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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Discretionary Advisory Committee on
Heritable Disorders in Newborns and Children
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April 13, 2015

The Honorable Sylvia Mathews Burwell
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Secretary Burwell:

The Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (Committee) is charged with making systematic evidence-based and peer-reviewed recommendations that include heritable disorders that have the potential to significantly impact public health for which all newborns should be screened.

During the Committee's February 2015 meeting, we reviewed the evidence-based report for the nominated heritable disorder – Mucopolysaccharidosis Type I (MPS I). Based on this report and deliberations of all associated clinical data, testing platforms, available treatments, benefits and harms, and the public health impact assessment, the Committee voted to recommend to you the following:

1. Expand the Recommended Uniform Screening Panel (RUSP) to include the addition of MPS I.
2. Provide federal funding to State newborn screening programs to implement the screening of MPS I, including further defining the most appropriate test platform and laboratory protocol and establishing short and long term follow up procedures.

Mucopolysaccaridosis Type I (MPS I) is an autosomal recessive lysosomal storage disorder (LSD) caused by deficiency of the enzyme α-L-iduronidase (IDUA). Individuals with MPS I are either missing or have insufficient IDUA enzyme activity. These defects prevent the proper recycling process, resulting in the storage of materials in virtually every cell of the body. As a result, cells do not perform properly which leads to progressive damage throughout the body. Specific treatments include enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT).

MPS I affects an estimated 0.54 to 1.85 persons per 100,000 newborns. The manifestations of MPS I can be severe or attenuated, which reflects a spectrum of age of

disease onset, severity and rate of progression. Severe MPS I is the dominant form, and is associated with an early onset of developmental delay followed by developmental regression, cardio-respiratory failure, and obstructive airway disease, with death occurring before the age of 10years. Individuals with attenuated MPS I may also have shortened life span depending on the form and may also suffer from respiratory disease, cloudy corneas, short stature, stiff joints, speech and hearing impairment, heart disease, hyperactivity, depression, and cardiovascular disease. Diagnosis is based on clinical findings, biochemical tests, and mutation analysis.

The Committee deliberated on the net benefits, certainty and feasibility of newborn screening for MPS I, and concluded that there is certainty that newborn screening would have a significant benefit in terms of cognitive outcomes. The benefits of early detection via newborn screening for children with MPS I on overall survival are not known due to small sample size studies and the duration of treatment within the studies. There is also evidence that newborn screening for MPS I is feasible as a component of state newborn screening programs.

Although data indicate that effective laboratory technology is available for newborn screening for MPS I additional research is needed to identify the most appropriate testing platform and protocol. The addition of MPS I to the RUSP will also enable the research to be performed to further examine the impact of early or pre-symptomatic detection and treatment of MPS I. The Committee also recognizes that although it is feasible for States to implement MPS I disease screening, the majority of newborn screening programs are currently unprepared to begin screening and will need a period of at least 3-5 years (based on the findings in the public health impact survey) and funding to obtain the necessary test platform and complete training on the appropriate protocol, as well as to establish treatment referral networks in order for successful implementation to occur.

We hope that early adopter States that are already moving forward with implementing screening for MPS I will be a source of additional evidence to confirm the efficacy of earlier detection from newborn screening compared to clinical diagnosis which occurs after onset of symptoms and provide data on implementation and quality improvement. In addition, the Committee recommends that funding be made available for States to include newborn screening for MPS I. I hope that currently funded newborn screening research projects, such as the NIH/NICHD Newborn Screening Translational Research Network, can be involved with States that decide to implement screening for MPS 1 to help develop evidence based algorithms for short and long term follow-up, and federal agencies such as the Centers for Disease Control and Prevention can provide assistance to develop evidence based approaches for the standardization of testing protocols and laboratory quality procedures.

The Committee strongly believes that screening for MPS I disease will lead to significant net benefits for infants born with this rare condition.

Sincerely yours,

Joseph A. Bocchini, Jr., M.D.
Chairperson

Enclosure:
Report - *Newborn Screening for Mucopolysaccharidosis Type 1 (MPS I): A Systematic Review of Evidence, Report of Final Findings*

cc: Debi Sarkar, M.P.H.
Designated Federal Official
Health Resources and Services Administration

Newborn Screening for Mucopolysaccharidosis Type 1 (MPS I):
A Systematic Review of Evidence
Report of Final Findings
Final Version 1.1

Prepared for:
MATERNAL AND CHILD HEALTH BUREAU

March 16, 2015

By

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We wish to acknowledge and thank Scott Grosse, PhD, Senior Health Economist with the Centers for Disease Control and Prevention, for his contributions throughout this review.

Table of Contents

Introduction

This report was developed to support the U.S. Secretary of Health and Human Services' Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (SDACHDNC) in making recommendations to the Secretary about whether Mucopolysaccharidosis (MPS I) should be added to the recommended uniform screening panel (RUSP). This report includes:

- The systematic evidence review of the potential benefits and harms associated with newborn screening for MPS I compared to usual care based on published and unpublished data;
- The decision-analytic model to estimate upper and lower bounds of impact on population-level health of adding newborn screening for MPS I compared to clinical detection and usual care; and,
- The public health system impact assessment to evaluate feasibility and readiness of states' newborn screening programs to adopt screening for MPS I.

Request for Review

MPS I was initially nominated to the SACHDNC for inclusion in the RUSP in May 2012. At that time, the Committee requested a systematic review of the potential benefits and harms of screening for MPS I disease, specifically to follow the final report of Pompe disease (May 2013). Following discussion of the Pompe report, the Advisory Committee placed the MPS I review on hold to establish and convene an Expert Advisory Committee to develop formal Public Health System Impact assessment procedures (April 2014).

Overview of Report

The condition review includes three major components: 1. Systematic evidence review, 2. Decision Model of Population-level Benefits, 3. Public Health System Impact Assessment. The following document includes Part I, Part II, and Part III, which report on findings from each of these components. These component report Parts follow an overall brief executive summary. Data tables are found in the Supplement at the end of this document.

Brief Executive Summary

Mucopolysaccaridosis Type I (MPS I) is an autosomal recessive lysosomal storage disorder (LSD) affecting an estimated 0.54 to 1.85 cases per 100,000 newborns. Although there are overlapping phenotypes, MPS I can be generally classified into two forms, severe and attenuated, based on the age of onset and severity. Severe MPS I is the dominant form, and is associated with multi-system involvement, including progressive and rapid developmental delay. Specific treatments include enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT). ERT is the mainstay of treatment for the attenuated form. However, HSCT, which allows for endogenous production of the missing enzyme, is used in the severe form because intravenous ERT does not penetrate the blood-brain barrier. MPS I can be screened for in dried-blood spots, and two States have implemented pilot screening programs following legislative mandates to screen for MPS I. One other State with a legislative mandate has not yet begun screening. Screening is complicated by the detection of pseudodeficiency. Diagnosis is based on clinical findings, additional biochemical tests, and mutation analysis. In some cases, it can be difficult at the time of a positive screen to determine the form of MPS I because there are many private mutations and clinical signs or symptoms might not be present in early infancy. Few data are available regarding the early or presymptomatic detection and treatment of MPS I on patient-level outcomes. Observational data suggest that detection through screening compared to usual clinical case detection will not alter mortality in the first three- years of life. However, indirect observational data suggest that there may be an impact on cognitive development. Because severe MPS I leads to progressive neurocognitive impairment, earlier HSCT may halt this progression sooner and lead to improved outcomes. The magnitude of this effect is unclear. The use of ERT prior to HSCT might help improve neurodevelopmental outcomes of severe MPS I. Using decision-analytic modeling, newborn screening would be estimated to detect 44 cases of MPS I (range: 22-89) in the United States annually, with at least 29 (range:13-62) being severe. Two States, Illinois and Missouri, have implemented pilot screening for MPS I. Challenges to adoption include the cost, needing to implement a technology and approach to detect a lysosomal storage disorder, and implementation of specific algorithms for short- and long-term follow-up.

Part I. Systematic Evidence Review of Newborn Screening for MPS I

Key Topic 1: What is the Natural History and Epidemiology of MPS I?

MPS I Disease Overview

Case Definition

Mucopolysaccaridosis Type I (MPS I) is an autosomal recessive lysosomal storage disorder (LSD) caused by deficiency of the enzyme α-L-iduronidase (IDUA).

MPS I is a progressive, multisystem disorder, with symptoms presenting across a continuum of disease severity. Although traditionally classified as one of three MPS I syndromes – Hurler syndrome, Hurler-Scheie syndrome, or Scheie syndrome – the clinical findings overlap and suggest a spectrum of disease. MPS I disease is often described as *severe* or *attenuated*, which reflect a spectrum of disease onset, severity, and treatment indications.

Epidemiology: Incidence Estimates under Clinical Detection

The evidence review identified ten reports of incidence estimates of MPS I from clinically detected cases in Europe, Australia, Asia, Africa, and in Cuba published since 2003.[1-10] The majority estimate the birth incidence of MPS I to be from *0.54 to 1.85 cases per 100,000.* These estimates were based on review of patient medical records in major hospitals, laboratory records, and interviews or surveys with patients or family members. Table 1.1, below, summarizes incidence estimates across studies. Most of the identified cases were of the severe form. The challenge of case ascertainment without screening of attenuated disease likely yields an underestimate of the birth incidence of this form.

Table 1.1. Prevalence Studies of MPS I: Clinical Detection

Pub Year	Authors	Study Region	Time Period	Est. Birth Incidence per 100,000
2012	Menendez-Sainz et al.	Cuba	1990-2005	1.01
2012	Krabbi et al.	Estonia	1985-2006	0
2009	Turkia et al.	Tunisia	1988-2005	0.63
2009	Lin et al.	Taiwan	1984-2004	0.11
2009	Vazna et al.	Czech Rep Slovakia	1978-2008	0.7 (CZECH) 1.32 (SLOV)
2009	Murphy et al.	Irish Republic	2001-2006	3.8*
2008	Malm et al.	Scandanavia: Sweden Norway Denmark	1975-2004	0.67 (SWED) 1.85 (NORW) 0.54 (DENM)
2008	Moore et al.	United Kingdom: England & Wales	1981-2003	1.07 (ENG & WALES)
2005	Baehner et al.	Germany	1980-1995	0.69
2003	Nelson et al.	Western Australia	1969-1996	0.93

**Predominantly Irish Traveller population*

Natural History of MPS I

Infants with MPS I typically appear normal at birth. In its severe form, onset of overt clinical symptoms usually occurs during the first or second year of life, with pervasive, multi-systemic involvement and rapid disease progression. In the attenuated forms, onset can occur by about age three years through 12 years, though may also occur later in adulthood, and typically progresses more slowly than the severe form. In contrast to the severe form, deterioration of musculoskeletal and cardio-respiratory functions have slower progression in attenuated MPS I. CNS involvement is not classically a component of attenuated MPS I. Table 1.2 outlines the broad spectrum and disease course of MPS I. There can be overlap across the spectrum, such as Hurler-Scheie, which can make it difficult to distinguish the forms at the time of presentation.

Table 1.2. MPS I Disease Spectrum and Progression of the Natural History

	SEVERE		**ATTENUATED**
Alt. Classification	**Hurler**	**Hurler-Scheie**	**Scheie**
ONSET AND PROGRESSION	Onset by 1 to 2 years Rapidly Progressive	Onset by 3 to 4 years	Onset variable, 2 to 12 years Less progressive problems
CARDIAC SYSTEM	Cardio-respiratory failure	Cardiovascular disease	Valvular heart disease
RESPIRATORY SYSTEM	Severe respiratory, obstructive airway disease	Respiratory disease	Upper airway infections
CNS/COGNITION & DEVELOPMENT	Progressive developmental delay	Little or no developmental delay	Normal intelligence
VISION & HEARING	Hearing loss	Decreased vision	Corneal clouding
MUSCLE & SKELETAL SYSTEMS	Coarse facial features Spinal deformity Skeletal Dysplasia	Skeletal abnormalities Joint stiffness, contractures	Joint stiffness Carpel tunnel syndrome
LIFE EXPECTANCY *(IF UNTREATED)*	Death < 10 years of age	Death in teens or 20s	Death in later life; most have normal life span

As of 2013, the MPS I Registry includes data on 1,046 MPS I patients[11] characterizing the natural history, symptoms, treatment, and course of disease progression. The natural history of MPS I was inferred from a 2014 report, using data from untreated patients and data prior to treatment initiation. For the 987 patients with natural history data, median ages of onset, diagnosis, and treatment initiation are, respectively, 0.5, 1.0 and 1.5 years of age for Hurler's disease (n=601, 60.9%); 1.8, 4.0, and 8.0 years of age for Hurler-Scheie disease (n=227, 23.0%); and 5.3, 9.4, and 16.9 years of age for Scheie syndrome disease (n=127, 12.9%).[11]

A report from 2012 of MPS I Registry data (n=891) described similar natural history trends, with additional information on frequency and ages of death.[12] Table 1.3 summarizes these natural life course data for MPS I patients.

Table 1.3 Median Age of Onset, Diagnosis, Treatment, and Death for MPS I Registry patients (N=891).

Disease Classification[‡]	N [%]	Age at Onset *in years* (range)	Age at Diagnosis *in years* (range)	Treatment Reported[§] [n]	Age at 1st Treatment *in years* (range)	Death Reported [n]	Age at Death *in years* (range)
SEVERE (Hurler)	**508** [57]	**0.5** (0-6.5)	**0.8** (0-23.8)	**438**	**1.4** (0.1-31.2)	**156**	**3.8** (0.4-27.2)
ATTENUATED	**306** [34.4]			**282**		**20**	
(Hurler-Scheie)	**209** [23.5]	**1.9** (0-12.2)	**3.8** (0-38.7)	(197)	**8.6** (0.3-47.2)	(16)	**17.4** (7.5-30.3)
(Scheie)	**97** [10.9]	**5.4** (0-33.8)	**9.4** (0-54.1)	(85)	**17.1** (3.1-62.9)	(4)	**29** (17.4-46.6)

[†]*MPS I Registry (from inception in 2003 through March 2010).*
Regions: 47% Europe; 35% No Amer; 15% Latin Amer, 3% Asia Pacific.
[§]*13% reported as untreated with ERT or HSCT.*
[‡]*8.6% undetermined (3.1%) or missing (5.5%) form classification.*

MPS I Screening and Diagnosis

Screening

Newborn screening for MPS I is based on measurement of IDUA enzyme activity levels in dried-blood spot (DBS) specimens. Current available high-throughput screening methods include fluorometric assay, immunocapture, and tandem mass spectroscopy (MS/MS). Recently, a digital microfluidics system has been developed that is based on a fluorometric assay. Measurement of IDUA enzyme activity can be multiplexed with assays to detect other lysosomal storage disorders (LSDs).

The feasibility of large-scale newborn screening for MPS I multiplexed with detection of other LSDs with both digitial microfluidics and MS/MS has been demonstrated. Researchers at the University of Washington have conducted a study evaluating anonymous dried-blood spots with MS/MS.[13] The Illinois state newborn screening program is using MS/MS with a different protocol in preparation to expand the state newborn screening panel. The Missouri state newborn screening program is using digital microfluidics. Newborn screening programs outside of the United States, including Taiwan and Italy, have reported use of fluorometric and comparative MS/MS methods for LSD-multiplex screening. Results from these research and public health screening programs are described in further detail in the pilot study screening studies section.

According to communication with expert investigator, Dr. Dieter Matern (9/29/2014 and 12/14/2014), researchers at the Mayo Clinic are conducting a comparative trial of these three different multiplex assays to screen for 13 LSDs, including MPS I, Friedrich's ataxia, Wilson's disease, and X-linked adrenoleukodystrophy.[14] Overall aims of the study are to identify effective and efficient screening approaches, and to provide comprehensive descriptions of resources needed to implement each approach. The study is prospectively analyzing 100,000 anonymous dried-blood spots provided by the California newborn screening program. Final results are not yet available.

Short-term Follow-up and Diagnostic Confirmation

The typical protocol for screening is that following a positive first screen for low IDUA activity with an enzyme assay from a dried-blood spot, repeat analysis of the same DBS sample is run to confirm the results. Positive repeat screens require follow-up contact with a parent to request a 2nd blood sample from the newborn to confirm low IDUA activity levels.

Positive screens for low IDUA levels on the second sample are referred to a specialty diagnostic testing center for confirmatory testing. The standard procedures to confirm a diagnosis of MPS I may include establishing low or undetectable IDUA enzyme activity levels in white blood cells, measuring glycosaminoglycan (GAG) urinary excretion levels which rise as a result of functionally low IDUA enzyme activity, molecular genetic testing for IDUA gene mutations known to be associated with MPS I. In all cases, newborns are also referred for clinical assessment by specialty providers.

Factors that Affect Detection and Diagnosis

Genetics of MPS I

There are approximately 100 known mutations associated with MPS I mutations reported in the Human Genome Database and MPS I Registry. The majority of known IDUA mutations are nonrecurring private mutations, making difficult the prediction of severity from uncertainties in genotype-phenotype correlation. However, at least 7 to 9 mutations have been identified with some recurrence, and can be reliably targeted in sequence analysis.[15,16] The frequencies of these mutations have been found to vary across continents and by ethnicity. In North America, two of the most commonly reported mutations are the nonsense mutations W402X and Q70X,[15] followed by A75T and 474-2a-->g.[17] Reported frequencies of these mutations in MPS I patients are 45% - 60% (W402X), 17% (Q70X),[15] and 7% (A75T and 474-2a-->g.[17] Most of these mutations are associated with the severe phenotype, although some heterogenous mutations with W402X and Q70X have been associated with milder, attenuated forms.[15]

Carriers. As an inherited autosomal recessive trait, individuals may inherit only one IDUA mutation for MPS I, and thus be a carrier but not have the disease. Because the IDUA levels of carriers of MPS I may be lower than normal, screening procedures to detect low IDUA levels may not be able to distinguish some MPS I carriers. Confirmatory IDUA levels, urine GAG measurements, and mutation analysis through genotyping help separate MPS I carriers from those likely to be affected by the disease.

Pseudodeficiency. Pseudodeficiency alleles of IDUA may yield artificially low levels of IDUA enzyme activity, leading to false-positive screening results. Recent pilot program results reported by the Missouri NBS program and Greenwood Genetic Center in South Carolina from initial pilot program results find that 25 of 41 positive screens referred for follow up have IDUA levels in an indeterminate "gray zone." Further molecular testing has identified at least four recurring IDUA gene sequence alterations among these newborns, the most common of which has an allele frequency of 2.8% in African-American newborns.[18] These findings suggest that the frequency of pseudodeficiency alleles is higher than previously reported.

Current Newborn Screening Programs and Research

The most relevant evidence regarding newborn screening programs comes from population-based pilot programs or evaluations of screening with diagnostic confirmation. Published reports of population-based pilot newborn screening for MPS I, with diagnostic confirmation have come from programs in Taiwan[19] and Italy.[20] A published report from researchers at the University of Washington presents results to evaluate MS/MS LSD-multiplex screening methods on anonymous dried-blood spots, with follow up genetic testing on these same DBS samples.[13] Other relevant unpublished results are from the Missouri and Illinois State screening programs, which had legislative mandates to screen for MPS I. These programs are conducting population-based pilot screening for MPS I as they finalize implementation procedures for full reporting.

Treatment Strategies for MPS I

Primary treatment strategies for MPS I seek to replace deficient IDUA enzyme levels. The main treatments include enzyme replacement therapy (ERT) with recombinant human IDUA and hematapoetic stem cell transplantation (HSCT).

Pharmacological Treatment: Laronidase

In 2003, the US Food and Drug Administration (FDA) approved Laronidase; Genzyme (Genzyme Corp., Cambridge, MA) for enzyme replacement therapy to treat MPS I. Recommended administration for this recombinant human IDUA (rh IDUA) enzyme replacement therapy (ERT) is through intravenous infusion typically every one to two weeks with infusion times lasting about four hours.

A major limitation of ERT is that it does not cross the blood brain barrier (BBB), and thus is considered suboptimal for the treatment of the CNS involvement associated with severe MPS I. Following promising animal model applications, a case study reports the use of intrathecal administration of enzyme replacement therapy (IT-ERT) as a way to address the inability of intravenous ERT to permeate the BBB in an adult patient with MPS I-Scheie syndrome presenting with symptomatic spinal cord compression.[21] The case report suggests that IT-ERT can be administered safely and facilitate a return to normal CSF GAG levels, as well as functional improvements in stability and gait control, ventilation, and pulmonary diffusion. Current treatment guidelines[22] recommend intravenous ERT (laronidase) for patients with MPS I meeting one or more of the following criteria: age > 2 years; age ≤2 years and expected to have the attenuated disease form; or age ≤2 years and developmental quotient <70 (or approximately 2 standard deviations below average). In January 2013, the Agency for Healthcare Research and Quality released a technical brief, "Enzyme-Replacement Therapies for Lysosomal Storage Diseases," including summaries of 5 studies of ERT studies of MPSI: http://www.effectivehealthcare.ahrq.gov/ehc/products/364/1368/TB12_EnzymeReplacementTherapies_FinalReport_20130102.pdf.

Hematopoietic stem cell transplantation (HSCT)

The primary treatment for the majority of children with severe MPS I is hematopoietic stem cell transplantation (HSCT), which can allow treated individuals to produce endogenous active IDUA (note: the term "hematopoietic cell transplantation (HCT)" is more correct because the treatment is based on an infusion of stem and progenitor cells; because of the predominant use of the term in the literature, we use HSCT). Current clinical guidelines recommend HSCT for patients with severe MPS I who are not yet 2 to 2.5 years of age and who have an estimated developmental quotient ≥ 70 (i.e., higher than two standard deviations below the mean).[22] Mortality from HSCT has been reported to be about 10-15%, with most transplant failures occurring within the first year. Estimating mortality from HSCT is challenging because of improvements in treatment over time and variations in outcomes by graft type (e.g., related or unrelated donor sources, HLA match) and patient characteristics (e.g., age, health status). Based on recent reports,[23]some institutions and providers now offer ERT to patients with the severe form at diagnosis, prior to transplantation as a way to slow or stabilize disease progression before transplant.

Conceptual Framework: Evaluation of Newborn Screening for MPS I

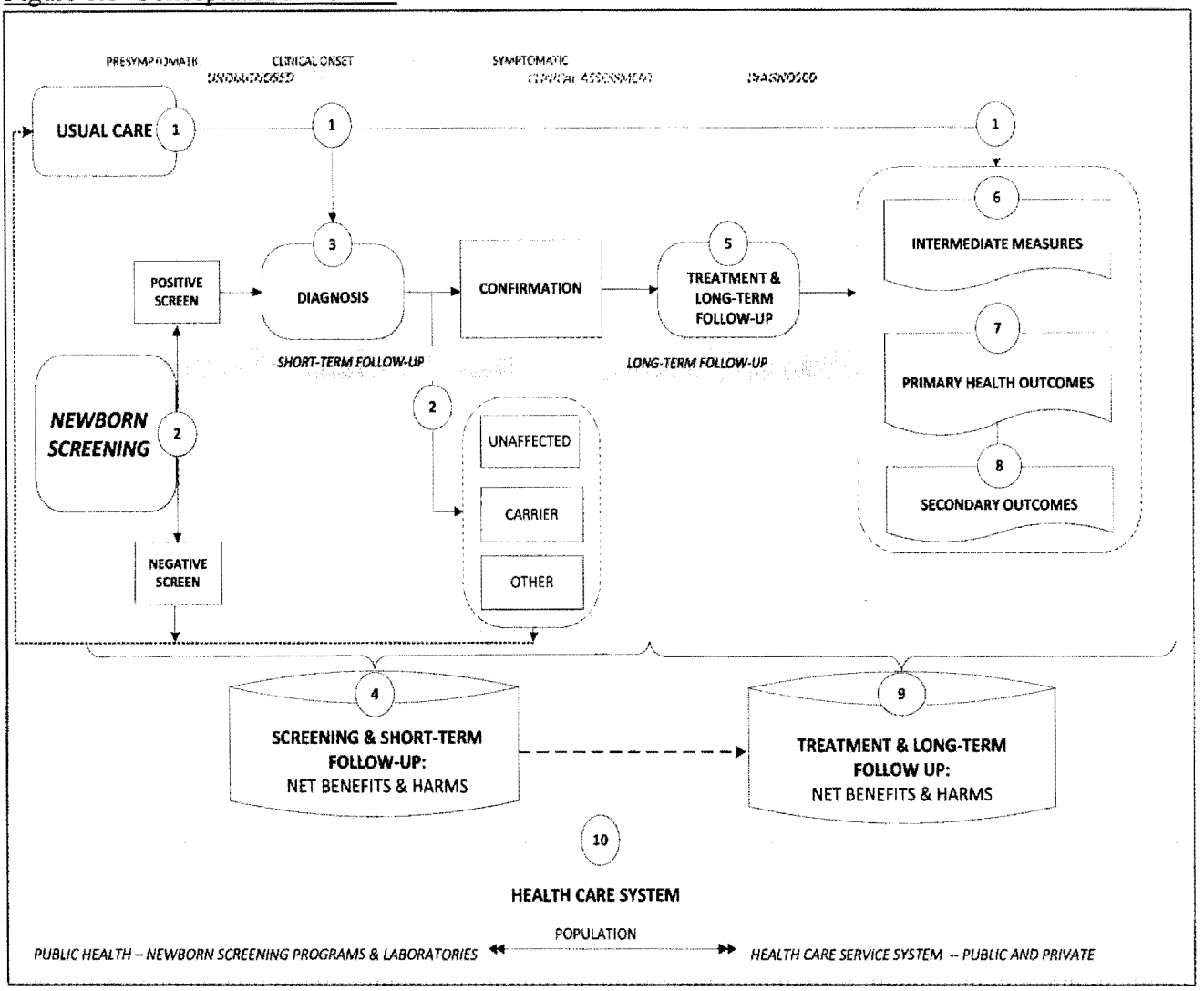
The overarching goal of this systematic review is to summarize the evidence regarding newborn screening for MPS I for the SDACHDNC in comparing the net benefits of newborn screening to usual clinical care. The conceptual framework (Figure I.1) illustrates the approach to assess the impact of newborn screening for MPS I.[24] Within the framework, ten broad Key Topic Areas (KTAs) organize detailed sets of Key Topic Questions (KTQs). KTQs specify the relevant considerations for all aspects of MPS I screening compared to usual care (i.e., clinical diagnosis). The framework is used as a tool to

ensure a comprehensive consideration of the benefits and harms of newborn screening for a particular condition. The framework is different than a decision-analytic model, which explicitly models the quantitative outcomes that might occur with newborn screening compared to usual care. As KTQs represent a comprehensive group of questions, they may overlap or appear on the conceptual framework more than once.

Standard clinical care for children with MPS I can be considered to occur over two distinct phases: the periods of time during which individuals are undiagnosed and diagnosed with MPS I. The time to diagnosis will vary, based on clinical factors including the nature and timing of symptom onset, and a wide array of other health care-related factors. The scale of the conceptual framework does not represent the variability of the time spent in the different various phases of clinical detection through usual care. In contrast, those newborns screening positive will have a period of time lasting from screening through diagnostic confirmation of MPS I, referred to as short-term follow-up. The length of time in short-term follow-up is dependent on the steps needed to rule-out the condition or establish the form of MPS I (i.e., severe or attenuated). After diagnosis through newborn screening, affected individuals enter the period of long-term follow-up. Newborn screening may not identify all cases.

Individuals with MPS I can be diagnosed following clinical presentation, then enter into treatment and long-term follow-up. These events may modify intermediate measures of health (e.g., biomarkers, changes in functional measures) or primary health outcomes (e.g., mortality, morbidity, quality of life). In contrast, newborn screening can identify individuals presymptomatically, leading to earlier diagnosis and entry into treatment and long-term follow-up. Earlier treatment and long-term follow-up could lead to differences in intermediate measures or primary health outcomes, or may prevent changes in these outcomes. Changes in intermediate measures or primary health outcomes can occur at any time over the lifespan of affected individuals. Both usual care and newborn screening occur within the context of the broader health care system, including public health and -private health care service arenas. A potential expansion of newborn screening services must consider the resources required and effects on the broader health care system.

Figure 1.1 Conceptual Framework



The conceptual framework organizes the main key topic areas that might be impacted if a new condition were added to the newborn screening panel. These Key Topic Areas are outlined briefly below. Within each of these Key Topic Areas, Key Questions specific to MPS I developed to guide the review of evidence regarding the impact are outlined in later sections of this report.

Key Topic Area 1 (background): EPIDEMIOLOGY, CLINICAL DETECTION, AND USUAL CARE. This KTA addresses the frequency of the target condition diagnoses in the absence of screening, the timing of clinical onset, diagnosis, treatment, and outcomes.

Key Topic Area 2: SCREENING. This KTA addresses the ability of screening approaches to distinguish newborns with and without the target condition and to predict form of the condition.

Key Topic Area 3: SHORT-TERM FOLLOW-UP AND DIAGNOSIS. This KTA evaluates the process of short-term follow-up of positive screens to confirm diagnosis and refer for follow-up care. KTA 3 also evaluates the availability, accessibility, and feasibility of timely confirmatory diagnostic testing and follow-up.

Key Topic Area 4: BENEFITS AND HARMS OF SCREENING AND DIAGNOSIS, UNRELATED TO TREATMENT. This KTA evaluates the benefits and harms that could result from newborn screening and early diagnosis unrelated to treatment. This KTA synthesizes the effects, both positive and negative, that may arise from newborn screening and diagnosis (unrelated to treatment). Many of these benefits and harms affect both child and family.

Key Topic Area 5: TREATMENT AND LONG-TERM FOLLOW-UP CARE. This KTA describes current treatment practices for the target condition, including approaches to treatment decision-making, implementation, and long-term management for those identified with the target condition through clinical detection with usual care and through newborn screening.

Key Topic Area 6: INTERMEDIATE OUTCOME MEASURES. This KTA considers the degree to which treatment and long-term follow-up affects intermediate measures (e.g., biomarkers, functional measures) over the life of those diagnosed with the condition and the degree to which earlier treatment leads to differences in these outcomes.

Key Topic Area 7: PRIMARY HEALTH OUTCOMES. This KTA evaluates the degree to which treatment and long-term follow-up with early detection affects primary health outcomes (e.g., mortality; added years of survival; disease progression), and the strength of association between the intermediate measures and the primary health outcomes as applicable.

Key Topic Area 8: SECONDARY OUTCOMES. This KTA describes other outcomes with early detection that affect treatment and long-term follow-up on patients and family caregivers.

Key Topic Area 9: TREATMENT AND LONG-TERM FOLLOW-UP—BENEFITS AND HARMS synthesizes the benefits and harms associated with treatment and long-term follow-up, comparing treatment outcomes resulting from usual care versus newborn screening.

Key Topic Area 10: PUBLIC HEALTH AND HEALTH CARE SYSTEM IMPACT. This topic addresses the projected impact of adding newborn screening for the target condition on population-level health, and on public health programs and health care services, relative to current detection and usual care for the condition.

Systematic Evidence Review Methods

The methods guiding this systematic evidence review are based on approaches outlined in the Condition Review Workgroup – Manual of Procedures - Rev (July 2012). These procedures are based on the AHRQ SER Methods Guide [25,26], and other established evidence review standards, with adaptations to address the nature of research on rare disorders (e.g., few large RCTs, primarily case series studies) and the established review and comment timeline of the Committee. This chapter outlines the procedures that guided the Systematic Evidence Review of newborn screening for MPS I Disease. Further details documenting the evidence review can be found in Appendix A.

Literature Search

We identified literature published in MEDLINE, EMBASE, and CINAHL databases from 1966 (the start of MEDLINE) to January 2015. The present review used the following keyword terms and their associated MeSH terms for each database:

Keywords and Associated MeSH Terms:

- *Mucopolysaccharidosis type I (MPS I)*
- *Hurler syndrome/disease*
- *Hurler-Scheie syndrome/disease (MPS I H/S)*
- *Scheie syndrome/disease* (MPS I S)
- *severe MPS 1*
- *attenuated MPS 1*
- *gargoylism*
- *alpha-L-iduronidase enzyme assay*

In consultation with the Condition Review Workgroup, an experienced medical librarian conducted the initial literature search. An initial screening of titles and abstracts was conducted by two independent reviewers for exclusion and inclusion; disagreements were reconciled through discussion or by a third independent reviewer as needed. Based on the available evidence, inclusion and exclusion criteria were narrowed further in the full-text screening. Reviewers screened the initially included articles with full-text screening using pre-developed data abstraction forms.

Article Screening

Inclusion criteria. Articles that reported on studies with human subjects and published in English were included. Because of the inability to conduct large scale, randomized trials for rare genetic disorders, all study designs were considered in the initial screening, including case reports, case series, observational, studies, uncontrolled, and controlled intervention trials.

Exclusion criteria. Non-human studies, studies with no English language abstracts, and articles with no new data were excluded.

Following preliminary screening of article titles, the inclusion and exclusion criteria were narrowed as follows:

For all other articles, inclusion criteria added to the criteria listed above were

- Any article addressing early detection or treatment was included

For all other articles:

- Publication date in 2003 or later
- N>5

Further details of the article screening procedures and flow diagram can be found in Appendix A.

To develop the data abstraction plan, identify issues in current research and practice, and describe the typical care standards for newborn screening and treatment procedures we conducted four expert panel teleconferences (July 10, 2012, November 4, 2014, January 6, 2015, and January 23, 2015) with invited members. In addition, individual interviews and communications (one-time and ongoing) were conducted with experts and stakeholders with relevant expertise. Table 4.1 lists the Technical Expert Panel members and other advisors contacted for this MPS I review.

Table 4.1a. Technical Expert Panel Teleconferences

TEP MEMBERS	**AFFILIATION**
Lorne Clarke	Dept of Medical Genetics Univ of British Columbia
Barbara Burton	Lurie Children's Hospital of Chicago
Patricia Dixon	Div of Medical Genetics LA County Harbor – UCLA Med Center
Joe Muenzer	Dept of Pediatrics and Genetics Univ of NC at Chapel Hill School of Medicine
Barbara Wedehase*	National MPS Society

Table 4.1b. Individual Expert Interviews

MPS I NBS - Individual Expert Interviews	**AFFILIATION**
Michael Gelb†	Dept. of Chemistry, Univ of Washington
Joan Keutzer (Genzyme)**	MPS I Registry, Genzyme Corporation
S. Rogers, MD/P. Hopkins (MO NBS)	MO NBS Program
Khaja Basheeruddin (IL NBS)	IL NBS Program
Dietrich Matern **	Mayo Clinic College of Medicine, Rochester MN

† Developer of the MS/MS instrument. Application pending for FDA-approved multiplex kit in partnership with PerkinsElmer.
*Nominator of MPS I disease for consideration to be added to the RUSP.
**Provided written responses to questions only.

Screening and Short-Term Follow-Up

1. What is the analytic validity or clinical validity of the screening approaches used to detect MPS I?
2. What diagnostic testing methods are available to confirm or identify (a) MPS I? (b) Severe MPS I? (c) Attenuated MPS I (or age of onset or disease severity?)

The most relevant evidence for the accuracy of newborn screening comes from population-based studies of newborn dried-blood spots with diagnostic confirmation. Studies meeting these criteria include 2 published reports of MPS I pilot newborn screening programs in Italy[20] and Taiwan.[19] Another study evaluated screening accuracy in anonymized dried-blood spots, with confirmation based on mutation analysis alone (i.e., no clinical follow-up).[13] We also summarize reports gathered through technical expert interviews with representatives from the Illinois and Missouri state newborn screening programs. We do not present findings of studies that analyzed dried-blood spots without either molecular testing or clinical confirmation of MPS I disease status.

Taiwan

In Taiwan, 35,285 newborns were screened for MPS I disease through a pilot program from 2008 through 2013 with a fluorescence enzyme assay for IDUA activity levels.[19] Of these newborns, 58 had low IDUA levels (<19.82 umol/L/L blood*20 h) at first screen. Repeat analysis of the original samples of these 58 found 19 with confirmed low IDUA levels (<9.03 umol/L/L blood*20 h). These 19 newborns were recalled for a retest, of whom 3 infants continued to have low IDUA levels. These 3 newborns were referred for diagnostic testing. Two of the 3 had low IDUA levels confirmed in leukocyte IDUA testing and MPS I diagnosis was confirmed by molecular genetic analysis.

Based on these findings, the epidemiology and screening test characteristics were as follows:

- 2 cases of MPS I were identified, yielding an estimated incidence: 1 in 17,643 (5.67 per 100,000)
- Calculated from the report, the overall positive rate based on the requirement for a second dried-blood spot was 0.054%
- Calculated from the report, the positive predictive value based on the second dried-blood spot was 10.5% (e.g., 2 of 19). Based on a binomial distribution, the 95% confidence interval is 1.3%-33.1%.
- Calculated from the report, the false positive rate after the second dried-blood spot was 5.1%. Based on a binomial distribution, the 95% confidence interval is 1.1%-14.4%.

Italy

One report[20] described a population-based screening study in Italy conducted between January 2010 and June 2012. Using a fluorometric assay, 3,403 newborns were screened for Fabry disease, Gaucher disease, Pompe disease, and MPS-I. IDUA enzyme levels <25% of the average control activities were found in 13 (0.38%) newborns. A second dried-blood spot was obtained for 13 newborns with low IDUA level, and the retest confirmed these levels in 3 newborns. Follow-up assay of whole-blood samples revealed normal IDUA enzyme activity. The threshold for a positive newborn screening test was higher than currently used in population-based screening. Therefore, it is difficult to generalize findings regarding the false positive rate. Although no cases were detected, the sample size was too small relative to the expected frequency of MPS I to expect any positive cases to have been found.

United States

University of Washington Study

One research study[13] evaluated MS/MS multiplex screening procedures for three LSDs anonymous dried-blood spots from the Washington State newborn screening program. For MPS I disease, a cutoff of IDUA activity ≤ 1.15 µmol/h/l, corresponding to $\leq$32% of the mean, was used. Of the 106,526 samples, 9 screened positive for low IDUA activity at the first tier.

Follow-up through mutation analysis of these 9 anonymous DBS samples revealed:

- 3 had mutations/nucleotide changes "consistent with MPS I disease"
- 1 carrier of a common MPS I mutation
- 3 had no identified nucleotide change
- 2 had low activity due to a poor dried-blood spot punch

Based on these findings, the epidemiology and screening test characteristics were:

- Overall birth prevalence of infants who "may eventually develop clinical symptoms of MPS I disease": 1/35,700 (95% CI: 1/43,000-1/11,100).
- The overall positive rate (calculated from the report): 1/6,561(95% CI: 4,098-11,261)
- The positive predictive value: 0.33% (95% CI: 0.08%-0.65%)
- False positive rate: 1/17,750 (95% CI: 1/7,250-1/31,900)

Because of the lack of information on phenotype, studies of anonymous dried-blood spots are not substitutes for true clinical epidemiology.

The investigators claim that the cost per sample is $1.03, including reagent purchase and equipment rental. No other costs (e.g., personnel time) were included in that estimate.

Illinois

Illinois issued a lesliative mandate to screen for MPS I disease in 2012 with two other LSDs, following prior mandate to screen for four other LSDs in 2007. After initially using a digital microfluidics platform, the program switched to MS/MS in 2011 to accommodate high volume and additional LSD conditions for multiplexing. Validation and pilot testing began in January and November 2014, respectively, in four birthing hospitals. According to IL NBS program contacts, from November 2014 through December 18, 2014, 17,300 newborns were screened.

Of the 17,300, 17 newborns were called out (0.1%) and repeated in triplicate before reporting. Referral results are as follows:

- 0 Confirmed MPS I
- 5 Cases of pseudodeficiency
- 0 Carriers
- 10 False positives
- 2 Pending
- 0 Lost-to-follow up

Missouri

Following legislation mandating MPS I screening (August 2009), the Missouri Newborn Screening Program has been pilot-testing newborn screening procedures statewide since January 15, 2013 using a digital microfluidics platform. As of December 2014, 174,636 dried-blood spots have been screened for MPS I disease, with the following confirmed results:

70 positive screens:

- 1 confirmed severe MPS I patient
- 3 carriers of MPS I disease
- 30 false positives (IDUA enzyme activity level in the normal range, carrier status unknown)
- 25 cases of pseudodeficiency
- 9 cases pending
- 2 newborns lost to follow-up

These findings suggest an overall prevalence of MPS I disease of 1/174,636. Overall, there were about 40 positive screens for every 100,000 newborns. Among those who tested positive and excluding those lost to follow-up or who are still pending diagnostic confirmation, the positive predictive value was 1.6%. However, these preliminary pilot study results results do not reflect current screening protocol in Missouri and should not be generalized. The initial phase of the pilot study used a very conservative (low) cutoff to minimize the risk of missed cases. The cutoffs have already been adjusted to increase the positive predictive value and will continue to be adjusted. These results show a high rate of pseudodeficiency mutations, with alleles particularly prevalent among African Americans.[18]

Adjusting the overall screening outcomes for the current IDUA enzyme activity threshold, the findings would be as follows:

42 Positive Screens:

- *1 confirmed severe MPS I patient*
- *2 carriers of MPS I disease*
- *11 false positives (IDUA enzyme activity level in the normal range, carrier status unknown)*
- *21 cases of pseudodeficiency*
- *7 cases pending*
- *1 newborn lost to follow-up*

In this case, there are about 24 positive screens for every 100,000 newborns. Among those who test postive and excluding those lost to follow-up or who are still pending diagnostic confirmation, the positive predictive value is 2.4%.

Treatment Outcomes for MPS I

- Does early initiation of treatment (HSCT and/or ERT) improve survival outcomes when the condition is detected early or through newborn screening compared with usual clinical care? How does this vary by phenotype?
- Does early initiation of treatment (HSCT and/or ERT) improve other outcomes (i.e., cognitive development) when the condition is detected early or through newborn screening compared with usual clinical care? How does this vary by phenotype?
- What other factors modify or affect treatment outcomes?

Primary Health Outcomes: Survival and Mortality

Evidence on the natural history of attenuated forms of MPS I indicates that relatively normal lifespans for mild cases (i.e., Scheie syndrome), and most moderate cases (i.e., Hurler-Scheie syndrome).[8] Therefore, the review on survival outcomes focuses on reports of severe MPS I and attenuated forms with early onset.

Severe MPS I: Mortality

The present review included reports published since 2003, the year that ERT (Laronidase) was approved by the Food and Drug Administration to treat MPS I. HSCT was being used to treat severe cases of MPS I prior to 2003. Reports reviewed here also include follow-up of MPS I patients with HSCT prior to 2003.

The literature search identified 17 case series treatment reports with >5 subjects with the severe form of MPS I. Table 6.1. summarizes the published treatment articles included in this review, sample size of MPS I cases, treatment type, ages of diagnosis and first treatment, and overall survival rates reported. The majority of identified articles for treatment of Severe MPS I presented outcomes of HSCT, with one report on outcomes of ERT only for MPS I patients less than 5 years of age,[27] described below. Further summary information for all of the studies can be found in the evidence tables in Appendix B. Some reports may overlap in cases presented (see Appendix B).

Overall, these studies indicate survival rates ranging from 63% to 100% at 1-year, and 53 to 100% at 5-years with clinical detection. Studies that report all subjects receiving first treatment before 2.5 years of age (the currently recommended age limit for HSCT), show 1-year survival rates ranging from 83% to 100%.[28-30]

One study reported use of ERT alone with severe MPS I patients.[27] This prospective, open-label, Phase I/II trial of 52 weeks of ERT with 20 young or severely affected MPS I cases (16 MPS IH), reported median ages of diagnosis and treatment of 15.6 months and 2.9 years, respectively. Among the 16 infants with severe MPS I, the survival rate was 87.5% at 1-year follow up.

Table 6.1. Characteristics and Survival Outcomes Severe MPS I in Published Reports

Publication		N	Treatment		Age in months (range)		% Survival			
Author	**Year**	**MPSI H**	**Type**	**Period**	**Diagnosis**	**1st Treatment**	**≤1 yr**	**2-3**	**3-4**	**5**
Wynn et al.	2009	18	HSCT + ERT	2004-2008	9 mos (3-19 mos)	ERT: 9.5 (3-19) HSCT: 11.5 (7-22)	89			
Gassas et al.	2011	23	HSCT	1989-2007	--	13.5 mos (4-24 mos)	*83*		78	
Sauer et al.	2009	12	SCT with Conditioning	2001-2008		14 mos (4–31 mos)	*100*	100		
Cox-Brinkman et al.	2008	22	HSCT+ERT	2003-2005	14 mos (1-28 mos)	14-18 mos (2-39 mos)	86			
Grigull et al.	2011	8	SCT with conditioning, FU		4.5 mos (1-12 mos)	14.4 mos (4-36 mos)	*100*	100		
Boelens et al.	2009	93	UCB (retro risk analysis)	1995-2007	--	15.6 mos (2.4-60 mos)	*77*		77	
Boelens et al.	2013	258	HSCT w/ conditioning, 48% +ERT	1995-2007	--	16.7 mos (2.1-228 mos)	*74*			74
Eisengart et al.	2013	19	HSCT + ERT v HSCT only	2005-on 2002-2005	--	17.5 mos	*100* 80	100		
Staba et al.	2004	20	UCBT	1995-2002	12 [11] mo (0 - 29 mos)	18 [16] mos (3-33 mos)	*85*	85		
Boelens et al.	2007	146	SCT	1994-2004	10.5 mos (0-55 mos)	18 mos (1-96 mos)	85			
Hansen et al.	2008	7	HSCT + RIC		--	18 mos (12-36)	*85.7*	85.7		
Bjoraker et al.	2006	41	HSCT	1983-2002	--	21.7 (4.1-73)	*98*			98
Souillet et al.	2003	27	HSCT, related & unrelated	1986-2001	11 mos (2 to 87 mos)	25 mos (14-96 mos)	*85*		85	
Orchard et al.	2010	74	HSCT only	1990-2003	--	--	*63*			53
Mitchell et al.	2013	25/53	HSCT	1992-2008	--	--	*83*			83
Moore et al.	2008		BMT	1981-2003			*96**		*65**	*65**
Wraith et al.	2007	16/20	ERT (52 wks) Phase I/II		15.6 mos (0 to 54 mos)	2.9 yrs (0.5–5.1 yrs)	90			

*estimated by visual inspection of survival curves

Factors That Affect Survival and Outcomes following HSCT

A 2013 study by Boelens et al.[31] reported on outcomes of transplantation with various hematopoietic stem cell sources after pre-transplant myeloablative conditioning. The study included registry records of 258 subjects with severe MPS I identified through registries who underwent HSCT between 1995 and 2007. Of these subjects, 19% (n=48) received at least 4 infusions of ERT prior to HSCT. HSCT donor sources included unrelated cord blood (n=116), unrelated with matched HLA (n=105), and related

sibling donors with matched HLA (n=37). The median age of HSCT was 16.7 months (range: 2.1 to 228 months). Overall 5-year survival was 74%, and event-free survival was 63%. After adjusting for year of transplantation and prior ERT, multivariate analysis of factors affecting event-free survival found that transplant age <16.7 months (p=0.03) increased chances of survival, while unmatched cord blood (p=0.031) or mismatched unrelated donor grafts (p=0.007) lowered chances of EFS.

A previous multivariate analysis of outcomes from the same study on 93 patients who received an unrelated cord blood transplant analysis found that use of a *pre-transplant conditioning regimen of cyclophosphamide and busulfan* (p=0.011) and a *shorter interval from diagnosis to transplant* (82% <4.6 months interval vs. 57% ≥4.6 months interval, p=0.046) predicted improved event-free survival rates at 3 years[32]

A retrospective analysis of 74 MPS IH patients transplanted at the University of Minnesota from 1990 to 2003, before institution-wide use of ERT prior to transplant, examined pre-transplant factors related to survival.[33] The overall survival of the sample at 1- and 5-years was 63% and 53%, respectively. Multivariate analysis found that *history of lower airway disease or pneumonia* were associated with significantly lower survival rates. Age at transplantation, presence of hydrocephalus, history of cardiovascular or upper airway obstruction were not associated with significant differences in survival.

A 2015 study by Aldenhoven and colleagues[34] examined long-term predictors of HCT outcomes for severe MPS I. Gathering records from 217 severe MPS I patients with successful engraftments conducted between 1985 to 2011 at major European and U.S.-based treatment centers, the investigators examined neurodevelopmental and organ system function to characterize outcomes and residual disease burden among MPS I HCT survivors. The median age of transplant in the final sample was 16 months (range: 2 – 47 months), and the median age at last follow-up was 9.2 years, with patients' post-transplant years of survival ranging between 3 years to a high of 23 years. Using univariate and multivariate analysis, results found that higher cognitive function pre-HSCT (developmental quotients >85) who were transplanted before 16 months of age had significantly better cognitive function post-HSCT than subjects with poorer pre-HSCT cognitive function who were >16 months of age at transplantation. Overall, the study identified considerable residual disease burden in the majority of surviving patients across a number of organ systems. Having IDUA levels that returned to normal levels following transplantation was associated with long-term prognosis and function in most organ systems.

Findings from the MPS I Disease Registry (*unpublished*)
We requested that Genzyme query the MPS I disease registry to examine overall survival among those with first treatment initiation before 8 months of age vs. after 8 months of age, for HSCT only, HSCT and ERT, and ERT only. The results appear in Table 6.2. Other health outcome data, including cognitive development, were insufficient for comparable analysis.

Summary. The 5-year overall survival rate for attenuated patients was 100%, regardless of the treatment type (HSCT only, ERT+HSCT, ERT only). Among severe MPS I patients, those who received first treatment at 8 months of age and older experienced comparable or relatively higher survival rates across 12 to 60 months follow up than patients for whom treatment was initiated before 8 months of age. Patients with severe MPS I receiving ERT only had higher rates of overall survival through 5-year follow up when compared to patients receiving HSCT only or ERT+HSCT. This finding was consistent across treatment initiation age groups (<8 months, ≥8 months of age). Overall, the small numbers of patients receiving treatment before 8 months of age limit conclusions. However, the most important limitation in interpreting this data is the inability to adjust for disease severity prior to treatment. The

results may be confounded because more severe cases were more likely to come to earlier identification but also have worse outcomes because of progression of the underlying disease.

Tables 6.2. Survival Rates for Severe and Attenuated MPS I By Age of First Treatment and Treatment Type, MPS I Registry (N=907), *Genzyme*.

Age of Treatment Initiation								
	Severe (MPSI-H)		Attenuated (MPSI-H/S)		Severe (MPSI-H)		Attenuated (MPSI-H/S)	
HSCT Only Patients (n=199)								
Survival Age *in months*	Age* < 8 months (n=10, median age =6.81)				Age* ≥ 8 months (n=189, median age = 17.07)			
12	8/10	80%			178/178	100%		
24	7/10	70%			157/178	88%		
36	7/10	70%			135/178	76%		
48	7/10	70%			131/178	74%		
60	7/10	70%			131/178	74%	11/11	100%
ERT + HSCT (n=192)								
	Age† < 8 months (n=30, median age = 5.20)				Age† ≥ 8 months (n=162, median age = 14.74)			
12	27/28	96%			154/154	100%		
24	25/28	89%			146/154	95%		
36	25/28	89%			139/154	90%		
48	24/28	86%			138/154	90%		
60	24/28	86%	2/2	100%	137/154	89%	8/8	100%
ERT Only (n=516)								
	Age* < 8 months (n=16, median age = 4.75)				Age* ≥ 8 months (n=500, median age = 89.16)			
12	10/11	91%			186/186	100%		
24	9/11	82%			184/186	99%		
36	9/11	82%			183/186	98.4%		
48	8/11	73%			182/186	97.8%		
60	8/11	73%	5/5	100%	180/186	96.8%	314/314	100%

**Age at first HSCT received or first infusion of ERT received, as applicable.*
†Age at first treatment, either ERT or HSCT, whichever came first.

Note: Survival is defined as the age at which patient will still be alive and is specified by a cutoff of 12, 24, 36, 48, 60 months.
It is presented as a first part of the statistic; the second part represents the total number of patients in the column.
Note: Patients who died and do not have valid date of death or discontinuation reported will be excluded from the analysis.

Output: tout_1.rtf

Program name: Y:\MPSI Registry\Data Requests\Year 2014\MDR-2014-1101_01_Keutzer\Survival_keutzer_AP.sas
Creation date: 10DEC2014 12:17

Summary

Overall, it is difficult to quantify the effect of early HSCT on survival in severe MPS I. One study[32] reported significantly better survival for transplants <16.7 months. However, the study included children with transplants up to 228 months of age. Because of worse survival for older children undergoing HSCT, clinical guidelines recommend that HSCT ordinarily be restricted to children under 24-30 months of age. Consequently, the findings of the Boelens et al. study are not informative as to whether survival is a function of age at transplantation within the recommended age range. The study by Orchard

et al[33] found no association of age at transplantation with survival. Similarly, the unpublished data from the MPS I registry indicate no difference in survival by age at HSCT

Secondary Outcomes: Cognitive Development

Because of the effects of severe MPS I on neurodevelopmental outcomes, cognitive outcomes were identified by the Technical Expert Panel as a key secondary outcome to target in this review. It is reported in the literature that children with untreated severe MPS I experience severe and progressive cognitive impairment and that further neurological deterioration can be halted with HSCT.[17] The question of relevance to this review is whether there is evidence that earlier treatment associated with early diagnosis results in better cognitive outcomes.

Severe MPS I

Five studies were identified that addressed cognitive functioning in children with severe MPS I who survived HSCT; three of these included cognitive outcome measures based on standardized assessments, with comparisons of baseline and repeated measures through at least 2-year post HSCT follow-up.[23,35,36] These three studies are reviewed below, in addition to relevant findings from other studies.[27,37]

A 2013 study, also outlined in the previous survival outcomes section of this report,[23] compared cognitive outcomes among 9 MPS I patients treated with HSCT and ERT and 10 MPS I patients treated with HSCT only. Subjects were enrolled sequentially at the University of Minnesota BMT Service, with HSCT only patients enrolled from 2002 – 2005, and HSCT + ERT patients enrolled from 2005 onward, when the institutional standard of care protocol changed to include ERT prior to HSCT. The mean age at HSCT was 17.5 months (sd 17.9 months). Neuropsychological assessment with the Mullen Scales of Early Learning were administered before HCT, and repeated at 1- and 2-year post-HCT follow up. The Early Learning Composite (ELC), an age-based standard composite score (mean ±SD. 100±15), reflects overall cognitive development and is an early estimate of IQ. Mean baseline ELC scores were 90.8 for the HCT only group and 84.0 for the HSCT + ERT group. The decline in mean ELC scores during the 2-year follow-up period was significantly less in the HCT + ERT group compared with the HCT only group, adjusted for length of hospital stay (p=0.031), 7.0 points for the HCT + ERT group and 17.8 points for the HCT only group. Eisengart et al. also report results in which they assigned scores of 0 to infants who died.

A 2014 study by Poe and colleagues[35] enrolled 31 patients with severe MPS I who had umbilical cord blood transplantation (UCBT), and underwent a neurodevelopmental evaluation at baseline, and every 6 to 12 months follow-up, with a median of 7 subsequent evaluations. Standardized assessments were used to assess cognitive, adaptive and language function. The authors report a "developmental quotient" of measured developmental age/calendar age to generate trajectories for each child derived from the Mullen Scales of Early Learning and Differential Ability Scales. The 31 patients were grouped according to age at transplantation into three subject: 2-8 months (n=6), 9-17 months (n=17), and ≥18 months (n=8), respectively, to compare developmental trajectories following transplantation. The authors note that in the case of the early translant group "family history permited early diagnosis and treatment" (*p. 751*). In a fixed effects model, younger age at transplantation was found to be a significant predictor of skill development in all areas. The youngest transplantation age group (2-8 months) demonstrated significantly better performance in cognitive function (p=0.001), receptive and expressive language (p=0.004 and p=0.01), and adaptive behavior (p=0.03) during the follow up period (median 7.3 years) than those transplanted after 8 months of age. In particular, the trajectories demonstrate significant deterioration over time in developmental quotients of the late transplanted group and no deterioration for the early transplanted group. Five of 6 early transplanted infants had a final developmental age equal to or greater than their calendar age compared with few of the 25 infants

transplanted after 8 months. However, the authors did not report mean scores for the three groups that would allow for comparison with findings from other studies. Similarly, potential confounding variables at baseline, such disease status, age of diagnosis, and family socioeconomic level, were not available from the authors within the timeline of this report, and thus there effects on outcomes cannot be assessed.

One other study[36] reported long-term cognitive outcomes post-HSCT on the basis of repeated standardized assessments. Malm et al. followed four children with severe MPS I transplanted between 11 and 18 months through at least 24 months post-HSCT. Three of the children had repeated cognitive assessments using the Griffiths Developmental Scale at 4.7-6.6 years of age. For those three children, gaps between chrononological and developmental age decreased with age, with average developmental quotients of 0.83 pre-HSCT, 0.76 first post-HCT assessment, and 0.97 at final assessment (calculations based on Table S2).

Another study[37] assessed IQ scores (Wechsler Abbreviated Scale of Intelligence) for 7 children or adolescents (mean age 12.6 years) with severe MPS I who had undergone HSCT at least 5 years earlier at a mean age of 14 months (range 5-20 months). Mean full scale IQ was 77.9 (SD 13.7). No difference was reported by age of transplantation according to the authors, but no details were provided.

Wraith et al.[27] graphed repeated developmental quotients (ratio of mental age to calendar age) based on the Griffiths Mental Developmental Scales for 16 children with severe MPS I who underwent ERT only. The children were enrolled between 0.5 and 5.1 years of age. All except 1 child had mental age less than calendar age at each assessment. All 7 children whose first assessment was at 36 months of age or later showed progressive deterioration, whereas 6 subjects whose first assessments were prior to 18 months of age appeared to have no further deterioration in developmental quotients.

Aldenhoven et al.'s 2015[34] retrospective study of predictors of long-term prognosis among 217 severe MPS I patients also examined predictors of cognitive function. This study, described in the previous section (see *Factors that Affect Survival and Outcomes of HCT*, p. 20), found that those who had cognitive function in the normal range (DQ/IQ>85) and a younger age at transplantation (<16 months) had significantly better long-term cognitive function than those with impaired cognitive function (DQ/IQ <85) and older age at transplantation (>16 months). When predictors of age at HCT and baseline cognitive function (DQ/IQ) were combined, investigators found that 71% of the patients who were older (>12 months of age) and had moderately- or severely- impaired cognitive function (DQ/IQ<70) at the time of HCT also had moderate or severe cognitive impairments by a median 9.2 years post-HCT follow up. In contrast, 14.7% of patients who were younger (<12 months of age) and had mild to normal cognitive function (DQ/IQ>70) at the time of HCT had moderate or severe cognitive impairment (DQ/IQ<70) by follow up ($p<0.001$).

Summary

Overall, it is difficult to quantify the effect of early HSCT on cognitive outcomes in severe MPS I. Although earlier treatment may improve developmental outcomes, based on the results of one study by Poe et al., quantifying the magnitude of benefit is difficult. The smaller study by Malm et al. suggests that long-term cognitive outcomes for children with severe MPS I transplanted up to 18 months of age may often be normal. Small numbers of observations, inconsistent categorization of age at transplant, lack of control for confounders related to disease status at the time of transplant and specific treatment, variable length of follow-up, use of different methods of assessment, and incomplete data are challenges that limit certainty of findings from the available evidence. Because of inconsistent and non-standard

scores and insufficient data or methods detail, cognitive outcome could not be used in the decision-analytic modeling.

What is the direct evidence that early treatment initiation with early detection improves outcomes?

No published reports were identified that address early or presymptomatic treatment initiation for HSCT following early detection of Severe MPS I. Two reports were found that describe case histories of 2 sets of siblings with Attenuated MPSI, in which older siblings facilitated early detection of MPS I in younger siblings.[38,39] These reports are described below.

Attenuated MPS I: Presymptomatic ERT Use

Two reports were identified that describe outcomes of early and later ERT initiation among siblings with attenuated MPS I. Gabrielli et al.[39] report five-year follow up outcomes of a 5-year old male, identified to have low IDUA at 3 days of age, and IDUA mutations similar to his 4.5 year old sister who had been diagnosed with attenuated MPS I (Hurler-Scheie). Prior to treatment initiation at 5 months of age, the male infant presented with no clinical symptoms other than elevated urine GAG levels. Within 4 months of ERT, urine GAG levels returned to normal levels. At 5-year follow-up, the patient showed no clinical signs except for mild corneal clouding. In contrast, his sister was diagnosed at 4.5 years, and began ERT at 5 years of age. At 5 years of ERT, her clinical symptoms of liver and spleen enlargement (hepatosplenomegaly), thick skin, joint stiffness, and shoulder movement showed moderate improvement, while cardiac function, skeletal problems, and corneal clouding had stabilized but not improved.

A brief report by Laraway et al.[38] describes three siblings, each with elevated urine GAGs consistent with MPS I before ERT, which significantly decreased once treatment began. The oldest sibling initiated treatment at age 6 years, with presenting symptoms of facial coarsening, reduced range of motion, mild corneal clouding, and cardiac involvement. Symptoms stabilized or slightly improved after one year of treatment, though require intervention. The middle sibling received ERT at 2.5 years of age, presenting with some clinical signs such as mild corneal clouding and cardiac involvement, though no joint stiffness. After 5 years of treatment, he shows little disease progression besides mild stiffness. He is generally asymptomatic, with functioning within normal limits. The youngest sibling began ERT at 4 months of age. After 5 years of ERT, she shows minimal clinical evidence of disease. Further information regarding diagnosis is not provided.

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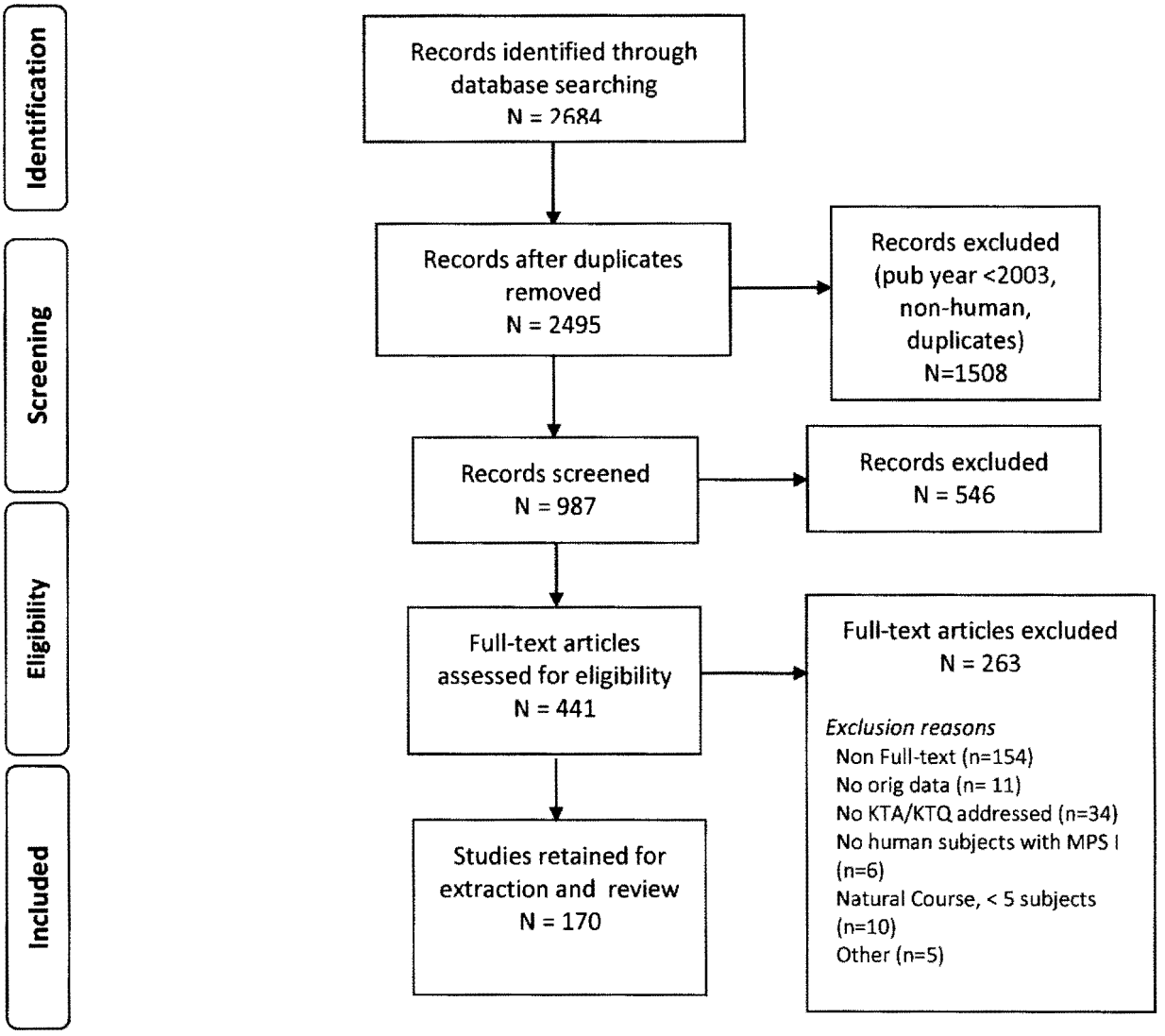
Appendix A. PRISMA Diagram of Published Literature Search



PART II. Decision Modeling to Estimate Population-Level Benefits for MPS I

Overview

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.[1] 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[2], 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 I, this approach was anticipated to aid in the estimation of the range of health outcomes that could be expected for universal newborn screening of MPS I compared with clinical identification.

Applying Decision Analysis to Screening for MPS I

Published literature for rare phenomena including MPS I is usually very limited with respect to data for prevalence, natural history, or response to treatment. Some new data have become available from screening pilot programs in two states. By utilizing modeling for this review, the Advisory Committee anticipated that a model would supplement the evidence base by providing projections of key health outcomes at the population level and highlight evidence gaps, thereby enhancing the overall decision making process.

Expert Panel Meeting Process

Clinical and scientific experts in the screening and treatment of MPS I were identified and invited to serve on an Expert Panel (see Appendix B for list of expert panelists). Expert panel members were asked to provide input on the structure of the decision analysis model, including the identification of key health outcomes to be included in the analysis. A series of three expert panel meetings (11/4/14; 1/6/15; 1/22/15) were conducted to identify sources and derive probabilities for each outcome in the model; to provide feedback on the structure of the initial and revised decision analytic model, including the relevant timeframe for key health outcomes; and to develop assumptions where little or no data were available. All meetings were conducted via webinar. Expert panel participants received a discussion guide prior to the meeting that included background information, 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 1. Timeline - Application of Decision Analytic Model for MPS I Screening

Date	Decision Analysis Milestones
2012	MPS I nominated for addition to uniform newborn screening panel; referred to external condition review group
Fall 2014	Initial development of decision analytic model to evaluate newborn screening for MPS I
Nov 2014	Technical Expert Panel 1 – Review Model Structure
Jan 2015	Technical Expert Panel 2 – Review Revised Model Structure and Input Assumptions
Jan 2015	Technical Expert Panel 3 – Review Revised Input Assumptions and Preliminary Results
Feb 2015	Final MPS-I evidence review report and decision analysis findings presented to Advisory Committee

Methods

An initial decision analysis model was developed concurrently with the evidence review process. The model was reviewed with the expert panel in November 2014 and during 2 separate meetings in January 2015. During each meeting, the structure, endpoints, data sources, and assumptions included in the model were reviewed by the expert panelists. A schematic of the MPS-I newborn screening decision model is shown in Figure 1a-b.

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

- Target population: Annual newborn cohort for the US, excluding newborns at higher risk for MPS I, of 4 million newborns.
- Interventions: A strategy of universal newborn screening (NBS) is compared with diagnosis through clinical identification (Clinical Identification). The analysis assumes that identified cases of severe MPS I will be treated with HSCT whether they are diagnosed through newborn screening or through clinical identification. In other words, the key difference in determining outcomes between the two modeled cohorts – newborn screened or clinically-identified – indicates the benefits of earlier diagnosis and treatment. In other words, infants identified through newborn screening are assumed to initiate treatment ([1] HSCT or [2] ERT followed by HSCT) at an earlier age than severe cases of MPS I identified through clinical identification.
- Timeframe: 1 year, 5 years
- Key health endpoints: Mortality

Two additional expert panel meetings were held in January 2015 to review the decision tree, proposed set of parameter inputs for the decision model, and preliminary results. Parameter inputs were based on published and unpublished data. The model structure and parameter estimates were revised following each expert panel based on additional data sources identified during the expert panel and supplemented

by expert opinion in cases where no data were available. The final set of parameter inputs and associated ranges for the analysis are shown in Tables 2 and 3 below.

Overall Approach

The model estimates outcomes for two identical cohorts of newborns not at higher risk for MPS I. Two strategies for identifying patients with MPS I are modeled: (1) newborn screening for all newborns not at higher risk for MSP-1, and (2) no newborn screening/identified via clinical identification. In the model, one cohort receives newborn screening for MPS I and one cohort does not.

The key endpoint is 5-year mortality. The model also estimates the number of newborns identified with each level of severity of MPS I (severe, attenuated, ambiguous phenotype) as well as screening program outcomes for the newborn screened cohort. Each parameter in the model is defined with a 'most likely' estimate and a range for sensitivity analyses. Ranges are projected for each outcome. The model was programmed using Treeage software.

Key Assumptions

MPS I Cases Identified

- The number of possible and confirmed MPS I cases is expected to be higher under newborn screening compared with clinical identification. There is little evidence to guide assumptions as to the magnitude of the increase in identified cases. The analysis uses a range of 0-20% more cases identified under newborn screening.
- The number of severe cases of MPS I is assumed to be the same under newborn screening or clinical identification. In other words, any "additional" cases of MPS I identified under newborn screening would be attenuated or of unknown phenotype.

Table 2. Key probability inputs, MPS I prevalence and subtypes[1]

	Universal newborn screening (NBS)				**Clinical Identification (CI)**			
MPS-I	**Most Likely**	**Min**	**Max**	**Sources**	**Most Likely**	**Min**	**Max**	**Sources**
Possible & Confirmed MPS I (all subtypes)	1.1 per 100,000	0.54 per 100,000	2.22 per 100,000	MO & IL pilot programs; Scott et al, 2013 Part I, Table 4.1a; Expert Opinion	1.0 per 100,000	0.54 per 100,000	1.85 per 100,000	Malm et al., 2008; Moore et al., 2008 Part I, Table 6.1
Distribution of Severity Conditional on Diagnosis of MPS I (Possible or Confirmed)								
Severe[2]	0.65	0.605	0.698	Derived using data from Beck et al, 2014; MO & IL pilot programs; expert opinion	0.714[3]	0.620	0.762	Beck et al, 2014; Malm et al, 2008; Moore et al., 2008; Assumption
Attenuated[2]	0.05	0.031	0.078		0.286[3]	0.238	0.380	
Unknown Phenotype[2]	0.30	0.224	0.364		N/A			

[1] 95% confidence interval derived using a binomial distribution
[2] within first few months of life
[3] By 5 years of age – assumes that only severe (Hurler) and attenuated (Hurler-Scheie) are diagnosed by 5 years of age

Identification, Diagnosis, and Treatment of Severe Cases of MPS I

- All identified severe cases of MPS I are expected to receive HSCT whether identified through newborn screening. Cases of MPS I for which ERT would be considered the preferred treatement option would be classified as attenuated.
- All cases of severe MPS I would be detected under newborn screening or clinical identification within the first 36 months of life, but at a later age of identification for CI. The difference in detection for newborn screening compared with clinical identifiction will be in the timing of identification, diagnosis, and initiation of treatment (not in the identification of missed cases). Cases identified through newborn screening are assumed to receive transplant several months earlier than those identified through clinical identification. The modeling results represent an estimate of the health benefits that could be associated with earlier diagnosis and treatment for newborn screening compared with clinical identification.
    - Some evidence suggests a survival benefit for earlier vs. later transplant, however, as noted in the evidence review, data available from the MPS I registry do not demonstrate a difference in survival for earlier vs. later age at transplant. The range of estimates in the model include the scenario in which there is not survival benefit. The upper bound included in the modeling estimates are based on data from the MPS I registry which evaluated outcomes for patients who received transplant before or after the median age of transplant for the cohort (16.7 months). This could represent a more optimistic estimate of the effect of treatment due to the greater
    - Evidence suggests there may be a benefit with respect to cognitive impairment for earlier vs. later transplant, however, there are not enough data available to quantitatively model this benefit. There was substantial discussion in the expert panels that earlier transplant would very likely result in preventing cognitive impairment but may not affect survival. Again, there is likely to be confounding due to the use of level of cognitive impairment and other clinical involvement as a factor used in selecting which patients were eligible for transplant.
- We do not make any assumptions about the additive effect of starting ERT prior to HSCT.
- The decision analysis does not include any specific assumptions regarding the use and timing of ERT for attenuated cases of MPS I identified through newborn screening. It is unclear what the recommended protocol will be for this cohort of newborns. The decision to initiate treatment is likely to be based on a number of factors, including results from confirmatory testing; type, severity and timing of onset of clinical signs and symptoms; as well as parent preference. Given the substantial uncertainty pertaining to the use of ERT in this cohort, the analysis will provide estimates of the number of cases likely to fall into this group but does not estimate health outcomes for this cohort.
- Cases classified as 'unknown phenotype' in the analysis are expected to have the same variability with respect to the initiation of ERT as attenuated cases of MPS I. The analysis will provide an estimate of number of cases likely to fall into this group but does not estimate health outcomes for this cohort.

Table 3. Post-HSCT outcomes for severe MPS I.[1]

a. **Mortality**

	Mortality, 1 year following HSCT	5-year Mortality post-HSCT
Screened/Receive Transplant		
Most Likely	0.07	-[2]
(Min, Max)	(0.05, 0.10)	
Sources	Table X/Treatment, cohorts receiving transplant 2002 and later; expert opinion	Derived
Clinically Diagnosed/Receive Transplant[3]		
Most Likely	0.07	-[2]
(Min, Max)	(0.05, 0.10)	
Sources	Table X/Treatment, cohorts receiving transplant 2002 and later; expert opinion	Boelens et al, 2013; Expert opinion

[1]Minimum and maximum values derived from 95% CIs assuming a binomial distribution. 1-year post-transplant outcomes estimated using data from studies that included study subjencts who received transplant in 2002 or later (to reflect newer success rates for transplant)
[2]Data are not reliable enough to provide a most likely estimate; only a range is estimated for this endpoint.
[3]Clinically-diagnosed cases are identified and treated at least several months later than cases identified under newborn screening.

a. **Survival**

	Survival, 1 year following HSCT	5-year Survival post-HSCT
Screened/Receive Transplant		
Most Likely	0.930	
(Min, Max)	(0.90, 0.95)	
Sources	Part I, Table 6.1/Treatment, cohorts receiving transplant 2002 and later	
Clinically Diagnosed/Receive Transplant[5]		
Most Likely	0.930	
(Min, Max)	(0.90, 0.95)	
Sources	Part I, Table 6.1/Treatment, cohorts receiving transplant 2002 and later	

[1]Minimum and maximum values derived from 95% CIs assuming a binomial distribution. 1-year post-transplant outcomes estimated using data from studies that included study subjencts who received transplant in 2002 or later (to reflect newer success rates for transplant)
[5]Clinically-diagnosed cases are identified and treated at least several months later than cases identified under newborn screening.

Results

Projected cases of MPS I (includes confirmed and possible cases):
We projected the annual number of MPS I cases (severe, attenuated, and unknown phenotype) that would be identified with newborn screening compared with clinical identification (Table 4):

- Projected annual cases of possible and confirmed MPS I identified through newborn screening would be 44 cases on average (based on an incidence 10% higher than under clinical identificatin) compared with 40 cases through clinical identification. The 4 additional cases identified through newborn screening are anticipated to fall into the attenuated/unknown phenotype category.

- Of these 44 identified cases:

  - Approximately 65% (range: 61-70%) cases would be severe MPS I.
  - Approximately 35% (range: 26-44%) would be classified as either attenuated or unknown phenotype. (Table 4)

- Compared with newborn screening, it is anticipated that all cases of severe MPS I would be identified through clinical identification but at a later age of identification than with newborn screening.

Table 4. Projected cases for newborn screening for MPS I compared with clinical identification for a cohort of 4 million children (U.S. population)

	Newborn Screening	**Clinical Detection**
Severe	28.6 (13 - 62)	28.6 (13 - 56)
Attenuated	2.2 (0.6 - 6.9)	11.4 (8.2 - 17.6)
Unknown Phenotype	13.2 (7.9 - 19.9)	--
Total MPS I (Confirmed & Possible)	**44** **(22 - 89)**	**40** **(22 - 74)**

Projected Health Outcomes for Cases of Severe MPS I
It is anticipated the earlier identification, diagnosis, and treatment of severe MPS I could result in improved health outcomes:

- Projected 5-year survival could result in improved health outcomes for newborn screening compared with clinical identification with the range of averted deaths in patients with severe MPS I estimated to range from 0-1.3 deaths.

Screening Outcomes

Projected number of true positives, false positives, true negatives and false negatives are listed in Table 5.

Table 5. Projected screening algorithm outcomes for newborn screening for MPS-I compared with clinical identification

	Per 100,000		Per 4 million	
	Newborn Screening (n)	**Range**	**Newborn Screening (n)**	**Range**
Total positive screens	35		1,400	
True positives*	1.1	0.30-3.2	44	22-89
False positive	34	26-43	1,356	1,059-1,708
Total negative screens	99,965		3,998,600	
True negatives	99,965	99,963-99,965	3,998,600	3,998,520 – 3,998,600
False negatives	0	0-2	0	0-80

*Includes possible and confirmed MPS I

Limitations

This analysis uses a simplified model to evaluate projected outcomes for identified cases of severe MPS I under a universal screening recommendation. The model includes projected survival but does not quantify additional health benefits that would likely be associated with earlier identification and treatment of cases of severe MPS I, such as cognitive impairment) nor does it include potential harms (e.g., adverse events associated with treatment) other than mortality rate following HSCT.

The analysis does not include a projection of the number of cases (attenuated or unknown phenotype) that would initiate ERT due to a lack of data on what recommended treatment protocols might be following the initation of newborn screening.

The analysis did not evaluate economic outcomes such as costs or cost-effectiveness of alternative screening modalities. The analysis did not consider health outcomes for identified cases of attenuated or unknown phenotype MPS-I but focused on estimation of health benefits for severe cases.

Summary

- Assuming an annual US newborn cohort of 4 million, not at increased risk for MPS I, newborn screening is projected to identify 44 cases, including severe, attenuated, and unknown phenotype.
- Of these 44 cases (range 22-89),
    - 29 cases are expected to be severe (range: 13-62).
    - 15 cases are expected to be attenuated or of unknown phenotype (range: 9-27).
- Earlier identification and treatment could result in lower mortality but currently available evidence do not consistently support this potential finding. The projected range of averted deaths by 5 years of age for newborns with severe MPS I is 0 to 2 deaths.
- Earlier identification and treatment may also result in improved cognitive and other health outcomes for severe cases. There was not enough evidence available to quantitatively estimate the anticipated benefit in cognitive and other health outcomes for cases identified and treated earlier due to newborn screening.
- Overall, the decision modeling highlighted the uncertainty reflected in the evidence base for estimating long-term outcomes (5 years or longer) associated with NBS for MPS I.

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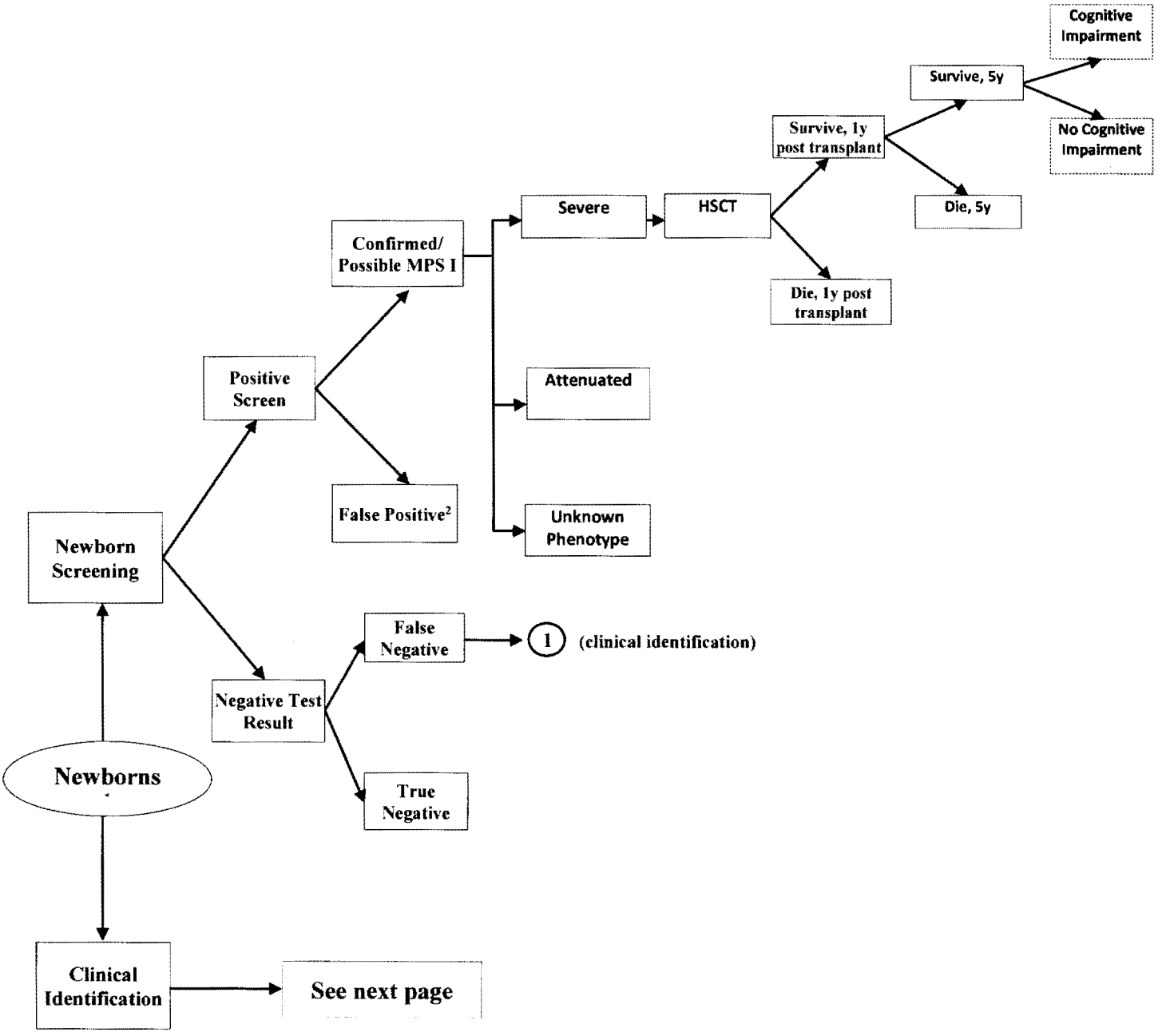
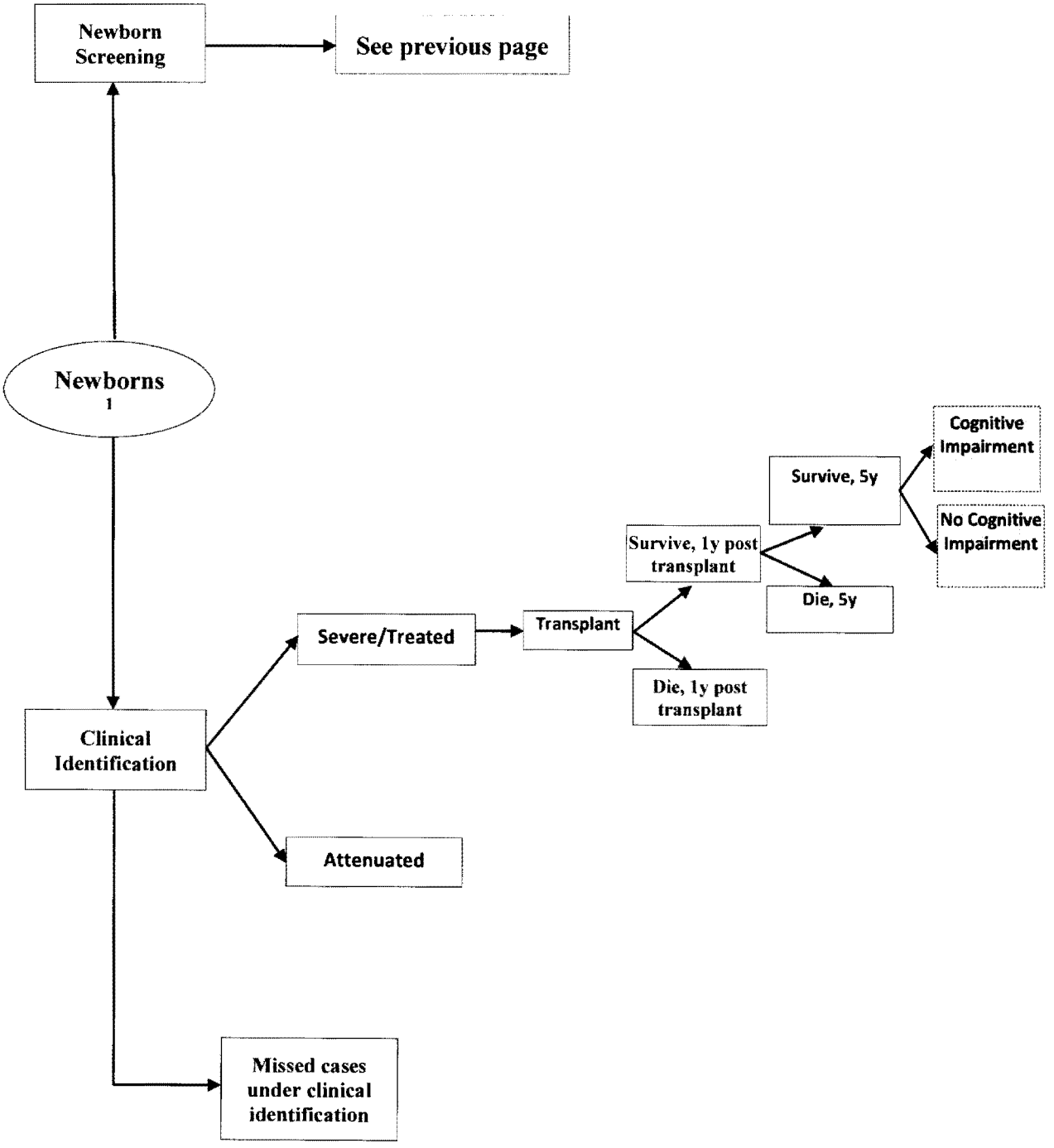
Figure 1.a. Schematic for MPS I Newborn Screening Decision Model (Screening Submodel)



[1]Not at high risk
[2]Includes true false positives, carriers, and pseudo deficiencies

Figure 1.b. Schematic for MPS I Newborn Screening Decision Model (Clinical Identification Submodel)



[1]Not at high risk

Part III. Public Health System Impact Assessment

Introduction

The purpose of this public health system impact assessment is to assess individual state newborn screening (NBS) programs' readiness and feasibility to implement screening for Mucopolysaccharidosis (MPS I).

Methods

The public health system impact assessment was based on web-based surveys of states that have not carried out any activities related to newborn screening for MPS I and detailed interviews of states that have begun any activity related to implementation of newborn screening for MPS I. The goal was to assess feasibility and readiness, as described in the subsequent section. In order to assure that respondents had familiarity with newborn screening for MPS I, a Fact Sheet was distributed and a webinar was held, as described below.

Feasibility and Readiness
Feasibility as defined by the CRW is based on the degree to which the following exist:

- An established and available screening test
- A clear approach to diagnostic confirmation
- Acceptable treatment plan, and
- Established approach to long-term follow-up plans

Some of the key issues related to feasibility extend beyond the public health system and into personal medical care services.

Readiness refers to the ability to adopt a condition into newborn screening and is classified as:

- Ready: most NBS programs could implement within 1 year
- Developmental Readiness: most NBS programs could implement within 1–3 years
- Unprepared: most NBS programs would take more than 3 years to implement

Fact Sheet
The fact sheet, which was created in collaboration with APHL, members from the CRW and individuals from state NBS programs, provided background information pertaining to MPS I to assist individuals with completing the survey (Appendix A). The fact sheet was sent to NBS program directors along with an MPS I survey. The MPS I fact sheet, included information such as incidence of the disorder, screening methods, resources/materials, workstation resources and capacity, personnel requirements, quality control and reported screening results, estimated costs, short-term follow up, and treatments.

The fact sheet provided information about two screening methods for MPS I: flow injection tandem mass spectrometry (MS/MS) and digital microfluidics, based on a Washington NBS research study using anonymous dried-blood spots and a Missouri pilot study with linked

specimens and clinical follow-up. Limitations of the fact sheet were that performance requirements (e.g., laboratory personnel, instrumentation) may not accurately reflect performance in any one particular state, cost data were based on projections, and there was little data regarding screening performance and health outcomes.

Survey

APHL developed a web-based survey instrument intended to evaluate states' readiness to implement comprehensive screening for MPS I. The survey was initially pilot tested with five NBS programs. Feedback from those programs was incorporated into the final survey instrument (Appendix B). The survey instrument included questions related to funding challenges, programmatic and system factors that may hinder or aid in implementation, and timeframe to complete implementation activities.

The survey link was sent to one state designee (e.g., program director) in 53 U.S. states and territories via email. NBS programs that contract services were given a slightly different version of the survey. The survey email emphasized that the individual completing the survey should collaborate with necessary stakeholders (e.g., laboratory experts, follow-up staff, medical specialists, Title V directors, advocates, public health commissioners) prior to completing the survey link. The time frame to complete the survey was from November 13, 2014 to January 7, 2015. All survey data was submitted electronically to APHL.

Interviews

NBS programs that had a requirement or other mandate to screen for MPS I, either as part of a pilot program or across the entire population were excluded from the web-based survey; instead, representatives from such NBS programs were interviewed by telephone. These respondents were informed to prepare for the interview by reviewing the questions and consulting with stakeholders in their public health system. Stakeholders were encouraged to be on the call. APHL designed a combination of open- and close-ended interview questions (Appendix C) meant to assess challenges and successes. The interview tool included questions related to the implementation process, screening methods, outcomes, timeframe for implementation, personnel, and follow-up issues. Interviews were conducted in December 2014.

Webinar and Outreach

APHL conducted a webinar on November 18, 2014, to discuss the purpose of the public health system impact assessment, benefits of completing the survey, and the MPS I factsheet.

APHL discussed the public health system impact assessment and survey at several meetings and conference calls. Additionally, emails were distributed to the Principal Investigators of the seven Genetics and Newborn Screening Regional Collaborative groups. The email discussed the importance of their input to ensure that the point of contact for each state in their region would follow through on completing the survey.

Throughout November and December 2014, APHL conducted active follow-up with survey non-responders through phone calls and emails to improve participation.

Data Analysis
Data were kept secure and reviewed for accuracy. Quantitative and qualitative data from the surveys were aggregated for analysis using Qualtrics and Excel. Interview data were de-identified for anonymity.

Results

Interview Analysis
The following state NBS programs were excluded from the web-based survey and completed in-depth interviews.

Table 1: NBS Programs Interviewed

Illinois	X		X
Missouri	X	X	
New Jersey	X		

The three state NBS programs that were interviewed were the only programs in the U.S. to have conducted MPS I pilots outside of a research setting or that had a mandate to screen. One program has performed MPS I screening for 23 months, a second for 3 months and a third program has not begun screening. All programs have been screening or plan to screen for multiple lysosomal storage disorders (LSDs). Specific findings from these screening activities are described in the systematic evidence review.

NBS program directors from each state explained that after receiving a mandate to screen, they completed an elaborate implementation process. Some considerations during this process included meeting with state Advisory boards and subcommittees to gather evidence and input, obtaining equipment, choosing and validating a screening method, developing clinical protocols, resolving database/Laboratory Information Management System (LIMS) issues, collaborating with medical specialists, and conducting pre-pilots.

NBS program directors discussed the following barriers with regards to implementing MPS I: cost and time involved with obtaining new equipment and making laboratory upgrades, hiring dedicated staff for testing, dealing with a high number of false positives and cases of pseudodeficiency, the intricacies and time required for the method validation process, the low incidence of the disorder, difficulty creating treatment algorithms, uncertainty regarding age of onset and how to handle unknown genotypes and ambiguous cases, and the broad burden on the medical system due to multi-system involvement of the disorder.

The NBS program directors discussed factors that have or will aid in implementation for MPS I. These factors include: increasing the potential yield of screening by multiplexing MPS I with other LSDs, conducting a pilot first prior to statewide screening, having infrastructure established (e.g., laboratory equipment, resources, and staff), and developing well-defined

protocols. They all highlighted the importance of having strong relationships, communication and expertise from staff as well as medical professionals and other partners.

NBS program directors chose a method based on their program's screening needs. Justification for selecting the flow injection MS/MS method was that it could be used to multiplex with all the LSDs, while justification for selecting the digital microfluidics method was that it was inexpensive and required no retrofitting and less staff time. The programs that were using or plan to use the MS/MS method, had to procure between 3 and 4 new MS/MS instruments dedicated to LSD screening through either purchase or rental bundled with reagents, a.k.a. reagent rental. They also purchased ancillary items such as centrifuges and 96 channel pipettors. The NBS program that was using digital microfluidics procured the analyzers through reagent rental and purchased ancillary items and a freezer.

Despite using different screening methods, the NBS program directors and colleagues were satisfied with the particular method they had chosen or were planning to use. Generally, some of the challenges that were seen when implementing a method included the time required to validate it, adjusting cutoffs to reduce false positives, not having quality control or proficiency testing materials available from the Centers for Disease Control and Prevention (CDC), and, for some programs, not having a Food and Drug Administration (FDA) approved kit is a negative. The program directors believed they would continue using the method they were using. Some indicated they would consider making minor tweaks, particularly if an FDA approved kit becomes available.

NBS program directors interviewed believed it would take at least 2 years to complete the entire implementation process from obtaining equipment to conducting statewide screening. These program directors believed it would take other programs less than one year or one to two years to perform each of the activities involved in the process such as validating the method, hiring staff, consulting with medical staff, obtaining equipment, and pilot testing.

NBS program directors discussed personnel and follow-up issues during the interviews. In general, it appeared that the digital microfluidics method required fewer FTEs than the flow injection MS/MS method (1.75 FTE vs. 3 FTE per 100,000 samples/year) to screen for multiple LSDs. Obtaining staff was thought to be a concern for the NBS program with a mandate to screen.

Some follow-up concerns that were discussed by the NBS program directors included: uncertainty regarding how to deal with cases of pseudodeficiency and mutations of unknown significance, duration of time required to follow-up these cases, developing clear and consistent follow-up protocols, uncertainty surrounding volume of cases that may require follow-up, having access to an established network of physicians that are geographically distributed, and deciding what to do with long-term outcome data.

When asked what advice NBS program directors had for other states to ensure smooth and timely implementation, they mentioned data sharing and creating flexible timelines, gathering facts and researching methods early, participating in the rule making process if possible, being proactive with partners, and creating protocols early.

Survey Analysis
A total of 39 completed surveys were received from 53 U.S. states and territories, for a response rate of 74%. Three state NBS programs were excluded from the analysis because they participated in the interview.

The following table categorizes the responsible party for providing NBS laboratory services for the programs (Note that more than one option could have been chosen).

Table 2: Characteristics of Survey Responders

Your own state's public health or NBS laboratory	26	72%
A contracted regional NBS laboratory or other not-for profit laboratory	9	25%
A contracted commercial laboratory	5	14%
Other - please specify:	2	6%
None of the above	0	0%

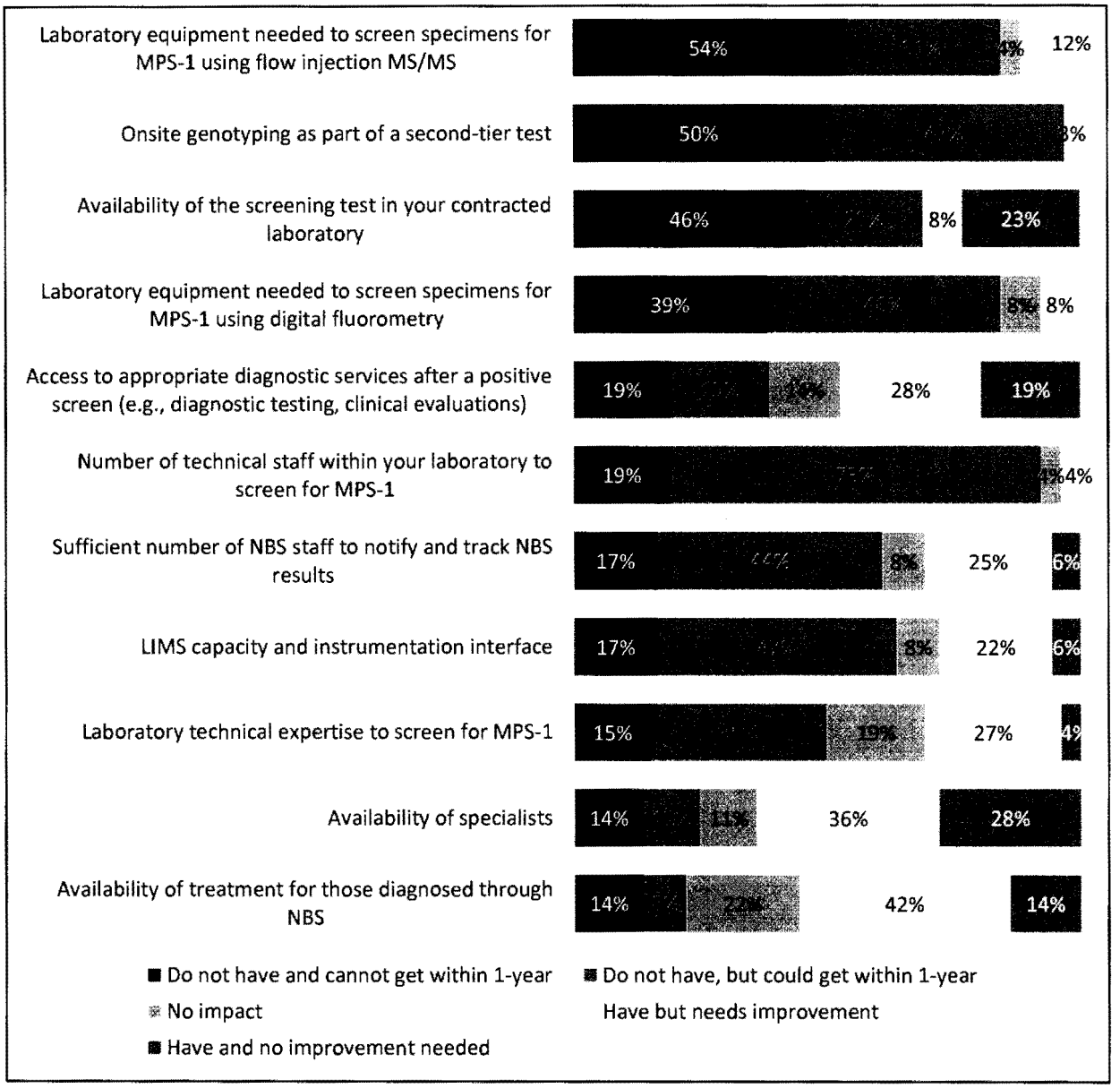
Table 3: Funding Challenges Related to NBS Program Activities for MPS I[1]

Providing the screening test	29	81%	5	14%	2	6%
Long-term follow-up for those with late-onset disease or who are carriers*	26	74%	7	20%	2	6%
Increasing your NBS fee	20	56%	14	39%	2	6%
Support to treatment for MPS I*	18	51%	13	37%	4	11%
Support to specialists in MPS I	17	47%	15	42%	4	11%
Short-term follow-up of abnormal screening tests, including tracking and follow-up testing	14	39%	17	47%	5	14%

*35 total responses yielded for this category

[1] Full question text: 5. Please categorize the funding challenges related to NBS program activities for MPS I in your state.

Figure 1: Factors Impeding or Facilitating Screening for MPS I[2]



[2]Full question text: 6a. Other than funding, certain factors related to MPS I might make screening easier or more challenging in your state. Please let us know the degree to which these factors impede or facilitate your ability to screen for MPS I in your state. In order to respond to these questions, assume that MPS I has been authorized for addition to your state's panel and that funds for both laboratory testing and follow-up are made available. To what extent do the factors below impede or facilitate the adoption of screening for MPS I in your state?

Table 4: Factors Impeding or Facilitating Screening for MPS I[3]

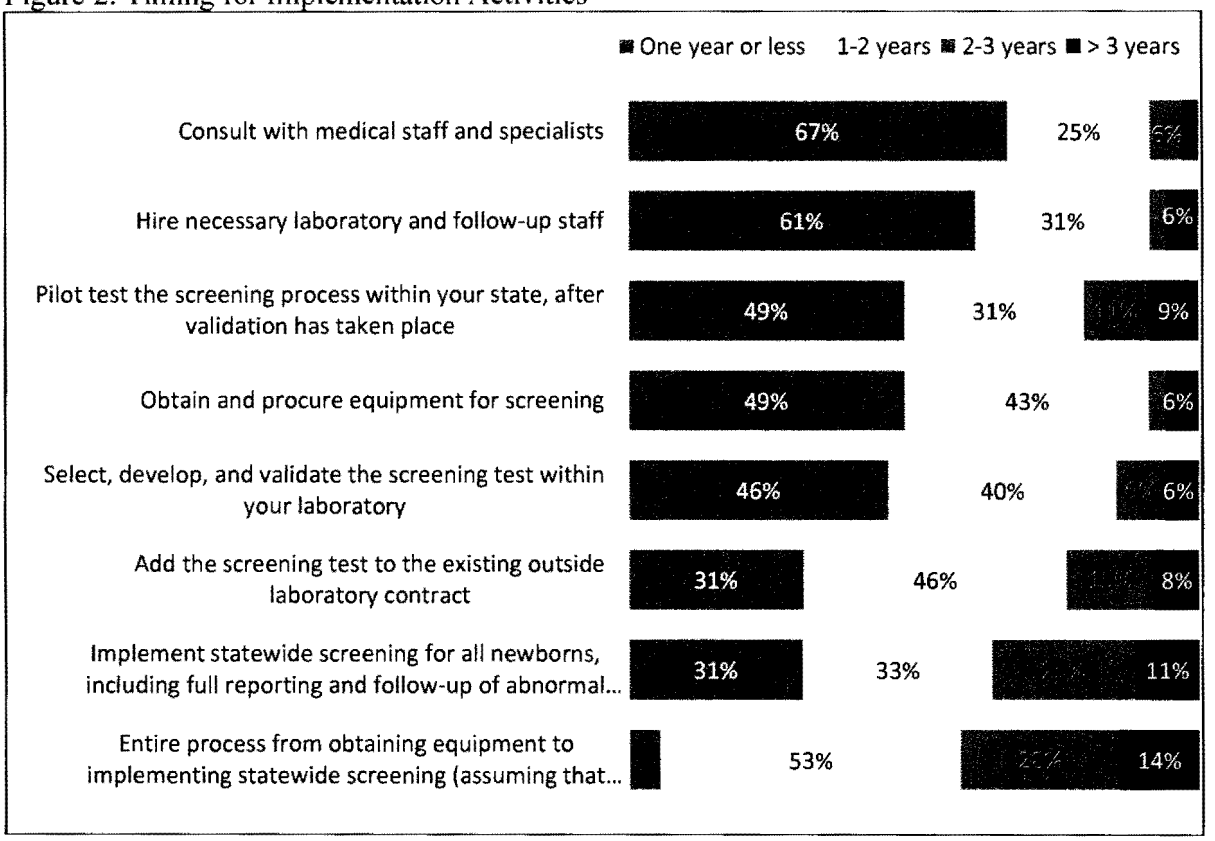
Cost per specimen to conduct screening (personnel, equipment, reagents)	13	36%	19	53%	1	3%	3	8%	0	0%
Other ongoing NBS program activities (e.g., addition of other conditions, other quality improvements)	11	31%	18	50%	0	0%	5	14%	2	6%
Predicted run time to screen for MPS I as it relates to other workload	8	22%	14	39%	0	0%	14	39%	0	0%
Extent to which screening protocol for MPS I has been demonstrated in other NBS programs	7	19%	7	19%	5	14%	4	11%	13	36%
Cost of treatment for newborns diagnosed with NBS	4	11%	21	58%	1	3%	9	25%	1	3%
Other non-NBS public health priorities within your state	4	11%	14	39%	0	0%	17	47%	1	3%
Expected clinical outcomes of newborns identified by screening	3	8%	14	39%	4	11%	6	17%	9	25%
Expected cost-benefit of screening in your state	3	8%	10	28%	3	8%	8	22%	12	33%
Advocacy for screening for this condition	0	0%	3	8%	4	11%	9	25%	20	56%

6c. What is the most significant barrier to NBS for MPS I in your state?
Multiple responses were captured for this question. Eighteen programs (50%) responded that funding and costs associated with implementation was the most significant barrier to implementation. NBS programs also responded that significant barriers included not having MPS I on the Recommended Uniform Screening Panel (RUSP), the condition not meeting criteria for screening, limited Enzyme Replacement Therapy (ERT) capabilities, as well as uncertainty regarding what to do with false positives and mild cases of the disorder.

[3] Full question text: 6b. Other than funding, certain factors related to MPS I might make screening easier or more challenging in your state. Please let us know the degree to which these factors impede or facilitate your ability to screen for MPS I in your state. In order to respond to these questions, assume that MPS I has been authorized for addition to your state's panel and that funds for both laboratory testing and follow-up are made available. To what extent do the factors below impede or facilitate the adoption of screening for MPS I in your state?

6d. What would most facilitate screening for NBS MPS I in your state?
Multiple responses were captured for this question. Nine programs (25%) responded that having treatment, clinical and outcome evidence showing the utility of screening would most facilitate implementation. Eight programs (22%) responded that funding associated with implementation would most facilitate screening. Other responses included approval of an FDA approved kit and addition to the RUSP.

Figure 2: Timing for Implementation Activities[4]



[4]Full question text: 7. How long would it take to achieve the following assuming that MPS I was added to your state NBS panel and funds were allocated today, with your current NBS program and laboratory infrastructure?

Summary

Most (79%) of the state NBS programs that were surveyed or interviewed reported that it would take between 1 and 3 years to implement screening for MPS I after approval and allocation of funds. Funding challenges, which should not be understated, were commonly reported in this assessment. Several other important barriers related to feasibility were reported, including uncertainty about cases of pseudodefiency, mutations of unknown significance, and long-term follow-up. The two states that have begun to offer screening for MPS I have used different approaches to the screening test and provide lessons about implementation. However, detecting a large number of false positives and cases of pseudodeficiency has been challenging for those states.

The majority of NBS programs were confident that they could complete many implementation activities in 2 years or less. For example, 80% of programs believed they could complete a pilot, 92% believed they could procure equipment and 86% believed they could validate a screening test in 2 years or less respectively. A major factor seen in aiding implementation was advocacy (56%).

The following specific issues were identified:

- No quality assurance/quality control (QA/QC) or proficiency testing materials have been made available by the CDC.
- There is no FDA-approved kit for MPS I, which can be a barrier to adoption in those states that are required to use FDA-approved assays.
- Establishing diagnosis after a positive screen, including predicting severity, can be challenging.
- The treatment protocol for those with an ambiguous phenotype or those with suspected attenuated disease is not clear, which can present challenges for newborn screening programs.

Although most respondents reported that screening for MPS I could be implemented between 1 and 3 years after funding was made available, it is critical to recognize that obtaining funding for the screening test was seen as a major challenge by 81%. Fifty-four percent of NBS programs surveyed stated they could not get additional MS/MS instrumentation for MPS I screening within one year, while 39% stated they could not get digital microfluidics equipment within one year. In general, NBS programs surveyed noted more difficulties obtaining equipment and getting the screening test approved within one year and fewer difficulties acquiring and training staff and getting access to specialists within one year.

Respondents also highlighted the potential efficiency of multiplex screening for the LSDs

There were several limitations to this evaluation. In many of the survey questions, respondents were asked to assume approval had occurred and funds were allocated. This was not meant to underestimate the importance and time commitment involved with these steps, but rather to have responders consider specific implementation activities outside of funding and legislation. It is

plausible to assume that getting approval and acquiring funds could add years to the timeframe for implementation. Additionally, although NBS program directors likely relied on experiences implementing other conditions, the questions in the survey were hypothetical and responses were subjective. Interviews assisted in gathering additional information pertaining to real world barriers and facilitators as well as screening outcomes.

Appendix A: PHSI Fact Sheet

Public Health System Impact Assessment:
Fact Sheet for MPS I Screening

Condition	MPS I
Description	Autosomal recessive Lysosomal Storage Disorder caused by a deficiency of alpha-L-iduronidase enzyme; many systems can be affected, including cardiac, respiratory, brain & CNS, and muscle and skeletal; the disease has three phenotypes, which include Hurler (severe form), Hurler/Scheie and Scheie (attenuated forms); current treatments for the disorder include hematopoietic stem cell transplantation (HSCT) for the severe form only and enzyme replacement therapy (ERT)
Expected Incidence	Clinical detection= ~0.54 to 1.15 per 100,000 births (all forms) Detection by laboratory screening= ~1 to ~3 per 100,000 births (all forms); estimates from Missouri pilot Clinically ~61% of all cases are severe, while ~39% are attenuated[5]

Measurement Method[6]	*Flow injection tandem mass spectrometry (PE-FIA MS/MS 2014)*	*Fluorometry by digital microfluidics platform*
Data Source(s)	Anonymous research study in collaboration with Drs. Ron Scott and Michael Gelb, and Washington NBS program	Missouri statewide newborn screening pilot with linked specimens and clinical follow-up
Screening Marker	Enzyme Activity	Enzyme Activity
Screening Strategy	Tagged synthetic substrate and measurement by tandem MS/MS	Four MU tagged synthetic substrate and measurement by fluorescence

Resources and Materials		
Minimum Instrumentation, Equipment and Requirements Necessary to Process 50,000 Specimens Annually (Includes Conventional	• Shaker/incubator • Multichannel pipettor • 2 MS/MS (Note: MS/MS cannot be multiplexed with amino acids and acylcarnitines)	• Shaker • Multichannel pipettor • 4 digital microfluidics analyzers

[5] Beck M. et al., 2014. The natural history of MPS I: Global perspectives from the MPS I Registry. Genetics in Medicine, 16, 759-765.
[6] Other methods not depicted here include LC-MS/MS and fluorometry on microtiter plate.

Redundancies)	• Nitrogen and exhaust • Plate centrifuge • Solvent/dryer	
Instrumentation Per Detection Workstation to Process 50,000 Annually	1 MS/MS	4 digital microfluidics analyzers
Equipment Suppliers and Availability of Kits, Reagents and Consumables	**MSMS** Perkin Elmer **Artificial Substrates (ASR):** Genzyme is the sole source, distributes through CDC; continued availability of these ASR substrates is unlikely. **Note:** Perkin Elmer (PE) and the University Washington have developed a 6-plex kit, pending FDA approval ~2016 **Consumables:** Routine purchase	**Digital Microfluidics** Baebies (formerly Advanced Liquid Logic, acquired by Illumina, Inc.) is the sole source for DMF instrument **Artificial Substrates:** Baebies is sole source **Consumables:** Baebies is sole source for purchase of microfluidics cartridges

Specimens (with Controls) Processed at One Workstation	80 to 96 specimens per plate x 1 plate per instrument x 1 instrument = 80 to 96 specimens	40 specimens per plate x 1 plates per instrument x 4 instruments per workstation = 160 specimens
Tech Time to Prepare Specimens (Extraction and Loading Cartridges)	Not available	1 hr.
Instrument Time	3 hrs. MS/MS (multiplexible) to get 1 plate	4 hrs. (multiplex 4 LSDs) to get daily results
Enzyme Incubation Time	16 hrs.	The enzyme incubation occurs very quickly within the cartridge on the platform during the instrument run time
Maximum Number of Specimens to Be Analyzed at One Workstation During An 8 Hour Shift	192 specimens	320 specimens
Space Requirements (Supporting Equipment Not Included)	23 x 32", 14 cu ft. (one MS/MS)	32 x 96" (fluorometry workstation)

FTE Needed to Process 50,000 Specimens Annually (From Sample Receiving Through Result Interpretation)	1 FTE (one MS/MS)	0.75 FTE
FTE Needed to Process 100,000 Specimens Annually	Not available	Not available

LIMs Adjustments	Not available	Not available
Training	Not available	Not available

Availability of Quality-Control Specimens	In development at CDC, but not yet validated	Proficiency testing materials in development at CDC but not yet validated (developed for Pompe); Routine plate controls and calibrators provided by Baebies
Reported Rate of Retests (Same Specimen)	Not available	~1% of total DBS specimens received will need to be re-punched and re-tested in duplicate due to a breach of the in-house cutoff
Reported Rate of Repeats (Independent Specimen)	Not available	~ 0.49% of specimens will require a repeat/independent specimen to be collected
Rate of Referrals[7]	Projected rate= 9/106,526 or ~8 per 100,000	Reported rate= 57/117,000 or ~45 per 100,000

[7] Caution is needed when comparing number of referrals for these methods. Data from WA specimens entailed retrospective, blinded specimens with no follow-up. Confirmation was by DNA testing. Missouri data was from a prospective population based pilot study with confirmatory testing, diagnosis and follow-up. Screening in Missouri began purposefully conservative to give the highest sensitivity before working to enhance specificity. Missouri's referral rate is expected to decrease once statewide screening is initiated.

Reported Outcomes[8]	#by type(s): (n=106,526 DBS) Confirmed= 3 Pseudo def= 0 Carriers= 1 False positives= 3 Poor punch= 2	#by type(s): (n=117,000 DBS) Confirmed= 1 Pseudo def= 24 Carriers=3 False positives= 24 Pending= 4 Lost to FU= 1

Equipment Cost (Overhead)	**Equipment purchase for use with reagents:** $220,000-$250,000 for one 1 MS assuming useful life of 10 years, straight-line depreciation of $220-225,000 per year; annual cost of maintenance contract and electricity of $33,200; instrumentation cost per specimen	Not available
Estimated Cost to Laboratory of Reagents or FDA-Approved Kit[10]	Stated costs to manufacture reagents range from ~$0.07-$.10 per specimen for each of the 6 LSDs; $0.42-$0.60 for 6 LSDs ~$0.12-0.15 per specimen for each of the 6 LSDs; ~$0.73-$0.88 for all (assumes 80,000 annual specimens, one-screen state, and one MS/MS)[11] Likely price to be charged by manufacturer will be no less than $1.00 per condition per specimen[6]	Not available
Estimated Reagent Rental Cost **(Includes Instruments, Reagents, Cartridges,**	Not available	Price charged by manufacturer likely to be no less than $1.00 per condition per specimen

[8] See above

[9] Cost estimates presented in this document have a high level of uncertainty at this point in time; the only high throughput clinical laboratory is running digital microfluidics.

[10] FDA kits are pending approval and costs are still unknown.

[11] Costs for instrumentation and maintenance will vary based on number of annual specimens screened; for example, it will double for states that screen 45,000 specimens vs. 90,000.

Estimated [illegible] Costs		
Service and Tech Support)		
Estimated Personnel Cost To Screen 50,000 to 100,000 Specimens Annually (Follow-Up Not Included)[12]	Level: Advanced Chemist Number: 2 $150,000 for 2 advanced chemist FTEs (salary, benefits overhead)	Level: Junior Chemist Number: 0.75 Assuming $100,000 for 1 Junior Chemist FTE (salary, benefits, overhead)
Estimated Diagnostic Assay Cost	$200-$600	$200-$600
Estimated Diagnostic Molecular Testing Costs	$1000-$2800 (full gene)	$1000-$2800 (full gene)

[illegible]	
Description	Approximately 10-20% FTE from follow-up staff is needed to make staff calls; Diagnostic centers handle positive specimens by conducting Iduronidase (IDUA) enzyme activity assay, urine glycosaminoglycan (GAGs), and genotyping; a geneticist interprets results (Missouri experience)
Case Definition Applicable to Neonatal Period	Iduronidase activity in leukocytes or in culture skin fibroblast must be <1% normal activity
Diagnostic Method & Criteria	Definitive MPS I= IDUA enzyme activity < 1% normal Supportive of diagnosis= Increased GAG levels in urine Genotyping can assist if a known pathogenic mutation is detected
Availability of Diagnostic Centers	There are ~4-5 diagnostic laboratories in the U.S.; Missouri utilizes Greenwood Genetics and Mayo Clinic to conduct genotyping; Missouri utilizes Greenwood Genetics, Mayo Clinic and UPenn for IDUA enzyme level diagnostics

Current Treatment [illegible]		
Description and Current Treatment Guidelines with Clinical Identification	**HSCT**= Recommended for patients 2 to 2.5 years with little cognitive decline (≤70 developmental quotient) **ERT** may be given in conjunction with HSCT (pre- and post-HSCT)	**ERT** = standard recommended treatment with current clinical identification
Specialty Providers or Centers	Availability of specialty providers and centers varies by state; each center usually has a defined region it serves; some patients may have to travel long distances to reach a treatment center; this could have major implications on patients who need ERT infusions every two weeks	

[12] Personnel costs will vary based on FTE for particular state and number of annual specimens.

Appendix B: PHSI Assessment – NBS Program Survey

MPS I Public Health Impact Assessment Survey

The purpose of this survey is to inform the Secretary of Health and Human Services Discretionary Advisory Committee about states' ability to add newborn screening (NBS) for Mucopolysaccharidosis I (MPS I) using information gathered from most of the states in the U.S.

Please refer to the MPS I screening factsheet to answer the following questions about the ability to add NBS for MPS I in your state. Please also note that only one person in each state has received this survey. We ask that you consult with others within your state, including laboratory and follow-up staff, medical professionals and specialists, prior to completing the survey.

Data Use Permission

The APHL NewSteps program would like to update your public state profile in the NewSteps Data Repository using data from questions 1-4 from this survey.

Will you give us permission to utilize this data?

- Yes, you have my permission
- No, you do not have my permission

1. Does your state currently include MPS I NBS as a part of the routine NBS panel or as any type of pilot evaluation?
   - Yes (end survey)
   - No

2. Within the last three years, has your state included...*Please check all that apply.*
   - MPS I as part of the routine NBS panel (*end survey*)
   - MPS -1 as any type of pilot evaluation (*end survey*)
   - None of the above (*go to question 3*)

3. Has there been a state-level decision to start screening for MPS I as part of NBS?
   - Yes (end survey)
   - No

4. **Which of the following provides NBS laboratory services for your state's NBS program?** P*lease check all that apply.*
   - Your own state's public health or NBS laboratory
   - A contracted regional NBS laboratory or other not-for profit laboratory
   - A contracted commercial laboratory
   - Other – please specify:
   - None of the above

5. Please categorize the **funding** challenges related to NBS program activities for MPS I in your state.

Providing the screening test				
Short-term follow-up of abnormal screening tests, including tracking and follow-up testing				
Support to specialists in MPS I				
Support to treatment for MPS I				
Long-term follow-up for those with late-onset disease or who are carriers				
Increase your NBS fee				

5a. Please describe any additional challenges.

6a. **Other than funding**, certain factors related to MPS I might make screening easier or more challenging in your state. Please let us know the degree to which these factors impede or facilitate your ability to screen for MPS I in your state. In order to respond to these questions, assume that MPS I has been authorized for addition to your state's panel and that funds for both laboratory testing and follow-up are made available.

To what extent do the factors below impede or facilitate the adoption of screening for MPS I in your state?

Factor						
Laboratory equipment needed to screen specimens for MPS I using flow injection MS/MS*						
Laboratory equipment needed to screen specimens for MPS I using digital fluorometry*						
Laboratory technical expertise to screen for MPS I*						
Number of technical staff within your laboratory to screen for MPS I*						
Availability of the screening test in your contracted laboratory~						
Onsite genotyping as part of a second-tier test						
LIMS capacity and instrumentation interface						
Sufficient number of NBS staff to notify and track NBS results						
Access to appropriate diagnostic services after a positive screen (e.g., diagnostic testing, clinical evaluations)						
Availability of specialists						
Availability of treatment for those diagnosed through NBS						

** Please respond to these factors if you selected "Your own state's public health or NBS laboratory" at question 4.*

~ Please respond to this factor if you selected "A contracted regional NBS laboratory or other not-for profit laboratory" or "A contracted commercial laboratory" at question 4.

6b. **Other than funding**, certain factors related to MPS I might make screening easier or more challenging in your state. Please let us know the degree to which these factors impede or facilitate your ability to screen for MPS I in your state. In order to respond to these questions,

assume that MPS I has been authorized for addition to your state's panel and that funds for both laboratory testing and follow-up are made available.

To what extent do the factors below impede or facilitate the adoption of screening for MPS I in your state?

Factor						
Predicted run time to screen for MPS I as it relates to other workload						
Other ongoing NBS program activities (e.g., addition of other conditions, other quality improvements)						
Extent to which screening protocol for MPS I has been demonstrated in other NBS programs						
Cost per specimen to conduct screening (personnel, equipment, reagents)						
Cost of treatment for newborns diagnosed with NBS						
Expected clinical outcomes of newborns identified by screening						
Expected cost-benefit of screening in your state						
Advocacy for screening for this condition						
Other non-NBS public health priorities within your state						

6b1. Please describe any additional factors.

6c. What is the most significant barrier to NBS for MPS I in your state?

6d. What would most facilitate screening for NBS MPS I in your state?

7. How long would it take to achieve the following assuming that MPS I was added to your state NBS panel and funds were allocated today, with your current NBS program and laboratory infrastructure?

Activity					
Obtain and procure equipment for screening					
Hire necessary laboratory and follow-up staff					
Consult with medical staff and specialists					
Select, develop, and validate the screening test within your laboratory					
Add the screening test to the existing outside laboratory contract~					
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 abnormal screens after validation and pilot testing					
Entire process from obtaining equipment to implementing statewide screening (assuming that some activities may occur simultaneously)					

~Please respond to this activity if you selected "A contracted regional NBS laboratory or other not-for profit laboratory" or "A contracted commercial laboratory" at question 4.

8. Please share any additional information regarding implementation of NBS for MPS-

9. Please provide information about the respondent:
   Name:
   Phone number:
   Email address:
   Job title

10. How long have you had this position?

- < 1 year
- 1-3 years
- 4-6 years
- 7-9
- More than 10 years

11. 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
- MPS I Specialists
- Primary care providers
- Advocates within your state for MPS I screening
- Others- please specify: _____
- None of the above

Thank you for completing the survey!

Appendix C: PHSI Interview Questions for State NBS Programs

MPS I Interview Questions For State NBS Programs

IMPLEMENTATION PROCESS

The first few questions deal with the implementation process and some of the decisions your program had to make. In what capacity are you screening for MPS I? How long have you been screening?

1. *(Those with mandate)* If you have not started screening, when do you plan to start?
2. (*For those who are in pilot stage*) How long do you anticipate to be in a pilot phase? Was this planned? Please explain.
3. Please tell us how you implemented/plan to implement MPS I.
4. *(For those who have started)* After having gone through this process, was there something you would have changed?
5. *(For those who have started)* Did you have any surprises with implementation? Please explain.
6. What has been/will be the most significant barrier to MPS I screening?
7. Is there something specific to your program that has/will aid in implementing MPS I screening?

METHODOLOGY

8. The next few questions deal with screening methodology.
9. What method are you using/do you plan to use to screen for MPS I?
10. Why did you choose x method?
11. Please explain what new equipment you needed to/will need to procure for this method?
12. *(If screening has begun)* Are you getting the outcomes you expected with this method? Please explain why or why not.
13. Have you had to adjust your cutoff? If so, why? Has this changed your outcomes?
14. Do you have concerns with the method you are using/planning to use? Please elaborate.
15. Will you continue using this method? Explain.

TIMEFRAME

16. In an attempt to better understand timeframe for a variety of implementation activities we would like to know how long it took/will take you to do the following (answer options < 1yr., 1-2 yrs., 2-3 yrs. >3 years):
    - Obtain and procure equipment for screening
    - Hire necessary laboratory and follow-up staff
    - Consult with medical staff and specialists
    - Select, develop, and validate the screening test within your laboratory
    - Add the screening test to the existing outside laboratory contract
    - 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 abnormal screens after validation and pilot testing
    - Entire process from obtaining equipment to implementing statewide screening (assuming that some activities occurred simultaneously)
17. What advice do you have for other state NBS programs in order to ensure smooth and timely implementation?

PERSONNEL AND FOLLOW-UP

18. The next few question are more specific and deal with personnel requirements and follow-up issues. Do 18you have staffing concerns with MPS I screening? If so, what are they?
19. How many FTEs and what level (education/experience) do you have for MPS I screening (technical only)?
20. This question pertains to follow-up. Do you have concerns with short-term and long-term follow up for MPS I? If so what are your concerns?

CONCLUSION

21. That concludes the formal part of the interview. Do you have anything else to add?
22. Name of respondent, title, how long in position.
23. Did you consult with anyone to prepare for the interview? If so, whom?

Supplement: Evidence Tables for MPS I Published Reports

283	M. Sauer, B.	Allogeneic blood SCT for children with Hurler's syndrome: results from the German multicenter approach MPS-HCT 2005	Bone Marrow Transplant	2009	SCT w condition reg	In an attempt to improve long-term engraftment and to reduce regimen-related toxicity (RRT), a prospective multicenter approach was initiated in Germany using a fludarabine-based radiation-free preparative regimen. The goal of the study was to determine whether this preparative conditioning regimen could provide sustained engraftment after allo-SCT from related and unrelated donors without an increased incidence and severity of transplant-related complications.	CASESERIES	12	SEV	12			Between March 2003 and January 2008, 12 consecutive children (7F, 4M, 1NR) with Hurler's syndrome underwent SCT. Median age at SCT was 14 months (range, 4-31 months).			Germany		see Table 1, 2 for pre- and post-transplant patient characteristics		ALIVE AND ENGRAFTED At a median follow-up of 29 months (range 2–85 months), all children engrafted and have either stabilized or improved neurological function. In total, 12/12 (100%) patients showed donor-derived engraftment with 9/12 (75%) having full and 3/12 having mixed hematopoiesis. One developed acute GVHD ≥grade II. RRT>grade II was observed in two patients.			Although SCT represents an effective treatment for children suffering from MPS IH, the procedure carries a significant risk of morbidity and mortality. *It is important to note that the protocol for this German multicenter approach was initiated before the cord blood results from Duke University were published in 2004 (Staba et al. 2004, NEJM, REFID 496). These impressive results must currently be considered to be the 'gold standard' for transplanting children with MPS IH. The event-free survival rate was 65%.				
5	R. Mitchell, I. Nivison-Smith, A. Anazodo, K. Tiedemann, P. J. Shaw, L. Teague, C. J. Fraser, T. L. Carter, H. Tapp, F. Alvaro, T. A. O'Brien	Outcomes of haematopoietic stem cell transplantation for inherited metabolic disorders: A report from the Australian and New Zealand Children's Haematology Oncology Group and the Australasian Bone Marrow Transplant Recipient Registry	Pediatr Transplant	2013	5-year survival HSCT	To report a retrospective analysis of 53 haematopoietic stem cell transplants for a number of inherited metabolic disorders performed at ANZCHOG transplant centres between 1992 and 2008	CASESERIES	53	SEV	25			The study evaluates HSCT for a wide array of inborn errors of metabolism MPS I not separately reported. Overall Median age at transplant was two yrs, with a range of 0–15 yr.			NonUS Ss	Australia		HSCT between 1992 and 2008.	Among MPS-IH patients (n=25): Five-yr survival among Hurler's patients = 83% (95% CI 68%-88%). All reported deaths within the first year. Five year survival for sibling donors (n=8) was 100% and for unrelated donors (n = 16) was 74%. Among the full study cohort (n=53): Five-yr survival was 78% (95%CI: 66%-90%), 11 (21%) deaths reported, all within the first year after HSCT.				Figure 1 Survival curve		Treatment harms not separately reported for MPS I	
292	R. F. Wynn	Use of enzyme replacement therapy (Laronidase) before hematopoietic stem cell transplantation for mucopolysaccharidosis I: experience in 18 patients	J Pediatr	2009	ERT pre-HSCT	To report on the outcome of the use of enzyme replacement therapy in conjunction with hematopoietic stem cell transplantation in 18 consecutive patients with severe mucopolysaccharidosis type I.	CASESERIES	18	SEV	18			The patient cohort comprised consecutive children under age of 2 years with MPS I Hurler who underwent HSCT at our center between February 2004 and January 2008. n=18 (10M, 8F) Med age at dx: 9 mos (rg: 3 - 19 mos) Med age at ERT start: 9.5 mos (rg: 3 - 19 mos) Med age at 1st transplant: 11.5 mos (rg: 7 - 22 mos); (Mean age= 12 mos) (4 patients had >1 transplant) (NOTE: 1 patient also reported in Cox-Brinkman et al., 2006 sample, REFID 403)			UK		Table 1-Patient characteristics and outcomes. Table 2-Summary of recent studies of HSCT in MPS IH	All patients weekly laronidase for 12 weeks before transplantation. Stem cell source and donor characteristics varied. Laronidase was continued during transplantation and until donor cell engraftment was documented. After transplantation, patients received immunosuppression, which was withdrawn after 3 to 6 months in the absence of GVHD. All patients were followed for a minimum of 6 months after transplantation. Most of the patients (14/18; 78%) received an unrelated donor transplant (9 cord donors and 5 adult donors). One patient presented with severe cardiomyopathy and an ejection fraction of only 3% to 4%; after 6 months of laronidase, his ejection fraction improved to 20%, and he was able to undergo HSCT.	At 6 month follow up, the overall survival and engraftment rate was 16/18 (89%). In the fully conditioned group, the alive and engrafted rate was 14/15 (93%). The survival rate following the first transplantation was 100% (18/18). Four (4) patients were transplanted >1 time, and 2 of these patients died. Specifically: Three (3) patients underwent a second transplantation, and 2 of them demonstrated sustained engraftment. The third patient died of GVHD after a third transplantation after having rejected her second graft. One patient experienced primary graft failure after full-intensity conditioning and an unrelated cord transplantation. This patient engrafted after a second cord transplantation but died of adenovirus infection 18 months later.							Key - ERT+HSCT
359	J. J. Boelens	Outcomes of hematopoietic stem cell transplantation for Hurler's syndrome in Europe: a risk factor analysis for graft failure	Bone Marrow Transplant	2007	2ndary data, risk anal	Allogeneic stem cell transplantation (SCT) before the age of 2 years halts disease progression. Graft failure limits the success of SCT. Study aims to analyze data on HS patients transplanted in Europe to identify the risk factors for graft failure, comparing outcomes in 146 HS patients transplanted with various conditioning regimens and grafts.	BMT database	146	SEV	146			All HS patients reported to the European Bone Marrow Transplant (EBMT)-registry between January 1994 and September 2004 were included. Since the follow-up of these patients was incomplete, an additional 'simple questionnaire' was prepared and sent to the various centers that transplanted these patients to complete the data set. From a total of 154 patients entered in the EBMT registry, questionnaires were completed in 146 patients (82 male/64 female) and were included in the analyses of outcomes. Patients were transplanted in 16 centers across Europe, with the majority from Manchester, Lyon, Dublin, London, and Paris. Median age of diagnosis: 10.5 (range 0–55) months Median age at transplant: 18 (range 2–96) months. Median Follow up after first SCT: 44 (range 6–120) months			Europe				MORTALITY /SURVIVAL The 'Survival' and 'Alive and Engrafted' rate after first transplant was 124/146 (85%) and 82/146 (56%), respectively. The overall 'Survival' and 'Alive and Engrafted' rate after one to three transplants was 118/146 (81%) and 111/146 (76%), respectively. At the time of analysis, some patients were awaiting a second graft. Twenty-two patients (15%) died after initial transplant, 19 from transplant-related causes (see Table 1). Infection, mainly viral, was the most prevalent cause of death.	MORBIDITY ASSOCIATED WITH SCT Acute GvHD (≥grade 2) was noted in 16% of patients (see Table 1) and was found to be independent of sex, age at transplant, matching, conditioning, cell source and donor relationship. A similar analysis for VOD (+parainfluenza III/enterocolitis) showed: for every month older in age, 12% less chance of developing VOD (OR 0.88; 95% CI 0.81–0.97; P ≤ 0.008), while Bu/Cy conditioning (OR 5.25; 95% CI 1.22–22.69; P ≤ 0.026) was a predictor for VOD.	UNIVARIATE PREDICTORS of ALIVE AND ENGRAFTED (TAB 2): Reduced Intensity Conditioning (RIC, p=0.005) T-Cell Depletion (TCD, p=0.001) HLA disparity/mismatch (p=0.014) Busulfan targeting (p=0.028) Moderators: HLA mismatch was NOT a predictor for Alive and Engrafted rates for Cord Blood donor recipients MULTIVARIATE PREDICTORS of ALIVE AND ENGRAFTED - similar to univariate results (Fig 2) except that Flud-MA regimens protected against graft failure KM SURVIVAL CURVES for Alive and Engrafted Outcomes: FIG 1a (Conditioning), 1b (TCD), 1c (Cell Source). OS - no significant univariate predictors	In this European retrospective study on the outcome of SCT for HS, T-cell depletion (TCD) and Reduced Intensity Conditioning (RIC) were found to be risk factors for graft failure. Busulfan targeting influenced engraftment positively, while cell source used (BM, PBSC or CB) did not influence the end point. CB, however, was found to be a predictor for achieving full donor chimerism associated with normal enzyme levels.	Tab 1, 2 (Univar, AE) Fig 1 (KM Curves, AE, conditioning, TCD, Cell source); Fig 2 (Multivar, AE)			N=146, Tx OUTCM risk, no early age (AK pls check)
42	J. B. Eisengart	Enzyme replacement is associated with better cognitive outcomes after transplant in Hurler syndrome	J Pediatr	2013	KTA10_PHI, HCT v HCT+ERT	To investigate whether intravenous enzyme replacement therapy (ERT) benefits cognitive function in patients with mucopolysaccharidosis type Ih (Hurler syndrome) undergoing hematopoietic cell transplantation (HCT).	EXPER	19	SEV	19			57.9% M (n=11) mean age at HCT 17.5 mos (17.3) BL ELC scores: Overall 87.6 (16.4) HCT only 90.8 (17.7) ERT+HST 84.0 (15.0)	US Sa					HST only, n=10 (2002-2005) ERT + HST, n=9 (2005 onward) serial enrollment, institutional change (Univ of MN BMT Service) in standard of care to include ERT+HCT, other pretransplant regimens were comparable across subjects. All had neuropsychological evals per protocol, BL/pre-HCT, 1 yr and 2 yr post HCT (Mullen Scales of Early Learning, score=Early Learning Composite (ELC) - overall cognitive development/early IQ estimate subdomain scores within ELC: Visual Reception Fine Motor Receptive Lang Expressive Lang	MORTALITY Death (reported only, not an outcome for primary analysis, adjusted ITT comparisons of ELC scores with deaths given ELC score of 0 at 1 and 2 yr FUs, and excluded death comparisons) HST only - 20% (2/10) deaths (@ 104 days and 231 days post-HCT) due to medical complications ERT+HST - 0% (0/9) deaths by 2 yr FU		COGNITIVE DEVELOPMENT Rate of decline in ELC scores over 2 years was significantly less in the ERT+HCT group v. HCT only group, after adjusting for BL ELC score and length of hospital stay (see Table III). HCT only group: loss of 12.84 points per year (95% CI: -20.23 to -5.46; p≤0.001) ERT+HCT group: loss of 3.84 points per year (95% CI: -7.57 to 0.18; p=0.89) Difference in rates, based on estimated rates of decline for each group, indicated ERT+HCT group lost 9.19 fewer points per year (95% CI: 0.85 - 17.54, p=0.031). When 2 deaths excluded, difference reduced to 5.40 points per year (95% CI: 0.5 - 10.29; p=0.031) (both statistically and clinically significant), see Table III and Figure 1.		Figure 1, Table 3			Key - cognitive outcome, HST only, HSCT+ERT
206	P. J. Orchard	Pre-transplant risk factors affecting outcome in Hurler syndrome	Bone Marrow Transplant	2010	pre-HCT risk factor	As enzyme replacement therapy (ERT) has become available, controversy has emerged in regards to whether the use of enzyme in the peri-transplant period is appropriate. An analysis was performed on 74 patients with Hurler syndrome transplanted at the University of Minnesota between 1990 and 2003, before our use of ERT associated with transplant, with the intention of determining if patients at higher risk during the transplant can be identified based on evaluations and events before transplantation.	TRO-COHO	74	SEV	74			74 sequentially patients with Hurler syndrome transplanted at the Univ of MN from 1990-2003 were evaluated. Time period is before institutional use of ERT with HCT in these patients.	US Sa	MN					MORTALITY/ OS Total (n=74), 33 deaths overall survival (OS), Kaplan-Meier est at 1 yr: 63% (95%CI: 51–74) at 5 yrs: 53% (95%CI 41–65) Table 1 shows Patient- and transplant-related factors and univariate analysis of OS at 1yr and 5 yrs Table 3 shows Disease-specific factors, and multiple regression of effects on 1yr and 5yr survival. Factors considered in the Cox regression: -Donor type (related vs URD matched vs URD mismatched vs UCB), p=0.12 -Age (<2 vs >=2), p=0.16 *-Gender (male vs female), p=0.01 -Conditioning (BU/CY vs CY/TBI (brain sparing) vs CY/TBI), p=0.88 -depletion (yes vs no), p=0.27 -CMV serostatus (negative vs positive), p=0.16 -time-dependent acute GVHD, hydrocephalus (yes vs no), p=0.75	Median age of patients with a VOD: 9 (range 4-18) months.		Factors not associated with differences in survival: Age, the presence of hydrocephalus, a history of cardiovascular issues or upper airway obstruction before transplant. Factors significantly associated with survival outcomes: patients who had a history of lower airway disease, including reactive airway disease or bronchiolitis, or a history of pneumonia.	Tbls 1, 3 for reg resp at, HCT, disease char on OS. Figs 1-3 survival curves of pulm/resp factors.			
198	K. J. Bjoraker, K. Delaney, C. Peters, W. Krivit, E. G. Shapiro	Long-term outcomes of adaptive functions for children with mucopolysaccharidosis I (Hurler syndrome) treated with hematopoietic stem cell transplantation	J Dev Behav Pediatr	2006	post HSCT LT adaptive function/qual o life	To investigate the development of various adaptive functions in children who have had hematopoietic stem cell transplant (HSCT) for Hurler syndrome and risk factors that are associated with the development of these functions. The study aims to show age related changes in children who have not had treatment for comparison with same age children who have had treatment.	CASECONTROL	41	SEV	41			Of 196 children in the Univ MN MPS-I database, 41 children with MPS I-H were identified who had HSCT, were followed for annually 2 to 7 years post-HSCT (1983-2002), and who had 3 or more Vineland Adaptive Behavior Scales records assessed before and after transplant. Of these 41, 40 are alive: 1 died of causes other than transplant or MPS I disease. Of the 41 children in the transplanted sample, 16F, 25M. Avg age at transplant: 21.7 mos (SD, 11; rg: 4.1 - 73 mos) Avg years follow-up from transplant: 87.2 months (SD: 46.5); (rg: 2 to 21 yrs); Average mental development (Bayley Scales-Infant Development or Mullen Scales-Early Learning) before HSCT: 83.9 (SD: 17.1). All children remain fully or partially donor-engrafted. Comparison group: From this database, comparison data are available on 43 children with 53 observations (a few had more than one observation). This group consists	US Sa	MN					Of 41 transplanted children, 1 death due to non-transplant, non-MPS I disease causes.	Multivariable analyses suggested only older age (9% less chance for every month older in age) to be a protector (OR 0.91; 95% CI 0.83–1.01).	ADAPTIVE FUNCTIONING/QUALITY OF LIFE: While standard scores decline over time, development of skills continue with a slower than average rate compared with peers. A cross-sectional nontransplanted comparison group showed more deficits after age 2 years than the transplanted group. In contrast to cognitive ability, age at transplant was not significantly associated with ultimate adaptive level. Baseline cognitive level before HSCT and growth of cognition after HSCT were associated with adaptive functions especially for communication and daily living skills. Socialization was predicted by cumulative medical risk factors, likely due to restricted social exposure in children with complicated transplant courses.	Overall, measurement of adaptive behaviors demonstrated that HSCT allows long-term slow improvement of functional outcomes for children with Hurler syndrome. Children with Hurler syndrome with good cognitive levels before HSCT and continued growth of cognition after HSCT show good adaptive functions				
294	L. A. Clarke	Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I	Pediatrics	2009	ERT LT Safety-Effic	To evaluate the long-term safety and efficacy of recombinant human alpha-l-iduronidase (laronidase) in patients with mucopolysaccharidosis I in the phase 3 extension trial (ClinicalTrials.gov identifier: NCT00146770). Additional data are provided on the clinical response to laronidase over 4 years of treatment.	EXPER	45			ATT	45	All 45 patients who completed a 26-week, double-blind, placebo-controlled trial of laronidase were enrolled in a 3.5-year open-label extension study. Mean patient age at baseline was 16 (range, 6-43) years. All patients had attenuated disease (84% Hurler-Scheie, 16% Scheie phenotypes). Clinical, biochemical, and health outcomes measures were evaluated through the extension phase. Changes are presented as the mean +/- SEM. 22 patients had initially received laronidase and 23 had initially received placebo. Eighty-two percent of patients were Caucasian, and 71% of patients were 18 years of age or younger. On average, patients had experienced symptoms for over a decade and had considerable disease burden.				Both	Tables 2 and 3 show baseline characteristics of the trial population.	Forty (89%) of the 45 subjects completed the initial trial. All patients who completed the trial received at least 80% of their scheduled infusions.	One patient died as a result of an upper respiratory infection unrelated to treatment. Antibodies to laronidase developed in 93% of the patients; 29% of the patients were seronegative at their last assessment.	P ≤ 0.093) against VOD.	RESPIRATORY FUNCTION Percent predicted forced vital capacity (FVC) remained stable, with a linear slope of -0.78 percentage points per year. MOBILITY The 6-minute walk distance (6MWT) increased 31.7 +/- 10.2 m in the first 2 years, with a final gain of 17.1 +/-16.8 m. RESPIRATORY/SLEEP APNEA improvements in the apnea/hypopnea index (AHI), decrease of 7.6 +/- 9 events per hour among the patients with significant baseline sleep apnea) and MOTION ...shoulder flexion (increase of 17.4° 3.6°) were most rapid during the first 2 years. ACTIVITIES OF DAILY LIVING/ DISABILITY Improvements in the Child Health Assessment Questionnaire/Health Assessment Questionnaire (CHAQ/HAQ) disability index (decrease of 0.31 - 0.11, signifying a clinically	This trial demonstrates the long-term clinical benefit and safety of laronidase in attenuated patients with MPS I and highlights the magnitude and chronology of treatment effects.	TABLE 5 Changes in Clinical Domains from Baseline to Final Assessment	Laronidase was found to be well tolerated and safe in most patients with an adverse event profile that was similar to that of the 26-week placebo-controlled trial. All patients experienced at least 1 adverse event; however, most adverse events were mild and were attributed to underlying disease rather than treatment. Adverse events	Wraith et al 2004 trial	

320	G. Stabile, D.	Outcome in six children with mucopolysaccharidosis type IH, Hurler syndrome, after haematopoietic stem cell transplantation (HSCT)	Acta Paediatr	2008	HSCT	Long-term follow-up of transplanted children has resulted in a recommendation to perform HSCT before 18–24 months of age. If performed before this period, studies suggest that child's mental ability is preserved, though bone deformities and other functions appear to be less improve. This study aims to follow-up six children with severe mucopolysaccharidosis type IH, Hurler syndrome, who were treated before 24 months of age with haematopoietic stem cell transplantation, with 3 children who receiving ERT from diagnose to engraftment.	CASESERIES	6	SEV	6	Six consecutive children born with Hurler syndrome in Sweden during the last 10 years who underwent HSCT (2000-2007). Median age of diagnosis: 14 months (range 9–20 months) Median age of HSCT: 18 months (range 11-24 months).			Sweden	Table S1 for more patient characteristics.	Each child was transplanted before they were 24 months. ERT was given to the 3 youngest patients following diagnosis until engraftment. Urine GAGs and L-IDUA levels were monitored 2–3 times during the first year after HSCT and then yearly after transplantation and as indicated. Follow up varied from 3 months for the youngest child to 7 years for the oldest. All children were assessed before and after transplantation with developmental status (Griffith Dev Scale), cardiac examination, ophthalmologic and audiologic investigations, neurologic (magnetic resonance imaging, nerve conduction studies), and growth and bone deformities	Urine GAG decreased in all children after HSCT, in the three children treated with ERT urine GAG levels decreased before HSCT.	COGNITIVE DEVELOPMENT DNA to two years after transplantation the children demonstrated some developmental delays in cognitive function. These final age were later followed by normalization. ORTHOPEDIC. Orthopaedic operations on the spine and hips and cervical tunnel syndrome were still required following transplantation. CARDIAC FUNCTION. Cardiac valve involvement remained progressive in the children. FACIAL FEATURES. All children besides the youngest have normalisation of their facial features after HSCT GROWTH. All children except the two youngest had growth retardation of between −2.9 SD's and −3.2 SD's in height. One child, with >−3SDs growth retardation received growth hormone treatment since transplantation.	The outcome of six children in this study confirms that early haematopoietic stem cell transplantation in mucopolysaccharidosis type I Hurler syndrome, preserves an affected child's mental ability. Matched, unrelated donor or umbilical cord transplants are effective at improving the survival of children with MPS IH. Current challenge is for pediatricians to recognize and diagnose severe MPSI early enough to allow transplantation <18months to preserve cognition.				
324	L.E. Polgreen, L. Tolar, M. Plog, J. H. Huhan, P. J. Orchard, C. B. Whitley, P. S. Miller, A. Parikh	Growth and endocrine function in patients with Hurler syndrome after hematopoietic stem cell transplantation	Bone Marrow Transplan t	2009		To investigate growth in patients with MPS IH after HSCT and described accompanying endocrine abnormalities.	CASESERIE S	48	SEV	48	A cohort of 48 patients (26 F) with MPS IH who had received HSCT between 1363 and 2005 were included. Sample selection: The medical records of 66 patients with MPS IH who received HSCT (marrow from unrelated or related donor or umbilical cord blood) at the University of Minnesota between September 1363 and April 2005, and who survived at least 1 year after HSCT, were reviewed to collect height, weight, endocrine and clinical data. All HSCT related data were obtained from the University of Minnesota Pediatric Blood and Marrow Transplantation Database.	US Se	MIN		Retrospective records review, per clearly stated inclusion/exclusion criteria.		GROWTH. The prevalence of short stature (height <−2 s.d. score; SDS) before HSCT was 5%, and increased to 71% at last follow-up (8.9+/−5.1 years after HSCT). Short stature was positively associated with increased age at HSCT (P=0.002) and TBI (P=0.009). In total, 33% had growth hormone deficiency and/or low insulin-like growth factor-1, one female patient had premature adrenarche, one precocious puberty and 27% had clinical or subclinical hypothyroidism. Growth failure is highly prevalent in children with MPS IH after HSCT. Children who had no TBI exposure and were younger at the time of HSCT had a better height outcome.	Growth failure is highly prevalent in children with MPS IH after HSCT. Children who had no TBI conditioning exposure and were younger at the time of HSCT had a better height outcome.				
331	J. Tolar, S. S	Combination of enzyme replacement and hematopoietic stem cell transplantation as therapy for Hurler syndrome	Bone Marrow Transplan	2008	ERT+HSCT	To determine whether enzyme replacement therapy (ERT) with alpha-iduronidase in the perits transplant period affects outcome of hematopoietic stem cell transplantation (HSCT) for MPS IH.	CASESERIE S	7	SEV	7	Between 2004 and 2007, seven patients received allogeneic HSCT with ERT (Table 1). Median age: 16.4 months (range 7.6 mos - 22.5 mos) Median number of ERT doses before HSCT: 10 (rg: 9 - 14) Number of ERT doses after HSCT: 8 All patients had severe IDUA mutations, with no L-IDUA production.	US Se	MIN		Median number of ERT doses before HSCT: 10 (rg: 11-14) Number of ERT doses after HSCT: 8 Outcomes assessed a mos before HSCT Follow up through Aug 2007 (med 1.1 years, rg: 6-28.5 mos)	Post transplant α-L-iduronidase activity in all patients, including the ones with high α-L-iduronidase antibody levels, was within normal range.	PULMONARY FUNCTION Pulmonary complications improved. Five out of seven MPS IH patients had two or more risk factors, a finding that observed to be associated with significant morbidity and mortality in MPS IH patients treated with HSCT alone. A majority of patients had significant pulmonary complications before ERT and HSCT but all are alive and well with a median follow-up of more than 1 year after HSCT. This suggests that ERT prior to HSCT is unlikely to alter engraftment. In addition, morbidity was acceptable, despite a previous history of pulmonary difficulties that suggested that these patients were high risk for these complications.	Investigators found potential benefits reduced pulmonary complications, and reduced overall morbidity, normalized IDUA levels with ERT + HSCT to = economical treatment of MPS IH patients with combination of ERT and HSCT therapy to further investigate its longer term effects.				
333	C. Taylor, P. Brady, A. O'Meara, D. Moore, F. Dowling, I. Hogarty	Mobility in Hurler syndrome.	J Pediatr Orthop	2006	mobility 8yrs post-HSCT	The effects of HSCT on associated musculoskeletal abnormalities remains unclear, and long-term data are limited. This study details the follow-up of 23 patients at a mean of 8 years after successful hematopoietic stem cell transplant.	CASESERIE S	23			23 Twenty-three patients who underwent allogeneic HSCT in the National MST Unit at Our Lady's Hospital, Dublin, between 1989 and 2003 were included in this study. Pretransplant conditioning entailed busulfan and cyclophosphamide. All patients were managed exclusively by the orthopaedic dept. 1st HSCT was undertaken at a mean of 9.4 months (range, 3-21 months); 5 underwent a second graft at a mean of 12 months after initial HSCT. Mean time after successful HSCT at assessment was 8.5 years (range, 19.2-1.7 years). At the time of report, patients' age ranged from 20.7 to 16 years			Ireland		Following HSCT, all patients underwent clinical examination at an annual multidisciplinary clinic. Serial radiological studies were reviewed to assess development and management of hip dysplasia and genu valgum.					
347	S. C. Dusing, D. B. Thorpe, M. D. Poe, A. E. Rosenberg, V. V. Mercer, M. S. Escolar	Gross motor development of children with Hurler syndrome after umbilical cord blood transplantation.	Phys Ther	2007	post UCBT motor development	The purpose of this study was to provide a description of gross motor development in children with Hurler syndrome after UCBT.	CASESERIE S	21	SEV	21	Total n=21, 11F 19 symptomatic/clinically identified: 11F, mean age at UCBT=17 ± mos, 8.2 mos sd 2 asymptomatic/identified early from family risk: 2F, mean age at UCBT=2.3 mos, 0.4 mos sd (15 of 21 reported in previous studies on UCBT outcomes)	US Se	WC		Longitudinal changes in gross motor abilities were documented on the gross motor subtests of the Peabody Developmental Motor Scales, second edition (PDMS-2).No 21 children with Hurler syndrome. Each child was assessed between 1 and 6 times after UCBT. The participants had a mean age (+/-SD) of 22.2+/-16.6 months at the time of the first assessment. The mean time (+/-SD) between UCBT and the first assessment was 16.2+/-16.3 months.	GROSS MOTOR DEVELOPMENT. The participants had marked gross motor delays, with a mean gross motor quotient 2 standard deviations below the mean for children who were developing typically. The rate of development differed between the subtests of the PDMS-2. The participants gained abilities at the slowest rate on the FINE/MANIP subtest and at the fastest rate on the locomotor subtest.	The participants had varying degrees of delay in different gross motor domains. While gaining new gross motor abilities over time, these children continued to have delays up to 48 months after UCBT.		15 of 21 children reported in previous study of UCBT outcomes (Table Stabile et al. 2004, NEJM) for clinical symptoms and cognitive development.		
357	K. S. Amos	Enzyme replacement therapy in 12 patients with MPS I-H/S with homozygous p.Leu490Pro mutation	J Inherit Metab Dis	2007	ERT H/S	We describe a cohort of 14 Hurler-Scheie patients homozygous for the p.Leu490Pro missense mutation in the alpha-L-iduronidase gene, 12 of whom who received ERT.	OSP-COHO	14		ATT	14	Now based in the UK, patients are all of Pakistani/Kashmiri descent, 66% were female, 11/14 (79%) had a sibling or cousin with MPS I and the parents are consanguineous in all cases. Median age at diagnosis: 1.8 years (range: antenatal diagnosis to 15.5 years).			UK of Pakistani/Kashmiri descent	Twelve of 14 were on ERT with recombinant human α-L-iduronidase (TOVA; Laronidase, Genzyme) Median age at start of ERT: 8.6 years (range 0.4–23.1 years). Median ERT duration: 22.5 months (range 2–71 months)	Clear improvement in the size of liver and spleen as well as reduction in urine glycosaminoglycans (GAGs) Mean (range) urine GAG levels in mg/mmol creatinine were 63.1 (28.9–107.6), 26.3 (10.9–41.4), 22.8 (12.3–41.1), 15.7 (9.2–24.8) and 16.3 (10.1–21.4) at commencement, 3 months post ERT, 6 months post ERT, 12 months post ERT and 24 months post ERT, respectively.	GROWTH Effects on growth were not clear as there does not seem to be an obvious trend of increase or decrease in height after commencement of ERT and this seems to be the case regardless of the age at which ERT was started.				NOTE: Short Report. Pers Summary text only
364	T. Lutke, A. M. Dieckmann, K. W. Sykora, F. Donnerstag, G. Schmidt, L. Gingelt	Developmental outcome in five children with Hurler syndrome after stem cell transplantation: a pilot study.	Dev Med Child Neurol	2007	developme nt post SCT	To report the developmental outcome (assessed by the Denver Developmental Screening Test, before and yearly after SCT) of four females and one male with MPSIH treated with a well-tolerated, fludarabine-based, radiation-free conditioning regimen for SCT in patients with Hurler syndrome	CASESERIE S	5	SEV	5	Now5. MPS I-H Mean age at SCT was 25 months (range 10–36mo). Mean age at last follow-up 71mo. range 42–87mo).			Germany		To assess follow-up, all patients were seen on a regular basis in the outpatient oncology and neuropediatric departments of Hannover Medical School. The mean follow-up time was 43.6 months (range 32–58mo; see Table II). Development was assessed with the Denver Developmental Screening Test (DDST) before SCT, and three to five follow up assessments. Social, adaptive, language, and motor behaviour were tested by the same physician at each assessment.	PSYCHOMOTOR DEVELOPMENT. None of the children showed psychomotor deterioration as in the classical natural course of the disease. All showed an improvement in psychomotor skills after SCT in longitudinal testing. Nevertheless, all of them still showed mild to pronounced psychomotor retardation. Psychomotor development was most compromised in the child treated at 36 months of age relative to those with SCT between 12 mos to 32 mos. The improvement in psychomotor development followed SCT with a latency of about 10 to 20 months.				
3647	M. D. Poe, S. L. Chaffin, M. L. Escolar	Early treatment is associated with improved cognition in Hurler syndrome	Annals of Neurology	2014	cognition-UCBT	The purpose of this article is to determine whether age at transplantation can predict cognitive outcomes.	CASESERIE S	31	SEV	31	(N=21 (53 children eligible, 1 declined to participate) 19 F, 16 M 29 Caucasian, 1 African-American Median age at transplantation = 13.8 months (range: 1.2–34.3); median baseline developmental quotient = 0.86 (range 0.48–1.34). 3 groups based on Median Age at Transplantation (MAT): Group 1 (n=6): 2 - 8 months MAT (med MAT 4.05 mos, rg 1.2-7.3) Group 2 (n=17): 9-17 months MAT (med MAT 12.3 mos, rg 10.9-17.7) Group 3 (n=8): >18 months MAT (med MAT 25.6 mos, rg 20.2-34.2) Developmental trajectories of Median age at Transplant (MAT) groups for cognitive skills.	US Se		Table 1 - Descriptive Statistics for the sample and by groups	Review of records for 31 patients with Hurler syndrome underwent umbilical cord blood transplantation (Jan 1997 to February 2013), and were evaluated at baseline and every 6 to 12 months thereafter. No patients received ERT, and all patients underwent a transplant conditioning regimen. All 31 patients underwent complete neurodevelopmental evaluation (median follow-up = 2.3 years, range = 0.1-11.7) and a median of 7.0 evaluations (range = 3-18). A standardized neurodevelopmental protocol was used to assess patients who were referred for pre- and post-transplant evaluation. Cognitive ability was assessed using the Mullen Scales of Early Learning and, in later years, the Differential Ability Scales.	COGNITIVE SKILLS. All children continued to gain cognitive skills after transplantation. Age at transplantation was a strong predictor of post-transplant cognitive development (p< 0.001; Table 2), with younger age at transplantation associated with greater gains during the follow-up period (p< 0.001). The interaction between baseline cognitive score and age was not significant (p = 0.34) and was removed from the final analysis. LANGUAGE SKILLS. Similar trajectories for receptive and expressive language to that of cognitive skills. ADAPTIVE BEHAVIOR. Younger age at transplant was associated with better post-transplant adaptive behavior development (p = 0.030). However, the rate of acquisition decreased over time (negative estimate for the age coefficient, p=0.001). AUDIOLOGICAL AND VISUAL FUNCTION. Severity of hearing loss and corneal clouding were similar across groups, regardless of age at transplantation.	Early age at transplantation is a strong predictor of cognitive, language and adaptive behavior outcomes. Children younger than 9 months at the time of transplant showed normal cognitive development. Results emphasize the need for early identification and treatment of Hurler syndrome and newborn screening. Challenges in newborn screening due to the lack of knowledge to predict phenotype and severity are acknowledged, since most patients appear to have private mutations.	Figures 1 -2 - Cog Dev trajectories, by MAT Group, Table 2 - Fixed effects regression model effects.			KEY - UCBT (cognitive outcomes. Age at transplant +Sinus infections outcomes

4	S. Lareway, C. Ikeen, J. Mercer, S. Jones, J. E. Wraith	Does early use of enzyme replacement therapy alter the natural history of mucopolysaccharidosis I? Experience in three siblings	Mol Genet Metab	2013	Some evidence re: pre symptomatic treatment	To present data from three siblings treated with enzyme replacement therapy at different ages which supports this finding. [benefit of pre symptomatic treatment]	CASESERIES	3			ATT_MPSI-HS_S	3	3 siblings homozygous for missense mutation p.Leu490Pro.			NonUS Ss	Sibling 1: ERT at 6 years Sibling 2: ERT at 2.5 years Sibling 3: ERT at 4 months	Sibling 1: After 5 years of treatment, cardiac valve disease stable, FVC improved from 41% to 53%, 6 minute walk test <10th percentile Sibling 2: After 5 years of treatment. 6 minute walk test is normal. no facial coarsening, FVC 81%, 6 minute walk test normal for age Sibling 3: After 5 years of treatment, mild corneal clouding, six minute walk test is within expected average, FVC 85%, no facial coarsening			KEY - 3 sibling case evidence for presymptomatic TX benefit
252	R. Y. Wang	Treatment reduces or stabilizes brain imaging abnormalities in patients with MPS I and II	Mol Genet Metab	2009		This study aims to determine the effects of hematopoietic stem cell transplantation (HSCT) and/or intravenous enzyme replacement therapy (ERT) on these abnormalities.	CASESERIES	5	SEV	1	ATT	2	5 patients: 3 MPS I (1 MPS I H, 2 MPS I Att, cog normal siblings), 2 MPS II	US Ss	CA		Patient 1 (severe MPS I) (genotype W402X/35del12) and received ERT followed by HSCT. Patients 2-5 - ERT only Retrospective chart and brain MRI study review, with independent review and scoring by 3 neuroradiologists blinded to age, specific diagnosis, cognitive status, type of treatment, date of treatment initiation. Follow up ranged from 13 to 51 months	Inter-observer variation in MRI scoring was minimal. Greatest abnormalities for each patient were found at initial MRI. All patients, including the ERT-only patients, demonstrated improved or unchanged MRI scores following treatment. Severity of white matter abnormalities or dilated perivascular spaces did not correlate with cognitive impairment; as such, extensive pre-treatment MRI abnormalities were noted in the older, cognitively normal MPS I sibling. In comparison, his younger sibling had only mild MRI abnormalities at the same age, after 4 years of ERT.	This study represents one of the first to document the CNS effects of ERT in MPS patients utilizing serial brain MR imaging studies, and raises several important observations. Brain MRI abnormalities typically become more pronounced with age; initiation of ERT or HSCT reversed or stabilized this trend in the MPS patients studied. In addition, earlier initiation of treatment resulted in decreased severity of imaging abnormalities. Possible mechanisms for these observations include improved cerebrospinal fluid dynamics, reduced central nervous system glycosaminoglycan storage via efflux through the blood-brain barrier (BBB), repair of damaged BBB, reduction in CNS inflammation, or ERT permeability through the BBB.		
385	M. V. Munoz-Rojas	Intrathecal enzyme replacement therapy in a patient with mucopolysaccharidosis type I and symptomatic spinal cord compression	Am J Med Genet A	2008	Innovative Tx- intrathecal (IT) laronidase	To report on the use of intrathecal (IT) laronidase in a MPS I patient with Spinal Cord Compression (SCC) who refused the surgical treatment, which carries a high risk for morbidity and mortality. SCC can occur from the build-up of GAGs within cervical meninges, and intravenous ERT does not typically cross the blood brain barrier	CASEREPORT	1			ATT	1	The patient is an adult male, 8th offspring of 12 children (5 females and 7 males) born from a nonconsanguineous, young and healthy couple. One sister and one brother were also affected and already deceased. The patient was born through a normal delivery. At age 23 he was diagnosed as having MPS I—Scheie syndrome. Clinical symptoms: corneal clouding, respiratory disease and obstructive sleep apnea, cardiac murmur, multiple joint contractures with carpal tunnel syndrome and dysostosis multiplex, neurological symptoms, including unstable and progressive spinal cord compression.			NonUS Ss	Since the patient presented with significant neurologic morbidity caused by spinal cord compression resulting from GAG storage and refused the standard surgical treatment, intrathecal enzyme replacement therapy (IT ERT) with recombinant laronidase was considered as an alternative therapy. After baseline evaluations, the patient received 4 intrathecal injections of 3 ml of a-L-iduronidase (approximately 1.74 mg of enzyme) at 1-month interval.		Although preliminary, this pioneer intrathecal ERT treatment yielded promising results, as there were no significant adverse events, and some clinical improvements. Patient had improvement in his gait and ability to rise when seated, 34% increased distance walked in the 12MWT, and increased baseline heart rate. No oxygen desaturation. Gait improved during treatment and was steadier and less ataxic. Additionally, a reduction in joint and/ or neuropathic pain was reported, along with a reduced need for pain medication. There were improvements in pulmonary diffusion tests and disappearance of right ankle clonus, a well-known sign of pyramidal dysfunction. IT laronidase injections through lumbar puncture is an emerging new therapy which appeared to be effective in this adult patient with attenuated	Adverse events included a minor bleeding at the last lumbar puncture and an increase in baseline heart rate during 12MWT. No other adverse events were observed or reported during or following IT ERT with laronidase.	*EXCL - but key IT ERT case

219	A. Tylki-Szym	Efficacy of recombinant human alpha-L-iduronidase (laronidase) on restricted range of motion of upper extremities in mucopolysaccharidosis type I patients	J Inherit Metab Dis	2010	ERT on ROM, ADLs	The aims of the study were to assess the effectiveness of enzyme replacement therapy (ERT) with laronidase on the range of motion (ROM) of upper extremities and influence on activities of daily living (ADLs) of patients with mucopolysaccharidosis type I (MPS I).	CASESERIES	17	SEV	10	ATT	7		17 patients born at term, MPS I dx at mean 5.9 yrs (rg 5mos - 39 yrs) Study enrollment at mean age 6.1 yrs (rg 1-39 yrs) Group 1 - MPSI-Severe (n=10, 58%) 8M, 2F Age at Dx: med 8.5 months, range 5mos to 7 yrs Age at BL: med 1 yr, range 1 yr to 10 yrs Age, Current: med 3.5 yrs, range 2 yrs to 14 yrs Group 2 - MPSI-Atten (n=7,47%) 5M, 2 F Age at Dx: med 4 yrs, rg: 1.5 to 39 yrs Age at BL: med 15 yrs, rg: 2.5 to 38 yrs Age, Current: med 19 yrs, rg: 6.5 to 42 yrs all patients had exhibited a range of clinical problems reflecting the multisystemic and progressive nature of the disease. The spectrum of symptoms included recurrent inguinal/umbilical hernias, chronic rhinitis, pulmonary disease, joint stiffness, corneal clouding	RUS Sx		Poland		patients were divided in two groups depending on their phenotype and the possibility to test passive or active ROM, and ADLs. Group 1: ten patients with MPS I-H passive range of motion in the upper extremities was assessed at the beginning of ERT and after 52–208 weeks of treatment Group 2: seven patients with MPSI-H/S (two with Hurler/Scheie, five with Scheie) the active range of motion in their upper extremities, as well as activities of daily life (ADL) was assessed at the beginning of ERT and after completion of 52–208 weeks of ERT Passive and active ROM was measured by a goniometer.		MOBILITY/ RANGE OF MOTION Early (<1yr) ROM impairment of upper extremities in children with MPS I became more severe over time, self-care difficult. ERT led to slower progression of symptoms, esp passive ROM in all patients. ACTIVITIES OF DAILY LIVING / DEVELOPMENT Patients with normal/slightly delayed mental development (Group 2) who began treatment between 2.5 and 39 yrs of age, had improvement of active shoulder flexion, followed by enhanced self-care. Patients with severe intellectual disabilities, difficulties introducing rehab due to lack of cooperation and motivation.	**Four years of observation: EARLIER introduction of ERT led to slower progression of symptoms. ERT for MPS I patients improves joint elasticity and decreases the restriction of motion. However, it cannot influence muscle strength, which requires physical exercise and rehabilitation. Rehab and self-care outcomes moderated by mental development.				
239	O. Gabrielli	Enzyme-replacement therapy in a 5-month-old boy with attenuated presymptomatic MPS I: 5-year follow-up	Pediatrics	2010	Case-presymptomatic ERT RS	To present the 5-year follow-up of a boy with attenuated MPS I who had laronidase therapy initiated at the age of 5 months and compare his clinical course to that of his older sister, who began treatment at 5 years of age after she had developed typical signs of MPS I.	CASESERIES	2			ATT										CORNEAL FUNCTION After 5 years of treatment, the younger sibling has not developed any clinical manifestations of MPS I except for mild corneal clouding. In contrast, although many of the older sibling's clinical features have improved after 5 years of treatment, her dysostosis multiplex, cardiac valve involvement, and corneal clouding, although stabilized, have persisted	Case of siblings suggests that early treatment of attenuated MPS I may significantly delay or prevent the onset of the major clinical signs, substantially modifying the natural history of the disease.				KEY presymptomatic ERT benefits with MPSI-Atten