WISCONSIN NEWBORN SCREENING (NBS) PROGRAM – CONDITION NOMINATION

Nomination of a Condition to the Wisconsin Newborn Screening Panel

Date of Nomination

07/18/2022

NOMINATOR	
Name Donald Basel, MD	Organization Children's Wisconsin
Affiliation (i.e., health professional, researcher, clinician, advocate) Clinician	
Address 8915 W. Connell Ct,Milwaukee, WI 53226	
Email Address dbasel@mcw.edu	Telephone Number 4142662979
CO-SPONSORING ORGANIZATION #1 (as appropriate, additional sponsors may be included on page 5)	
Name Mei Baker, MD	Organization Wisconsin State Laboratory of Hygiene
Affiliation (i.e., health professional, researcher, clinician, advocate) Public Health Laboratory Director	
Address 465 Henry Mall, Madison WI 53706	
Email Address mei.baker@slh.wisc.edu	Telephone Number 608-262-5494

Condition	**STATEMENT**
Nominated Condition	MPS1
Description of Disorder	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 has a chronic and progressive disease course involving multiple organs and causes joint disease, cardiorespiratory compro-mise, and death by 18 months if not treated. Attenuated MPS I exhibits similar symptoms; however, the rate of progression andseverity of complications is delayed and patients rarely show neuro-logical involvement beyond learning disabilities. 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. Early presymptomatic detection of MPS I via newborn screeningmay result in improved neurocognitive outcomes through earlierenzymatic replacement therapy (ERT) and hematopoietic stem celltransplant (HSCT), even though improvement in mortality has not been established. Diagnosis is based on clinical findings, additional biochemical tests, and mutation analysis.
Screening Method	Measurement of low enzyme activity in dried blood spot (DBS). Confirmed by DBS glycosaminoglycan (GAG) measurement.

Gene	alpha-L-iduronidase (IDUA)
OMIM or other names for condition	Hurler (MPS IH; 607014), Scheie (MPS IS; 607016), and Hurler-Scheie (MPS IH/S; 607015)
Case Definition	Low IDUA enzyme activity and elevated GAGs in DBS

NOTE: Please reference each statement/answer with the corresponding reference number listed in **Key References**.

CRITERION	
Criterion 1: Mandated testing should be limited to conditions that cause serious health risks in childhood that are unlikely to be detected and prevented in the absence of newborn screening.	
Timing of Clinical Onset	*Relevance of the timing of newborn screening to onset of clinical manifestations. Must cause serious health risks in childhood that are unlikely to be detected and prevented in the absence of newborn screening.* 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. Mucopolysaccharidosis type I (MPS I) newborn screening was added to the recommended uniform screening panel (RUSP) in 2016 (Heath Resources and Services Administration, 2019). Early presymptomatic detection of MPS I via newborn screening may result in improved neurocognitive outcomes through earlier enzymatic replacement therapy (ERT) and hematopoietic stem cell transplant (HSCT), even though improvement in mortality has not been established (Kemper, 2015). HSCT is the standard of care for infants diagnosed with severe MPS I and is recommended before the age of 2. Even with limited evidence, MPS I is perceived by healthcare providers as a favorable condition to screen due to improved efficacy and availability of therapeutic options (Lisi & McCandless, 2016). This makes early identification of MPS I via newborn screening fit RUSP criteria of an available treatment which requires presymptomatic initiation. A recent study published by (Stapleton et al., 2020) suggests that general screening of new-borns by both blood GAGs and enzyme assays may be a sensitive two-tiered strategy for the diagnosis of MPS patients. This will reduce the false positive rate associated with the pseudodeficiency allelles.
Criterion 2: For each condition, there should be information about the incidence, morbidity and mortality, and the natural history of the disorder.	
Incidence	*Determined by what method(s): pilot screening or clinical identification?* 0.54-1.85 cases per 100,000. Clinical identification

Severity of Disease	*Morbidity, disability, mortality, spectrum of severity, natural history*. In its severe form, children develop pervasive, multi-systemic involvement andshow rapid disease progression, with death occuring typically in early childhood if untreated. In the attenuated forms, onset occurs in childood of 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 but disability from musculoskeletal complications is not infrequent. •Severe MPS I. Infants appear normal at birth. Typical early manifestations are nonspecific (e.g., umbilical or inguinal hernia, frequent upper respiratory tract infections before age 1 year). Coarsening of the facial features may not become apparent until after age one year. Gibbus deformity of the lower spine is common and often noted within the first year. Progressive skeletal dysplasia (dysostosis multiplex) involving all bones is universal, as is progressive arthropathy involving most joints. By age three years, linear growth decreases. Intellectual disability is progressive and profound but may not be readily apparent in the first year of life. Progressive cardiorespiratory involvement, hearing loss, and corneal clouding are common. Without treatment, death (typically from cardiorespiratory failure) usually occurs within the first ten years of life. •Attenuated MPS I. Clinical onset is usually between ages three and ten years. The severity and rate of disease progression range from serious life-threatening complications leading to death in the second to third decade, to a normal life span complicated by significant disability from progressive joint manifestations and cardiorespiratory disease. While some individuals have no neurologic involvement and psychomotor development may be normal in early childhood, learning disabilities and psychiatric manifestations can be present later in life. Hearing loss, cardiac valvular disease, respiratory involvement, and corneal clouding are common. There is no easily measurable biochemical differences between MPS I-H / MPS I-HS / MPS I -S [Muenzer 2004] and the clinical findings overlap to some degree. There has been some encouraging work [Kingma 2013] in methodologies aiming to predict phenotypic severity in the first month of life but there is also good genotype-phenotype correlation. Data from 538 individuals within the international MPS I registry [Clarke et al 2019] show close correlation between genotype and phenotypic outcomes. Complete loss of IDUA enzyme activity, often due to homozygosity or compound heterozygosity of the common p.Gln70Ter or p.Trp402Ter pathogenic variants, is associated with severe MPS I. Any combination of two "severe" variants leads to severe MPS I. In individuals with severe MPS I, 68% (257/380) had two variants that would be predicted to severely disrupt gene transcription or translation, 76 of the remaining 123 individuals (20%, 76/380) had recurrent variants, and 47 (12.4%, 47/380) had at least one unique variant. .

Criterion 3: Conditions identified by newborn screening should be linked with interventions that have been shown in well-designed studies to be safe and effective in preventing serious health consequences.	
Urgency	How soon after birth must treatment be initiated to be effective? Urgent but not emergent. It would prevent up to 2 deaths before age 5 years due to the disease each year. The implementation of specific management would depent on the severity of the disease. In severe MPS I-H, HSCT should occur within the first few months of life.

Efficacy (Benefits)	Extent of prevention of mortality, morbidity, disability. Treatment limitations, such as difficulty with acceptance or adherence. Treatment of manifestations: Infant learning programs/special education for developmental delay; physical therapy, orthopedic surgery as needed, joint replacement for progressive arthropathy, atlanto-occipital stabilization; spinal cord decompression for cervical myelopathy; cerebrospinal fluid shunting for hydrocephalus; early median nerve decompression for carpal tunnel syndrome based on nerve conduction studies before clinical manifestations develop; special attention to anesthetic risks; hats with visors/sunglasses to reduce glare, corneal transplantation for ophthalmologic involvement; cardiac valve replacement as needed and bacterial endocarditis prophylaxis for those with cardiac involvement; tonsillectomy and adenoidectomy for eustachian tube dysfunction and/or upper airway obstruction; ventilating tubes; hearing aids as needed; CPAP for sleep apnea; gastrointestinal management for diarrhea and constipation. Primary disease focused interventions • Hematopoietic stem cell transplantation (HSCT) for children with severe MPS I. Outcome is significantly influenced by disease burden at the time of diagnosis (and thus, by the age of the individual). HSCT can improve cognitive outcomes, increase survival, improve growth, reduce facial coarseness and hepatosplenomegaly, improve hearing, prevent hydrocephalus, and alter the natural history of cardiac and respiratory symptomatology. HSCT has lesser effects on the skeletal and joint manifestations, corneal clouding, and cardiac involvement. HSCT alters the course of cognitive decline in children with severe MPS I; cognitive outcome is greatly influenced by the degree of cognitive impairment at the time of transplantation. Due to the morbidity and mortality associated with HSCT, it is currently recommended primarily for children with severe MPS I. • Enzyme replacement therapy (ERT) with laronidase (Aldurazyme®), licensed for treatment of the non-CNS manifestations of MPS I, improves liver size, linear growth, and mobility and joint range of motion; slows progression of respiratory disease; and improves sleep apnea in persons with attenuated disease. The age of initiation of ERT influences the outcome. • Gene Therapy : currently experimental but will be a consideration for treatment in the near future. Prior to the implementation of NBS programs for MPS1, early intervention through hematopoietic stem cell transplantation (HSCT) for the most severe form, Hurler syndrome (MPS IH), was predicted to improve cognitive outcomes. Consistent evidence from peer-reviewed studies suggests that transplantation in the first year of life is associated with improved developmental quotient or intelligence quotient and continued cognitive growth, with earlier age of treatment associated with improved outcomes. Available evidence suggests that cognitive functioning and attention can still lag behind unaffected age-matched children, leading to the need for special education services. Verbal and nonverbal cognitive abilities outcomes may be affected differently by HSCT.
Potential Harms	Potential medical or other ill effects from treatment. Requires potentially harmful interventions. Hematopoietic stem cell transplant is a high risk procedure which requires lifelong monitoring but in experienced centers outcomes from HSCT outweighs the risk of the disease. Similarly, enzyme replacement therapy requires ongoing administration of the manufactured enzyme through an infusion. The medical risks of infusion reactions, port infections etc need to be considered but again the benefit of ERT outweighs the risk of no intervention.
Criterion 4: The interventions should be reasonably available to affected newborns.	

Modality	*Drug(s), diet, replacement therapy, transplant, surgery, other. Include information regarding regulatory status of treatment.* Treatment is through FDA approved ERT or HSCT. For MPS I-H, HSCT is accepted as the definitive treatment to slow the neurological disease progression but it is only available at selected centers. In WI, there are two pediatric HSCT centers which can offer this treatment. To date it is the only therapeutic approach that alters the natural history of neurocognitive disease in MPS I. ERT is most effective for non-CNS manifestations and used in the milder forms of the disease, MPS I-SH or MPS I-S or in MPS I-H if there is a delay in access to HSCT. There is a clinical trial looking at outcomes for individuals who have undergone HSCT and then treated with ERT.
Availability	*Describe scope of availability and note any limitations.* HSCT is available at the 2 major academic centers in WI, Children's Wisconsin in Milwaukee and American Family Children's Hospital in Madison. There is a center of excellence in Minnesota which has extensive experience with HSCT in MPS1.
Criterion 5: Appropriate follow-up should be available for newborns that have a false positive newborn screen.	
Follow-up for False Positives	*Define the follow-up process.* Consistent with existing Wisconsin NBS practices, the state NBS laboratory at WSLH will communicate the positive MPS I screening result to the primary care provider and the metabolic center designated to engage in confirmatory testing and short term follow-up. At the center, the metabolic geneticist will reach out to the primary care provider to provide further consultation and to reach out to the baby's family about the initial appointment where confirmatory testing will be performed. This confirmatory testing will assess for deficient activity of the lysosomal enzyme α-L-iduronidase (IDUA) and coordinate gene testing to assist with the identification of severe MPS I-H. This will help determine those who: 1) do NOT have a disorder and they can be discharged from further follow-up or 2) DO have a disorder and differentiate the severe from the attenuated forms of MPS I. The newborns identified with severe MPS-I will be referred for HSCT at a specialised center.
Criterion 6: The characteristics of mandated tests in the newborn population should be known, including specificity, sensitivity, and predictive value.	
Screening test(s) to be used	*Description of the high volume method, instrumentation and if available as part of multi-analyte platform.* The IDUA enzyme activity will be measured using the NeoLSD MSMS kit from Perkin Elmer, which is already being used in the Wisconsin NBS laboratory for Pompe disease screening. The method consists of 18-hour incubation of DBS punches in the kit substrate and internal standard. Following incubation, samples are purifeid and analyzed using liquid chromatography-mass spectrometry. Samples with IDUA activity below 15% of the daily median will be selected for second-tier testing by DBS GAG measurement. If second tier testing is positive, the screen will be reported as a positive. If the second tier test is negative, the lab will request a repeat after one week. The kit is a multiplex assay that measures enzyme activity of IDUA, GAA, and GALC for early identification of MPS I, Pompe, and Krabbe diseases, respectively. The activity of GALC will be reviewed for sample quality control purposes, but only the results for IDUA and GAA will be reported for screening purposes.
Modality of Screening	*Dried blood spot, physical or physiologic assessment, other* DBS
Does the screening algorithm include a second tier test? If so, what type of test and availability?	*Dried blood spot, physical or physiologic assessment, other* Specimens with IDUA enzyme lower than 15% of the daily median will be confirmed by biochemical second tier testing, consisting of DBS GAG quantitation by liquid chromatography-tandem mass spectrometry

Clinical Validation	*Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation, positive predictive value, false positive rate, analytical specificity, sensitivity.* A published pilot study for MPS1 newborn screening was performed in Illionois over 15 months. The study included 219,793 infants. Of screened infants, 151 screened positive with 1 individual confirmed to have MPS I by follow-up testing (urine GAGs and leukocyte IDUA activity testing). Thirty positive-screened indivuals were discovered to have psuedodeficiency alleles. The positive predictive value was 0.66% with a false positive rate of 99.3%. It was noted by the authors of the study that the false positive rate was impacted by the conservative cut-off values used in the screening process. No false negatives were reported in this study. The high false positive rate observed in this study is likely due to the lack of second-tier testing. In this nomination, we have included plans for second tier testing by DBS GAG measurement, which would result in a lower false positive rate. A smaller pilot study from Japan screened 18,222 samples over 3 years. This study measured IDUA activity and GAGs in DBS. While the study was not large enough to identify a true MPS I case, the false positive rate using this method was much lower at 0.21%.
Analytic Validation	*Limit of detection/quantitation, detection rate, reportable range of test results, reference range. Include regulatory status of test, information about reference samples and controls required for testing and availability of or potential for external quality assurance system, e.g., QC and PT for both screening and confirmatory tests.* Assay performance statistics below have been obtained from the manufacturer, Perkin Elmer, using the QSight MD 210 screening system. The assay is FDA approved and performance statistics indicate that the method is can be used to effectively screen for MPS1. Because the assay is FDA approved, the method will only require verification, a more streamlined and shorter process than validation. Precision: Precision was determined by measurement of 105 replicates of 5 different standards with mean measured concentrations ranging from 0.76 to 16.4 µmol/L/hr. Results were reported as coefficient of variation (CV%). Repeatability ranged from 7.0 to 15.1 CV%. Within lab variation ranged from 8.9 ti 15.6 CV%. Between lot variation ranged from 0.5 to 3.3 CV%. Total variation across all replicates ranged from 8.9 to 15.8 CV%. Linear range: Linearity was maintained for IDUA activity measurement between 0.08 and 22.3 µmol/L/hr. Lower limit of detection: The lower limit of detection was obtained from 75 measurements of low IDUA activity samples. Lower limit of detection was determined to be 0.13 µmol/L/hr. Lower limit of quantitation: Lower limit of quatitation was determined to be 0.19 µmol/L/hr. At this level, CV% was determermined to be 21.1%.

Potential Secondary Findings	*May other disorders be identified by the screening test for the nominated condition?* ☐ Yes ☒ No ***If yes:*** • *How should that identification be handled—should those screening results be disclosed to the physicians or parents?* • *Would that disorder(s) meet the outlined criteria?* ☐ Yes ☐ No o *If yes, please prepare a separate nomination form for the secondary disorder(s)* o *If no, what criteria does it not meet?*

Summary of Population-based Pilot Study(ies)

Location of Prospective Pilot	Illinois
Number of Newborns Screened	219,793
Number of Positive Results	*Positive by primary test versus 2nd tier test if applicable.* By enzyme activity only: 151
False Positive Rate; False Negative Rate (if known)	*False positive by primary test versus 2nd tier test if applicable.* By enzyme activity only: False positive rate = 99.3% ; False negative rate = 0%
Number of Infants Confirmed with Diagnosis	*How are diagnosis confirmed [clinical, biochemical, molecular]?* confirmed by biochemical determination by urine GAG content and leukocyte IDUA activity.
Criterion 7: If a new sample collection system is needed to add a disorder, reliability and timeliness of sample collection must be demonstrated.	
Is this a new sample collection system?	*If yes, demonstrate reliability and timeliness of sample collection process, including data collection, analysis, and reporting of new results.* No
Criterion 8: Before a test is added to the panel, the details of reporting, follow-up, and management must be completely delineated, including development of standard instructions, identification of consultants, and identification of appropriate referral centers throughout the state/region.	
Considerations of Screening and Diagnostic Testing	*False positives, carrier detection, invasiveness of method, other* As mentioned above, the screening method for MPS1 is part of a multiplex assay that is already being run in the Wisconsin NBS laboratory for the detection of Pompe disease. As such, the addition of MPS1 screen will require minimal changes to the current screening procedure. In the event of a positive screen, the laboratory will contact the primary care provider, as well as appropriate metabolic consultants. Confirmatory testing will be coordinated between these healthcare providers.
Is test FDA cleared/approved	*Include availability of information, sole source manufacturer, etc.* Yes, the kit used for enzyme testing is produced by Perkin Elmer. Information on the assay is available from the manufacturer website: https://www.perkinelmer.com/product/neolsd-msms-kit-3093-0020. The GAG measurement assay is not FDA approved.
List all CLIA or CAP certified labs offering testing in the US	*Link to GeneTests, and Genetic Test Reference if applicable.* https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=mps1

Follow-up and management process	*Development of standard instructions, identification of consultants, identification of appropriate referral centers throughout the state/region, follow-up for results, management of ongoing care, education, and outreach.* Follow up for MPS1 begins with consultation with a physician specializing in genetic and/or metabolic diseases with the goal of confirmation of the diagnosis and assessment of disease severity. Infants are diagnosed with MPS1 when confirmatory testing supports the diagnosis of MPS1 from the screening test measuring IDUA activity and GAGs from the NBS punch card. Confirmatory testing includes blood for IDUA enzyme activity and urine for GAGs. If these are positive, confirming a diagnosis, then IDUA gene sequencing will be performed in order to differentiate between the 3 clinical forms; MPS I-H, MPS I-H/S, MPS I-S. Families of infants with MPS I should receive information about MPS I using resources for newly diagnosed families as a guide, (e.g., see https://www.babysfirsttest.org/newborn-screening/conditions/mucopolysaccharidosis-type-i, https://www.mps1disease.com/patients/about/what-is-mps1/; https://mpssociety.org/support/newly-diagnosed/). They should also receive early genetic counselling with the goal of identifying at-risk family members, who may be at risk for the milder disorder. Multidisciplinary care is required for patients with MPS I and screening of affected systems including skeleton, eye, heart, hearing, neurology, GI, and ENT should be performed regularly. The infants with severe MPS I-H will be transitioned to specialty care for HSCT, infants with milder disease should be assessed for the benefit of ERT based on their disease severity.
Criterion 9: Recommendations and decisions should include consideration of the costs of the screening test, confirmatory testing, accompanying treatment, counseling, and the consequences of false positives. The mechanism of funding those costs should be identified. Expertise in economic factors should be available to those responsible for recommendations and decisions.	
Screening test	IDUA enzyme activity assay and GAG measurement in DBS
Confirmatory testing	Molecular analysis of the IDUA gene and urine GAG measurement
Treatment	ERT is standard of care. HSCT is used in severe presentations.
Counseling	Counseling can be performed at any of the regional centers
False positives	False positives would result in unnecessary confirmatory testing
Mechanism of funding	NBS for MPS1 would need to be funded through the NBS fee.

Key References to support each criterion. Please list and attach as PDF(s). If mailing, include hard copies.	
#	**Criterion 1**
	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
	Lisi EC, McCandless SE. Newborn Screening for Lysosomal Storage Disorders: Views of Genetic Healthcare Providers. J Genet Couns. 2016 Apr;25(2):373-84. doi: 10.1007/s10897-015-9879-8. Epub 2015 Aug 29. PMID: 26315880. Stapleton M, Kubaski F, Mason RW, Shintaku H, Kobayashi H, Yamaguchi S, Taketani T, Suzuki Y, Orii K, Orii T, Fukao T, Tomatsu S. Newborn screening for mucopolysaccharidoses: Measurement of glycosaminoglycans by LC-MS/MS. Mol Genet Metab Rep. 2020 Jan 10;22:100563. doi: 10.1016/j.ymgmr.2019.100563. PMID: 31956510; PMCID: PMC6957835.
	Criterion 2
	Parini R, Deodato F, Di Rocco M, Lanino E, Locatelli F, Messina C, Rovelli A, Scarpa M. Open issues in Mucopolysaccharidosis type I-Hurler. Orphanet J Rare Dis. 2017 Jun 15;12(1):112. doi: 10.1186/s13023-017-0662-9. PMID: 28619065; PMCID: PMC5472858.
	Kingma SD, Langereis EJ, de Klerk CM, Zoetekouw L, Wagemans T, IJlst L, Wanders RJ, Wijburg FA, van Vlies N. An algorithm to predict phenotypic severity in mucopolysaccharidosis type I in the first month of life. Orphanet J Rare Dis. 2013 Jul 9;8:99. doi: 10.1186/1750-1172-8-99. PMID: 23837464; PMCID: PMC3710214. Clarke LA, Giugliani R, Guffon N, Jones SA, Keenan HA, Munoz-Rojas MV, Okuyama T, Viskochil D, Whitley CB, Wijburg FA, Muenzer J. Genotype-phenotype relationships in mucopolysaccharidosis type I (MPS I): Insights from the International MPS I Registry. Clin Genet. 2019;96:281–89
	Criterion 3
	Grosse SD, Lam WKK, Wiggins LD, Kemper AR. Cognitive outcomes and age of detection of severe mucopolysaccharidosis type 1. Genet Med. 2017 Sep;19(9):975-982. doi: 10.1038/gim.2016.223. Epub 2017 Jan 26. PMID: 28125077; PMCID: PMC5763496.
	Criterion 4

Schmidt M, Breyer S, Löbel U, Yarar S, Stücker R, Ullrich K, Müller I, Muschol N. Musculoskeletal manifestations in mucopolysaccharidosis type I (Hurler syndrome) following hematopoietic stem cell transplantation. Orphanet J Rare Dis. 2016 Jul 8;11(1):93. doi: 10.1186/s13023-016-0470-7. PMID: 27392569; PMCID: PMC4938899.

Muenzer J. The mucopolysaccharidoses: a heterogeneous group of disorders with variable pediatric presentations. J Pediatr. 2004;144:S27–34

Aldenhoven M, Jones SA, Bonney D, Borrill RE, Coussons M, Mercer J, Bierings MB, Versluys B. van Hasselt, Wijburg FA, van der Ploeg AT, Wynn RF, Boelens JJ. Hematopoietic cell transplantation for mucopolysaccharidosis patients is safe and effective: results after implementation of international guidelines. Biol Blood Marrow Transplant. 2015a;21:1106–9.

Aldenhoven M, Wynn RF, Orchard PJ, O'Meara A, Veys P, Fischer A, Valayannopoulos V, Neven B, Rovelli A, Prasad VK, Tolar J, Allewelt H, Jones SA, Parini R, Renard M, Bordon V, Wulffraat NM, de Koning TJ, Shapiro EG, Kurtzberg J, Boelens JJ. Long-term outcome of Hurler syndrome patients after hematopoietic cell transplantation: an international multicenter study. Blood. 2015b;125:2164–72.

Shapiro EG, Nestrasil I, Rudser K, Delaney K, Kovac V, Ahmed A, Yund B, Orchard PJ, Eisengart J, Niklason GR, Raiman J, Mamak E, Cowan MJ, Bailey-Olson M, Harmatz P, Shankar SP, Cagle S, Ali N, Steiner RD, Wozniak J, Lim KO, Whitley CB. Neurocognition across the spectrum of mucopolysaccharidosis type I: age, severity, and treatment. Mol Genet Metab. 2015;116:61–8

Kunin-Batson AS, Shapiro EG, Rudser KD, Lavery CA, Bjoraker KJ, Jones SA, Wynn RF, Vellodi A, Tolar J, Orchard PJ, Wraith JE. Long-term cognitive and functional outcomes in children with mucopolysaccharidosis (MPS)-IH (Hurler syndrome) treated with hematopoietic cell transplantation. JIMD Rep. 2016;29:95–102

Polgreen LE, Lund TC, Braunlin E, Tolar J, Miller BS, Fung E, Whitley CB, Eisengart JB, Northrop E, Rudser K, Miller WP, Orchard PJ. Clinical trial of laronidase in Hurler syndrome after hematopoietic cell transplantation. Pediatr Res. 2020;87:104–11.

Criterion 5

Criterion 6

Burton BK, Charrow J, Hoganson GE, Waggoner D, Tinkle B, Braddock SR, et al. Newborn Screening for Lysosomal Storage Disorders in Illinois: The Initial 15-Month Experience. The Journal of pediatrics. 2017;190:130-5. Epub 2017/07/22. doi: 10.1016/j.jpeds.2017.06.048. PubMed PMID: 28728811.

Kubaski F, Suzuki Y, Orii K, Giugliani R, Church HJ, Mason RW, et al. Glycosaminoglycan levels in dried blood spots of patients with mucopolysaccharidoses and mucolipidoses. Molecular genetics and metabolism. 2017;120(3):247-54. Epub 2017/01/10. doi: 10.1016/j.ymgme.2016.12.010. PubMed PMID: 28065440; PubMed Central PMCID: PMC5346460.

Maccari F, Galeotti F, Mantovani V, Zampini L, Padella L, Rigon L, et al. Composition and structure of glycosaminoglycans in DBS from 2-3-day-old newborns for the diagnosis of mucopolysaccharidosis. Analytical biochemistry. 2018;557:34-41. Epub 2018/07/17. doi: 10.1016/j.ab.2018.07.007. PubMed PMID: 30009765.

Stapleton M, Kubaski F, Mason RW, Shintaku H, Kobayashi H, Yamaguchi S, et al. Newborn screening for mucopolysaccharidoses: Measurement of glycosaminoglycans by LC-MS/MS. Molecular genetics and metabolism reports. 2020;22:100563. Epub 2020/01/21. doi: 10.1016/j.ymgmr.2019.100563. PubMed PMID: 31956510; PubMed Central PMCID: PMC6957835

	Criterion 7
	Criterion 8
	Muenzer J, Wraith JE, Clarke LA. Mucopolysaccharidosis I: management and treatment guidelines. Pediatrics. 2009;123(1):19-29. Epub 2009/01/02. doi: 10.1542/peds.2008-0416. PubMed PMID: 19117856.
	Criterion 9

Additional Co-sponsoring Organizations

CO-SPONSORING ORGANIZATION #2	
Name Roberto Mendez, PhD	Organization Wisconsin State Laboratory of Hygiene
Affiliation (i.e., health professional, researcher, clinician, advocate) Public Health Laboratory Director	
Address 465 Henry Mall, Madison, WI 53706	
Email Address Roberto.Mendez@slh.wisc.edu	Telephone Number (608) 265-5968
CO-SPONSORING ORGANIZATION #3	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Telephone Number
CO-SPONSORING ORGANIZATION #4	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Telephone Number
CO-SPONSORING ORGANIZATION #5	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Telephone Number

Submission Checklist	
☒	Nomination form
☒	Conflict of Interest Forms completed by Nominator and all Co-Sponsoring Organizations
☒	PDF(s) or hard copies of references

Contact information of Nominator: dbasel@mcw.edu

Submit Nominations to: DHSWICongenitalDisorders@wisconsin.gov
Or mail to:

WI Division of Public Health
Newborn Screening Program
1 West Wilson Street – Room 233
Madison, WI 53703