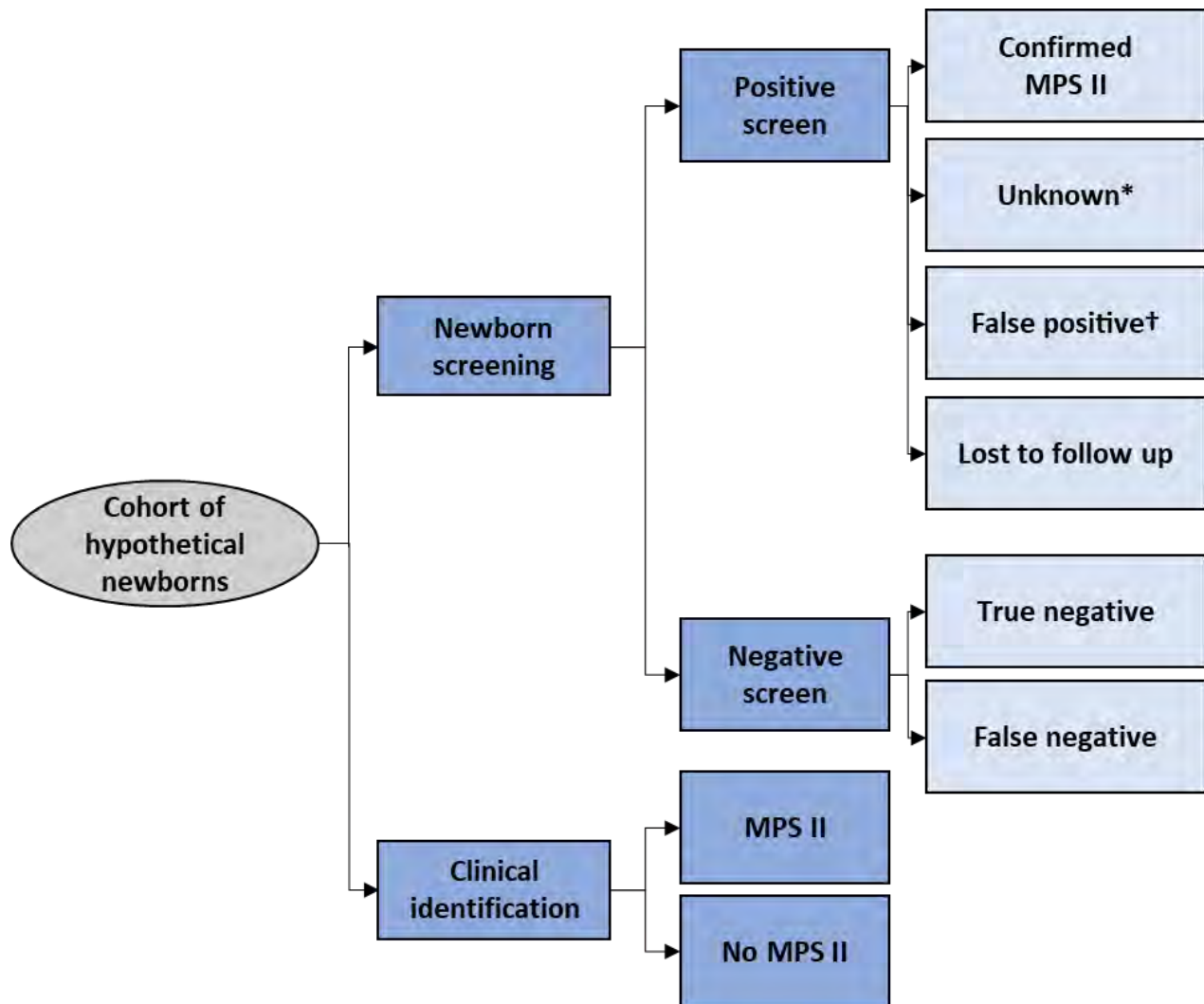
**Table 8. Timeline of Decision Analytic Modeling for MPS II Disease Screening**

<b>Date</b>	<b>Milestone</b>
May 2021	MPS II disease nominated for addition to uniform newborn screening panel; referred to external ERG
July 2021	TEP meeting #1
August 2021	Initial development of decision analytic model to evaluate newborn screening for MPS II disease
September 2021	TEP meeting #2 – review model structure and preliminary evidence review summary
January 2022	TEP meeting #3 – review revised model structure, input assumptions, and preliminary model output
February 2022	Final MPS II evidence review report and decision analysis findings presented to ACHDNC

### **Methods**

An initial decision analysis model was developed concurrently with the evidence review process. The initial model was reviewed with the expert panel in September 2021. A schematic of the final MPS II newborn screening decision model is shown in Figure 1.

Figure 1. MPS II Model Schematic



\*Includes patients with no diagnosis but still being followed

†Includes patients without MPS II and those with biochemical pseudodeficiencies

The key features of the decision analytic model are as follows:

- Target population: Annual newborn cohort for the United States (i.e., 3.6 million newborns).
- Interventions: Universal newborn screening compared with diagnosis through clinical identification.
- Timeframe: ~6 months for newborn screening; lifetime for clinical identification.
- Key endpoints: Screening outcomes (positive screens, confirmed MPS II, cases with no diagnosis but still being followed, false positives (including cases of biochemical pseudodeficiency), and cases of clinically identified MPS II.

Parameter inputs were based on published and unpublished data. The model structure and parameter estimates were revised following each TEP meeting based on additional data sources

identified and supplemented by expert opinion in cases where no data was available. The final set of parameter inputs and associated ranges for the analysis is shown in Table 10.

**Overall Approach**

The model estimates outcomes for two identical cohorts of newborns for MPS II, one cohort receives newborn screening for MPS II and one cohort does not. The key endpoint is number of cases of confirmed MPS II. The model also estimates screening outcomes. Each parameter in the model is defined with a point estimate and a range reflecting plausible estimates. The model was programmed using Treeage Pro Healthcare 2021 R2.1 (Williamstown, MA).

The evidence base on natural history and treatment effectiveness was insufficient to support the modeling of longer-term outcomes for individuals with MPS II. The evidence review identified substantial heterogeneity in reported outcome measures, which was made more complex by the lack of standardized key markers of disease progression. Without quantitative evidence of additional benefits associated with earlier diagnosis and treatment, the modeling of long-term outcomes was not feasible.

Previous decision analytic models for the evidence review process have been able to project outcomes at least through infancy. Since this could not be done for MPS II, two systematic appraisals were conducted to inform future research activities to collect the necessary data for outcome modeling. These included a review of outcome measures included in clinical trials or observational studies of MPS II, and study designs of key effectiveness studies from previous condition reviews.

**Key Assumptions**

As described in the SER, the birth prevalence of MPS II in the United States is unknown. The likely range is from 0.13 to 2.16 per 100,000 births, with a midpoint of 0.67 per 100,000 births.

The estimated probability of outcomes from screening including probability and range of having a positive screen, identifying MPS II, identifying cases with diagnostic uncertainty needing follow-up, false positive screens, and cases lost to follow-up were based on data from the Illinois and Missouri newborn screening programs (Table 10).

**Table 9. Estimated Birth Prevalence of MPS II Based on Clinical Case Detection and Newborn Screening**

<b>Description</b>	<b>Most Likely</b>	<b>Range (min-max)</b>	<b>Source</b>
Birth Prevalence of MPS II, clinical identification	0.67 per 100,000 live births	0.13 – 2.16 per 100,000	Published literature on the prevalence of MPS II <sup>†7</sup>
Birth prevalence of MPS II, newborn screening	1.6 per 100,000	1.5 – 1.6 per 100,000*	Illinois and Missouri Newborn Screening Data

\*Minimum and maximum values derived from 95% confidence interval assuming a binomial distribution

**Table 10. Parameter Inputs, Newborn Screening for MPS II**

**a. Summary Data from Illinois and Missouri Newborn Screening Programs**

Category	Missouri		Illinois		Combined	
	n	Incidence (per 100,000)	n	Incidence (per 100,000)	n	Incidence (per 100,000)
Total newborns screened	68,640	-	546,000	-	614,640	-
Positive screen	11	16.0 per 100,000	71	13.0 per 100,000	82	13.3 per 100,000
MPS II after a positive screen	1	1.5 per 100,000	9	1.6 per 100,000	10	1.6 per 100,000
Diagnostic uncertainty leading to follow-up after a positive screen	5	7.3 per 100,000	5	0.9 per 100,000	10	1.6 per 100,000
Positive screen is false	3	4.4 per 100,000	52	9.5 per 100,000	55	8.9 per 100,000
Loss to follow-up after a positive screen	2	2.9 per 100,000	5	0.9 per 100,000	7	1.1 per 100,000

**b. Parameter Inputs**

Probability	Most likely	Range (min-max)	Source
Positive screen	13.3 per 100,000	9.6 – 14.5 per 100,000*	Illinois and Missouri Newborn Screening Data
MPS II after a positive screen	12%** (1.6 per 100,000)	9% - 13%** (1.5 – 1.6 per 100,000)†	
Diagnostic uncertainty leading to follow-up after a positive screen	12% (1.6 per 100,000)	7% - 45% (0.9 – 7.3 per 100,000)†	
Positive screen is false‡	67% (8.9 per 100,000)	27% - 73% (4.4 – 9.5 per 100,000)†	
Loss to follow-up after a positive screen	9% (1.1 per 100,000)	7% - 18% (0.9 – 2.9 per 100,000)†	

\*95% confidence interval derived using binomial distribution.

\*\* Conditional probability given a positive screen, ranges for conditional probability based on IL and MO experiences

† Range represents range of data from Illinois and Missouri screening programs

‡ Includes biochemical pseudodeficiency

## Results

### Projected Cases of MPS II

We projected the annual number of confirmed MPS II cases that would be identified with newborn screening in the United States, with 3.6 million births per year, compared with clinical identification.

Using combined data from the Illinois and Missouri screening programs, the projected number of positive screens referred for follow-up per year is 480 (range: 346-523) each year for a United States newborn cohort of 3.6 million. These newborns would require confirmatory testing. Following confirmatory testing, an estimated 59 (range: 44-61) newborns would be diagnosed with MPS II. The projected number of false positives each year is 322 (range: 131-352) newborns (Table 11). Based on screening experiences in Illinois and Missouri, there would be 41 (range: 34-87) newborns with a positive screen lost to follow-up.

**Table 11. Projected Cases from Newborn Screening for MPS II Compared to Clinical Identification for a Cohort of 3.6 million Children in the United States**

	<b>Newborn Screening</b>	<b>Clinical Identification</b>
Positive screen	480 (346 - 523)	-
MPS II identified	59 (44 - 61)	24 (5 - 78)
Diagnostic uncertainty requiring follow-up	59 (34 - 218)	-
False positive	322 (131 – 352)	-
Lost to follow-up	41 (34 -87)	-

## Systematic Appraisals – Findings and Recommendations for Future Research

### Outcome Measures

A systematic appraisal of 14 clinical trial and observational studies of MPS II identified substantial heterogeneity in outcome measures and underscored the absence of key standardized markers of disease progression. Previous modeling analyses used key markers of disease progression such as death or time to required ventilator-assistance. Table 12 lists the set of outcome measures used in at least 2 MPS II studies. Given the substantial heterogeneity of the outcome measures used, one recommendation from this systematic appraisal for future research would be the development of a core outcomes set for the measurement of disease progression in MPS II for use in clinical trials, observational studies, and patient registries.

**Table 12. Outcome Measures in MPS II Studies**

<b>Outcome or Measure</b>	<b>Clinical Trials (N=5)</b>	<b>Observational Studies (N=9)</b>
Urine GAG level	5	4

Liver and spleen volume/size	5	5
EKG or cardiovascular involvement	3	5
Developmental, cognitive, or functional outcomes	2	7
6MWT	4	1
Pulmonary function	4	1
Neurological status (heterogeneous measures)	0	5
Joint mobility (heterogeneous measures)	4	2
Survival	-	4

### **Study Designs from Previous Evidence Reviews**

A review of the key studies used to estimate the benefits associated with earlier diagnosis and treatment of patients with SMA, X-ALD, and MPS I identified several common elements of study design. Five out of 6 studies utilized the inclusion of a cohort of pre-symptomatic patients, either compared over time in a single-arm study or compared to a cohort of symptomatic patients using retrospective chart review, to measure the effect of earlier diagnosis and treatment.<sup>76-83</sup> Pre-symptomatic patients were typically identified through family testing (e.g., sibling or carrier identification) but also included some patients identified through pilot newborn screening programs. The 6<sup>th</sup> study conducted a prospective cohort study of clinically identified patients with varying ages at treatment initiation.

Future research to better understand MPS II could take advantage of a core outcome set and registry data to compare standardized outcomes at specific ages based on age of diagnosis and treatment initiation.

### **Limitations**

The analysis used a simplified model to evaluate projected screening outcomes for identified cases of MPS II by newborn screening in the United States. Limited data were available for many parameter inputs. Insufficient data were available to project long-term outcomes for MPS II, either through newborn screening or clinical identification. The birth prevalence of MPS II in the United States is unclear, making comparisons of number of identified cases with and without screening to be characterized by substantial uncertainty.

Given the rare nature of newborn screened conditions, data are typically scarce for conditions being considered for addition to the RUSP. Compared with other conditions that have been nominated and considered for addition to the panel, data for the consideration of MPS II were considerably sparser.

### **Summary**

- Newborn screening would identify a greater number of cases of MPS II compared with clinical identification.
- The number of cases requiring follow-up because of diagnostic uncertainty is similar to the number of cases of MPS II diagnosed immediately following newborn screening.
- If cases lost to follow-up had further evaluation, estimates from this model could change.

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- This is the first condition considered by the ACHDNC since the incorporation of decision modeling that there has been insufficient evidence to model any outcomes beyond case identification to quantify the potential benefits of screening.



## 4 ASSESSMENT OF THE PUBLIC HEALTH IMPACT OF NEWBORN SCREENING FOR MUCOPOLYSACCHARIDOSIS TYPE II

In partnership with the ERG, the Association of Public Health Laboratories (APHL) evaluated state newborn screening programs' capability to screen for MPS II according to the Manual of Procedures. The purpose of the public health impact assessment is to assess the readiness and feasibility of NBS programs to implement screening for MPS II. Readiness refers to the ability to adopt MPS II newborn screening into the program's existing panel and is classified as ready (could implement within one year), developmental readiness (could implement within 1 to 3 years), and unprepared (would take more than 3 years). Feasibility is based on the degree to which there is an established and available screening test, a clear approach to diagnostic confirmation, an acceptable treatment plan, and an established approach to long-term follow-up.

The public health system impact assessment focuses on the time that it takes to implement newborn screening for MPS II. However, there are several activities that must take place within a newborn screening program to prepare for implementation that is difficult to capture in this evaluation. This includes obtaining the authority to screen, receiving any necessary legislative agreement, identifying the technology for screening, and ensuring the availability of short-term follow-up resources. Newborn screening programs vary in the steps needed to add a new condition and these steps can add several years to the process of implementation.

### Methods

#### *Survey Administration*

APHL, the ERG, and representatives from state newborn screening programs currently screening for MPS II developed a fact sheet (see Appendix C) to provide baseline knowledge about MPS II newborn screening to survey respondents. The fact sheet provided information on the incidence of MPS II, screening methods, resources and materials needed for screening, workstation capacity, personnel requirements, the process for quality control, the process for reporting screening, the process for short-term follow-up, typical treatments, and summary information about treatment outcomes and costs from programs already screening for MPS II. The screening outcomes included on the factsheet were what was known at the time of the webinar in September 2021; programs provided subsequent updates that were included elsewhere in this report. APHL also hosted a webinar in September 2021 to prepare potential respondents for the survey.

A web-based survey approved by the Office of Management and Budget, was designed to assess readiness and feasibility components to add MPS II onto state NBS panels. The survey was administered to 53 public health programs in the United States via email from September 20 to October 30, 2021. The survey focused on the elements directly related to public health programs and not personal medical care services. The email with the survey link emphasized the importance of working collaboratively with stakeholders in the state (e.g., laboratory experts, follow-up staff, medical specialists, Title V directors, advocates, public health commissioners) to complete the survey. All survey results were submitted directly to APHL for analysis. In October 2021, reminders were sent to survey non-respondents.

#### *Interviews*

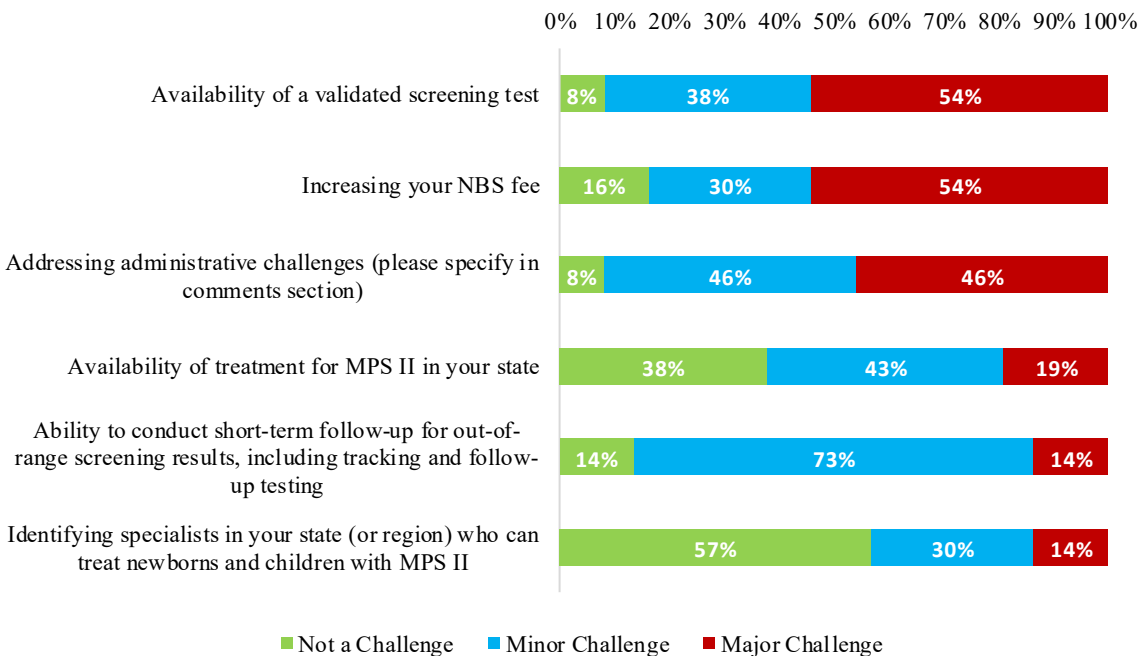
Representatives from newborn screening programs that had begun screening for MPS II or who had a mandate to screen for MPS II were interviewed by APHL. In addition to the newborn screening program designee, relevant stakeholders were encouraged to join in the interview. These interviews focused on better understanding facilitators and barriers to MPS II newborn screening and to collect information on screening outcomes. To provide further context, representatives from three additional newborn screening programs were interviewed to understand how recent changes to the RUSP might impact adoption of MPS II newborn screening.

## Survey Results

Overall, 42 of 53 newborn screening programs (79%) responded to the survey. Thirty-seven programs were included in the analysis and five were excluded due to having a mandate/screening for MPS II and an interview was requested. Among the respondents, 23 were from the public health or newborn screening laboratory, 7 from programs that contract newborn screening laboratory services regionally, 4 came from laboratory where there was a state university laboratory for which there is an intra-state agency agreement, and 3 from programs that contract newborn screening laboratory services commercially.

Most respondents (84-92%) considered the availability of a validated screening test, increasing NBS fees, and addressing administrative challenges to be challenges for implementing MPS II. The distribution of implementation challenges is as follows.

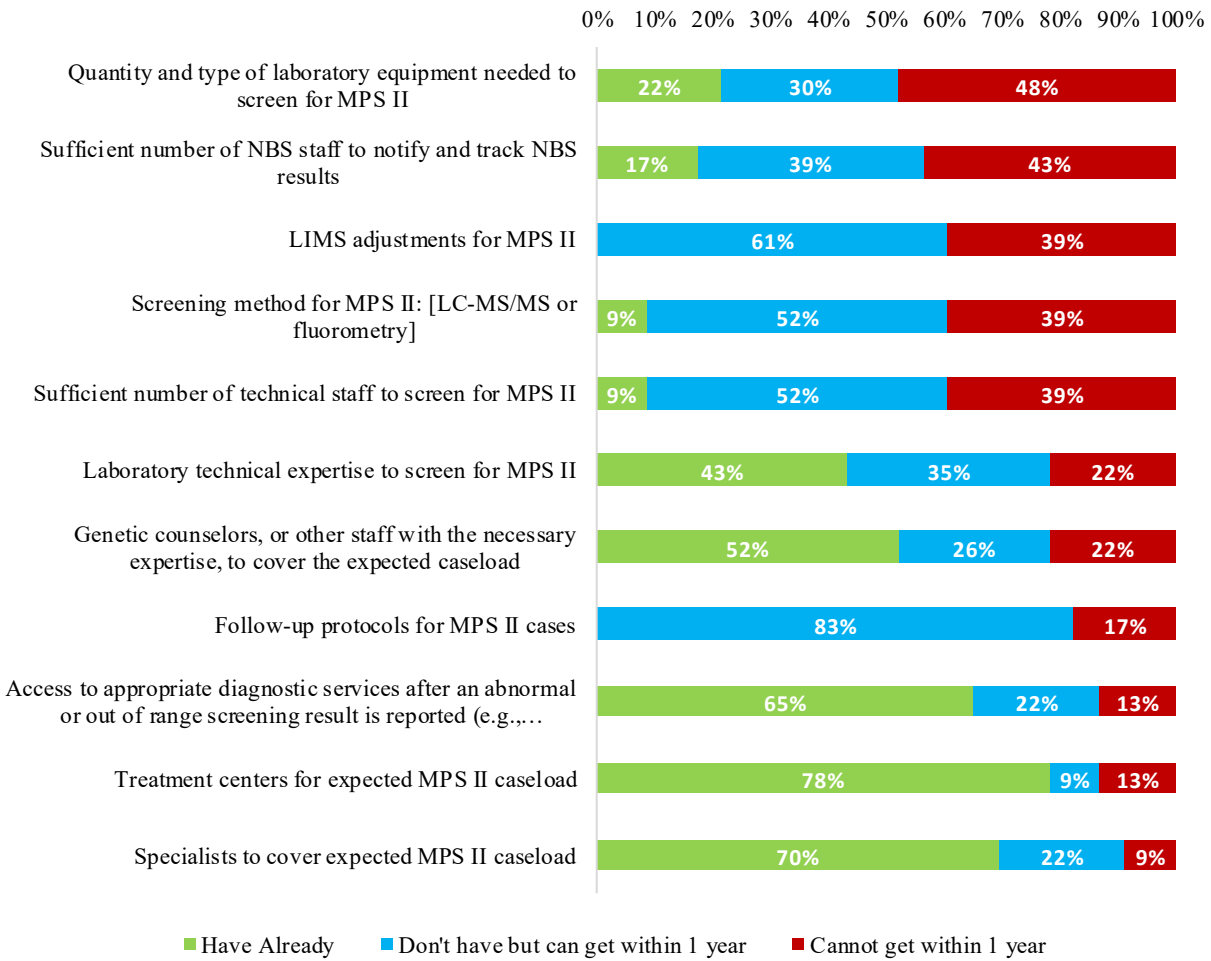
**Figure 2. Reported Barriers to MPS II Newborn Screening**



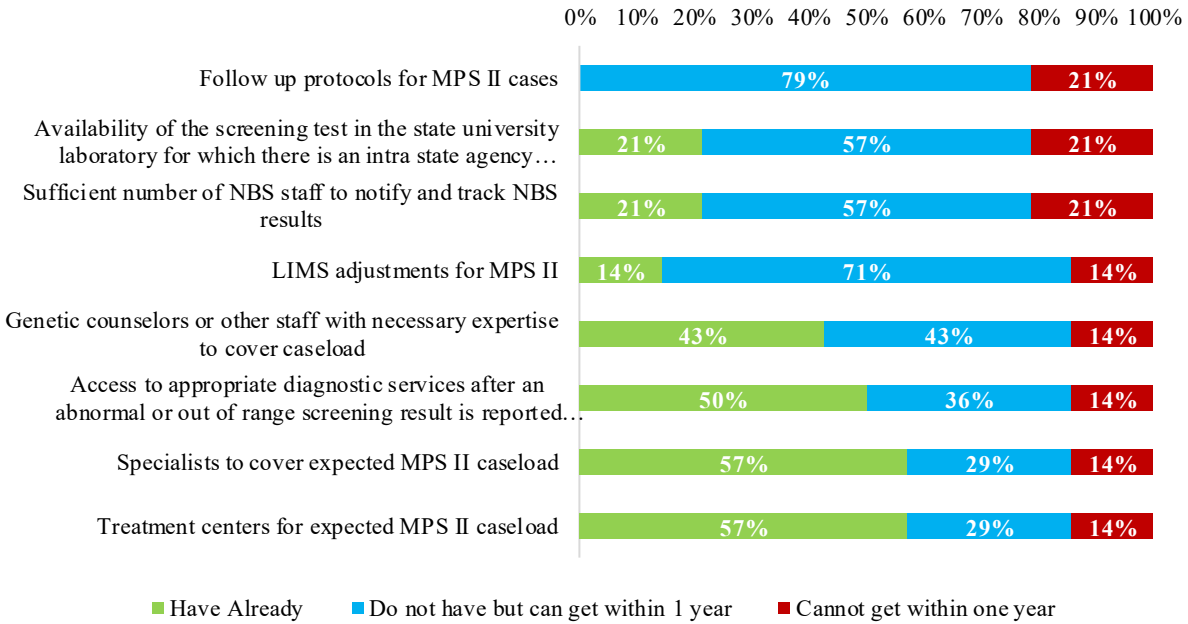
About half of the respondents reported not having the necessary equipment for MPS II newborn screening and that it would take at least a year to obtain it. Some (39%) reported not having sufficient laboratory staff within one year. Although most (>65%) reported having access to diagnostic services, specialists, and treatment center necessary for the potential caseload generated by MPS II newborn screening, nearly half (43%) reported challenges with having

sufficient short-term follow-up staff within a year. Similar to respondents from state public health laboratories, 57% of contracted or state university laboratory respondents indicated that they already had treatment centers and specialists to cover expected MPS II caseload. The following figures illustrate the resources that are available to implement MPS II for NBS programs and those that are needed.

**Figure 3. Resources Needed For Own State’s Public Health or NBS Laboratory**

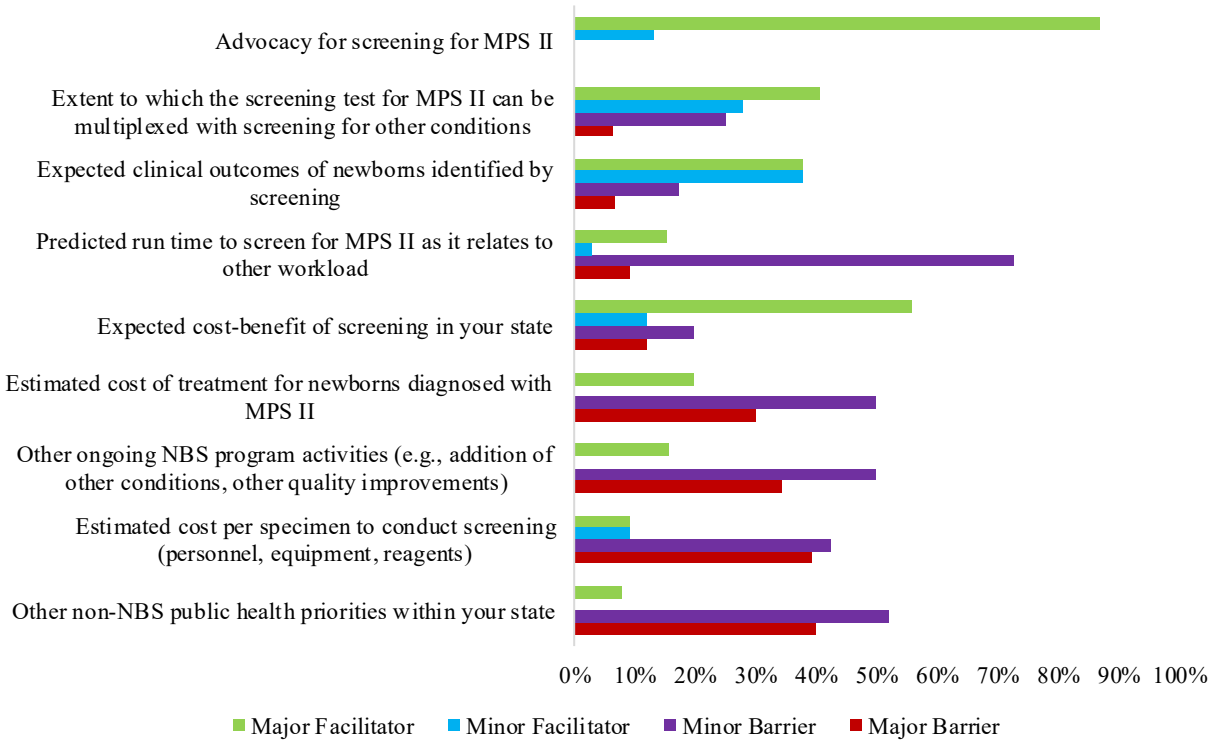


**Figure 4. Resources Needed For Contracted or State University Laboratories with Intrastate Agreement**



Most respondents reported that MPS II newborn screening advocacy and the expected cost-benefit of MPS II screening were potential facilitators. The extent to which MPS II could be multiplexed with other conditions in newborn screening was a barrier for 30%. Other barriers cited by most respondents included the challenge of ongoing newborn screening program activities, the cost per specimen of screening, and other public health priorities other than newborn screening. These barriers and facilitators are summarized in the following figure.

**Figure 5. Barriers and Facilitators of MPS II Newborn Screening**



Among the open-ended responses for barriers to screening, programs most frequently cited staffing issues and competing priorities [COVID, other newborn screening projects, Laboratory Information Management System (LIMS), adding other conditions]. The facilitator that was cited most frequently was obtaining funding and getting fee increases.

Most newborn screening programs (62%) reported that it would take from 1-3 years to implement MPS II newborn screening. Half of the 12 newborn screening programs that screen for the most recent conditions added to the RUSP (Pompe disease, spinal muscular atrophy, and x-linked adrenoleukodystrophy) reported that they could implement MPS II newborn screening in 1-2 years, compared to 13% that of the 15 programs that screen for some of these conditions, and 10% of the programs that do not screen for these conditions. Please see the following two figures for additional detail.

Figure 6. Estimated Time It Would Take to Implement MPS II Screening in Your State

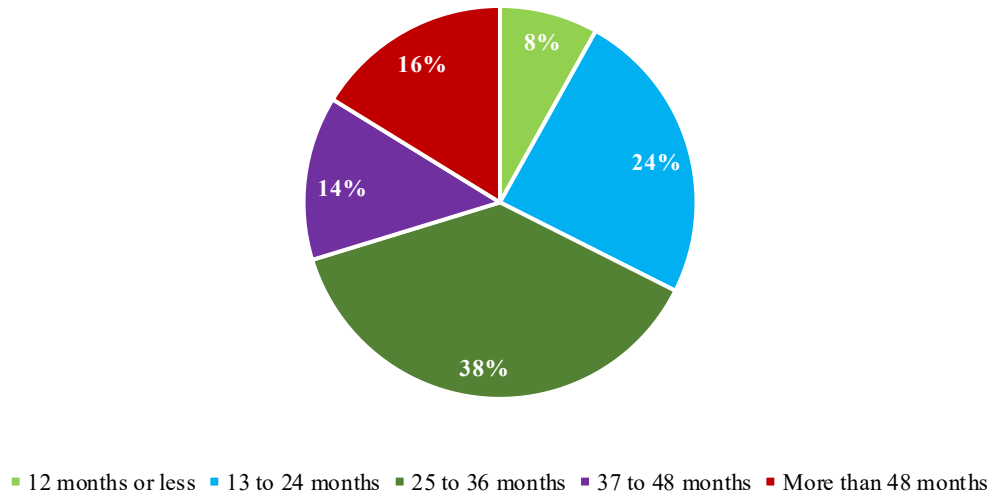
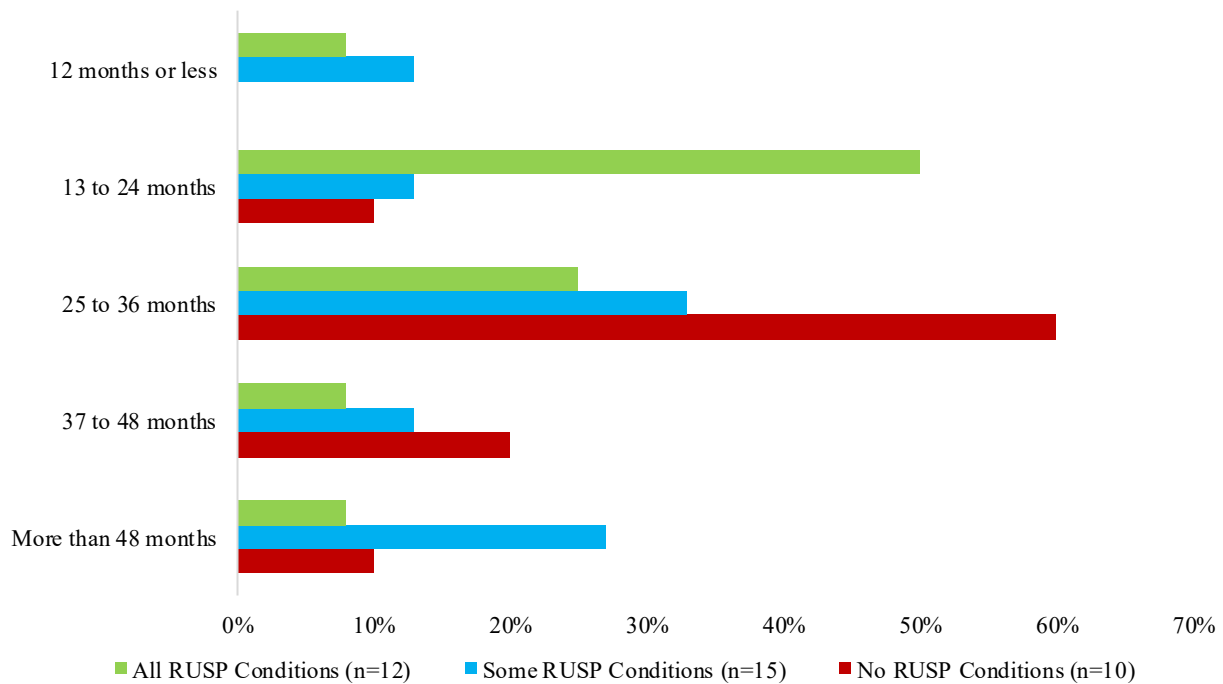


Figure 7. Estimated Time It Would Take to Implement MPS II Screening in Your State Stratified by States that Screen for All of the Latest Four RUSP Conditions, Some of the Latest RUSP Conditions and None of the RUSP Conditions



### Interviews with Programs that Have Universal MPS II Newborn Screening

By December 2021, two state newborn screening programs, Illinois and Missouri, had adopted universal MPS II newborn screening.

Since 2015, Illinois has used tandem mass spectrometry (MS/MS) to screen for several lysosomal storage disorders, including Fabry disease, Gaucher disease, and Niemann-Pick A/B disease, and Krabbe disease (added in 2017) that are not included in the RUSP. The addition of MPS II newborn screening occurred in 2017 and is based on the same method, MS/MS with liquid chromatography. In their process, MPS II can be multiplexed with newborn screening for other LSDs. However, this requires a separate punch with a separate buffer and incubation step prior to injection into the mass spectrometer. The incubation period requires approximately 3 hours if the screening test is to be multiplexed with LSDs other than Krabbe disease newborn screening or up to 17 hours if the MPS II screening test is also multiplexed with Krabbe disease newborn screening. Reported advantages of liquid chromatography as a second-tier assay is its ability to reduce false positives by better separation of analytes. However, liquid chromatography columns require additional staff training and more frequent maintenance than traditional MS/MS.

Missouri began universal screening in 2018 following a mandate in 2017. A fluorometric enzymatic assay is used for MPS II screening. This method was selected because it is the same platform used to screen for other LSDs in the program and because of the small amount of laboratory space required.

Staff from the Illinois and Missouri newborn screening both reported that their assays provided good separation of positive and negative screens. Furthermore, they report that the second-tier GAG test significantly reduced false positives. The ability of being able to multiplex MPS II with other LSDs was seen as an advantage. Additionally, each program reported that MPS II newborn screening did not require much additional staff time. Approximately 0.5 to 1.0 new full-time equivalent laboratory technicians were required for laboratory screening and less than 1 new position was needed for follow-up. Clinical follow-up services were integrated into the existing partnerships already in place.

### **Interviews With Programs Planning for MPS II Newborn Screening**

North Carolina has received funding from the National Institutes of Health for a pilot test of MPS II newborn screening. The Research Triangle Institute is working with the state newborn screening program to develop the screening approach, with a plan to begin sometime in the first half of 2022.

The New York screening program is now evaluating whether to adopt liquid chromatography MS/MS screening for MPS II. In addition, there is a research program, Screen Plus, operating in pilot hospitals in the state that will offer MPS II newborn screening. However, this project is still new.

West Virginia has a new mandate to screen for MPS II but has not begun specific activities yet.

### **Interviews With Programs Not Currently Considering MPS II Newborn Screening**

These three programs highlighted challenges of funding, hiring staff, laboratory space, and updating their LIMS. Although the relative magnitude of these barriers varied, none of the programs were concerned about the challenges of short-term follow-up or access to treatment.

### **Readiness**

The majority of NBS programs (~62%) stated that it would take them more than one year, but less than three years to implement screening for MPS II, which would make them developmentally ready to implement MPS II. Readiness varies greatly across the country,

however, programs that have already added all RUSP conditions to their NBS panels have generally reported being able to complete implementation activities quicker than those that have not.

### **Feasibility**

Not all NBS programs are screening for LSDs, however, those that are may be in a better position to begin screening for MPS II. Although most laboratories use MS/MS to screen for LSDs, some use digital microfluidics to screen for other disorders and so it may make sense for these laboratories to use fluorimetry. Regardless of approach, all programs will need to modify their information systems to accommodate MPS II newborn screening.

### **Summary of Key Findings**

- Illinois and Missouri are the only newborn screening programs with universal MPS II newborn screening. Some MPS II newborn screening pilot work is occurring in North Carolina and New York. West Virginia has a mandate but has not yet begun screening.
- The ability to multiplex MPS II newborn screening is an important facilitator. However, multiplexing requires an additional punch and some additional incubation time.
- Challenges to MPS II newborn screening implementation include issues of funding, staffing, and competing priorities.
- Most newborn screening programs (62%) believed that selecting and validating the MPS II newborn screening test, purchasing equipment, hiring the additional staff, and developing the follow-up protocol would take 1 to 3 years.

### **Newborn Screening Program Costs of Screening for MPS II**

Representatives from the Illinois and Missouri newborn screening programs were interviewed to estimate the costs of MPS II newborn screening. Laboratory testing for MPS II is typically conducted by program staff alongside testing for other LSDs. The Illinois newborn screening program was already screening for other LSDs with MS/MS and Missouri was doing so with a digital microfluidics platform when MPS II newborn screening was adopted. Therefore, it is challenging to break out costs specific to MPS II testing.

The estimates of the additional cost of adding MPS II from the program perspective, above and beyond the fixed costs of an existing NBS program, varied between \$2 and \$6 per infant. The bulk of the estimated costs reflected the costs of equipment, reagents, and added laboratory technician and laboratory scientist time for first-tier screening. Depending on the technology, volume of specimens, and configuration, one additional full-time equivalent (FTE) technician may be required. If new equipment is required, costs may be toward the upper end of this range of costs. The frequency of positive first-tier results that require further testing varies across programs, depending in part on cutoff values. Second-tier GAG testing performed at an outside laboratory may cost \$120 per specimen, inclusive of transportation. However, because of low positive first-tier screening rate, this cost spread across all screened newborns is low. The same is true of short-term follow-up cost. The need to modify a newborn screening program's LIMS, can be an important fixed cost of implementing MPS II newborn screening.



## Appendix A. SYSTEMATIC EVIDENCE REVIEW TECHNICAL METHODS

### Literature Search

The following tables list the search terms for each of the four databases that were queried to identify articles for the systematic evidence review. The initial literature search was conducted for references published from January 1, 2001 to June 10, 2021, and a bridge search was conducted to update the references with publications from June 10, 2021 through January 1, 2022 (publications through December 31, 2021).

#### PubMed

Set	Terms	1/1/01-6/10/21	6/10/21-1/1/22
#1	(((((Mucopolysaccharidosis II[MeSH Terms]) OR (Mucopolysaccharidosis type II) OR (MPS II) OR (Hunter Syndrome)) OR (iduronate-2-sulfatase deficiency)) OR (I2S deficiency)) OR (idursulfase)) OR (idursulfase[Supplementary Concept])		
#2	English, Humans, 2001-present		
#3	#1 AND #2	2088	64

#### EMBASE

Set	Terms	1/1/01-6/10/21	6/10/21-1/1/22
#1	'mucopolysaccharidosis type ii' OR 'mps ii' OR 'hunter syndrome'/exp OR 'hunter syndrome' OR 'hunter`s syndrome' OR 'hunters syndrome' OR 'hurler hunter syndrome' OR 'glossitis, hunter' OR 'hunter disease' OR 'hunter glossitis' OR 'hunter hurler disease' OR 'hunter hurler syndrome' OR 'hurler hunter disease' OR 'mckusick 30990' OR 'mucopolysaccharidosis 2' OR 'mucopolysaccharidosis ii' OR 'mucopolysaccharidosis type 2' OR 'mucopolysaccharidosis type ii' OR 'iduronate-2-sulfatase deficiency' OR 'i2s deficiency' OR idursulfase		
#2	Limits: (2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py)		
#3	#1 AND #2	2240	84

**CINAHL**

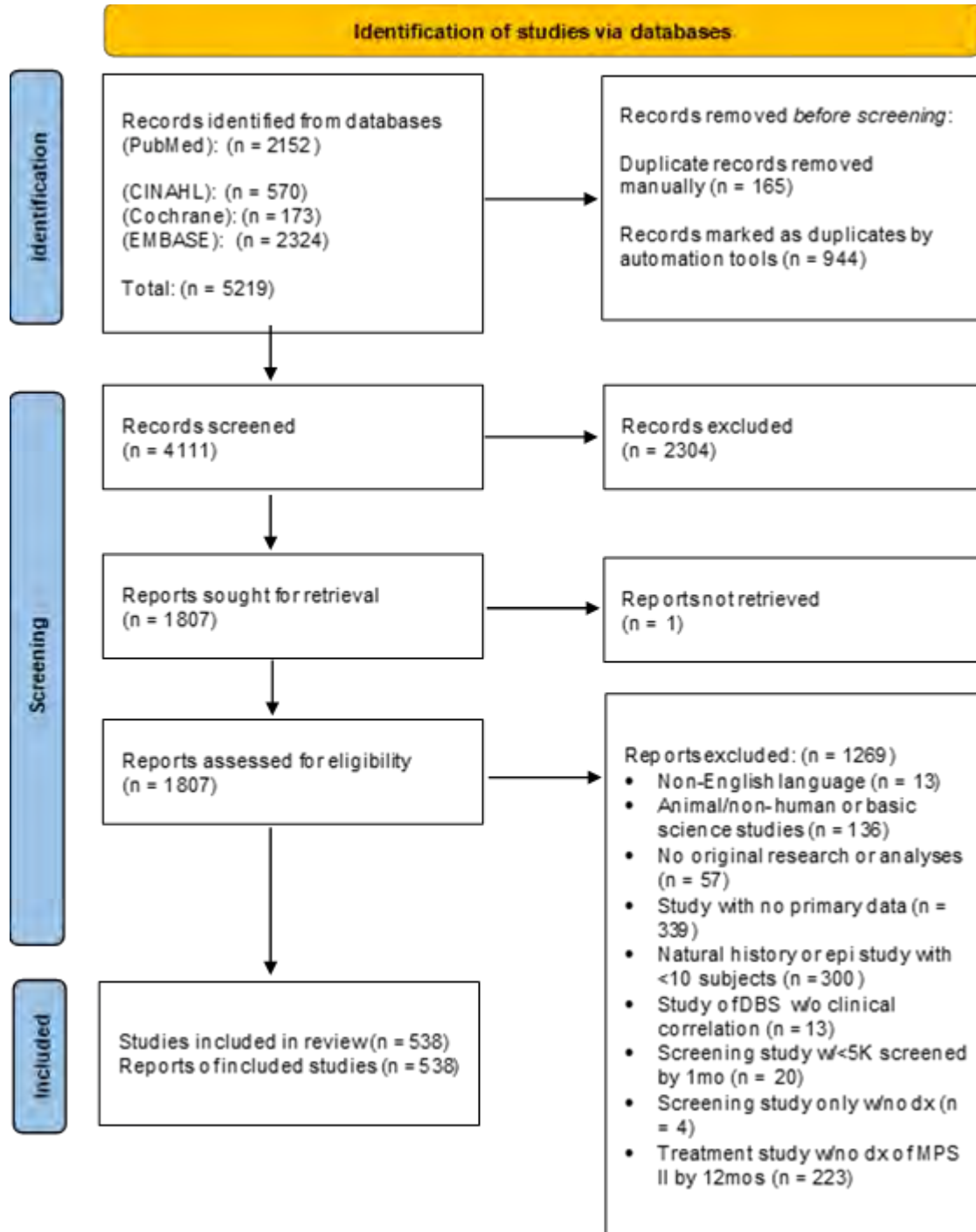
Set	Terms	1/1/01-6/10/21	6/10/21-1/1/22
#1	'mucopolysaccharidosis type ii' OR 'mps ii' OR 'hunter syndrome' OR 'iduronate-2-sulfatase deficiency' OR 'i2s deficiency' OR 'idursulfase'		
#2	Limits: 2001-present, English		
#3	#1 AND #2	544	26

**Cochrane Library**

Set	Terms	1/1/01-6/10/21	6/10/21-1/1/22
#1	'mucopolysaccharidosis type ii' OR 'mps ii' OR 'hunter syndrome' OR 'iduronate-2-sulfatase deficiency' OR 'i2s deficiency' OR 'idursulfase' (all additional word variations searched)	173	0

The following figure describes the process leading to the articles included in this review.

**Figure 8. Identification of Studies Via Databases**



### **Quality Assessment of Screening and Treatment Reports**

Following the methods for developing reports for the ACHDNC, the risk of bias was assessed for the published reports of MPS II newborn screening in the United States and for published reports comparing treatment with idursulfase in the first year of life versus treatment that was begun later based on clinical identification.

#### *Screening Studies*

A modified version of the QUADAS-2 was used to assess the risk of bias for screening studies.<sup>84</sup> This assessed the risk of bias related to newborn selection, standard use of a screening test, standard application of a reference standard, and the appropriate flow and timing of screening.

**Burton BK, Hoganson GE, Fleischer J, Grange DK, Braddock SR, Hickey R, Hitchins L, Groepper D, Christensen KM, Kirby A, Moody C, Shryock H, Ashbaugh L, Shao R, Basheeruddin K. Population-Based Newborn Screening for Mucopolysaccharidosis Type II in Illinois: The First Year Experience. J Pediatr. 2019 Nov;214:165-167.e1.**

The risk of bias of this report is low. Consecutive newborns were screened with a well-defined screening test, standard tests were used to establish the diagnosis, and the flow and timing of screening was appropriate for newborn screening.

**Burton BK, Hickey R, Hitchins L. Newborn screening for mucopolysaccharidosis type II in Illinois: An update. International Journal of Neonatal Screening. 2020;6(3).**

The risk of bias of this report is low. Consecutive newborns were screened with a well-defined screening test, standard tests were used to establish the diagnosis, and the flow and timing of screening was appropriate for newborn screening.

**Bilyeu H. WJ, Vermette L., Klug T. Validation and Implementation of a Highly Sensitive and Efficient Newborn Screening Assay for Mucopolysaccharidosis Type II. International Journal of Neonatal Screening. 2020;6(4):79.**

The risk of bias of this report is low. Consecutive newborns were screened with a well-defined screening test, standard tests were used to establish the diagnosis, and the flow and timing of screening was appropriate for newborn screening. The prospective assessment of newborn screening focuses on the number of samples tested, not individual newborns. However, outcomes of screening are reported based on the number of newborns referred and identified with MPS II.

#### *Treatment Studies*

A modified version of the National Heart, Lung, and Blood Institute (NHLBI) study quality assessment tools were used to evaluate case series. Although sibling studies are sometimes referred to as case-control studies, these are more properly considered well-matched case series, because in case-control studies cases and controls are distinguished by outcomes, not exposure. Findings from the HOS were also evaluated as a large case series. Cohort studies have clearly defined population-level entry criteria. In contrast, the HOS is a volunteer registry with variable duration of subject participation and some subjects have been retrospectively added.

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In general, case series have risk of bias related to selective identification, measurement bias because assessment is often not blinded, and confounding because of the many uncontrolled factors related to treatment and outcomes. Sibling studies provide a more natural comparator and can minimize confounding. The following table outlines the risk of bias (green – adequately addressed; yellow – uncertain, black – not relevant). Because of the risk of bias, no overall assignment is provided. However, the comments provide a qualitative assessment.

**Table 13. Risk of Bias in Case Series**

Reference	Objective Clear	Case Definition	Consecutive Cases	Comparable Subjects	Intervention Clear	Outcomes Defined	Follow-up Adequate	Results Clear	Comments
Grant et al. (2022) <sup>56</sup>									Well-described sibling report, with detailed outcomes at standardized ages.
Lampe et al. (2014) <sup>49</sup>									Multi-institutional case report. It is unclear if consecutive cases were selected.
Muenzer et al. (2021) <sup>50</sup>									Detailed report from the HOS. There is a risk that consecutive cases were not enrolled in the HOS. The length of follow-up time was variable by outcome and outcomes are not consistently reported at standardized ages.
Tomita (2021) <sup>53</sup>									Sibling report with standardized outcomes.
Tylki-Szmanska (2012) <sup>52</sup>									Sibling report with standardized outcomes.

## Appendix B. PUBLIC HEALTH SYSTEM IMPACT

### Fact Sheet

This fact sheet provides newborn screening programs with background information on MPS II so they can complete a public health impact assessment survey that evaluates their program's readiness and feasibility to add MPS II onto their newborn screening panels. The factsheet discusses background information pertaining to the condition, screening methods, resources/materials, screening results, personnel requirements, costs, short-term follow up, and treatment for MPS II. Contact Jelili Ojodu (jelili.ojodu@aphl.org) for more information.

Condition	MPS II
<b>Description</b>	Mucopolysaccharidosis Type II (MPS II), also referred to as Hunter syndrome, is an X-linked lysosomal storage disorder (LSD) caused by the deficiency of the enzyme iduronate-2-sulfatase (I2S), which is needed to break down complex sugars, glycosaminoglycans (GAGs) within the lysosomes. MPS II is caused by mutations in the <i>IDS</i> gene. Phenotype is often difficult to predict at diagnosis due to many private mutations. The severe form is characterized by progressive intellectual disability, the development of characteristic facial features, progressive joint stiffness that can limit mobility, and progressive involvement of the liver, spleen, and heart. The attenuated form is not associated with the same degree of intellectual disability but the other features can be similar.
<b>Expected Incidence</b>	Based on clinical detection, MPS II is present in 0.2-2.5 per 100,000 live births Screening detections to date are <sup>1</sup> : Illinois: ~1.7/100,000 live births Missouri: ~1.5/100,000 live births

First-Tier Screening Methods	
<b>Screening Strategy and Markers</b>	First tier screen can be done by either a fluorometric assay or liquid chromatography tandem mass spectrometry (LC-MS/MS) or flow injection MS/MS to measure I2S activity. MPS II may be multiplexed with some other LSDs using MS/MS, but an independent punch is required because MPS II testing requires a separate buffer and separate incubation step prior to injection. Flow injection MS/MS can accommodate multiplexing MPS I with some of the LSDs including Pompe. However, in order to multiplex MPS II with other LSDs such as Gaucher, Fabry, Krabbe, LC-MS/MS is required.

### Second-Tier Screening Methods

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<b>Screening Strategy and Markers</b>	Second-tier testing is based on measuring GAGs, which can be done on the dried-blood spot (DBS), and can help rule-out pseudodeficiency. Sequencing on the DBS may be helpful if a known mutation is identified. Second-tier testing is typically not performed at the NBS laboratory. <sup>1</sup>
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<b>Resources and Materials</b>
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<b>Minimum Instrumentation, Equipment and Requirements Necessary to Process 100,000 Specimens Annually (Includes Conventional Redundancies)</b>	First tier screen entails either fluorometric assay or MS/MS to evaluate I2S activity. If MS/MS is used, the assay can be multiplexed with other LSDs that are not MPS I/II markers. <sup>1</sup>
<b>Equipment Suppliers and Availability of Kits, Reagents and Consumables</b>	Fluorometry is not FDA approved and requires a laboratory developed test. Baebies supplies FDA-registered analyte specific reagents (ASRs). <sup>1</sup>  MS/MS is ideally performed with an LC column for better separation of analytes. <sup>1</sup>

<b>Workstation Resources and Capacity</b>
---

<b>Instrument Time</b>	2 hour incubation (fluorometric assay). <sup>1,2</sup>  3 hour incubation and 24 hours to run the assay after injection when screening is combined with other LSDs. <sup>1</sup>
<b>Maximum Number of Specimens to Be Analyzed at One Workstation In A Day</b>	Missouri can run 1440 samples/day with one dried-blood spot per newborn. <sup>1</sup>  Illinois can run 700 samples/day using one dried-blood spot per infant (multiplexed for multiple LSDs). <sup>1</sup>
<b>Minimum Space Requirements (Supporting Equipment Not Included)</b>	For fluorometry, the footprint is small and requires 35 sq ft of countertop space. <sup>1,2</sup>  For LC-MS/MS, two LC-MS/MS devices would be needed to have one as a back-up. <sup>1</sup>

<b>Personnel Requirements</b>
-------------------------------

<b>FTE Needed to Process 100,000 Specimens Annually</b>	The laboratory requires between 0.5 and 1 FTE for either method. <sup>1</sup>  The follow-up requires less than 1 FTE. <sup>1</sup>
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<b>Other Considerations</b>
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<b>LIMs Adjustments</b>	Variable (dependent on vendor)
<b>Training</b>	Laboratory training for LSDs, VOUS, carrier status, and pseudodeficiency reporting if 2 <sup>nd</sup> tier sequencing is conducted. <sup>1</sup>



QC and Reported Screening Results	
<b>Availability of Quality-Control Specimens</b>	QC specimens available from CDC. <sup>1</sup>
<b>Reported Rate of Repeat Requests (Independent Specimen)</b>	Many NBS programs may not need a borderline category for MPS II due to the assay's excellent separation of normal and positive results. <sup>1,2</sup>
<b>Reported Rate of Second-Tier Test</b>	N/A
<b>Rate of Referrals<sup>1</sup></b>	<b>Missouri</b> ~14/100,000 <b>Illinois</b> ~13/100,000
<b>Reported Outcomes<sup>1</sup></b>	<p><b>Missouri</b> # by type(s): MPS II = 3 in ~200,000 infants screened Carriers = None detected (no females identified to date; protocol/algorithm the same for males and females) False positives = 10 (3 pseudodeficiency; 7 normal) False negatives = None detected</p> <p><b>Illinois</b> # by type(s): MPS II = 8 in 468,470 infants screened (2 verified severe; 6 classification unconfirmed) Carriers = None detected to date False positives = 39 (30 pseudodeficiency; 9 normal) False negatives = None detected</p>

Estimated \$\$ Costs	
<b>Estimated Cost (Total)</b>	Missouri has estimated that it costs ~\$5/infant to test for MPS II using fluorometry. <sup>1</sup>
<b>Estimated Cost to Laboratory of Reagents or FDA-Approved Kit</b>	N/A
<b>Estimated Reagent Rental Cost</b>	N/A
<b>Estimated Personnel Cost To Screen 50,000 to 100,000 Specimens Annually (Follow-Up Not Included)</b>	N/A
<b>Estimated Diagnostic Assay Cost</b>	N/A
<b>Estimated 2<sup>nd</sup> Tier GAG Testing Costs</b>	N/A

Short-Term Follow-Up	
<b>Description</b>	A clinician will repeat the I2S assay to confirm enzyme levels are low and then request urine GAGs. If urine GAGs are not

	elevated, clinician will assume pseudodeficiency or possibly Multiple Sulfatase Deficiency. If urine GAGs are elevated, the clinician will assume MPS II. The clinician will conduct physical exam along with family history, and may sequence the IDS gene. <sup>1</sup>
<b>Case Definition</b>	X-linked lysosomal storage disorder due to the dysfunction of the <i>IDS</i> gene. There are two forms of the disorder: severe and attenuated, with a wide range of phenotypic expression. The attenuated form is not associated with the same degree of intellectual impairment.
<b>Diagnostic Method &amp; Criteria</b>	<ul style="list-style-type: none"> <li>• Low I2S enzyme activity</li> <li>• Elevated plasma/urine GAGS</li> <li>• IDS mutation</li> <li>• Clinical findings</li> <li>• Family history (siblings can have same form of disorder)</li> </ul>
<b>Availability of Diagnostic Testing Laboratories</b>	The diagnostic testing can be performed in a number of laboratories.

<b>Current Treatment(s)</b>	
<b>Description and Current Treatment Guidelines with Clinical Identification</b>	<p>Enzyme replacement therapy (ERT), Elaprase (idursulfase), was approved by the FDA for treatment of individuals with MPS II. Idursulfase does not cross the blood brain barrier. Clinicians recommend early treatment, as damage from MPS II cannot be reversed. ERT is intensive and requires 3-4 hour infusions weekly. Some individuals develop antibodies that can decrease the efficacy of the therapy.<sup>1</sup></p> <p>Stem cell transplantation can replace the missing enzyme but is associated with a greater risk of death and may not reduce the risk of intellectual disability in those with severe disease.</p> <p>Gene therapy and other therapies are in development and being tested.</p>

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**Survey**

The purpose of this survey is to inform the Secretary of Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children (Committee) about states' ability to add newborn screening (NBS) for MPS II using information gathered from most of the state and territorial NBS programs in the U.S. Your input will provide valuable information and aid the deliberations of the Committee.

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Please refer to the MPS II screening factsheet to help you answer the following questions about the ability of your state or territory to add screening for MPS II to your NBS program. Please consult with others, as needed, including laboratory and follow-up staff, medical professionals and specialists, to complete the survey. When unsure about a response, please provide your best estimate. If you were to answer every question, we estimate it will take an average of 10 hours to complete this form.

1. Within the last three years, has your state: *(check all that apply)*
  - Included [condition x] as part of the routine NBS panel? *(end survey)*
  - Planned, implemented, or completed any type of pilot study or pilot evaluation for MPS II? *(end survey)*
  - Issued a mandate or state-level decision to start screening for MPS II? *(end survey)*
  - None of the above *(go to question 2)*
  
2. Which of the following entities provide NBS laboratory services for your state’s NBS program?
  - Your own state’s public health or NBS laboratory
  - A state university laboratory for which there is an intra-state agency agreement
  - A contracted regional NBS laboratory
  - A contracted commercial laboratory
  - Other – please specify: \_\_\_\_\_

NBS programs consider many factors when deciding to add a condition to their NBS panel. The following question asks you to consider, in general, how much the following factors would be an issue in considering adding MPS II to your NBS panel.

3. Please indicate if the following implementation factors for MPS II would present a major challenge, a minor challenge, or would not be a challenge, given the current status of the NBS Program in your state.

Factor	Major Challenge	Minor Challenge	Not a Challenge	Comments
Availability of a validated screening test in your state				
Ability to conduct short-term follow-up for out-of-range screening results, including tracking and follow-up testing				
Identifying specialists in your state (or region) who can treat newborns and children with MPS II				
Availability of treatment for MPS II in your state				
Increasing your NBS fee				
Addressing administrative challenges (please specify in comments section)				

4. Please describe any additional overarching challenges.
-

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For questions 5-7 please assume that MPS II has been authorized for addition to your state’s panel and funds for laboratory testing and follow-up have been made available.

5. The following question considers the various resources needed (e.g. human resources, facilities, etc) by your NBS program in order to implement screening for MPS II.

5.a. Please complete the following table if you answered “your own state’s public health or NBS laboratory” on question #2. If your answer on question #2 was any of the other options, please skip to 5.b.

5.a. Resources Needed	Have Already	Do not have but can get within 1 year	Cannot get within 1 year	Comments
Screening method for MPS II:: fluorometry or MS/MS				
A second-tier screening approach for MPS II: GAG testing				
Quantity and type of laboratory equipment needed to screen for MPS II				
Laboratory technical expertise to screen for MPS II				
Sufficient number of technical staff to screen for MPS II				
LIMS adjustments for MPS II				
Sufficient number of NBS staff to notify and track NBS results				
Access to appropriate diagnostic services after an abnormal or out of range screening result is reported (e.g., diagnostic testing, clinical evaluations)				
Genetic counselors, or other staff with the necessary expertise, to cover the expected caseload				
Specialists to cover expected MPS II caseload				
Treatment centers for expected MPS II caseload				
Follow-up protocols for MPS II cases and carriers				

SKIP PATTERN (respondents fill out either 5.a. or 5.b., but not both)

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5.b. Please complete the following table if you answered “a state university laboratory for which there is an intra-state agency agreement”, “a contracted regional NBS laboratory”, “a contracted commercial laboratory”, or “other – please specify” on question #2.

5.b. Resources Needed	Have Already	Do not have but can get within 1 year	Cannot get within 1 year	Comments
Availability of the screening test in the state university laboratory for which there is an intra-state agency agreement, or contracted regional laboratory, or commercial laboratory				
LIMS adjustments for MPS II				
Sufficient number of NBS staff to notify and track NBS results				
Access to appropriate diagnostic services after an abnormal or out of range screening result is reported (e.g., diagnostic testing, clinical evaluations)				
Genetic counselors, or other staff with the necessary expertise, to cover the expected caseload				
Specialists to cover expected MPS II caseload				
Treatment centers for expected MPS II caseload				
Follow-up protocols for MPS II cases				

6. Please indicate the degree\* to which these factors impede or facilitate your ability to adopt screening for MPS II in your state.

Factor	Major Barrier	Minor Barrier	Minor Facilitator	Major Facilitator	Not Applicable
Predicted run time to screen for MPS II as it relates to other workload					
Extent to which the screening test for MPS II					

can be multiplexed with screening for other conditions					
Other ongoing NBS program activities (e.g., addition of other conditions, other quality improvements)					
Estimated cost per specimen to conduct screening (personnel, equipment, reagents)					
Estimated cost of treatment for newborns diagnosed with MPS II					
Expected clinical outcomes of newborns identified by screening					
Expected cost-benefit of screening in your state					
Advocacy for screening for MPS II					
Other non-NBS public health priorities within your state					

*\*Major barrier- Will prevent testing from being implemented effectively and/or timely.*

*\*Minor barrier- May compromise testing so it is not performed effectively and/or timely.*

*\*Minor facilitator- May allow testing to be done effectively and/or timely.*

*\*Major facilitator- Will allow testing to be done effectively and/or timely.*

7. Please describe any additional factors that impede or facilitate adoption of screening for MPS II in your state.

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8a. What are the most significant barrier(s) to screening for MPS II in your state?

8b. What would most facilitate screening for MPS II in your state?

9. Please estimate the time it would take your NBS program to initiate screening for MPS II in your state (i.e. get authority and funds to screen for MPS II, go through administrative processes,

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meet with your state NBS committees and complete all activities needed to implement and commence screening for all newborns in your state)?

- 12 months or less
- 13 to 24 months
- 25 to 36 months
- 37 to 48 months
- More than 48 months

10. The question above related to the overall timeline. We recognize some of the activities happen in tandem and some cannot begin until a previous activity has been completed. Please estimate the total time needed, in general, for each individual activity listed below within your NBS program. If needed, please consult with laboratory and follow-up staff, medical professionals and specialists, prior to completing the survey.

Please complete the following table if you answered “your own state’s public health or NBS laboratory” on question #2. If your answer on question #2 was any of the other options, please skip to 10.b.

10a.

Activity	12 months or less	13 – 24 months	25 – 36 months	37 to 48 months	> 48 months	Not Applicable	Comment
Obtain authorization to screen for MPS II							
Availability of funds to implement screening for MPS II							
Meet with Advisory committees and other stakeholders							
Obtain and procure equipment for screening for MPS II							
Hire necessary laboratory and follow-up staff							
Select, develop, and validate the screening test within your laboratory IF you are NOT multiplexing							
Select, develop, and validate the screening test							

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within your laboratory IF you ARE multiplexing							
Develop a screening algorithm, follow-up protocols, and train follow up staff							
Set up reporting and results systems for added condition (e.g., LIMS)							
Collaborate with specialists and clinicians in the community to determine which diagnostic tests will be recommended upon identification of an out of range NBS result							
Conduct an internal validation study for MPS II							
Pilot test the screening process within your state, after validation has taken place							
Implement statewide screening for all newborns, including full reporting and follow-up of a normal screens after validation and pilot testing							

SKIP PATTERN (respondents fill out either 10.a. or 10.b., but not both)

10b.

Activity	12 months or less	13 – 24 months	25 – 36 months	37 to 48 months	> 48 months	Not Applicable	Comment
Obtain authorization to screen for MPS II							
Availability of funds to implement screening for MPS II							



Meet with Advisory committees and other stakeholders							
Develop follow-up protocols, and train follow up staff							
Set up reporting and results systems for added condition (e.g., LIMS)							
Collaborate with specialists and clinicians in the community to determine which diagnostic tests will be recommended upon identification of an out of range NBS result							
Add the screening test to the existing outside laboratory contract							
Implement statewide screening for all newborns, including full reporting and follow-up of a bnormal screens after validation and pilot testing							

11. Are there any special considerations regarding MPS II that need to be taken into account when assessing the impact on the public health system? (e.g. variants of unknown significance, pseudodeficiencies, age of onset, access to specialists, access to treatment, cost of treatment, etc) Please describe:

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12. Please share any additional information regarding implementation of NBS for MPS II.

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13. Please provide information about the respondent:

Name:

Phone number:

Email address:

Job title:

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14. Who did you consult with to answer these questions? *Please check all that apply.*
- State NBS laboratory experts
  - Other NBS program staff
  - State NBS advisory board
  - State Title V Director
  - [Condition x] Specialists
  - Primary care providers
  - Advocates within your state for [condition x] screening
  - Others- please specify: \_\_\_\_\_
  - None of the above

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