Secretary's Advisory Committee on Newborn Screening Meeting

Friday, September 19, 2025

Report on the Nomination to Add Early Infantile Krabbe Disease with Psychosine at or above 10 nmol/L 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 early infantile Krabbe disease with psychosine at or above 10 nmol/L to the Wisconsin mandatory newborn screening (NBS) panel. Krabbe disease was nominated on March 17, 2025 by Zoë Culshaw-Klein, a Master of Science Genetic Counseling student with the Medical College of Wisconsin, and co-sponsored by Dr. William Rhead, Clinical Professor of Pediatrics at the University of Wisconsin School of Medicine and Public Health. The Metabolic Subcommittee (April 11, 2025) and the Umbrella Committee (May 2, 2025) met previously and concluded that early infantile Krabbe disease with Psychosine at or above 10 nmol/L meets all of the criteria for inclusion on the NBS. The Secretary's Advisory Committee met to discuss the nomination further.

Early infantile Krabbe disease is an autosomal recessive neurodegenerative disorder caused by pathogenic variants in the *GALC* gene, which result in a deficiency of the enzyme galactocerebrosidase (GALC). This enzyme is responsible for breaking down psychosine and other sphingolipids. When GALC activity is absent or severely reduced, psychosine accumulates to toxic levels, leading to demyelination and widespread destruction of oligodendrocytes and Schwann cells in the central and peripheral nervous

systems. The early infantile form of Krabbe disease typically presents within the first six months of life with irritability, feeding difficulties, hypotonia, spasticity, seizures, and developmental regression, and without early treatment, results in death usually by two years of age. The condition can be identified through measurement of GALC enzyme activity in dried blood spots followed by second-tier measurement of psychosine. The early infantile form is defined as onset prior to 1 year of life.

At the time of this report, eleven other states (Illinois, Indiana, Kentucky, Georgia, Missouri, New Jersey, New York, Ohio, Pennsylvania, Tennessee, and Texas) screen for Krabbe disease, and the U.S. Secretary of Health officially added early infantile Krabbe disease to the Recommended Uniform Screening Panel (RUSP) on July 1, 2024.

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

Early infantile Krabbe disease presents in otherwise healthy newborns, with a median onset of severe neurologic symptoms around 4 to 6 months of age. These include irritability, feeding difficulties, stiffness, developmental delay, and seizures. Without early intervention, affected infants experience rapid neurodegeneration and death, usually within the first two years of life. Hematopoietic stem cell transplantation (HSCT) is the only effective treatment and must be performed within the first 30 to 45 days of life to

slow disease progression and preserve neurologic function. Without newborn screening, diagnosis typically occurs after irreversible neurological damage has occurred making the treatment far less effective. **All eight members voted that early infantile Krabbe disease meets Criterion 1.**

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

Krabbe disease occurs in approximately 1 in 100,000 to 250,000 live births in the United States, with the early infantile form comprising about 62% of cases. Without treatment, death typically occurs by two years of age for those with the infantile form of the disease. Mortality results from respiratory failure resulting from poor muscle tone or infections from aspiration. The natural history of the disease is well documented in both U.S. and international studies, demonstrating consistent clinical onset, progression, and outcomes. **All eight members voted that early infantile Krabbe disease meets Criterion 2.**

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.

Hematopoietic stem cell transplantation (HSCT) is the current standard of care. When performed within the first 30 days of life before the onset of symptoms, HSCT significantly prolongs survival and improves neurologic outcomes compared to untreated or later-treated infants. Studies have shown that psychosine (the substance responsible for neurological decline in patients with Krabbe) levels decrease following transplantation. Infants treated presymptomatically show markedly improved neurological symptoms and

survival, whereas treatment after symptom onset yields poor outcomes. Specifically infants treated with HSCT prior to symptoms have a median survival rate of 15.5 years, infants treated after symptoms have a median survival of 5 years, and untreated infants had a median survival of 2.2 years. Individuals who receive treatment prior to the onset of symptoms are able to live relatively normal lives until their early teens. Risks of HSCT include a 10% treatment-related mortality rate, graft-versus-host disease, and long-term motor and speech difficulties, but the benefits of early treatment substantially outweigh these risks. The developmental delays associated with HSCT are typically less significant than what is seen in untreated infants. Additionally, while HSCT improves outcomes for patients, it is not curative for Krabbe disease. Even with treatment, long term motor and speech difficulties are expected. The treatment has been demonstrated to be more effective at treating the central nervous system concerns then the peripheral nervous system concerns. **All eight members voted that early infantile Krabbe disease meets Criterion 3.**

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

Wisconsin infants can receive HSCT at Children's Wisconsin in Milwaukee, a FACT-accredited bone marrow transplant center with experience in metabolic disorders. Transplant centers at Lurie Children's Hospital (Chicago, IL) and the University of Minnesota (Minneapolis, MN) also offer HSCT for Krabbe disease and are accessible to Wisconsin families who wish to seek treatment elsewhere. An international cord blood registry aids in the identification of donor matches for transplant. There is a strong likelihood that WI Medicaid will cover HSCT. **All eight members voted that early infantile Krabbe disease meets Criterion 4.**

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

Infants with low GALC activity and psychosine below 10 nmol/L on confirmatory testing are classified as false positives for early infantile Krabbe disease. Families with children who are determined to have false positives will be offered genetic counseling. Genetic counseling and education are provided to explain that the child is -at low risk for early infantile Krabbe disease. Newborns with normal/reduced GALC enzyme, elevated psychosine, and normal molecular testing for the *GALC* gene may be offered sequencing of the *PSAP* gene to test for Saposin A deficiency. **All eight members voted that early infantile Krabbe disease meets Criterion 5.**

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

The screening process includes first-tier measurement of GALC enzyme activity via FDA-approved multiplex MS/MS assay and second-tier psychosine measurement on the same dried blood spot, performed by Mayo Clinic Laboratories. Programs using psychosine as a second-tier test report the low false positive rates. Wisconsin will employ a psychosine cutoff of 10 nmol/L or greater to identify infants at significant risk for early infantile disease. Based on data from other states the false positive rate at this cutoff is predicted to be <.001%. Screening is 100% sensitive, has a high positive predictive value with second tier testing, and no false negatives have been reported from other states already screening for the condition. No additional conditions are expected to be detected by this assay, except in rare cases of Saposin A deficiency (PSAP), which can be

distinguished via molecular testing. Saposin A deficiency does not meet the established criteria for screening. **All eight members voted that early infantile Krabbe disease 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; Krabbe disease screening uses the same dried blood spot collected for existing NBS tests.

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

Infants with low GALC enzyme activity and psychosine ≥10 nmol/L will be urgently referred to a genetics or neurology specialist capable of coordinating HSCT within 30–45 days of birth. Early inpatient admission may be pursued to expedite evaluation and treatment. Confirmatory testing will be pursued while coordinating HSCT**. All eight members voted that early infantile Krabbe disease 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.*

Wisconsin currently utilizes a six-enzyme multiplex panel that includes *GAA* activity measurement for Pompe disease screening; this assay can be extended to Krabbe disease at no additional first-tier cost. Second-tier psychosine testing is estimated to cost $60–$100 per sample, with approximately 50–150 samples anticipated annually depending on the enzyme cutoff used. Confirmatory testing and HSCT are typically

covered by insurance or Medicaid. **All eight members voted that early infantile Krabbe disease meets Criterion 9.**

As early infantile Krabbe disease was determined to fulfill all nine criteria, a motion was made to approve the nomination of early infantile Krabbe disease. 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
David Wargowski MD