State of Wisconsin
Department of Health Services
Tony Evers, Governor
Karen E. Timberlake, Secretary

February 3, 2021

Kevin and Judy Cushman
[redacted]

Joanne Kurtzberg, MD
2400 Pratt Street
Durham, NC 27705

Dear Mr. and Mrs. Cushman and Dr. Kurtzberg:

Thank you for submitting a nomination on March 9, 2020, to add Krabbe disease to the Wisconsin newborn screening panel of conditions.

When we receive a nomination to add a condition to the Wisconsin panel, we follow a careful process to ensure it is thoroughly reviewed using established criteria. You can read more about this process, and the committees involved, at https://www.dhs.wisconsin.gov/newbornscreening/process-additions.htm .

The Metabolic Subcommittee considered the Krabbe disease nomination on April 17, 2020, and concluded that Krabbe disease did not meet criteria 3 and 4, and that more information was needed to determine whether it met criteria 8 and 9. Conditions added to the Wisconsin mandatory newborn screening panel must meet all nine criteria. The subcommittee forwarded their comments to the Newborn Screening Advisory Umbrella Committee (Umbrella Committee).

On May 1, 2020, the Umbrella Committee, composed of newborn screening specialists, also reviewed the Krabbe nomination and made the same conclusion as the Metabolic Subcommittee.

Finally, on May 15, 2020, the Secretary's Advisory Committee on Newborn Screening (SACNBS) reviewed the nomination, as well as the comments of the Metabolic Subcommittee and Umbrella Committee. The SACNBS also concluded that Krabbe disease did not meet the required criteria. A motion was made to table the nomination of Krabbe disease while advocates collaborate with experts to further delineate processes for appropriate follow-up of infants who have a confirmed concerning result for Krabbe, including identification of consultants and referral centers.

Based on the review by the SACNBS, the Department has made the difficult decision that Krabbe should not be added to the Wisconsin newborn screening panel at this time. The Department will continue to closely monitor the data from states that have added Krabbe to their

newborn screening panels. We encourage you or others to resubmit the nomination once processes for appropriate follow-up of infants who have a confirmed concerning result for Krabbe are in place, including identification of consultants and referral centers. We look forward to a time when children born with Krabbe can lead full and healthy lives.

Thank you for your interest and support for the Wisconsin Newborn Screening Program.

Sincerely,

Karen E. Timberlake
Interim Secretary

Enclosure:

The full report of the SACNBS is enclosed, and will also be posted on the DHS website's Krabbe Disease – Nomination Process page. (https://www.dhs.wisconsin.gov/newbornscreening/krabbe-nomination-process.htm).

Secretary's Advisory Committee on Newborn Screening Meeting

Friday, May 15, 2020

Report on the Nomination to Add Krabbe Disease

to the Newborn Screening Panel in the State of Wisconsin

On May 15, 2020, the Secretary's Advisory Committee on Newborn Screening met via Zoom to discuss the nomination to add Krabbe disease to the Wisconsin mandatory newborn screening (NBS) panel. Krabbe disease was initially nominated and reviewed in 2015; at that time, the motion was turned down due to insufficient evidence for safe and effective treatments. Recently, Krabbe disease was re-nominated by Kevin and Judy Cushman, Wisconsin residents and parents of Collin Cushman, who was diagnosed with Krabbe disease at the age of 13 months and died at age 8 from complications of the disease. The Metabolic Subcommittee (Apr 17, 2020)) and the Umbrella Committee (May 1, 2020) met previously and concluded that Krabbe disease did not meet criteria 3 and 4, and that more information was needed to determine whether it met criteria 8 and 9 (criteria are detailed below). The Secretary's Advisory Committee met to discuss the nomination further.

Krabbe disease, also known as globoid cell leukodystrophy, is a lysosomal storage disease that causes demyelination and neuromotor disability. It is an autosomal recessive disease caused by mutations in the *GALC* gene, which encodes the enzyme galactosylceramidase. This enzyme is responsible for the breakdown of galactolipids. Lack of functioning enzyme results in aberrant accumulation of galactosylceramide and psychosine and formation of globoid cells within the central nervous system, impairing

normal nerve conduction. Clinical manifestations of Krabbe disease most commonly include generalized muscle weakness and spasms, irritability, developmental delays, seizures, visual and hearing impairments, and respiratory distress. Individuals with late-onset Krabbe disease develop similar symptoms of motor impairment (e.g. ataxia) and visual impairment but are typically less severely affected compared to infantile-onset forms of the disease.

At the time of this report, seven other states - Illinois, New Jersey, New York, Kentucky, Missouri, Ohio, and Tennessee - screen for Krabbe disease.

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*. The most common form of Krabbe disease is infantile onset. This form is not readily detectable at birth but typically presents within the first year of life with muscle weakness, irritability, difficulty feeding, and delayed motor milestones. Symptoms may progress to include regression of motor development, muscle contractures, and respiratory distress. Untreated, affected children rarely live past the age of 2 years. Without newborn screening, Krabbe disease is unlikely to be detected early enough to prevent or ameliorate its serious health consequences. Therefore, the eight voting members of the committee unanimously agreed that Krabbe disease meets Criterion 1.

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

available describing the epidemiology and natural history of Krabbe disease. The overall incidence of Krabbe disease is approximately 1 in 100,000 to 400,000 live births. With an annual birth count of 60,000 infants, Wisconsin could expect approximately 0-2 new diagnoses a year through NBS. The morbidity and mortality of infantile-onset Krabbe disease is significant, with most affected individuals dying in early childhood. Morbidity during the short lifespan includes failure to thrive, motor delay, seizures, and respiratory insufficiency. Late-onset forms of Krabbe disease have a more variable presentation but typically inflict vision and motor impairments that compromise quality of life. There were 7 votes in favor of Krabbe disease meeting Criterion 2 and 1 vote for more information, particularly with regard to late-onset forms.

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*. Historically, treatment of Krabbe disease had been limited to symptomatic management. More recently, stem cell or bone marrow transplant (BMT) has been shown to delay the progression of motor disease in infantile-onset Krabbe disease, particularly if undertaken within the first 30 days of life. However, BMT does not fully treat or cure the disease. Furthermore, BMT poses a number of health risks, including potentially fatal complications. No enzyme replacement therapy or gene therapy is available at this time. Given the promising but limited evidence to support BMT as a treatment for Krabbe disease, 4 members voted that Criterion 3 was met, one member voted that it was not, and 3 members voted in favor of more information.

Fourth, *the interventions should be reasonably available to affected newborns.* Only a handful of centers across the country perform bone marrow transplants for Krabbe disease. Duke University has a well-established program and is considered a leader in the field. No centers in Wisconsin have undertaken the treatment, and it remains to be seen how readily these capacities could be developed within the state. In the meantime, patients would likely need to travel out of state to undergo BMT at established treatment centers. Six members believed that Krabbe met Criterion 4, while 2 members felt more information was needed.

Fifth, *appropriate follow-up should be available for newborns who have a false positive newborn screen.* With second tier testing for psychosine, the false positive rate for Krabbe disease is near zero. For the rare but theoretically possible cases of false positives, referrals could be made to out-of-state specialists and experts in Krabbe for further testing and follow-up. Given its inherent risks, treatment with bone marrow transplant is only undertaken in the setting of definitive laboratory diagnosis of the disease. All eight members voted that Krabbe 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 (experience, natural history, or literature).* To date, there are have been no known false positive results in screening for the infantile form of Krabbe disease. Second-tier testing by psychosine level or DNA sequencing is reliable without known false positives based on testing programs in other states. The false negative rate is unknown but thought to be vanishingly small. Given the high sensitivity and specificity

of current testing methods, the committee agreed unanimously that 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*. This criterion does not apply to Krabbe disease, as the screening test employs existing collection methods used to test for Pompe disease.

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*. Unlike the diseases currently on the NBS panel which were nominated by a physician scientist who championed the effort, Krabbe disease was nominated by an affected family. The necessary organizational structures within the medical community have yet to be developed. At this time, appropriate steps to follow-up a positive screening result for Krabbe disease are not clearly defined in the state of Wisconsin. There were no votes for Krabbe disease meeting Criterion 8; three committee members voted that it does not meet the criterion and five voted for more information.

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 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 cost of adding a screening test for Krabbe disease to the dried blood spot card would be nominal (on the

order of $1-4 per card), as Pompe disease is already being screened by analogous testing methods. The cost of secondary testing for psychosine, which is a send-out lab to Mayo Clinic, was also considered and estimated at around $100 per test. An estimated 20-30 second-tier tests will be required annually, which the committee felt was a reasonable expense to take on. Treatment of Krabbe disease is generally expected to be covered by health insurance, though concerns were raised regarding Medicaid coverage of treatment. No formal economic analysis has been performed to the committee's knowledge. Five members voted that Krabbe meets Criterion 9, while 3 were in need of further information.

Given concerns that Krabbe disease did not clearly meet all the criteria (especially criterion 8), a motion was made to table the nomination of Krabbe disease while advocates collaborate with experts to further delineate appropriate follow-up of infants who test positive on NBS, including identification of consultants and referral centers. The motion to table was seconded, then unanimously approved by the committee.

Respectfully Submitted

Norman Fost MD MPH (Chair)
Mei Baker MD
Jeffrey Britton MD
Christine Brown
Arthur Derse MD JD
Ousmane Diallo MD PhD
Stephen Leuthner MD MA
Kevin Josephson MS, CGC
David Wargowski MD
Sharon Fleischfresser MD MPH (non-voting)

Guests who asked to speak:
Dr. Greg Rice, University of Wisconsin School of Medicine and Public Health

Dr. Joanne Kurtzberg, Duke University
Dr. Michael Gelb, University of Washington
Judy Cushman, parent of children with Krabbe Disease
Kevin Cushman, parent of children with Krabbe Disease
Senator Patrick Testin (Wisconsin legislature)
Stacy Pike-Langenfeld, Krabbe Connect
Anne Rugari, parent of children with Krabbe Disease
Anna Grantham, Hunters Hope Foundation
Dr. Marie Escolar, University of Pittsburgh (written comment)
Dr. Donald Basel (Medical College of Wisconsin)
Dr. Dietrich Matern (Mayo Clinic)