Secretary's Advisory Committee on Newborn Screening Meeting

Friday, September 19, 2025

Report on the Nomination to Add Mucopolysaccharidosis Type II (MPS II; Hunter syndrome) to the Newborn Screening Panel in the State of Wisconsin

On September 19, 2025, the Secretary's Advisory Committee on Newborn Screening met via Zoom to discuss the nomination to add Mucopolysaccharidosis Type II (MPS II; Hunter syndrome) to the Wisconsin mandatory newborn screening (NBS) panel. MPS II was nominated on March 26, 2025 by Emily Singh, MS, CGC, a genetic counselor with the Medical College of Wisconsin, and co-sponsored by Dr. Roberto Mendez, Assistant Director of Newborn Screening with the Wisconsin State Laboratory of Hygiene. The Metabolic Subcommittee (April 11, 2025) and the Umbrella Committee (May 2, 2025) met previously and concluded that MPS II meets all of the criteria for inclusion on the NBS. The Secretary's Advisory Committee met to discuss the nomination further.

Mucopolysaccharidosis Type II (MPS II) is an X-linked lysosomal storage disorder caused by pathogenic variants in the *IDS* gene encoding iduronate-2-sulfatase (I2S). Deficiency of this enzyme leads to progressive accumulation of the glycosaminoglycans (GAGs) dermatan sulfate and heparan sulfate in multiple tissues. This accumulation produces a multisystem disease affecting the airway, heart, bones, and central nervous system. MPS II is classified as either severe (formerly neuronopathic) or attenuated (formerly non-neuronopathic), based on the presence of neurologic involvement. About two-thirds of cases are classified as the severe form. Patients with

MPS II may also have the following features: characteristic facial features, macrocephaly, macroglossia, hearing loss, spinal stenosis, short stature, dysostosis multiplex, hepatosplenomegaly, hoarse voice, carpal tunnel, and cardiac and airway disease. Without treatment, individuals with the severe form typically live only into their second decade; those with the attenuated form may live into their fifth or sixth decade.

At the time of this report, two states (Illinois and Missouri) screen for MPS II, and New York has a pilot program to gather information about MPS II screening. The U.S. Secretary of Health and Human Services added MPS II to the Recommended Uniform Screening Panel (RUSP) on August 2, 2022.

Conditions added to the Wisconsin mandatory newborn screening panel must meet nine criteria. Emily Singh, being a co-nominator, abstained from the voting. The Chair did not vote.

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 II is a progressive and life-threatening disease. Infants are asymptomatic at birth, and the earliest signs and symptoms in the first 1-2 years of life are not enough to distinguish infants with the condition from those without. The median age symptom onset is 1.5 years and the median age of diagnosis is 3.3 years. By the time clinical features raise suspicion, significant and irreversible organ damage has often occurred. Early detection through newborn screening allows timely evaluation and initiation of therapy

before severe somatic or neurologic manifestations develop. **All seven members voted that MPS II meets Criterion 1.**

Second, for each condition, there should be information about the incidence, morbidity, and mortality, and the natural history of the disorder.

Before NBS implementation, the U.S. birth prevalence was estimated at 0.26 to 0.67 per 100,000 births, or approximately 1 in 150,000 to 380,000 births. However, recent population screening data from Illinois (586,323 infants screened) and Missouri (288,892 infants screened) report birth prevalence rates of 1.4 per 100,000 or 1 in 73,000–96,000. The Advisory Committee on Heritable Disorders in Newborns and Children review estimated a prevalence of 1.6 per 100,000. Natural history data from the Hunter Outcome Survey (HOS) demonstrate progressive multisystem involvement including neurologic (84%), cardiovascular (82%), and skeletal (>60%) involvement. Without treatment those with the severe form of the condition may live into their 20's, and those with the attenuated form may live into their 50's or 60's. **Six committee members voted that MPS II meets criteria 2, one desired more information.**

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.

The standard therapy for MPS II is enzyme replacement therapy (ERT) with idursulfase (Elaprase®), approved by the FDA in 2006 as a once-weekly IV infusion. ERT improves urinary GAG levels, reduces hepatosplenomegaly, and stabilizes cardiac function and mobility, particularly when initiated early. A systematic review confirmed consistent benefits on somatic manifestations. Respiratory outcomes have not been

shown to improve consistently across studies. While ERT does not cross the blood-brain barrier and thus does not halt CNS decline in severe cases, it is safe and clinically effective for systemic disease. More data is needed to assess developmental outcomes for early treated individuals. The median survival age is 21.2 years in untreated individuals, and 33 years in those treated with ERT. Infusion-related reactions (primarily fever, rash, urticaria, or vomiting) are common but manageable; anti-idursulfase antibodies occur in ~50% of patients but rarely alter outcomes. Emerging therapies (including intrathecal ERT and gene therapy) are in clinical trials. **Five committee members voted that MPS II meets Criterion 3, one wanted more information on the efficacy of very early treatment versus later treatment, and one wanted more information in regards to the impact of treatment on central nervous system involvement.**

Fourth, the interventions should be reasonably available to affected newborns.

Enzyme replacement therapy is already administered at several locations across the state that have established infusion programs for lysosomal storage disorders. Home infusion is possible after stabilization and insurance approval. **All seven members voted that MPS II meets Criterion 4.**

Fifth, appropriate follow-up should be available for newborns who have a false positive newborn screen.

The Wisconsin State Laboratory of Hygiene (WSLH) will communicate positive MPS II results to the infant's primary care provider and designated metabolic center for confirmatory testing. Follow-up includes enzyme analysis of I2S and a second sulfatase to exclude multiple sulfatase deficiency, urinary GAG analysis, and molecular testing of the IDS gene. Infants with normal results or pseudodeficiency variants will be classified

as false positives and will be offered genetic counseling. Genetic counseling and education are provided to explain that the child is not at risk for disease. **All seven members voted that MPS II meets Criterion 5.**

Sixth, the characteristics of mandated tests in the newborn population should be known, including specificity, sensitivity, and predictive value.

Screening for MPS II uses measurement of I2S enzyme activity in dried blood spots by Revvity NeoLSD MS/MS platform, after a separated incubation step, the enzyme activity assessment is multiplexed with Pompe disease. Samples with low activity undergo second-tier GAG analysis on the same DBS, performed by Mayo Clinic Laboratories. Pilot data from Illinois and Missouri show that second-tier GAG testing reduces false positives substantially (10.6 per 100,000 in Illinois, 4.2 per 100,000 for Missouri). The Wisconsin lab would rerun tests in the uncertain range which should significantly lower the false positive rate. Based on information out of Illinois and Missouri the sensitivity of screening is 100%, the negative predictive value is 100%, and positive predictive value is 99.9%. No unrelated conditions would be identified except multiple sulfatase deficiency in rare cases, which would only emerge during confirmatory testing. **All seven members voted that MPS II meets Criterion 6.**

Seventh, if a new sample collection system is needed to add a disorder, reliability and timeliness of sample collection must be demonstrated.

No new sample collection system is required; testing will utilize existing dried blood spots collected for current NBS assays.

Eighth, before a test is added to the panel, the details of reporting, follow-up, and management must be completely delineated.

Follow-up for MPS II will mirror existing protocols for metabolic conditions. The WSLH laboratory will report screening positive results to the infant's primary care provider and metabolic specialist. Confirmatory testing and diagnosis will occur at Children's Wisconsin and the Waisman Center. Infants confirmed to have MPS II will receive multidisciplinary care involving genetics, dental, audiology, cardiology, ENT, orthopedics, pulmonology, neurology, neurosurgery, GI, and other specialties depending on specific patient needs, along with social work and family support resources. Infants will be assessed to see if they are a candidate for treatment. If they are to be given ERT they will begin ERT at an infusion center, and possibly eventually transition to home infusion. **All seven members voted that MPS II meets Criterion 8.**

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.

Adding MPS II to the panel requires purchase of additional reagents and send-out second-tier testing for GAGs, increasing the NBS card fee by an estimated $6 per newborn. Confirmatory testing, ERT, and counseling will be covered through insurance and the Congenital Disorders Grant at designated centers. These resources are also available to cover the cost of care for false positives. **All seven members voted that MPS II meets Criterion 9.**

As Mucopolysaccharidosis Type II was determined to fulfill all nine criteria, a motion was made to approve the nomination of MPS II. The motion to approve was seconded, then unanimously approved by the committee.

Members of the Committee

Norman Fost MD MPH (Chair)
Mei Baker MD
Jeff Britton MD
Arthur Derse MD JD
M. Bruce Edmonson MD MPH
Tim Kruser MD
Stephen Leutner MD
Emily Singh MS CGC (Abstaining)
David Wargowski MD