DEPARTMENT OF HEALTH AND HUMAN SERVICES

Advisory Committee on Heritable Disorders in Newborns and Children
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www.hrsa.gov/advisory-committees/heritable-disorders

March 15, 2022

The Honorable Xavier Becerra
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Secretary Becerra:

This letter is to inform you of a new recommendation from the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC or Committee). The ACHDNC provides advice and recommendations concerning heritable disorders, newborn screening, and childhood screening. The objective of the ACHDNC is to enhance states' abilities to reduce morbidity and mortality in newborns and children who have, or who are at risk for, heritable disorders. The ACHDNC makes systematic evidence-based recommendations regarding conditions for inclusion on the Recommended Uniform Screening Panel (RUSP): the list of conditions you recommend states screen for at birth as part of their state universal newborn screening programs. Newborn screening is a state public health function. Most states screen for the majority of disorders on the RUSP.

The Committee uses a rigorous process to identify conditions to recommend to you for inclusion on the RUSP. Multi-disciplinary teams nominate conditions by submitting information on key topics including natural history, screening methods and outcomes of pre-symptomatic or early initiation of treatment. If the Committee determines there is sufficient evidence, an independent external group conducts a systematic evidence-based review, which includes an analysis of information and data obtained from published and gray literature, technical experts, pilot programs and a state public health impact assessment survey on implementation of newborn screening for the nominated condition. The Committee develops its recommendation on whether to add a condition to the RUSP based on the findings of the evidence-based review and deliberations using a decision matrix to guide the decision-making process.

On February 9, 2022, the Committee voted to send you the recommendation to add the nominated condition Mucopolysaccharidosis Type II (MPS II) to the RUSP. This recommendation is based upon Committee deliberations and findings from the evidence-based review for MPS II, which includes detailed information on clinical data, testing

platforms, available treatments, benefits and harms, an assessment of the public health systems impact, and public comment.

MPS II, also referred to as Hunter syndrome, is an X-linked lysosomal storage disorder affecting many different parts of the body, resulting in debilitating disease. It is caused by mutations in the iduronate-2-sulfatase (*IDS*) gene leading to dysfunction of the enzyme iduronate-2-sulfatase (I2S). This condition primarily affects males and impairs the body's metabolism leading to the accumulation of two glycosaminoglycans (GAGs). Based on clinical detection, MPS II has an estimated incidence between 0.13-2.16 per 100,000 live births. For pilot studies in Illinois and Missouri, screening detections are 1.6 per 100,000.

Infants with MPS II do not have symptoms at birth; however, once the disease progresses it is typically classified as either severe or attenuated. Approximately 60 percent of individuals with MPS II have the severe form with symptoms appearing between 2-4 years of age. With attenuated MPS II, symptoms typically begin around 4 years of age. Common health problems experienced by individuals with both forms of MPS II include changes in facial appearance, enlarged liver and spleen, cardiac valve disease, enlarged tonsils and adenoids that can lead to obstructive sleep apnea, reduced lung functioning, skeletal disease, and progressive joint stiffness impairing mobility. Severe MPS II also results in damage to the central nervous system (CNS) leading to significant behavior problems and progressive intellectual impairment. Left untreated most individuals with the severe form of MPS II die between 10-20 years old. Individuals with attenuated MPS II typically live into adulthood but often experience premature mortality.

In the U.S., enzyme replacement therapy (ERT) is the only U.S. Food and Drug Administration-approved treatment for MPS II. ERT is administered through weekly intravenous infusion taking several hours. Studies demonstrate that early initiation of ERT extends life and slows disease progression allowing for increased mobility and ability to perform daily living activities including toileting and bathing with more independence. Family members and caregivers cited better quality of life for children who initiated ERT pre-symptomatically. Intravenous ERT does not cross the blood-brain barrier and individuals with the severe form of MPS II experience minimal improvements to cognitive functioning. Current research is exploring the effectiveness of intrathecal and intraventricular ERT and gene therapy to improve CNS outcomes.

Newborn screening tests measure I2S enzyme activity in dried-blood spots using tandem mass-spectrometry or fluorometry. Dried-blood spot GAG levels can be used as a second-tier test to reduce false positives. The Centers for Disease Control and Prevention has developed quality assurance/quality control and proficiency testing materials for newborn screening laboratories to aid in the implementation of testing for MPS II. Sixty-two percent of states responding to the public health impact assessment indicated that it would take between 1 and 3 years to implement screening for MPS II. For the two states piloting newborn screening for MPS II (Illinois and Missouri), there have been no reported missed cases.

The Committee deliberated on the net benefits, certainty of available evidence and feasibility of newborn screening for MPS II and concluded that there is moderate certainty of significant benefits to infants identified with MPS II through newborn screening. In addition, the Committee found that most states would need 1-3 years to begin

implementation of screening for MPS II and screening, testing and treatment in state newborn screening systems are feasible.

Through the evidence-based review, the Committee found that MPS II has a reliable screening test and evidence of improvements in somatic outcomes with early initiation of treatment. The Committee acknowledges that there is a lack of long-term outcomes data for MPS II and noted that this is a challenge the Committee will continue to face as increasingly rare conditions are nominated for inclusion on the RUSP. In its deliberations, the Committee noted the burden on states to implement new RUSP conditions without additional funding and the potential harms to families of newborns identified with uncertain diagnostic results.

Weighing all of these factors, the Committee determined that screening for MPS II will lead to significant benefits for infants born with this rare condition, their families and caregivers and respectfully requests you accept the recommendation to add MPS II to the RUSP.

Sincerely,

/s/

Cynthia M. Powell, MD, FACMG, FAAP
Chairperson

Enclosure:
Report - *Evidence-based Review of Newborn Screening for Mucopolysaccharidosis Type II*

cc: Soohyun Kim, MPH, CPH
Acting Designated Federal Official
Health Resources and Services Administration