Secretary's Advisory Committee on Newborn Screening
Friday, March 6, 2020

Report on the Nomination to add Pompe Disease to the Newborn Screening Panel in the State of Wisconsin

On March 6, 2020, the Secretary's Advisory Committee on Newborn Screening met at the Wisconsin State Laboratory of Hygiene in Madison, Wisconsin to review a nomination to add Pompe disease to the Wisconsin mandatory newborn screening panel. This meeting followed the meetings of the Metabolic Subcommittee on September 6, 2019 and the Umbrella Committee on December 6, 2019. Pompe disease was initially nominated on August 26, 2019 by Michael and Stephane Clubb, with co-sponsors Melissa Swainston, Genevive Faucher, Gregory Rice, MD, Mei Baker, MD, and Robert Steiner, MD. The Secretary's Advisory Committee voted unanimously in favor of the addition.

Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive condition. Homozygous or compound heteroyzygous pathogenic variants in the *GAA* gene, which encodes the enzyme acid alpha-1,4-glucosidase (GAA), result in aberrant accumulation of glycogen within lysosomes, which disrupts normal cellular function of cardiac and skeletal myocytes. In lay language, glycogen is a storage form of glucose, needed for energy throughout the body, and affected individuals cannot convert the glycogen to glucose. Thus, it accumulates in muscle cells, including the heart, gradually destroying the ability of the muscle cells to work properly.

Clinical manifestations of Pompe disease are varied but include hypertrophic cardiomyopathy (enlarged and poorly functioning heart muscle), hypotonia (floppy muscles throughout the body), generalized muscle weakness, and respiratory distress. Individuals with infantile-onset Pompe disease (with symptoms of cardiomyopathy presenting prior to 12 months of age) are typically more severely affected than those with late-onset form, though presentation and disease course range across a wide spectrum.

In 2015, Pompe disease was added to the national Recommended Uniform Screening Panel following the recommendation of the US Department of Health and Human Services (DHHS) Advisory Committee on Heritable Disorders in Newborns and Children, and the approval of the Secretary of DHHS. Wisconsin implemented a pilot screening program from July 2017 through March 2019, the results of which were favorable and motivated nomination of Pompe to the state panel. Currently, 19 states screen for Pompe disease, including Minnesota, Michigan, and Illinois.

Conditions added to the Wisconsin mandatory newborn screening panel must meet nine criteria. The committee considered each criterion in turn.

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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. Infantile-onset Pompe disease is not readily detectable at birth and typically presents with failure to thrive, muscle weakness, hypotonia, respiratory distress, and cardiomyopathy at a median age of 4 months. Untreated, the condition is generally fatal by 2 years of age. Initiation of treatment with enzyme replacement therapy prior to symptom onset improves survival and outcomes. Late-onset

Pompe disease, which is also diagnosed by the newborn screening test, can also be treated with enzyme replacement therapy to slow or prevent development or progression of disease.

Second, for each condition, there should be information about the incidence, morbidity, and mortality and the natural history of the disorder. Extensive literature has been published on the epidemiology and natural history of Pompe disease nationally and internationally. About 10-30% of Pompe cases are infantile. The overall incidence of infantile-onset Pompe disease is approximately 1 in 30,000 to 40,000 live births. Infantile-onset Pompe disease carries a mortality of >90% in the first 2 years of life; morbidity during the lifespan includes failure to thrive, motor delay, respiratory insufficiency, and heart failure due to cardiomyopathy. Late-onset Pompe disease presents in childhood in over 50% of cases. Given disease variability, mortality is more difficult to ascertain but has been estimated around 15%. Significant delays in diagnosis following symptoms onset, typically a decade, results in harm in the form of extensive workups with invasive testing and delays in disease-modifying treatment. State-specific incidence is available from the Wisconsin Pompe Pilot Program, in which 108,862 infants were screened with 13 confirmed positive cases. All of these cases were late- onset, giving an incidence of 1 in 8374 live births in Wisconsin. No false positive, false negative, or infantile-onset cases were identified during the pilot study.

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. Enzyme replacement therapy in infantile-onset Pompe disease has been shown to reduce the risk of death by 95% in addition to significant reductions in the need for invasive ventilation. Improvement in cardiac

function, motor skills, and long-term outcomes were also observed. Treatment is most effective when started before symptoms develop. Enzyme replacement therapy has also been shown to benefit patients with late-onset Pompe disease, with observed improvements in muscle strength and lung function when initiated early.

Fourth, the interventions should be reasonably available to affected newborns. Enzyme replacement therapy with either Myozyme or Lumizyme is now considered standard of care and is routinely covered by health insurance companies. Lumizyme is widely available, whereas Myozyme has more limited availability.

Fifth, appropriate follow-up should be available for newborns who have a false positive newborn screen. Among the 108,862 infants included in the pilot study of Pompe screening in Wisconsin, there were 0 false positives. While this does not preclude the possibility of future false positive results, it suggests the rate will be low. A follow-up process to evaluate such cases, including echocardiogram, further testing, education, and genetic counseling, is in place.

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). In the Wisconsin Pompe Pilot Program, all 13 positive cases were identified by first tier testing (enzyme activity) and confirmed by second-tier testing (molecular diagnosis). There were no false positives and there are no reported false negatives at this time. These data suggest high sensitivity and specificity of the testing procedure.

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

does not apply to Pompe disease, as the screening test employs existing collection methods. Measurement of GAA enzyme activity can be done on the dried blood spots that are now collected on filter paper for other newborn screening tests.

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 Pompe disease will follow the typical flow for other disorders on the Wisconsin newborn screening panel. In the event of a positive test, the state lab contacts the metabolic consultants, who then contact the primary care provider (PCP). The metabolic specialist and PCP then work together to coordinate necessary confirmatory testing, clinical evaluations such as echocardiograms, and initiation of treatment as necessary. Genetic counselors will also be involved in communication and care coordination.

Finally, recommendations and decisions should include consideration of the costs of the screening test, consideration of 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. The committee determined that the addition of a screening test for Pompe disease would be funded through the newborn screening fee, which hospitals pay to the state laboratory. A fee increase on the order of $8-10 per card may be necessary to offset the added cost of Pompe testing. Treatment of Pompe disease is generally covered by health insurance.

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

Respectfully Submitted,

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