Secretary's Advisory Committee on Newborn Screening Meeting

Friday March 3, 2023

Report on the Nomination to Add Mucopolysaccharidosis 1 to the Newborn Screening Panel in the State of Wisconsin

On March 3, 2023, the Secretary's Advisory Committee on Newborn Screening (SACNBS) met via Zoom to review the nomination to add mucopolysaccharidosis 1 (MPS-1) to the Wisconsin mandatory newborn screening (NBS) panel. MPS-1 was nominated by Dr. Donald Basel, MD (Children's Wisconsin) with co-sponsor Dr. Roberto Mendez, PhD (State of WI Newborn Screening Laboratory). The nomination was reviewed by Metabolic subcommittee which recommended acceptance, leading to presentation to the Umbrella Committee meeting on December 2, 2022, which also recommended acceptance. The SACNBS voted unanimously in favor of adding MPS-1 to the Wisconsin NBS panel.

MPS-1 is a rare progressive autosomal recessive lysosomal storage disorder also known as Hurler syndrome. The incidence of MPS-1 is estimated to be 1.50 - 1.85 cases per 100,000 newborns. Both males and females are equally affected. There are two forms of MPS-1 - severe and attenuated. Severe MPS-1 can lead to death in the first ten years of life without treatment. Attenuated MPS-1 presents between the ages of 3 and 10, commonly resulting in early death in the second to third decade, but can also lead to substantial physical or mental disability (e.g. progressive joint or cardiorespiratory issues and/or developmental delay) without an effect on life expectancy. Affected individuals have a deficiency of the lysosomal enzyme a-L-iduronidase (IDUA) leading to build up of intracellular components, glycosaminoglycans (GAGs), eventually leading to tissue damage and organ dysfunction.

Initial Screening for MPS-1 involves use of tandem mass spectrometry to detect IDUA enzyme activity in a dried blood spot (DBS). Second tier analysis for those samples initially identified to have low enzyme activity increases specificity by measuring levels of GAGs that accumulate in cells because of the IDUA enzyme deficiency in those affected by MPS-1. If a diagnosis of MPS-1 is confirmed, infants are seen by a pediatric genetics/metabolism specialist for discussion of starting enzyme replacement therapy and/or preparing for hematopoietic stem cell transplantation (HSCT) if it is indicated.

MPS-1 was added to the national Recommended Uniform Screening Panel (RUSP) in 2016. 30 states including Michigan, Minnesota, Indiana, and Illinois screen for MPS-1 though it is unclear which states, if any, utilize two tier analysis. Conditions added to the Wisconsin mandatory newborn screening panel must meet nine criteria. The Secretary's Advisory Committee considered and voted on each criterion in turn.

First, *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.* MPS - 1 is not detectable clinically until symptom development occurs in early or late childhood,at which point symptoms can not be reversed. MPS -1 can cause brain, cardiorespiratory, joint, muscular, and skeletal system symptoms including developmental delay, learning difficulties, hearing loss, vision loss, heart disease/failure, respiratory infections, lung disease, joint stiffness, skeletal deformities, and early mortality. MPS-1 can not be cured, however, there are two treatments that can prevent further progression of symptoms by helping to improve IDUA activity levels., Early diagnosis is key to success of these treatments. The two treatment options are enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT).

Second, *for each condition, there should be information about the incidence, morbidity, and mortality and the natural history of the disorder*. Extensive literature on the epidemiology and natural history of MPS-1 describes an incidence of approximately 1 in 100,000 live births each year for the severe form and 1 in 500,000 for the attenuated form. Untreated MPS-1 can lead to extensive morbidity and/or early mortality. Based on studies of newborn screening of lysosomal storage disorders in Illinois and Missouri there are pseudo deficiency alleles that contribute to high false positive rates in MPS -1 Newborn screening, illustrating the need for an additional second tier test.

Third, *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*. Diagnosis of MPS-1 early on during infancy allows for earlier discussion and implementation of enzyme replacement therapy (ERT) and HSCT if indicated (e.g. severe form). ERT currently is licensed for treatment of the non-CNS manifestations of MPS-1, as the infusion is not able to cross the blood brain barrier. The earlier an infant is able to begin ERT, the more encouraging the outcome. HSCT is only indicated at this time in patients with severe MPS-1 and outcomes correlate with age at time of HSCT. HSCT is currently recommended between the ages of 1 and 2 years old for those with severe MPS-1. There are ongoing clinical trials investigating the use of blood brain barrier penetrating forms of ERT as well as intravenously introduced gene editing therapeutics with the goal of increasing the affected individual's deficient enzyme.

Fourth, *the interventions should be reasonably available to affected newborns*. It is expected that ERT will be available at specialized pediatric medical centers. HSCT for MPS-1 is available at two centers in Wisconsin.

Fifth, *appropriate follow-up should be available for newborns who have a false positive newborn screen.* All infants who screen positive with low IDUA enzyme will enter second tier testing for confirmation by examining levels of GAGs. Families will only be notified of an abnormality if both the first and second tier tests are abnormal. Concerns were voiced about vulnerable child syndrome in children with false positive tests, with a recommendation that affected families be followed to ensure that they understand that a false positive does not indicate an illness. There was discussion that this concern with false positive tests is present with many tests on the newborn screening panel, and that continued efforts are needed by primary care, genetics, and research teams for continued improvement in this area.

Sixth, *the characteristics of mandated tests in the newborn population should be known including specificity, sensitivity, and predictive value or other convincing medical evidence (experience, natural history, or literature).* MPS-1 newborn screening methods include tandem mass spectrometry, which is already used for many other diseases in the newborn screening program. The initial test measures the activity of the deficient enzyme (IDUA). The second tier test proposed measuring GAGs in DBS has been shown to decrease false positivity rates. Missouri was the first US state to screen for MPS-1 utilizing only single tier testing. Within the first six months of the Missouri pilot study, 43,701 newborns were screened. 27 newborns screened positive for a lysosomal storage disorder. Three had confirmed MPS-1 genotype (one individual with confirmed MPS-1 and two individuals with variants of undetermined significance). Seven newborns were found to have pseudo-deficiency. Two newborns were noted to be carriers and 16 newborns had false positive results., In Illinois newborn screening for MPS-1 (utilizing only single tier testing), pseudo deficiencies were more frequent than true deficiencies.

Therefore, based on previous studies and the plan to include a second tier analysis (measurement of GAGs) 0-3 false positives per year are expected. The second tier test is not yet developed within the Wisconsin Newborn Screening laboratory and would require development. If unable to be developed, positive test results on first tier analysis (IDUA enzyme activity levels) could be sent to Mayo Clinic Laboratories for evaluation where a second tier test is available.

Seventh, *if a new sample collection system is needed to add disorder, reliability and timeliness of sample collection must be demonstrated.* This criterion does not apply to MPS-1, as the screening test suggested will employ existing collection methods; measurements of IDUA and GAGs can be completed on DBS collected on filter paper.

Eighth, *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.* Reporting, follow up, and management for identified cases of MPS -1 will follow the typical workflow for other metabolic disorders on Wisconsin newborn screening panel. In the event of both an abnormal 1st and 2nd tier test, the state lab will contact the infant's primary care provider (PCP) and a consulting clinical geneticist. The geneticist and PCP will then work together to communicate the positive screen result to parents and coordinate confirmatory testing. These tests can take place over the next 2-4 weeks. HSCT needs to be instituted between 1-2 years of age. The start of potential therapies is time sensitive, as treatment with ERT leads to better outcomes if started before symptoms present, with timing dependent on classification of disease and corresponding onset and progression. If confirmatory testing supports a diagnosis of MPS-1, initial clinical evaluations will be arranged with appropriate sub-specialists. Genetic

counselors will be involved in communication, education, care coordination, and counseling at-risk family members. Families of newly diagnosed infants will be directed to print and online resources.

Finally, *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 cost for the first tier test is negligible because it will utilize an already ongoing testing process. The second tier test will require about $0.50 per sample for development of assay or sending samples to Mayo Clinic to complete the second tier analysis. This proposed expense should be able to be covered by current funding methods, if the current budget deficit is addressed. Accompanying treatment for MPS - 1 if diagnosis confirmed would be covered by private and state health insurance.

The committee was unanimous in agreement that MPS-1 met conditions 1-9 (with the exception of condition 7, which does not apply to MPS-1). A motion was made and seconded to add MPS-1 to the NBS panel. The committee then voted unanimously in favor of recommending the addition of MPS-1 to the required newborn screening panel in Wisconsin.

Members of the Committee
Norman Fost MD MPH (Chair)
Mei Baker MD
Jeff Britton MD
Arthur Derse MD JD
Kevin Josephson MS CGC
Tim Kruser MD
David Wargowski MD

Not attending
Stephen Leutner MD
Bruce Edmonson MD MPH