

Secretary's Advisory Committee on Newborn Screening  
Monday, January 25, 2016

*Report on Nomination to Newborn Screening for Krabbe Disease in Wisconsin*

The advisory committee considered two major issues relating to a nomination to add Krabbe disease to the mandatory newborn screening panel in Wisconsin: (1) whether recent research on Krabbe disease, developed since the Metabolic Subcommittee and Umbrella Committee considered the issue, should affect the committee's recommendation, and (2) whether Krabbe disease should be added to the mandatory newborn screening panel in Wisconsin at this time

*(1) Should recent research on Krabbe disease affect the committee's recommendation?*

Krabbe disease is a rare lysosomal storage disorder, affecting roughly 1 in 400,000 people, with an early-infantile and late-onset form. The early-infantile form of the disease, if untreated, is fatal in childhood.. The Metabolic Subcommittee had previously recommended against adding Krabbe disease to Wisconsin's mandatory newborn screening panel. The subcommittee members reasoned that—although Krabbe disease had devastating effects—the screening test had an unacceptably high false positive rate, which was compounded by difficulty in distinguishing true- from false-positive cases with follow-up testing. Furthermore, despite some literature suggesting that early detection of the disease via newborn screening improved outcomes, no further studies had demonstrated that therapeutic intervention (namely, stem-cell transplantation) improves either quantity or quality of life in the long term. Before the Advisory Committee made its final recommendation about the nomination to add Krabbe disease to the mandatory newborn screening panel, however, the committee wished to review recent research on Krabbe disease at Duke University. The committee reasoned that this research might provide new evidence that there

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existed interventions that could improve either the quantity or quality of life of infants with Krabbe disease.

The committee heard the following evidence (via telephone) from Dr Joanna Kurzberg, professor of pediatrics and pathology at Duke University, and director of the stem cell transplant program there. Research at Duke suggested that stem-cell transplantation could improve functional outcomes and length of life, but only if performed on pre-symptomatic infants; transplants on symptomatic children did not significantly improve their quantity or quality of life. The committee also heard that the Duke research team expected that augmented therapies could further improve the outcomes of affected infants. For these reasons—together with a belief that ancillary testing could rapidly confirm the diagnosis of Krabbe disease—Dr Kurtzberg strongly supported newborn screening for Krabbe disease. This support, however, was conditional on it being the case that Wisconsin could be prepared, within 1-2 days of an infant receiving a positive screen for Krabbe disease, to refer this infant for treatment. The committee also heard that the recent research at Duke University had not yet been peer-reviewed or published.

The committee also heard from several families who have been affected by the birth of a child with Krabbe Disease and State Senator Julie Lassa, all of whom spoke in favor of newborn screening for Krabbe Disease.

### *(2) Should Krabbe disease be added to the mandatory newborn screening panel in Wisconsin?*

The committee then considered whether Krabbe disease met each of the following nine criteria:

1. 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.
2. For each condition, there should be information about the incidence, morbidity and mortality, and the natural history of the disorder.

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3. 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.
4. The interventions should be reasonably available to affected newborns.
5. Appropriate follow-up should be available for newborns that have a false positive newborn screen.
6. The characteristics of mandated tests in the newborn population should be known, including specificity, sensitivity, and predictive value.
7. If a new sample collection system is needed to add a disorder, reliability and timeliness of sample collection must be demonstrated.
8. 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 referral centers throughout the state/region.
9. 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 unanimously agreed that criteria 1, 2, and 7 were met, and a majority of committee members agreed that criterion 6 was met. However, the committee unanimously agreed that more information was required to know whether criteria 3 and 9 were met, and a majority of committee members agreed that more information was required to know whether criteria 5 and 8 were met. On criterion 4, the committee divided evenly between those who believed that it was met and those who believed that further information was required to know whether it was met.

Against the view that criterion 4 was met, some committee members argued that it was uncertain whether the state could refer for treatment infants who screened positive for (and were then confirmed as **Page 4 of 6**

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having) Krabbe disease within a short enough period of time for therapeutic intervention to be beneficial. In support of their concerns, these members noted that one would expect a confirmed positive screen only once every six to seven years. Other committee members, however, expressed confidence that mechanisms could be put in place to refer affected infants for treatment within an appropriate time period. Some committee members also argued that it was uncertain whether every child in the state was insured for the intervention required to treat Krabbe disease (e.g., children without insurance who were not Medicaid-eligible). Another committee member argued, in response, that he had never heard of a child not receiving therapy because of a lack of insurance. However, this committee member agreed that it did not follow that the families of these children had not encountered significant financial hardship.

With regard to criteria 5 and 8, some committee members argued that while they could not *presently* say that these criteria were met, they were confident that the criteria *would* be met, should Krabbe disease be added to the mandatory screening panel. Other committee members replied that, whether or not one could be confident that follow-up and confirmatory testing procedures could be put in place, there was uncertainty about the psychosocial effects of introducing mandatory screening for Krabbe disease. One committee member also pointed out that confirmatory testing for Krabbe disease was imperfect, and thus that some infants could end up in a 'limbo' state—i.e., one in which clinically they presented without problems, but it would not be known when, or if, they would develop problems.

Given the committee's view that Krabbe disease did not meet all of the criteria for inclusion in the mandatory newborn screen panel, most committee members argued that it would be inappropriate to recommend that Krabbe disease be added to the panel at this time. In further support of this view, committee members argued that:

- (a) the treatment for the disease involved risky interventions; **Page 5 of 6**

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- (b) there was uncertainty which treatment centers in Wisconsin could take on cases of Krabbe disease;
- (c) there was not an outline of the process that would be followed in Wisconsin from the moment of a first positive screen, nor suitable follow-up in place for infants identified as being at risk;
- (d) that the data presented by the Duke research team, while promising, could not be given great credence until it had been peer-reviewed and published; and
- (e) that while the committee members recognized the devastating impact of the disease on affected infants and families, there was also a need not to cause harm to other infants and families.

Some committee members expressed concern that a vote not to recommend inclusion might discourage further development of the Krabbe nomination. These members favored a vote to 'table' the nomination. Other committee members replied that—as in the case of other nominations that the committee had previously considered—a vote not to recommend addition to the mandatory screening panel at the present time did not constitute a vote recommending that Krabbe disease never be added to the panel.

The following motion was moved and seconded: *That the Krabbe Disease nomination proposal be tabled pending the acquisition and development of more information, and that resubmission was encouraged when the unanswered questions could better be answered.* A majority of the committee voted in favor of this motion, and the meeting concluded.

This report was approved unanimously by the members of the Committee.

Respectfully Submitted:

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