Expedited Evidence-Based Review of Newborn Screening for Krabbe Disease
Final Report: February 1, 2024

Prepared for:
MATERNAL AND CHILD HEALTH BUREAU

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Rationale for the Expedited Review

In February 2023, after considering an evidence-based review[1] and public comments, the ACHDNC voted against recommending to the Secretary of Health and Human Services that Krabbe disease with expected onset of signs and symptoms within 36 months after birth (i.e., early infantile and late infantile Krabbe disease) be added to the Recommended Uniform Screening Panel (RUSP) for newborn screening. A summary from the Chair of the ACHDNC identified the need for additional information regarding the impact of hematopoietic stem cell transplantation (HSCT) on early infantile Krabbe disease and additional information on outcomes for infants identified through newborn screening as at-risk of late infantile Krabbe disease.

In July 2023, Krabbe disease was renominated for consideration for the RUSP. The 2021 nomination included first-tier screening galactocerebrosidase (GALC) enzyme activity testing and second-tier psychosine concentration testing. Unlike the previous nomination, this nomination is for the detection of infantile Krabbe disease (i.e., significant and progressive neurologic impairment within 12 months after birth with death in early childhood without targeted treatment) and not later-onset phenotypes. The nominators proposed that a second-tier psychosine ≥10 nM be considered positive to avoid detection and thus follow-up of infants with later-onset phenotypes of Krabbe disease.

In August 2023, the ACHDNC voted to expedite consideration of infantile Krabbe disease for the RUSP. Because an evidence-based report addressing the full spectrum of Krabbe disease was presented to the ACHDNC in February 2023, this expedited report focuses only on changes to the key questions if newborn screening specifically targets the detection of infantile Krabbe disease.

Approach for the Expedited Review of Newborn Screening for Infantile Krabbe Disease

This is the first expedited review for a condition reconsidered for the RUSP. The report builds on the previous evidence-based review of newborn screening for infantile Krabbe disease and focuses on the following key questions approved by the Chair of the ACHDNC:

1. What is the clinical validity of newborn screening for infantile Krabbe disease with a two-tier dried-blood spot screening algorithm (i.e., first-tier low GALC enzyme activity and second-tier psychosine ≥10 nM)?
2. What is the impact of newborn screening for infantile Krabbe disease compared with usual case detection on the timing of diagnosis, the timing of treatment, the risk of mortality, or on neurodevelopmental outcomes?
3. What are the benefits and negative consequences for families of newborn screening for infantile Krabbe disease compared with usual case detection?
4. What are the potential population-level outcomes for screening all newborns in the United States with the proposed two-tiered screening algorithm for infantile Krabbe disease, with the second-tier test positive if the dried-blood spot psychosine concentration is ≥10 nM?

Key questions 1, 2, and 3 are addressed with an updated systematic evidence review following the procedures outlined in the previous Krabbe disease newborn screening evidence-based review. In addition, newborn screening programs that include psychosine second-tier testing, currently with a threshold ranging from 1 to 2 nM, were surveyed to provide information regarding expected screening outcomes if a threshold of dried-blood psychosine ≥10 nM had been used to prompt further evaluation. Key question 4 is addressed using decision analysis as outlined in the previous Krabbe disease newborn screening evidence-based review updated to reflect the proposed two-tiered screening algorithm. This expedited evidence-based review does not assess the readiness and feasibility of newborn screening for infantile Krabbe disease. However, the previous report assessed readiness and feasibility for newborn screening for Krabbe disease with expected onset by 36 months after birth.

Technical Expert Panel

The Technical Expert Panel (TEP) for the previous Krabbe disease newborn screening evidence-based review was reconvened for this expedited evidence-based review.

Table 1. Technical Expert Panel Members

Name	Affiliation
Anna Grantham*	Programs Director, Hunter's Hope Foundation
Amanda Ingram, RN	Director, Pediatric Case Management, Tennessee Department of Health
Joanne Kurtzberg, MD*	Professor of Pediatrics and Pathology, Director of the Marcus Center for Cellular Cures, and Director of the Pediatric Blood and Marrow Transplant Program, Duke University
Dietrich Matern, MD, PhD*	Professor of Laboratory Medicine and Pathology, Medical Genetics, and Pediatrics, Mayo Clinic
Joseph Orsini, PhD*	Deputy Director of the Newborn Screening Program, New York State Department of Health
Samantha Vergano, MD	Division Director of Medical Genetics and Metabolism, Children's Hospital of The King's Daughters
Robert T. Stone, MD	Associate Professor of Neurology and Pediatrics, University of Rochester Medical Center
Jacque Waggoner*	Chief Executive Officer, Hunter's Hope Foundation

*Also, a nominator of infantile Krabbe disease to the RUSP

The TEP met virtually on December 13, 2023, to review the scope of the review and methods, to discuss preliminary findings, and to identify additional sources of relevant data. The TEP was given opportunity to review a draft of this report before it was submitted to the ACHDNC.

Published Literature Search

The following table lists the search terms and number of articles identified from each of the databases queried to identify articles for the systematic evidence review. The search covers the

time from the date of the last search for the previous Krabbe disease newborn screening evidence-based review, January 10, 2023, to November 22, 2023.

Table 2. Published Literature Search

Database	Search Terms	Number of Articles Identified
PubMED	("Leukodystrophy, Globoid Cell"[Mesh] OR "Globoid Cell Leukodystrophy"[tw] OR "krabbe disease"[tw] OR "krabbe's disease"[tw]) Filters: English, Humans	15
CINAHL	(MH "Leukodystrophy, Globoid Cell") OR "globoid cell leukodystrophy" OR "krabbe disease" OR "krabbe's disease") Limiters: English, Humans Expanders - Apply equivalent subjects Search modes - Find all my search terms	1
EMBASE	('globoid cell leukodystrophy'/exp OR 'globoid cell leukodystrophy' OR 'krabbe disease') AND [humans]/lim AND [english]/lim AND [10-01-2023]/sd NOT [25-11-2023]/sd	86
Number of Articles After Removing Duplicates		86

A list of references to each of the articles appears in the Appendix. Based on title and abstract screening, none of these articles provided additional information addressing key questions 1, 2, or 3. In addition to published articles, two additional peer-reviewed manuscripts were considered. The nomination of infantile Krabbe disease referenced a peer-reviewed article related to family attitudes was excluded from the 2023 evidence-based review based on study quality, but is now discussed as part of key question 3.[2] The TEP also identified a peer-reviewed article evaluating potential disparities by race and ethnicity that was not identified by the published literature search because it was released by the journal as a "pre-proof," also discussed as part of key question 3.[3]

Grey Literature Search

This expedited review also includes relevant abstracts presented at research or clinical meetings. Members of the TEP were asked to identify relevant meetings that occurred after January 10, 2023. One abstract from the 2023 WORLD*Symposium* on lysosomal diseases (February 21-26, 2023) described outcomes of Krabbe disease newborn screening in Pennsylvania.[4] This abstract was not included in this evidence-based report because the Pennsylvania newborn screening program provided current information for this report. No relevant abstracts were identified from the 2023 Pediatric Academic Societies' Annual Meeting (April 27-May 1, 2023) or the 2023 Association of Public Health Laboratories / International Society for Neonatal Screening Newborn Screening Symposium (October 15-19, 2023).

The TEP also identified two abstracts to be presented at the 2024 WORLD*Symposium* on lysosomal diseases (February 4-9, 2024). Although a listing of presentations for this 2024 meeting are not yet publicly available, members of the TEP knew about these abstracts since

they are co-authors. One abstract presents findings from a survey of the 8 state newborn screening programs that include psychosine as a second-tier test, of which 7 responded. [5] Findings from this abstract are not included in this report because the Evidence Review Group independently surveyed these newborn screening programs regarding their screening results and all 9 newborn screening programs that include psychosine second-tier testing responded. A second abstract, addressing Krabbe disease outcomes, is described as part of key question 2. [6]

Summary of Sources of New Evidence

This expedited evidence-based review now includes:

- Information provided from the state newborn screening programs that include dried-blood spot psychosine testing as a second-tier test, including expected sensitivity and specificity with the psychosine concentration threshold ≥ 10 nM for a positive screen.
- A survey of families regarding attitudes about Krabbe disease newborn screening[2]
- An analysis of health disparities related to Krabbe disease identification[3]
- An analysis, available as an abstract and poster, of outcomes for infantile Krabbe disease with HSCT around 1 month of age that extends a report described in the previous evidence-based review[6]

Key Question 1: Clinical Validity of Infantile Krabbe Disease Newborn Screening

The RUSP nomination for infantile Krabbe disease newborn screening specifies first-tier screening with low GALC enzyme activity and second-tier dried-blood spot screening with psychosine, with diagnostic referral for psychosine ≥10 nM. As described in the previous evidence report, there is variability in the approach that newborn screening programs use to screen for Krabbe disease, with some screening for specific variants in addition to measuring GALC enzyme activity and/or psychosine concentration. Screening with only GALC enzyme activity and psychosine concentration, as nominated, would reduce referrals for later-onset phenotypes.

As described in the previous evidence report, low GALC enzyme activity can lead to elevation of psychosine, which is cytotoxic and leads to the signs and symptoms associated with Krabbe disease. Psychosine levels ≥10 nM in early infancy are associated with earlier and more rapid progression of symptoms than in individuals with Krabbe disease who have lower levels of psychosine in early infancy. Psychosine testing became generally available after 2015. Advances over time have improved the sensitivity of psychosine in dried-blood spots. [7] However, it is not currently available for routine high-throughput newborn screening, and thus is recommended only as a second-tier screening test. In the United States, four clinical laboratories, one research laboratory, and one commercial vendor have collaborated to ensure congruence in psychosine measurement. [8]

Psychosine is highly specific for Krabbe disease. Increasing the threshold for a positive second-tier psychosine screening test would decrease the number of less severe phenotypes that would be detected. To determine the impact, data regarding dried-blood spot psychosine sensitivity (i.e., proportion of cases of infantile Krabbe disease with psychosine ≥10 nM) and specificity (i.e., proportion without infantile Krabbe disease, including those without Krabbe disease or with a later-onset phenotype, with psychosine <10 nM) were evaluated.

Sensitivity of Dried-Blood Spot Psychosine ≥10 nM for Infantile Krabbe Disease

According the TEP, the risk of missing a case of infantile Krabbe disease with newborn dried-blood spot psychosine < 10 nM is nearly zero (i.e., the sensitivity of psychosine ≥10 nM for infantile Krabbe disease is nearly 100%). One article, described in the previous review, discussed 26 cases of infantile Krabbe disease with available dried-blood spot psychosine (9 identified through newborn screening and 17 based on symptoms) and reported a range of psychosine from 10 nM to 108 nM (median: 48.5 nM, interquartile range: 26.5-59.8 nM). [7]

The previous evidence review described a retrospective study published in 2017 of stored dried-blood spot samples from 6 subjects with early infantile Krabbe disease (0-6 months) dried-blood spot psychosine concentration ranging from 5.2 to 44 nM. [9] The TEP raised concern about the stability of the psychosine in these stored dried-blood spots leading to falsely low measures.

An abstract presented at the 2022 WORLD*Symposium* on lysosomal diseases meeting identified 131 subjects with Krabbe disease or at high-risk of developing Krabbe disease. From these, 24 had dried-blood spots "collected during evaluations between August 2010 and September 2021." [10] This abstract, included in the previous evidence-based review, found that "Newborn psychosine levels were found to be associated with onset of disease. Some babies with infantile-onset had newborn psychosine as low as 2-6 nmol/L." and concluded "Based on these findings, we provide recommendations for newborn screening psychosine interpretation in babies with lower cut-off level of 2-6 nmol/L which is below the current 10 nmol/L cut-off for predicting the infantile phenotype." [10] The abstract is not clear about the time between the collection of the dried blood-spots and the psychosine analysis. However, given that the dried-blood spots were collected as early as 2010, the study might have falsely low psychosine measures for at least some of the samples due to lack of psychosine stability.

The previous evidence-based report also described an infant with initial dried-blood spot GALC that had low enzyme activity, psychosine concentration of 1.2 nM, and compound heterozygosity for two *GALC* variants considered likely pathogenic, who was initially considered to have late-onset Krabbe disease based on a repeat psychosine concentration of 2.6 nM and a normal neurologic exam. [11] Ultimately this subject was diagnosed with infantile Krabbe disease and died at 26 months of age. However, the authors of the report caution that given the atypical course, this infant might have had a secondary or alternate diagnosis.

Specificity of Dried-Blood Spot Psychosine ≥10 nM for Infantile Krabbe Disease

One article, described in the previous review, described eleven cases of late-onset Krabbe disease (9 identified through newborn screening and 2 based on symptoms), one of whom had a dried-blood psychosine ≥10 nM (12 nM, at age 460 days). The other ten had dried-blood spot psychosine concentrations from 2.1 nM to 9.7 nM (median: 3.9, interquartile range: 3.1-7.3 nM). [7]

Findings from State Newborn Screening Programs

Overall Screening Results

Nine state newborn screening programs currently include psychosine as a second-tier screening test following first-tier screening for low GALC enzyme activity. Ohio and New Jersey screen for Krabbe disease but do not include second-tier psychosine testing. As described in the previous review, Kentucky does not have a specific GALC enzyme activity threshold, but instead uses multivariate recognition software.[12] The approach to second-tier testing is variable by newborn screening program. For example, among samples with psychosine in the ranges from 1 to 2 nM, some programs test for common variants associated with Krabbe disease, and some consider whether GALC enzyme activity is persistently low in follow-up samples. No state newborn screening program currently uses psychosine ≥10 nM to determine which infants to refer for diagnostic follow-up.

These nine newborn screening programs were requested to provide the number of infants screened over the time period when psychosine was part of their testing algorithm, the number of infants with a positive first-tier screen using their current algorithm, the number of infants with a positive first-tier screen who had psychosine ≥10 nM, the number of these infants diagnosed with infantile Krabbe disease, and a list of infants with known or suspected later-onset cases identified by the newborn screening program's current algorithm that would not have been identified if the only second-tier test was psychosine ≥10 nM. Newborn screening program were asked to classify a case as having infantile Krabbe disease if the infant would be expected to develop significant and progressive signs and symptoms in the first year of life and have a high risk of mortality in early childhood. These data were collected from the newborn screening programs separately and independently from the data collected for the previous evidence-based review and reflect different time periods and the completion of diagnostic evaluation for some cases previously still in follow-up.

Table 3. Screening Results Reported by State Newborn Screening Programs

Screening Program	Period	Number Screened	Positive First-Tier	Psychosine ≥10 nM	Infantile Krabbe Disease	Known or Suspected Later-Onset Cases not Detected with Psychosine≥10 nM
GA	9/30/21-11/30/2023	329,661	63 (19.1 per 100,000 screened)	1 (1.6% of positive first-tier screens)	1 (3.0 per million screened)	0
IL*	12/1/2017-9/30/2023	848,000	600 (70.8 per 100,000 screened)	5 (0.8% of positive first-tier screens)	5 (5.9 per million screened)	12 (14.2 per million screened)
IN	7/2020-11/2023	272,077	148 (54.4 per 100,000 screened)	0	0	10 (36.8 per million screened)
KY	2/15/16-6/30/23	404,626	128 (31.6 per 100,000 screened)	2 (1.6% of positive first-tier screens)	2 (4.9 per million screened)	0

MO	3/20/2020-8/31/2023	232,721	401 (172.3 per 100,000 screened)	3 (0.7% of positive first-tier screens)	1 (4.3 per million screened)	1 (4.3 per million screened)
NY	1/1/2021-9/30/23	572,197	38 (6.6 per 100,000 screened)	0	0	2 (3.5 per million screened)
PA	5/21/2021-10/31/2023	316,918	43 (13.6 per 100,000 screened)	1 (2.3% of positive first-tier screens)	1 (3.2 per million screened)	3 (9.5 per million screened)
SC	5/15/2023-11/27/2023	29,748	16 (53.8 per 100,000 screened)	0	0	0
TN	7/1/2017-9/30/2023	545,085	68 (12.5 per 100,000 screened)	1 (1.5% of positive first-tier screens)	1 (1.8 per million screened)	5 (9.2 per million screened)
Total		3,551,033	1,505 (42.4 per 100,000 screened)	13 (0.9% of positive first-tier screens)	11 (3.1 per million screened)	33 (9.3 per million screened)

*In Illinois, no information from the newborn screening program is available about the 5 cases of infantile Krabbe disease. However, information was obtained from a treatment center in Illinois regarding 4 of these cases of infantile Krabbe disease.

Infantile Krabbe Disease Case Detection

Based on the information from the state newborn screening programs, using psychosine ≥10 nM as the only second-tier test, the number of cases of infantile Krabbe disease ranged from 0 in Indiana, New York, and South Carolina, which collectively screened about 874,000 infants, to 5 cases of infantile Krabbe disease in Illinois, which reported screening 848,000 infants. Based on 3.55 million screened newborns described for this report, the overall infantile Krabbe disease case detection rate with psychosine ≥10 nM is about 3.1 per million infants screened.

False Positive Second-Tier Tests

Only Missouri reported false positive second-tier tests with psychosine ≥10 nM. According to this program, the referral laboratory for psychosine testing contaminated two simultaneously submitted samples with psychosine standard when preparing calibrators on the same bench. This led to 3-day hospitalization for evaluation of these infants before the suspected error was confirmed by testing the dried-blood sample in a different laboratory. The laboratory has changed its processes to prevent such an incident form happening again.

False Negative Second-Tier Tests

No program reported that they would miss a case of infantile Krabbe disease with a psychosine ≥10 nM. Pennsylvania reported a set of twins that they classified as late-onset infantile Krabbe disease with psychosine levels of 5.2 and 4.9 nM who both received HSCT around 100 days after birth. The program reported that the treating physician stated that "Those two children were assessed to be at high risk for the late infantile onset form of Krabbe so they did not need to be transplanted within the first 30 days of life." The TEP highlighted that HSCT in the first year does not necessarily imply infantile Krabbe disease. The TEP further underscored that treatment

centers have different thresholds for HSCT for later-onset Krabbe disease. This evidence report therefore did not classify these cases as false-negative second-tier tests for infantile Krabbe disease. These are examples of later-onset cases of Krabbe disease that would not be identified by newborn screening if the only second-tier test was psychosine ≥10 nM.

Later-Onset Krabbe Disease

The rationale for second-tier psychosine testing with a threshold of 10 nM is to decrease the identification of later-onset Krabbe disease (i.e., any phenotype other than infantile Krabbe disease, ranging from onset later in childhood or in adulthood) relative to current practice. No cases of later-onset Krabbe disease would have been identified by the newborn screening programs with psychosine ≥10 nM among the 3.55 million newborns screened as described in this report. This threshold also eliminates the detection of later-onset Krabbe disease across the total population of infants screened of about 9.29 per million infants screened.

Key Question 2: Impact of Infantile Krabbe Disease Newborn Screening Compared with Usual Case Detection

Outcomes of Cases Identified Through Newborn Screening Reported by Screening Programs

Other than Illinois, the state newborn screening programs described six cases of infantile Krabbe disease identified through newborn screening with dried-blood spot psychosine ≥10 (see Table 3). The Illinois newborn screening program was not able to provide a description of the cases of infantile Krabbe disease identified through newborn screening. However, a treatment center in Illinois was able to provide the following information about 4 of the 5 cases.

The following is a brief description of the 11 cases listed in table 3:

- One case with no follow-up information
- Two cases with follow-up and HSCT declined
- One case with HSCT declined, with death at 14 months
- HSCT at 24 days, now 5 years old
- HSCT at 30 days, now 3 years old
- HSCT at 1 month, now 2 years old, preparing for gene therapy to address persistent health problems including developmental impairment
- HSCT at 34 days and again at 169 days, now 2 years
- HSCT at 35 days, death around 7 months due to graft vs. host disease.
- HSCT at 40 days, now almost 5 years
- HSCT at 42 days, gene therapy at 24 months, now 28 months old

In summary, of the cases with follow-up information about HSCT, 3 of 10 (30%) families declined HSCT, of which one case of infantile Krabbe disease is known to have died. Of those who received HSCT, 6 of 7 cases (86%) who received HSCT are alive to at least 2 years (median 2.5 years, range 2-5 years).

New Research Findings

An abstract that will be presented at a 2024 conference[6] provides an update on the status of 5 of 6 infants described in the previous evidence review who received HSCT around 1 month of age for infantile Krabbe disease after identification through newborn screening (one family could not be reached) [13] and an additional infant not in the original report with infantile Krabbe disease

who was also identified through newborn screening and underwent HSCT around 1 month of age. Subjects were recruited consecutively after referral for HSCT. This study includes 2 of the of the 11 cases of infantile Krabbe disease described in table 3, of which 7 were treated with HSCT as described above.

The parents of the subjects in this study were contacted by a pediatric neuropsychologist to complete a Vineland Adaptive Behavior Scales, third edition (Vineland-3) and the Pediatric Quality of Life Inventory (PedsQL), a brief generic scale to measure overall quality of life. The Vineland-3 measures 11 standardized subscales (population mean 15, standard deviation 3), which lead to four adaptive domains (communication, daily living skills, socialization, and motor skills) and an overall adaptive behavior composite (each with population mean 100, standard deviation 15) and the PedsQL leads to 2 standardized subscales, physical and psychosocial health, leading to an overall score (population mean 100, standard deviation 15). The authors of the poster provided the Vineland-3 and PedsQL scores for this evidence-based review.

The characteristics of the subjects are provided in Table 4 by age at neurodevelopmental assessment. As a cross-sectional study, each subject was assessed with the Vineland-3 and PedsQL once and appears only once in each of the following figures.

Table 4. Subject Characteristics from the Abstract

Psychosine (nM)	*GALC* Genotype	Age at HSCT (days)	Age at Neurodevelopmental Assessment (years)
70	30kb del (het, path); c.1851del(p.try617) (het, path); c.550C>T (p.Arg184Cys) (het, VUS)	32	2.2
35	c.1723_1724insT (p.G575Vfs*10) and c.1913G>T (p.G638V) [het, path]; c.1685T>C (p.I562T) [het, Pseudo]; c.742G>A (p.D248N) [het, Pseudo]	40	4.7
38	30kb deletion (het, path) and [c.1270C>T 9p.Gln424Ter)] (het, path)	28	5.2
83	c.387c->g (homo, path); c.1885T->C (pseudo), c.550 C->T (pseudo)	31	5.8
61	p.W629MfsX9 (Trp629MetfsX9); p.I562T (Ile562Thr) // delEx8-Ex9partial; p.I562T (Ile562Thr); p.R184C (Arg184Cys)	24	6.9
24	30kb deletion (loss of exons 11-17) (het, path*) and exon	39	7.1

	4-c.379C>T (p.R127X) (het, path); (c.1161+6532_polyA+9kbdel)		

The Vineland-3 adaptive behavior composite score (figure 1, based on data provided by the authors) was below the population mean and varied by subject. For all subjects, the motor skills composite score was the lowest, but was the same as the communication composite score for one subject (figure 2, based on data provided by the authors). As highlighted in the poster, all subjects had markedly decreased gross motor subscores.

Figure 1. Vineland-3 Adaptive Behavior Composite Scores

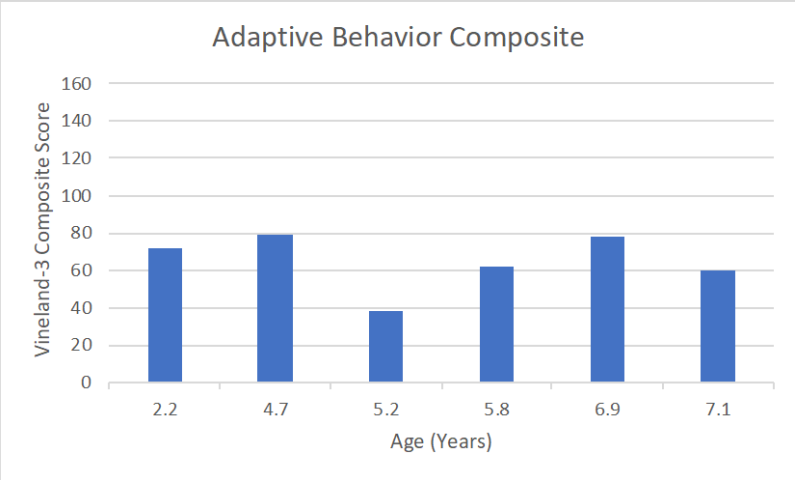


Figure 2. Vineland-3 Scores

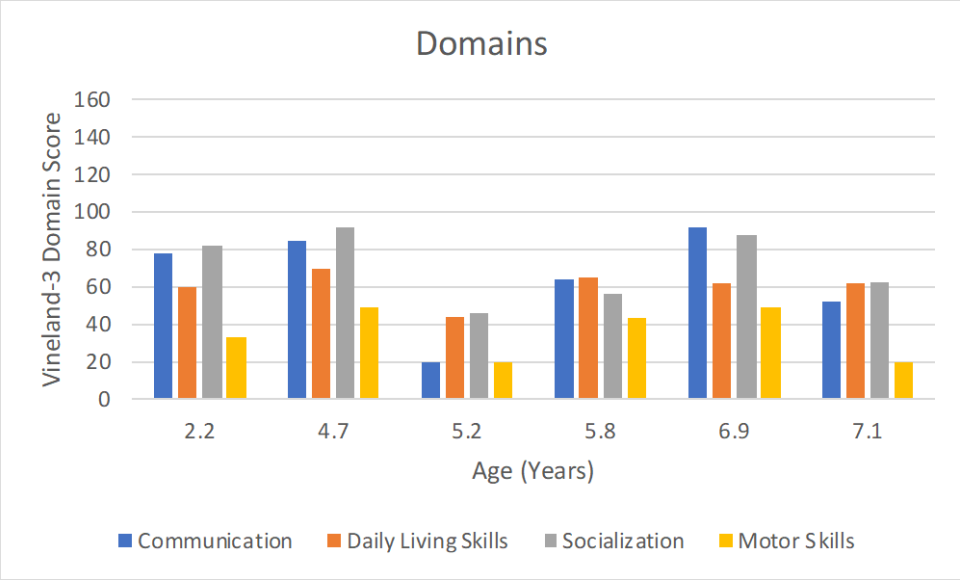
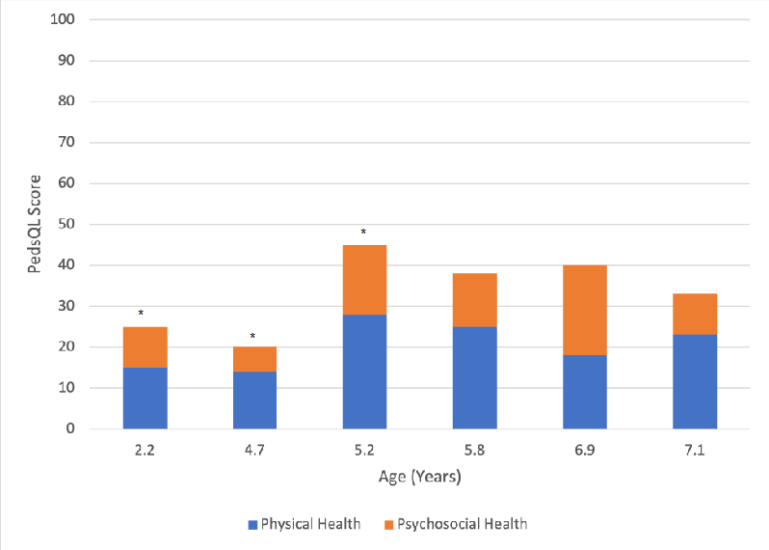


Figure 3 provides the overall PedsQL score by age along with the physical and psychosocial health subscales. Since the three youngest subjects were not in school, the school functioning subscales were not completed, which could decrease the overall PedsQL score. As noted in the

poster, subjects "generally performed poorly on physical functioning scores, while social, emotional, and school functioning scores were higher…" The parents of one subject, age 7 years, report, according to the poster, "He met all of his IP goals at 98% or higher and will be moving to the Gen Ed setting for the majority of the day…."

Figure 3. PedsQL Results

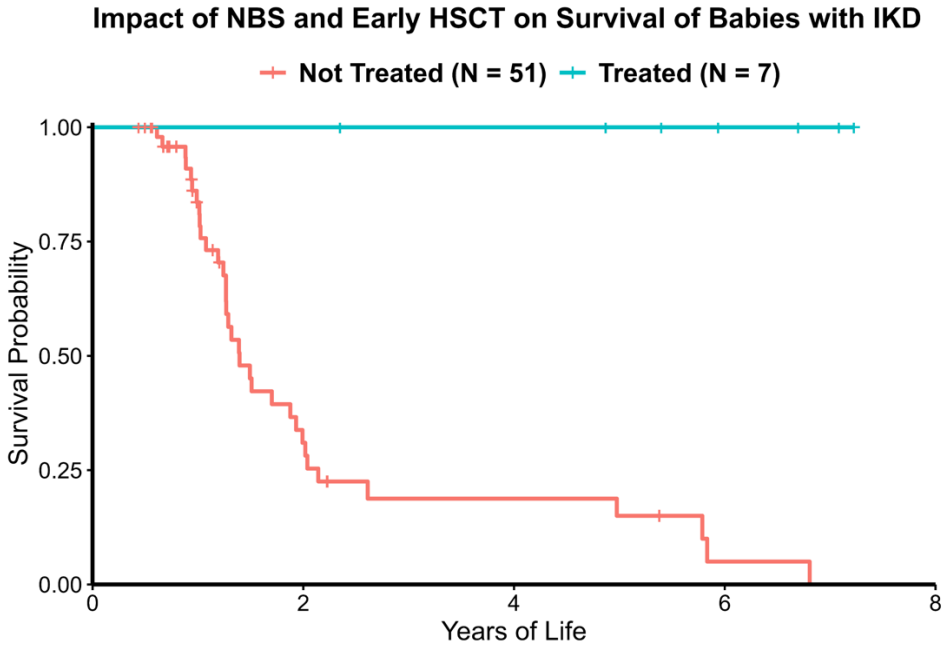


*School functioning subscales not completed

The poster concludes that unlike the expected history of infantile Krabbe disease without early HSCT, all subjects are alive. The abstract also notes that "All [subjects] have deficits, which are most significant in areas affecting gross motor function. In contrast, social, communication, psychosocial, emotional and school performance were stronger and in the adequate range in half of the children tested."

In addition to the functional outcome information, the poster presents a survival curve (figure 4) comparing these seven subjects to 51 subjects with infantile Krabbe disease born in states that do not offer screening and who were detected based on signs and symptoms in their first year of life and who did not qualify for HSCT based on their disease status. The mortality risk of those not treated with HSCT is similar to what is expected based on the previous evidence-based review. The survival of those who received HSCT in this analysis is based on 7 consecutive cases (the six cases described above and the one case that could not be reached). This analysis does not include subjects who died related to HSCT-related complications or whose families refused HSCT, and thus does not reflect the survival following newborn screening, which would be lower than what is presented. However, even taking this limitation into account, HSCT around the first month of life for infantile Krabbe disease is associated with decreased risk of mortality. The population-level modeling (Key Question 4) presents an analysis of what would be expected following newborn screening.

Figure 4. Survival Curve



Key Question 3: Benefits and Negative Consequences for Families of Infantile Krabbe Disease Newborn Screening

Family Experiences and Perspectives

The published literature review for the previous evidence report identified one study addressing family attitudes about Krabbe disease newborn screening based on 170 respondents to an online survey from December 2019 to February 2020.[2] All respondents were impacted by having a family member with Krabbe disease. Overall, nearly all respondents (97%) "feel that KD NS should be implemented in every state."[2] This study was excluded from the previous evidence-based review because of the likely low response rate. The survey was sent to potentially overlapping subjects included in the Hunter's Hope Foundation registry (n=439), the foundation's Facebook (n=12,954), Instagram (n=3,073), Twitter (n=3380), author social media platforms (n=806, n=18,958), another international group for families affected by Krabbe disease (n=793), and other international groups affected by leukodystrophies (n=2,666 and n=1,467). No response rate was reported and the survey method does not allow for a response rate to be calculated. Although the number of families impacted by Krabbe disease is much lower than the total number surveyed, the response rate is likely to be low, impacting external validity. As described in this report, the survey also does not assess attitudes about Krabbe disease newborn screening among those not directly affected by the condition. We did not identify other reports assessing attitudes towards Krabbe disease newborn screening.

No new study was identified that evaluated family experiences or perspectives related to Krabbe disease newborn screening.

Health Disparities

Public health newborn screening can potentially reduce disparities in care because all infants have access to screening. One publication compared the racial and ethnic distribution of cases of Krabbe disease, regardless of phenotype, identified through newborn screening with those of children identified in a database of free-standing children's hospitals in the United States. [3] The publication reports that the proportion of Krabbe disease among Black or Asian individuals identified through newborn screening was twice as high as in the hospital dataset. It also reported that within the hospital dataset, non-Hispanic White patients had a lower average time gap from first presentation to diagnosis (64 days) compared with non-Hispanic Black children (101 days), Asian children (136 days), and Hispanic children (120 days). The findings were not statistically significant, which could be due to the low statistical power given the rarity of Krabbe disease. According to the first author, the date of first presentation was the date of the first hospitalization, regardless of discharge diagnosis.

This analysis only considered hospitalization at these particular children's hospitals. Some of the major Krabbe disease treatment centers are not included in this dataset and no outpatient data was available for the analysis. There is also the risk of misclassification of race and ethnicity. Among the subjects in the hospital database, race and ethnicity for 20 (11%) were listed as "Other" and for 7 (4%) race and ethnicity were missing. In contrast, none of the state health departments reported "other" or missing race and ethnicity information.

This study was rated as low quality because it did not consider outcomes by phenotype, excluded major Krabbe disease treatment centers, the risk of misclassification of race and ethnicity, and because determining the timing of symptom onset and diagnosis is not possible only from hospital administrative claims.

No other studies evaluating health equity were identified.

Key Question 4: Potential Population-Level Outcomes of Infantile Krabbe Disease Newborn Screening

The previous evidence-based report evaluated the potential impact at the population level of Krabbe disease newborn screening if adopted by all newborn screening programs in the United States compared to clinical case detection in the absence of Krabbe disease newborn screening. The previous analysis included both infantile and later-onset phenotypes. In response to the revised nomination in this expedited review, the decision-analytic model was updated to reflect screening for infantile Krabbe disease only, not later-onset phenotypes, using a screening algorithm in which only infants with dried-blood spot psychosine ≥10 nM would be referred for diagnostic evaluation.

Applying Decision Analysis to Krabbe Disease Newborn Screening

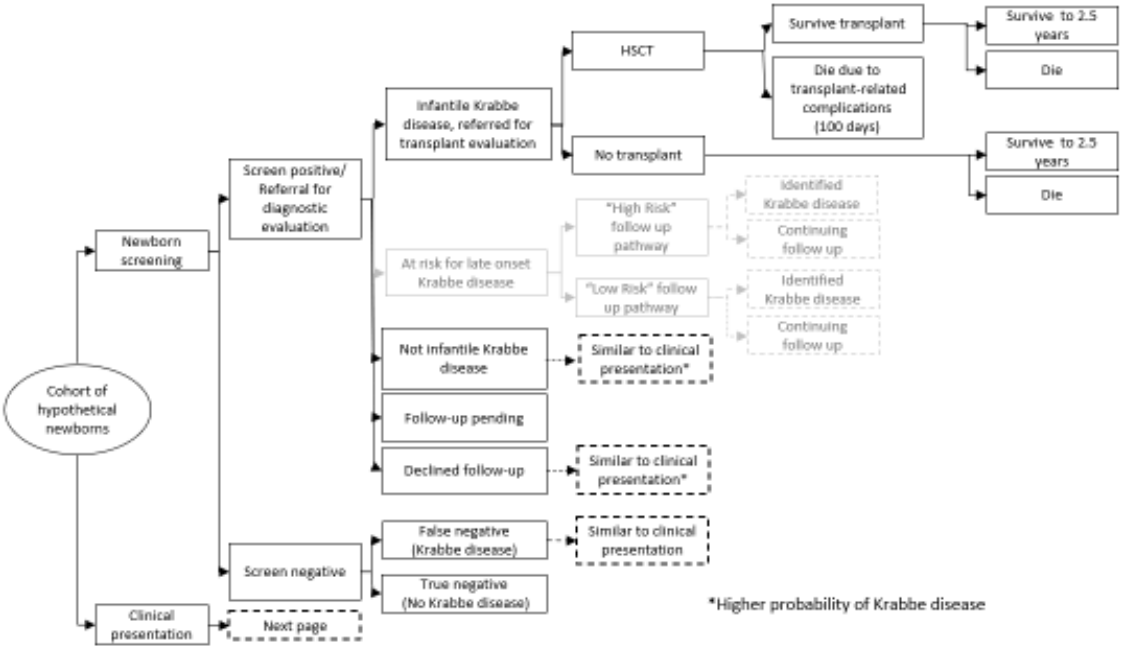
For this expedited review, we used updated data from state newborn screening programs to revise the screening parameters included in the simulation model. Parameters in the model are based on published and unpublished data, as described in the methods section.

Methods

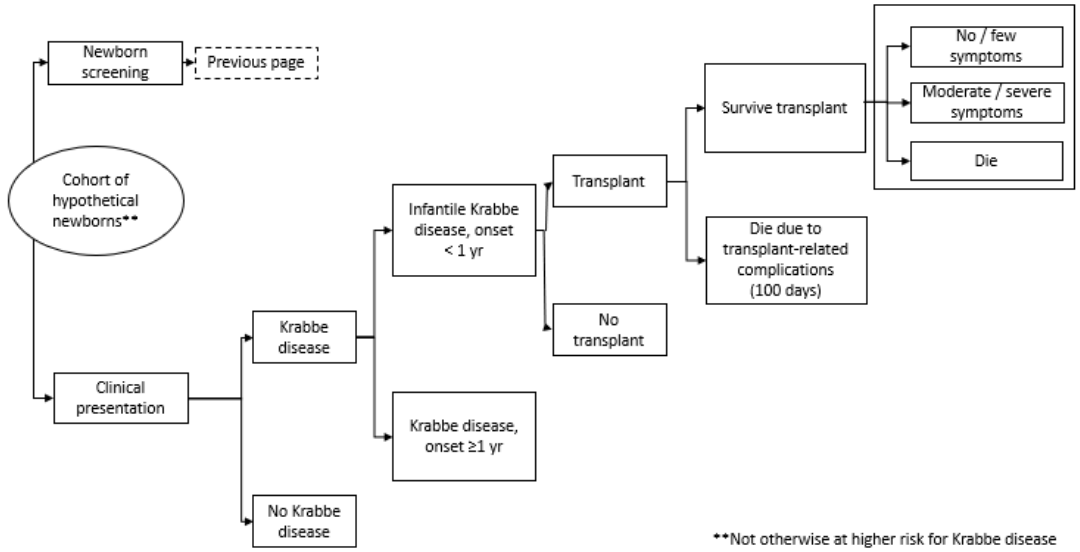
A schematic of the infantile Krabbe disease newborn screening decision model is shown in Figure 5.

Figure 5. Model Schematic

a. Newborn screening using the revised nomination screening algorithm†



b. Clinical presentation



*Only newborns with low GALC enzyme activity and psychosine ≥10 nM referred for diagnostic evaluation. Health states shown in gray were included in the previous modeling analysis and are not included in the analysis of the revised nomination.

Key Assumptions

The target population reflects the annual newborn cohort for the US (i.e., 3.65 million newborns) not otherwise known to be at high risk for infantile Krabbe disease. Strategies included in the model were universal newborn screening for infantile Krabbe disease using the screening algorithm from the revised nomination compared with diagnosis of infantile Krabbe disease through clinical presentation. The time horizon for the analysis is 2.5 years and reflects screening outcomes and short-term outcomes of newborns who receive HSCT.

Screening outcomes included positive screens, confirmed cases of infantile Krabbe disease and false negative and false positive screening results. Clinical presentation outcomes include the number of cases of infantile Krabbe disease identified before and after 1 year of age. Additional outcomes include the number of infants who receive HSCT and survival to 100 days after HSCT.

Parameter inputs were based on published and unpublished data and supplemented by expert opinion in cases where no data were available. The model structure and approach to the revised analysis were confirmed at the TEP meeting in November 2023.

Overall approach

The model estimates outcomes for two identical cohorts of newborns for infantile Krabbe disease, one cohort that receives newborn screening for infantile Krabbe disease and one cohort that does not. Each parameter in the model is defined with a point estimate and a range of values reflecting plausible estimates. The model was programmed using Treeage Pro Healthcare 2023 (Williamstown, MA).

Estimated transition probabilities for screening outcomes were revised for this expedited review using updated data from the state newborn screening programs with adjustments. Since individual state newborn screening programs use different algorithms for determining which newborns are referred for diagnostic follow-up, state programs were asked to submit updated data that reflects screening outcomes if a referral for infants with psychosine concentration ≥10 nM (Table 3). Ranges for the parameter inputs were derived assuming a binomial distribution (Tables 5 and 6).

Probabilities related to the cases of infantile or not infantile Krabbe disease identified through screening, recommendation for HSCT, and of surviving HSCT were derived from state-reported data, published data, or both, and reviewed by the technical expert panel (Table 5). Relevant probabilities for the clinical presentation cohort were derived from the literature and expert assumption (Table 6).

For this analysis, the incidence of infantile Krabbe disease has been updated from the previous analysis to be identical to the incidence of infantile Krabbe disease derived from newborn screening program data. In the previous model, clinical identification estimates were based on historical published data. Differences in timing of identification, definitions of the phenotypes of Krabbe disease, threshold for offering HSCT, and study populations are likely contributors to the difference between these historical published estimates and the lower observed incidence from newborn screening programs. Given the approximately 3.5 million infants have been screened thus far, the observed incidence is likely a more accurate estimate. As with many rare conditions, there is often substantial uncertainty about incidence.

The evidence on treatment effectiveness was insufficient to support the modeling of quality of life at any age or survival beyond 2.5 years for individuals with Krabbe disease.

The modeling analysis conducted base case and uncertainty analyses for screening and clinical outcomes.

Table 5. Newborn screening parameters

Parameter*	Most likely value	Range	Source
Screen positive/referral for diagnostic evaluation	0.30977 per 100,000	0.15464 – 0.55426 per 100,000	Primary data (updated) from state newborn screening programs
Infantile Krabbe disease/referral for diagnostic evaluation given positive screen	1 (0. 30977 per 100,000)†	0.72 - 1	
Not infantile Krabbe disease given positive screen	0	0 – 0.28	
Negative screen			
True negative	1	0.9999986 - 1	
False negative	0	0 – 0.0000014	
Identified with infantile Krabbe disease			
Received HSCT	0.88	0.62 – 0.98	[13,14]; primary data from state newborn screening programs (from previous analysis)
No HSCT	0.13	0.02 – 0.38	
Received HSCT			
Survive HSCT	0.89	0.67 – 0.99	[15]
Died due to HSCT-related complications within 100 days	0.11	0.01 – 0.33	
Survival at 30 months of age			
HSCT, if did not die within 100 days	1	0.59 – 1	[13,14]
No HSCT	0.23	0.14 – 0.35	[16]

*Using the revised nomination screening algorithm: only newborns with second-tier testing psychosine concentration ≥10 nM referred for diagnostic evaluation.

†Incidence at the population level

Table 6. Clinical presentation parameter inputs

Description	**Most Likely**	Range **(min-max)**	**Source**
Krabbe disease	0.662 per 100,000	0.236 – 1.18 per 100,000	[17], Primary data (updated) from state newborn screening programs
Infantile Krabbe disease	0.47	0.40 – 0.53	[18], Primary data (updated) from state newborn screening programs
Krabbe disease, not infantile	0.53	0.47 – 0.60	
Clinical presentation <1 year			
HSCT	.1	0 – 0.2	Modeling assumption
No HSCT	.9	0.8 - 1	
Received HSCT			
Survive HSCT	0.89	0.67 – 0.99	[15]
Died due to HSCT-related complications within 100 days	0.11	0.01 – 0.33	
Survival at age 30 months			
Survival given infant has received HSCT, if did not die within 100 days	1	0.59 - 1	[13,14]
Die given infant has received HSCT	0	0 – 0.41	
Survival given infant has not received HSCT	0.23	0.14 – 0.35	[16]
Die given infant has not received HSCT	0.77	0.65 – 0.86	

Results

Under a policy of infantile Krabbe disease newborn screening, 11.3 infants (range: 5.6 – 20.2) are estimated for referral for diagnostic testing due to a positive screen annually assuming an annual newborn cohort of 3.65 million newborns. Each of these infants are projected to be identified with likely infantile Krabbe disease (Table 7a) and referred for HSCT, of whom 9.9 (range: 3.5 – 19.9) would be expected to receive HSCT and 1.4 (range: 0.3 – 2.2) would not receive HSCT, either due to ineligibility based on disease status or declined by family. Of those infants receiving HSCT, 1.0 (range: 0.3 – 1.2) would be expected to die from complications within 100 days of transplant. By 30 months of age, 9.2 infants would be alive and 2.1 (range: 0.5 – 4.0) would be expected to have died (1.0 from HSCT and 1.1 from Krabbe disease). (Table 7c)

Under a policy of clinical presentation in the absence of newborn screening, 24.2 infants (range 8.6–43.3) would be identified with Krabbe disease. Of these, 11.3 (range: 4.0 – 20.2) would be expected to present with symptoms in the first year of life and 12.9 (range: 4.6 – 23.0) would be expected to present later (Table 7b). 1.1 clinically identified infants (range: 0.0–4.0) would be expected to receive HSCT. By 30 months of age, 7.9 (range 3.5 – 10.6) would be expected to have died either from HSCT complications or Krabbe disease progression (Table 7c).

Table 7. Projected outcomes for an annual cohort of 3.65 million newborns

a. With Krabbe disease newborn screening using the revised nomination screening algorithm*

	Most Likely Number of Cases (range)
Screen positive/ referral for diagnostic evaluation given positive screen	11.3 (5.6 – 20.2)
Infantile Krabbe disease/referral for diagnostic evaluation given positive screen	11.3 (5.6 – 20.2)
Not infantile Krabbe disease	0 (0 – 5.6)
False negative	0 (0 – 5.4)

b. Without Krabbe newborn screening, with case identification based on clinical presentation

	Most Likely Number of cases (Range)
Krabbe disease	24.2 (8.6 – 43.3)
Infantile	11.3 (4.0 – 23.0)
Not infantile	12.9 (4.6 – 20.2)

c. Projected outcomes at 2.5 years of age for newborn screening compared with clinical presentation

	Newborn Screening*	Clinical Presentation	Difference Between Newborn Screening and Clinical Presentation
Received HSCT by 1 year	9.9 (3.5 – 19.9)	1.1 (0 – 4.0)	8.8 (3.3 -16.6)
Died from complications of HSCT	1.0 (0.1 – 4.1)	0.1 (0 – 0.4)	0.9 (0.1 – 4.1)
Survive HSCT	8.9 (2.3 – 19.7)	1.0 (0 – 4.0)	7.8 (2.3 – 15.7)
Did not receive HSCT by 1 year	1.4 (0.1 – 7.8)	10.2 (2.8 – 23.0)	-8.8 (-15.9 - - 1.9)
Died from infantile Krabbe disease by age 30 months	1.1 (0.0 – 10.1)	7.8 (1.8 – 19.7)	-6.7 (-11.7 - - 0.7)
Total who died by age 30 months	2.1 (0.1 – 14.2)	7.9 (1.8 – 19.7)	-5.8 (-10.4 – 0.5)

*Using the revised nomination screening algorithm: only newborns with second-tier testing psychosine concentration ≥10 nM referred for diagnostic evaluation.

Limitations

The model was restricted to evaluating mortality at 2.5 years of life. Evidence regarding other outcomes, including quality of life or neurologic status, and for outcomes beyond 2.5 years was insufficient for modeling. The model cannot assess the impact of Krabbe disease identification, and treatment outcome on family members or society.

Summary

With universal infantile Krabbe disease newborn screening, this analysis predicts that 11.3 infants (range: 5.6 – 20.2) annually would be diagnosed with infantile Krabbe disease and be referred for evaluation for HSCT. Of these, 9.9 (range: 3.5 – 19.9) would receive HSCT. Of the infants who received HSCT, 1.0 (range: 0.3 – 1.2) would die from complications of HSCT within 100 days and all others would be alive at 2.5 years.

Without universal Krabbe disease newborn screening, relying on clinical presentation, 11.3 (range: 4.0 – 23.0) infants would present before age 1 year, of whom 1.1 (range: 0 – 4.0) would

be eligible for and receive HSCT. Of the remaining 10.2, 7.8 (range: 3.5 – 10.6) infants would be expected to die from Krabbe disease by age 2.5 years.

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