Evidence-Based Review of Newborn Screening for Krabbe Disease: Final Report

Prepared for:
MATERNAL AND CHILD HEALTH BUREAU

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Overview

This executive summary highlights key findings from the complete report developed for the United States Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) regarding Krabbe disease newborn screening (NBS). This summary is not intended to replace the complete report, which describes the methods for evidence identification and synthesis and provides a full discussion of findings. This summary instead provides a high-level review of findings from the complete report

Krabbe Disease: Epidemiology and Clinical Course

Krabbe disease (OMIM #245200) is an autosomal recessive lysosomal disorder associated with low functional levels of the enzyme galactocerebrosidase (GALC), leading to the death of myelin-producing cells and neurons. Krabbe disease has variable presentation of age. Although there are evidence gaps regarding the distribution of Krabbe disease phenotypes, it is likely that the majority of those with Krabbe disease will develop signs and symptoms by 36 months of age. Typical presentation in infancy includes feeding problems and significant irritability, and, without treatment, developmental regression and death in childhood. The birth prevalence across all phenotypes is typically described as 1 per 100,000, however gene frequency studies suggest that the birth prevalence could be as high as 8.3 per 100,000 live births.

Newborn Screening for Krabbe Disease

The condition nominated to the ACHDNC for consideration for the Recommended Uniform Screening Panel is Krabbe disease with the expected onset of signs and symptoms by 36 months. The nominators recommend first-tier dried-blood spot GALC enzyme activity screening followed by second-tier dried-blood spot psychosine concentration screening if the GALC enzyme activity level is low. In the United States, ten newborn screening programs include newborn screening for Krabbe disease. All programs measure GALC enzyme activity as the first-tier screen. GALC enzyme activity can be multiplexed with MS/MS when screening for other lysosomal disorders. There is also a fluorometric test that is not currently multiplexed with other newborn screening tests. Most of these ten programs have added second-tier tests, including dried-blood spot psychosine concentration and *GALC* gene molecular analysis. Second-tier psychosine concentration testing improves screening specificity. *GALC* gene molecular analysis can help with predicting phenotype, especially when a specific 30-Kb deletion associated with significant disease involvement is identified.

Diagnostic evaluation includes measuring clinical samples for GALC enzyme activity and psychosine concentration, *GALC* molecular testing if not previously done, physical exam, neurophysiological studies, neurologic imaging tests, and cerebrospinal fluid (CSF) protein concentration. Staging systems to assist with diagnosis and related follow-up and treatment recommendations are available.

Based on current screening algorithms used by these ten newborn screening programs, the overall referral rate for diagnostic testing is about 14.3 per 100,000 newborns screened (range: 0.6–54 per 100,000 newborns screened). This has led to the identification of about 0.36 cases of

Krabbe disease with expected onset in the first 12 months per 100,000 newborns screened and about 1.46 cases of Krabbe disease at high risk of onset after 12 months per 100,000 newborns screened.

Treatment for Krabbe Disease

The established specific treatment for Krabbe disease with projected onset before 36 months is hematopoietic stem cell transplant (HSCT). The goal is for HSCT to be completed before the development of significant signs or symptoms of Krabbe disease. For infants with early infantile Krabbe disease (i.e., signs or symptom onset in the first 6 months of life), HSCT is recommended by 4 to 6 weeks after birth, before significant disease involvement. Without newborn screening and a family history, early infantile Krabbe disease is often not diagnosed until the time period for HSCT has passed. For those with late infantile Krabbe disease (i.e., signs or symptom onset from 6 to 36 months of life), HSCT is recommended before the onset of significant signs or symptoms. The key factor considered by experts to impact treatment outcomes is the degree of existing Krabbe disease involvement at the time of HSCT based on a complete neurological assessment, and so somewhat later HSCT can be effective. Available case series suggests that HSCT can extend life for early infantile and late infantile Krabbe disease, but the impact on neurologic outcomes and other outcomes are more variable. No studies were identified that assessed the impact of HSCT on quality of life or on family functioning. These gaps in evidence are common for rare disorders. HSCT has a risk of morbidity and mortality within 100 days of transplant. Some families of infants with Krabbe disease choose not to have their child receive HSCT.

Impact on the Health of the Population

With universal Krabbe disease newborn screening of the 3.65 million infants born in the United States annually, using the available evidence, 74.8 (range: 55.8 – 98.2) infants would be expected to screen positive and be referred for diagnostic evaluation, leading to the identification of 15.3 (range: 5.8 –28.1) infants with infantile Krabbe disease and 54.9 (range: 33.1 –70.1) infants at risk for late onset Krabbe disease. In contrast, without universal Krabbe disease newborn screening, relying on clinical presentation using estimates from the available data, 18.8 (range: 11.2 –31.3) infants with Krabbe disease would be expected to present before age 1 year and 21.4 (range: 16.5 –21.4) would present later. With newborn screening, the number of infants who would die by age 30 months with Krabbe disease would be 2.9 (range: 2.3 –3.2) compared with 13.2 (range: 9.6 –17.0) without newborn screening, a difference of 10.3 (range: 7.3 –13.8) deaths by 30 months based on the available data. Insufficient evidence is available to model outcomes past 30 months of age or to predict quality of life or patient- or family-centered outcomes.

Impact on Public Health Systems

The estimated additional cost from the program perspective of adding Krabbe disease, above and beyond the fixed costs of an existing NBS program, varied between $2 and $7 per infant screened based on interviews with newborn screening programs. The bulk of the estimated costs reflected the costs of equipment, reagents, and added laboratory technician and laboratory scientist time for first-tier screening. Determining costs specific to Krabbe disease newborn screening can be challenging for newborn screening programs because Krabbe disease is

generally multiplexed with other lysosomal disorders. However, the costs that newborn screening programs reported for Krabbe disease newborn screening fell within this range.

This report does not assess the cost of Krabbe disease treatment.

Overall, 34 of the 44 programs that do not include Krabbe disease newborn screening (77%) responded to a survey, with 36% reporting that it would take less than 2 years to implement Krabbe disease newborn screening if it were recommended, 47% reported that it would take 2 to 3 years, 12% that it would take 3 to 4 years and 3% that it would take more than 4 years. Significant barriers include other ongoing newborn screening program priorities and the perceived access to timely HSCT for those identified through newborn screening.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children
APHL	Association of Public Health Laboratories
CNS	Central Nervous System
COMPHET30	Compound Heterozygous for the *GALC* 30-Kb Deletion
CSF	Cerebrospinal Fluid
EEG	Electroencephalogram
ERG	Evidence-based Review Group
FDA	United States Food and Drug Administration
FTE	Full-time Equivalent
GALC	Galactocerebrosidase
G-tubes	Gastrostomy tubes
HHS	Health and Human Services
HSCT	Hematopoietic Stem Cell Transplant
HOM30	Homozygous for the *GALC* 30-Kb Deletion
LIMS	Laboratory Information Management System
MRI	Magnetic Resonance Imaging
MS/MS	Tandem Mass Spectrometry
NBS	Newborn Screening
NP	Not Presented
RUSP	Recommended Uniform Screening Panel
TEP	Technical Expert Panel
US	United States

1. SCOPE AND METHODS OF THE REVIEW

Scope of the Review

This report was developed to support the Secretary of Health and Human Services (HHS) Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) in making recommendations to the Secretary, HHS, about whether NBS for infantile and late infantile Krabbe disease should be added to the Recommended Uniform Screening Panel (RUSP).

The condition review will present the evidence regarding the likely benefits and harms of expanding the RUSP to include Krabbe disease newborn screening, including the estimated health impacts of population-based screening for Krabbe disease in the US, and an estimate of the potential impact of Krabbe disease newborn screening on state NBS programs. The review focuses on the decision-making criteria considered by the ACHDNC. The Evidence-based Review Group (ERG) does not make specific recommendations to the ACHDNC about addition of a condition to the RUSP.

Nomination and Request for Review

In 2010, the ACHDNC decided against recommending Krabbe disease to be added to the RUSP because of gaps in knowledge about strategies for reliably identifying infants with Krabbe disease considered eligible for hematopoietic stem cell transplant (HSCT) and gaps in knowledge about the effectiveness of HSCT. Krabbe disease was nominated again for consideration to be added to the RUSP in 2021 and referred for evidence review in 2022 based on advancements related to screening, including second-tier psychosine testing, which can decrease false-positive screening results, and expansion of knowledge regarding outcomes of HSCT. Psychosine testing was not generally available until 2015.

Target of Newborn Screening

The condition nominated for addition to the RUSP is infantile or late infantile Krabbe disease, defined by the nominators as those infants with expected onset of signs or symptoms by 36 months of age. The classification of Krabbe disease has changed over time. This report will refer to cases with onset in the first 6 months after birth as early infantile Krabbe disease and those with onset from 7-36 months as having late infantile Krabbe disease. Because Krabbe disease can present across a wide spectrum of ages with no clear specific dividing age regarding natural history, the classifications are somewhat arbitrary. Many sources of available data, including information from state newborn screening programs, aggregate those with expected onset of symptoms in the first year of life. To reduce confusion, this report will provide specific ages when possible. However, this report often focuses on those with Krabbe disease in the first year of life because of the focus in published reports on detecting early infantile Krabbe disease for HSCT.

Krabbe disease can be diagnosed prenatally by molecular genetic analysis. The postnatal diagnosis of Krabbe disease is based on low GALC enzyme activity and elevated psychosine concentration in clinically obtained samples (i.e., not through newborn screening), physical exam, and additional specific neurologic tests, including brain magnetic resonance imaging (MRI), nerve conduction studies, electroencephalogram (EEG), auditory and visual evoked potentials, and the cerebrospinal fluid (CSF) protein concentration. Findings of elevated

psychosine concentration and molecular analysis of the *GALC* gene can help establish the diagnosis and help predict the expected timing of onset of signs or symptoms for those individuals who are asymptomatic. Staging systems and related recommendations for follow-up and treatment have been developed.

Methods for the Systematic Evidence Review

The methods guiding the systematic evidence review followed approaches outlined in the Condition Review Workgroup – Manual of Procedures (2012, 2014) and revised in 2016 to address requirements in the 2014 Reauthorization of the Newborn Screening Saves Lives Act (Public Law No: 113-240, 12/18/2014). These methods address the limited evidence that is typically available for rare conditions and the recognition that the evidence base for conditions considered for NBS is often rapidly changing. These methods were also developed to be completed within the timeline required for the ACHDNC. This section describes specific procedures that guided this Condition Review of Krabbe disease NBS.

Published Literature Search

The ERG identified published research articles from MEDLINE, EMBASE, CINAHL, and the Cochrane library using the following MeSH terms and associated key words for each database: "leukodystrophy, globoid cell" and the key words "globoid cell leukodystrophy," "Krabbe disease," and "Krabbe's disease." The search focused on articles published on January 1, 2010, and later. Published articles could be included if the full text was written in English and included human subjects and they met the criteria for at least one key question.

Appendix A lists the specific search criteria for each database and process leading to article inclusion. As described in the manual of procedures, each database was searched and identified articles were placed into an electronic database. Two reviewers independently evaluated the titles and abstracts for potential inclusion. If either reviewer thought that the article was potentially relevant, then the full text of the article was reviewed. For excluded articles, both reviewers had to agree on the reason for exclusion based on a hierarchical list.

Gray Literature and Unpublished Data

Following the Manual of Procedures, this report considers relevant abstracts presented at research or clinical meetings. See Appendix A for further detail. The only findings considered in this report that have not undergone peer review are Krabbe disease newborn screening results provided directly from NBS programs and unpublished meeting presentations (e.g., meetings sponsored by advocacy groups) without specific description of peer review but directly address key questions.

Key Questions for Evidence Review of Krabbe Disease Newborn Screening

The following describes the key questions for the systematic evidence review and the inclusion/exclusion criteria for published articles to provide evidence for each of the key questions.

1. What are the analytic and the clinical validity of newborn screening strategies currently in use to identify infants with Krabbe disease with expected onset of signs or symptoms by 36 months after birth?

Relevant study designs include cross-sectional, case-control, longitudinal (retrospective or prospective), or randomized studies. The studies should include at least 5,000 infants at average risk (e.g., not expected to have Krabbe disease based on family history) screened for Krabbe disease in the first month of life with diagnostic outcome data on those who screened positive. Screening parameters of interest include sensitivity, specificity, positive predictive value, negative predictive value, reliability, diagnostic yield, and the cost of screening. Although studies of anonymized dried-blood spots are important in the development of NBS tests, this evidence-based review focuses on studies of dried-blood spots linked to specific newborns, which provides direct insight into the validity of NBS for the targeted condition.

2. What is the impact of newborn screening for Krabbe disease with expected onset of signs or symptoms by 36 months after birth compared with usual case detection relative to the timing of diagnosis, the timing of treatment, the risk of mortality, or on neurodevelopmental outcomes?

Relevant study designs include longitudinal (prospective or retrospective observational or interventional) studies with at least 6 months of follow-up after diagnosis (or until death if that occurred before 6 months of treatment follow-up). Studies should include at least one subject diagnosed with Krabbe disease with expected onset of symptoms by 36 months of age. Outcomes of interest include mortality, cognitive development, social and emotional development, speech and language development, fine motor development, gross motor development, muscle tone, movement disorders, and the presence of epilepsy or seizure frequency.

3. What are the negative consequences for infants and families of Krabbe disease newborn screening?

Relevant study designs include cross-sectional, case-control, longitudinal (retrospective or prospective), randomized, case reports, and case series studies. Studies should include at least one newborn screened in the first month after birth for Krabbe disease. Outcomes include any reported adverse event related to NBS for Krabbe disease for the infant or the family, including the harms related to false-positive or false-negative screening, the harms of identification of the targeted condition (i.e., Krabbe disease with expected onset by 36 months of life), or identification of later-onset Krabbe disease (i.e., Krabbe disease with expected onset after 36 months of life).

In addition to these key questions, the ERG considered contextual questions that provide insight into the benefits and harms of Krabbe disease newborn screening but for which the evidence-base does not allow for systematic review.

1. What are the current approaches to Krabbe disease newborn screening and to establish the diagnosis of Krabbe disease and predict phenotype after a positive screen?
2. What clinical practice guidelines are available for the diagnosis or treatment of Krabbe disease with onset projected within 36 months after birth?
3. What is the availability and accessibility of specialists to provide care for newborns with a positive Krabbe disease newborn screen?
4. How accessible is timely HSCT for Krabbe disease diagnosed through newborn screening?

Technical Expert Panel

A panel of Technical Experts was convened to advise the development of this report. Members of this Technical Expert Panel (TEP) are listed in Table 1. The first meeting (August 8, 2022) reviewed the scope of the review and methods, outlined the process of Krabbe disease newborn screening, diagnosis, and treatment, and identified current issues in research and health care delivery for children suspected or known to be affected with Krabbe disease. The second TEP meeting (September 30, 2022) focused on issues related to diagnosis following newborn screening and early treatment of Krabbe disease. The third TEP meeting on January 5, 2023, focused on assessing the potential population health impact of Krabbe disease NBS. The TEP was given an opportunity to review a draft of this report.

Table 1. List of 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 Krabbe disease to the RUSP

2. REVIEW OF EVIDENCE: KRABBE DISEASE NEWBORN SCREENING

Epidemiology and Natural History of Krabbe Disease

Overview

Krabbe disease (OMIM #245200) is an autosomal recessive lysosomal disorder associated with low functional levels of the enzyme galactocerebrosidase (GALC),[1] also referred to as galactosylceramidase. GALC degrades certain galactolipids, including psychosine. Low GALC enzyme activity can lead to death of myelin-producing oligodendrocytes and Schwann cells, and the accumulation of globoid cells, which are macrophages that cluster around areas of active demyelination.[1,2] The clinical findings associated with Krabbe disease are due to white matter damage in the central nervous system (CNS) and demyelination in the peripheral nervous system. Some individuals with low GALC enzyme activity have GALC biochemical pseudodeficiency, in which the enzyme activity appears low but these individuals do not have Krabbe disease. Additional evaluation is necessary to distinguish biochemical pseudodeficiency from Krabbe disease and to predict the expected Krabbe disease phenotype.

Natural History of Krabbe Disease

Krabbe disease has a broad spectrum, with variation over the age at which signs and symptoms develop. Earlier development of signs and symptoms is associated with more severe illness and a more rapid progression. Some infants develop findings associated with Krabbe disease in the first month of life, suggesting that disease progression can begin *in utero*. The projected phenotype is typically classified based on the age of disease onset. Over time the age categories and terms that have been used for these age categories have changed.

One report[3] describes a systematic review of case reports and case series from 1982 to 2017. Cases were grouped into four categories based on disease onset: early infantile (0-6 months), late infantile (7-36 months), juvenile/adolescent (37-180 months), and adult-onset (>180 months). Table 2 summarizes the distribution of cases, the age of onset, and the overall survival.

Table 2. Distribution of 248 reported cases of Krabbe disease from a published systematic review[3]

	Early Infantile (0-6 months)	Late infantile (7-36 months)	Juvenile/Adolescent (37-180 months)	Adult-Onset (>180 months)
Number (%)	98 (39.5%)	57 (23%)	46 (18.5%)	42 (16.9%)
Age of onset (median months (range))	4 (3–5)	14 (10–24)	48 (48–72)	384 (165.9–516)
Survival	Median: 1.5 years	Median: 9.5 years	80% alive at 16 years	88% alive at 19 years

One report described a cross-sectional evaluation of patients in Germany in a national network from 2003-2017.[4] Of the 51 potential subjects, 13 were excluded because of missing data. None were identified presymptomatically. Most (71%) had early infantile Krabbe disease (0–6 months) and 7% had late infantile onset (7–12 months). Among these subjects, signs and symptoms at disease onset included agitation and irritability (80%) and movement problems and/or developmental regression (63%).

One report described 88 subjects with either onset or diagnosis of Krabbe disease at ages 0–5 months during 1999–2018.[5] Of these, 13 were identified based on family history. Of the remaining 75, the median age that symptoms were identified by the family was 4 months (range: 0–6 months) and the median age of diagnosis was 6 months (range: 3–15 months). Common symptoms at diagnosis included irritability (54%), feeding difficulties (36%), and spasticity (33%).

This report[5] also described the longitudinal natural history of Krabbe disease by censoring data after HSCT (26 received HSCT after their first visit) or when subjects were no longer followed (33 did not have follow-up after their first visit). Overall, 29 subjects who had not received HSCT were followed longitudinally for a median of 3 visits. Cognitive function was low, with significant regression. By 7 months of age, nearly 80% did not have head control and could not sit independently. Most (80%) had quadriparesis between 10 and 12 months of age, and by 24 months, all had quadriparesis. By 10 months of age, all subjects had abnormal auditory brainstem response. After 12 months of age, all subjects had gastrostomy tubes (g-tubes). All subjects had abnormal visual evoked potentials by 18 months of age and by 2 years of age, most (93%) had severe or complete inability to visually track. After 24 months of age, 94% of subjects had scoliosis. Overall, 70% of subjects died by 2.5 years of age and 80% by 6 years of age.

Another report from the same group of investgators[6] described 35 subjects with onset of signs or symptoms of Krabbe disease between 6 and 36 months of age from 2000 to 2017, with 11 subjects followed longitudinally for a median of 2 times (range: 2 – 8) until HSCT, loss-to-follow-up, or the end of the study period. Three subjects were diagnosed based on family history. The median age at diagnosis was 17.8 months of age (range: 0–39 months), with a median delay in diagnosis after initial development of signs or symptoms of 3.5 months (range: 0–21 months). Common initial symptoms included developmental regression (41%), irritability (38%), abnormal gait (22%), motor delay (16%), and abnormal muscle tone (13%). Most (72%) developed feeding problems by a median age of 12.5 months. Overall, 12 (34%) died, with a median survival time to 6.7 years of age. Vision problems were common, with 48% developing disconjugate gaze and 56% with abnormal pupillary light responses. Overall development was significantly lower than expected, with some having regression. By 40 months, all were below the 5th percentile for cognitive function.[6]

Determining the distribution of Krabbe disease phenotype from these published reports is challenging because of possible ascertainment, referral, and publication biases. In addition, determining the age at onset of symptoms can be difficult because of variability in how cases are identified and recall bias. As previously described, one study estimated that the proportion of individuals with Krabbe disease with onset by 12 months to be 78%[4] and another study estimated the proportion to have onset by 36 months to be 63%.[3] Additional work with population-based case detection is needed to describe the distribution of Krabbe disease by age of onset of signs and symptoms.

GALC and Pathogenic/Likely Pathogenic Variant Frequency

The *GALC* gene is located on chromosome 14 (14q31). The *GALC* gene, which was first cloned and sequenced in the 1990s, is about 60-Kb and has 17 exons.[7,8] According to the Genome Aggregation Database (https:/gnomad.broadinstitute.org, accessed January 19, 2023), more than 1400 variants of the *GALC* gene have been described. Of these, 62 have been classified within the database as "pathogenic/likely pathogenic" and 179 as "benign/likely benign." Many of the unclassified variants in this database are unlikely to be pathogenic. There are 964 *GALC* gene variants listed in the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar, accessed January 19, 2023), a curated database developed to assist the medical genetics community. Of these 423 are considered benign or likely benign, 340 as pathogenic or likely pathogenic, 207 are of uncertain significance, and 55 have conflicting interpretations. The benign variants include those shown to predict a biochemical pseudodeficiency state, where the protein reduces function *in vitro*, but retains enough enzyme activity *in vivo* to not cause disease.

The most common variant associated with severe disease is a 30-Kb deletion (ClinVar allele ID 1675125) that extends from the middle of intron 10 and continues beyond exon 17.[9] Those who are homozygous for this 30-Kb deletion are expected to develop early infantile Krabbe disease. The allele frequency of this variant is about 1 per 2,711.[10] In studies prior to newborn screening, the frequency of the 30-Kb deletion (homozygous or with another variant) in subjects with infantile Krabbe disease ranged from 24% to 66%.[11-13] Other than this deletion, the most common pathogenic single nucleotide or small deletion/duplication variant has an allele frequency of about 1 per 9,960.[14]

The New York newborn screening program has categorized variants based on whether they are expected to be pathogenic but without respect to expected phenotypic severity. The information provided for this report appears in Appendix B.

Birth Prevalence

The birth prevalence of Krabbe disease is commonly reported as about 1 per 100,000 births. This estimate is supported by a population-based study in Finland, which estimated the birth prevalence based on diagnosed cases to be 1.1 per 100,000 (95% confidence interval: 0.23–3.1 per 100,000).[15] However, other studies suggest a higher birth prevalence. A review of registries in Sweden between 1980 and 2009 estimated the birth prevalence of Krabbe disease to be about 1 per 39,000 live births (i.e., 2.6 per 100,000 live births).[16] Another study estimated the birth prevalence of Krabbe disease based on the distribution of pathogenic variants, including those associated with adult-onset disease, of the *GALC* gene in the Genome Aggregation database to be 1 in 12,080 live births (i.e., 8.3 per 100,000 live births).[17] In contrast, the British Paediatric Surveillance Unit system from 1997 to 2014 estimated the birth prevalence to be about 1 per 204,080 (i.e., 0.5 per 100,000).[18] Another study reported an even lower birth prevalence (about 1 per 310,000 or 0.3 per 100,000).[19] This study likely underestimates the prevalence because it only included cases identified treated in selected centers and then used an estimated population denominator, which could lead to a falsely low numerator and an inflated denominator. Determining the birth prevalence for rare conditions can be challenging and lead to an underestimate if there is incomplete case identification or the duration of follow-up is not sufficiently long for cases to be identified.

Krabbe Disease Newborn Screening

Overview of Screening

The primary strategy for identifying infants with Krabbe disease through newborn screening is by identifying infants with low GALC enzyme activity. The sensitivity of GALC activity measurement is reduced in premature infants because normal GALC activity is approximately 3-fold higher in preterm infants, which could potentially lead to false negative screening results.[20,21] It is unclear whether this is a meaningful problem in population screening or if routine repeat newborn screening of preterm infants for Krabbe disease would be warranted, as it is for some other conditions on the RUSP.

To increase the specificity (e.g., decrease false-positive referrals) of screening for Krabbe disease with expected onset in the first 36 months, many newborn screening programs include second-tier dried-blood spot psychosine testing. Second-tier *GALC* molecular analysis can also help identify cases, especially those that need urgent referral.

Psychosine Testing

Psychosine is considered to be a reliable biomarker for Krabbe disease because it is elevated when GALC enzyme activity is insufficient and because psychosine is cytotoxic, leading to the signs and symptoms associated with Krabbe disease. Currently, the threshold for normal psychosine is 2 nmol/L. Psychosine testing became available after 2015. A retrospective analysis of stored dried-blood spot samples in a research laboratory from 75 newborns without Krabbe disease estimated the normal range based on four standard deviations above and below the mean of psychosine concentration to be 0–0.7 nmol/L.[22] In contrast, the range of psychosine concentration among six subjects with early infantile Krabbe disease (0–6 months) was 5.2–44 nmol/L; one subject with late onset Krabbe disease (6–48 months) had psychosine of 5.0 nmol/L, and for one subject with juvenile onset (4–18 years), the level was 2.3 nmol/L. Although an abstract from another group reported that "some babies with the infantile-onset had newborn [dried-blood spot] psychosine as low as 2-6 nmol/L,"[23] psychosine concentrations are typically even higher. Multiple published studies[24-28] and meeting presentations[23,29-31] have found that psychosine concentration in dried-blood spots or red blood cell lysates can distinguish unaffected individuals from those with Krabbe disease and help predict the timing of the onset of signs or symptoms.

The threshold used for abnormal psychosine concentration is an important factor in case detection. One case report[32] describes an infant with low GALC enzyme activity identified through newborn screening with a dried-blood spot psychosine concentration of 1.2 nmol/L and two likely pathogenic *GALC* variants. On repeat testing with a separate dried-blood spot specimen, GALC enzyme activity was low and psychosine concentration was 2.6 nmol/L, below the 3 nmol/L threshold that was considered normal at the time but that would now be considered elevated in the moderate range. The infant had a normal neurologic examination and was scheduled for close follow-up. At 3 months of age, the infant was irritable and found to have a dried-blood spot psychosine concentration of 0.8 nmol/L. At 7 months, he was still found to be irritable and had a dried-blood spot psychosine concentration of 2.0 nmol/L. By 10 months, he had developmental regression and a dried-blood spot psychosine concentration of 1.0 nmol/L. By 12 months, the infant was diagnosed with Krabbe disease based on clinical and imaging

studies. The infant died at 26 months of age. Given the atypical presentation and findings on MRI, the report cautions that it is possible that the infant had a secondary diagnosis.

Elevated psychosine alone is not diagnostic of Krabbe disease. One case report found that psychosine concentration could also be elevated in saposin A deficiency, a very rare metabolic condition.[33] When this subject was 18 months old, the psychosine concentration was 12 nmol/L, above the current threshold of 2 nmol/L considered to be abnormal. Saposin A facilitates the GALC enzyme reaction and therefore is similar to Krabbe disease, including the recommendation for HSCT. Because saposin A deficiency is so rare, this report does not further address the condition.

Diagnosis and Prediction of Expected Phenotype after a Positive Krabbe Disease Screen
Staging systems based on neurologic findings, neurophysiologic testing, and imaging are available to help establish the diagnosis of Krabbe disease.[34,35] These have been modified over time with growth in knowledge about Krabbe disease. The approach to diagnosis and phenotype prediction has evolved over time.[36] An *ad hoc* task force of clinical experts, public health experts, and advocates convened during 2015–2017 to improve the specificity of screening and timeliness to HSCT. The task force recommended first-tier GALC enzyme activity screening followed by second-tier testing for the 30-Kb *GALC* deletion with consideration of *GALC* genotyping and psychosine testing. At the time of these recommendations, evidence regarding psychosine testing was still developing. The task force recommended referral for HSCT for infants who had elevated psychosine concentration and/or who were homozygous for the 30-Kb deletion, with full *GALC* molecular analysis and additional diagnostic evaluation to occur in parallel to avoid delays in treatment.

In 2021, a consensus report provided recommendations about follow-up management for infants with a positive Krabbe disease newborn screen (i.e., low GALC activity with or without psychosine testing or molecular analysis).[37] If psychosine concentration was not measured as part of the newborn screen, it should be measured urgently. According to this consensus report, Infants with psychosine concentration ≥10 nmol/L are likely to have early infantile Krabbe disease and should be referred immediately for HSCT. Infants with psychosine concentration ≥2 and <10 nmol/L are considered to be "at-risk for late onset Krabbe disease" defined as developing expected signs and symptoms after 6 months of age. These infants should be referred for evaluation by a specialist within 2–4 weeks after birth during which time GALC enzyme activity can be retested in leukocytes to confirm the newborn screen and the *GALC* genotype assessed, if not previously obtained. Infants can then be placed into a high-risk for late onset Krabbe disease follow-up pathway if they are found to have a severe genotype or into a low-risk pathway. Expert clinical opinion is used when there is uncertainty about the potential severity of the genotype. Finally, according to this consensus report, infants with GALC enzyme activity above the range reported in affected patients and psychosine concentration <2 nmol/L are considered to be unaffected, with no follow-up necessary unless other concerns arise. Clinical judgment is required; for example, an infant known to have pathogenic genotype would warrant additional follow-up even if subsequent measures of GALC enzyme activity and/or psychosine testing were within the normal range.

The follow-up pathway for individuals who are asymptomatic but at risk of late infantile disease includes a schedule of clinical exams and neurodiagnostic studies that is more frequent for higher risk individuals.[37] The high-risk follow-up pathway includes obtaining a brain MRI, a nerve conduction study, and psychosine concentration measurement by 2 months and then every 4 months through 20 months and then at 26 months, 2.5 years, and 3 years. From 3 to 12 years of age, annual evaluation should include neurologic exam, MRI brain and psychosine level. From 12–18 years of age, these evaluations should be done every 2–5 years. Nerve conduction study is optional after 3 years of age. Clinical exams, without the requirement for additional testing, is recommended at 2 months, 4 months, 8 months, 12 months, 16 months, 18 months, 22 months, and 24 months. In contrast, the low-risk follow-up pathway includes a brain MRI, a nerve conduction study, and psychosine concentration measurement at 18 months, and a brain MRI every 2–5 years until 18 years. Otherwise, clinical exams are recommended by 6 months, at 12 months, and thereafter to coincide with brain MRI.

Published Reports of Krabbe Disease Newborn Screening Case Identification

New York

New York began newborn screening for the full spectrum of Krabbe disease in 2006 using tandem mass spectrometry (MS/MS) to measure GALC enzyme activity and second-tier *GALC* sequencing for those with low enzyme activity.[20,21] The MS/MS test for GALC enzyme activity is currently multiplexed with screening for other lysosomal disorders.

Over time, the criteria for referral for diagnostic follow-up was modified to minimize false positives. Initially, all infants with low enzyme activity were referred. This changed to referral of all infants with GALC enzyme activity ≤8% of the daily mean value and those between 8.1% and 10% with one or more disease-causing variants or a variant of unknown significance. From 2006 to 2015, 2.2 million infants were screened for Krabbe disease. Of these 712 had low GALC enzyme activity and underwent second-tier molecular analysis, leading to referral for diagnostic evaluation of 319 infants. This led to the diagnosis of 5 cases of early infantile Krabbe disease and an additional 55 "high- or moderate-risk" for later onset Krabbe disease as they were referred to at the time.[21]

One report described outcomes from the infants identified through Krabbe disease screening in New York from August 2006 to August 2014.[34] Of the 14 classified as at high risk for later-onset Krabbe disease, one was reclassified as moderate risk at age 4 based on higher GALC enzyme activity. Five were classified as having early infantile Krabbe disease. Outcomes for these infants are described in the treatment section.

Missouri

Missouri began newborn screening for the full spectrum of Krabbe disease in 2012 with samples tested in New York using the New York approach until 2015, when screening switched to a plate-based fluorescence assay.[21] This assay requires a separate punch from the dried-blood spot and is not multiplexed with other screening.

During the 3 years of testing during which samples were sent to New York from Missouri, there were about 230,700 infants screened, 107 infants who required second-tier molecular testing, and 54 infants referred for diagnostic follow-up, none of whom had two known disease-causing

variants. According to a published report, "As of December 16, 2015, all of the screen-positive infants…remain asymptomatic."[21]

Illinois
From December 2017 through December 2020, Illinois screened 494,147 for Krabbe disease with first-tier GALC enzyme activity using MS/MS.[38] Infants with enzyme activity ≤16% of the batch median were repeated and those ≤13% had second-tier psychosine concentration testing for the 30-Kb deletion and *GALC* sequencing. Infants were referred for diagnostic follow-up if the psychosine level was ≥8.7 nM or if they were homozygous for the 30-Kb deletion. Infants with two pathogenic variants were also referred even if the psychosine concentration was <8.7 nM. This report does not describe how the psychosine threshold was set. Overall, 838 infants required repeat testing for enzyme activity ≤16% and 299 underwent second-tier testing. This led to the identification of 2 infants referred for HSCT (psychosine 10 nM and heterozygous pathogenic alleles; psychosine 35 and heterozygous likely pathogenic alleles). There were also 6 cases of suspected late onset Krabbe disease (median psychosine concentration: 3, range: 2–6 nM).

Kentucky
Kentucky sends samples to Mayo Clinic for Krabbe disease and other lysosomal disorders (i.e., Pompe disease, mucopolysaccharidosis type I). First-tier testing is with GALC enzyme activity with MS/MS, with multivariate recognition software to improve the accuracy of screening, followed by second-tier psychosine measurement when needed.[39] Of the 55,161 specimens from February 2016–February 2017, 11 required second-tier testing, leading to one case of Krabbe disease by 7 days of life, with HSCT by 24 days of life.

Krabbe Disease Newborn Screening in the United States
Ten newborn screening programs in the United States currently screen for Krabbe disease (Table 3), each of which responded to a survey from APHL. These programs reported that since beginning screening, 28 infants with Krabbe disease with expected onset prior to 12 months of age have been identified from among 7,407,982 newborns screened (0.38 per 100,000 or 1 case per 264,570 newborns screened). As is typical, each program has modified and refined its approach to screening over time. Therefore, this report focuses on outcomes from the current screening approaches used by these programs.

Table 3 describes the current approach to Krabbe disease newborn screening. First-tier GALC enzyme activity testing is done in-house for 8 of the programs. As previously described, GALC enzyme activity testing can be multiplexed with testing for other lysosomal disorders when using MS/MS but doing so increases the initial incubation time to up to 18 hours. All 8 programs that include second-tier psychosine testing contract this service out, with results typically available in 2 days. Six of the programs also test for the presence of the 30-Kb deletion concurrently with psychosine testing, with results typically available in 2 days. Of these six programs, five also conduct full sequencing of the *GALC* gene. New York sequences the *GALC* gene routinely when low GALC enzyme activity is identified.

Table 3. Current approach to Krabbe disease newborn screening '

Newborn Screening Program	Year Screening Began	First-Tier GALC Enzyme Activity Testing	Second-Tier Psychosine Testing	Psychosine Cutoff	*GALC* 30-Kb deletion testing concurrent with psychosine testing	*GALC* Sequencing
Georgia	2021	In-house, MS/MS	Mayo Clinic	2.0	No	No
Illinois	2017	In-house, MS/MS	PerkinElmer	1.5	Yes	Yes
Indiana	2020	In-house, MS/MS	PerkinElmer	1.5	Yes	Yes
Kentucky	2016	Sent to Mayo Clinic	Mayo Clinic	2.0	Yes	Third-Tier
Missouri	2012	In-house, Fluorometric	Mayo Clinic	2.0	No	No
New Jersey	2019	In house, MS/MS	No	N/A	No	No
New York	2006	In-house, MS/MS	Mayo Clinic since 2022	2.0	Yes	Yes
Ohio	2016	In house, MS/MS	No	N/A	No	No
Pennsylvania	2021	Sent to PerkinElmer	PerkinElmer	1.5	Yes	Yes
Tennessee	2017	In-house, MS/MS	PerkinElmer	1.5	Yes	Yes

The following table (Table 4) describes screening outcomes following the programs' current approaches for the indicated screening periods, grouped by general approach to screening.

Table 4 Screening outcomes from the program's current approach.

Newborn Screening Program	Screening Period	Number of Infants Screened	Referrals per 100,000 Screened	Krabbe Disease with Expected onset in the first year per 100,000 Screened [additional follow-up]	At-Risk for Onset after 12 months per 100,000 Screened	Pending Classification, Declined Follow-up, Lost Referrals
Referral Based on GALC Enzyme Activity Alone						
Ohio	April 2020-Sept 2022	808,816	54.0	0.4 (n=3)*	1.2 (n=10)*	Pending: 20 Declined: 36 Lost: 1
New Jersey	July 2019-Sept 2022	312,158	28.9	0 (n=0)	2.2 (n=7)*	Pending: 8 Declined: 0 Lost: 4
Referral Based on GALC Enzyme activity, Psychosine Concentration, and/or *GALC* 30-Kb Deletion						
Missouri	March 2020-Aug 2022	168,042	11.9	0.6 (n=1) [HSCT at 31 days]	1.2 (n=2)	Pending: 0 Declined: 0 Lost: 1
Tennessee	July 2017-Sept 2022	421,481	13.8	0.2 (n=1) [HSCT at 36 days]	0.5 (n=2) [Asymptomatic, no HSCT]	None
Referral Based on Psychosine Concentration and/or *GALC* 30-Kb Deletion						
Georgia	Sept 2021-Sept 2022	144,000	0.7	0.7 (n=1) [Family elected no HSCT]	0	None
Illinois	Oct. 2021-July 2022	98,721	8.1	0	2.0 (n=2)*	Pending: 2 Declined: 0 Lost: 0
Indiana	July 2020-Oct 2022	172,803	6.4	0	2.3 (n=4)*	None
Kentucky	Feb 2016-Sept 2022	330,555	0.6	0.6 (n=2) [HSCT at 24 and 30 days]	0	None
New York	March 2018-Sept 2022	985,726	7.3	0.2 (n=2)† [No HSCT based on psychosine and lack of symptoms]	2.5 (n=25)*	None
Pennsylvania	May 2021-Aug 2022	167,537	11.3	1.8 (n=3) [HSCT at 34 days, 101 days, 150 days]	0.6 (n=1)	Pending: 2 Declined: 0 Lost: 0

*No further follow-up data available from the program and no additional relevant report.
†A meeting abstract[40] reports that these two infants later received HSCT at 18 months, implying potential misclassification in this table. This table was developed based on information provided to APHL.

Across these newborn screening programs, based on their current screening approaches for Krabbe disease newborn screening, 3.6 million newborns have been screened. The average referral rate was 14.3 per 100,000 newborns screened (range: 0.6 to 54 per 100,000 newborns screened). Differences in newborn screening referral rates are not clearly related to the referral criteria. Referral has led to the identification of 13 cases of Krabbe disease with expected onset in the first 12 months after birth (0.36 per 100,000 newborns screened) and 53 cases with expected onset after 12 months (1.46 per 100,000 newborns screened).

According to information gathered by APHL, Ohio has reported that 36 with a positive screen have declined further follow-up and one has been lost to follow-up, representing about 8% of all potential referrals. This program also reports that 20 infants are pending classification either because the diagnostic process has not been completed or the results have not yet been reported to the newborn screening program. New Jersey reported that there are 8 pending classification and 4 with a positive screen lost to follow-up. Illinois and Pennsylvania each report 2 pending classification with no losses to follow-up. Missouri reported 1 positive screen lost to follow-up. There are no other reports of positive screen referrals who were lost to follow-up or declined follow-up. Overall, there are 32 cases pending classification, 36 who screened positive who declined follow-up, and 6 who were lost to follow-up, representing about 10% of all positive cases. The likelihood that these 74 referrals have Krabbe disease is uncertain. One newborn screening program, which makes referrals based on GALC enzyme activity alone without second-tier testing, accounted for most (77%) of these positive screens that are pending, declined or lost to follow-up.

Cost of Krabbe Disease Newborn Screening

The estimated additional cost from the program perspective of adding Krabbe disease, above and beyond the fixed costs of an existing NBS program, varied between $2 and $7 per infant screened. The bulk of the estimated costs reflected the costs of equipment, reagents, and added laboratory technician and laboratory scientist time for first-tier screening.

Key Findings: Newborn Screening for Krabbe Disease

- Krabbe disease newborn screening with first-tier GALC testing has been implemented in ten states and can be multiplexed with screening for other lysosomal disorders. Most newborn screening programs use psychosine second-tier testing to reduce false-positive screens, including the three most recent newborn screening programs to add Krabbe disease newborn screening (each staring in 2021). One of the programs that does not use second-tier testing accounts for the majority of cases that are pending, declined further follow-up, or are lost to follow-up. There is variation in the use of *GALC* molecular analysis. Although there is heterogeneity, the average referral rate is about 14.3 per 100,000 screened, with identification of about 0.39 cases of Krabbe disease with expected onset in the first 12 months per 100,000 newborns screened and about 1.39 cases of suspected Krabbe disease with expected onset after 12 months per 100,000 newborns screened.
- There is a small risk of a false-negative with second-tier psychosine testing. One subject[32] with early infantile Krabbe disease and a non-elevated initial dried-blood spot psychosine concentration based on the threshold at the time of testing has been described.

There is also uncertainty about the diagnosis of Krabbe disease in this infant. There is also a potential risk of false-negative GALC enzyme activity testing, such as in preterm infants, although no case was identified in this review.
- Some families opt out of HSCT.
- Programs have been able to coordinate timely HSCT after screening.

Overview of Krabbe Disease Treatment

HSCT was established as treatment for Krabbe disease in 1998, based on a case series of five subjects with Krabbe disease treated at 2 months, 2 years, 7 years, 8 years, and 11 years.[41] A subsequent report, published in 2005, described 25 subjects with Krabbe disease treated with unrelated umbilical-cord blood HSCT.[42] Of these 25, 11 were diagnosed prenatally or shortly after birth due to family history. According to one of the authors, all 11 had siblings who died from infantile Krabbe disease, 7 were homozygous for the 30-Kb deletion, 1 had other high-risk variants, and *GALC* gene information was not immediately available for 3. These 11 subjects received HSCT at a median age of 18.5 days, when they were still reported to be asymptomatic. Although described as asymptomatic, 4 had "subtle motor abnormalities." The other 14 were diagnosed from 4 to 9 months after birth based on symptoms and received HSCT from 142 to 352 days. Key findings regarding differences in outcomes from the group that was asymptomatic compared with the symptomatic group included:

- Survival: There were no deaths in the asymptomatic group, with a median follow-up of 36 months after HSCT. In contrast, 6 of the 14 infants in the symptomatic group survived for a median follow-up of 41 months after HSCT. Deaths in the symptomatic group were attributed to progressive disease (n=4), graft-versus-host disease (n=1), aspiration pneumonia (n=1), adenoviral infection (n=1), and complications after liver biopsy for graft-versus-host disease.
- Gross Motor Development: Of the 10 of 11 in the asymptomatic group with follow-up, one had severe delays and four had mild-to-severe delays, and two developed truncal weakness and lower extremity spasticity. Those in the symptomatic group who survived had a "developmental level equivalent to that of a one-month-old."
- Fine Motor Development: Of the 10 of 11 in the asymptomatic group with follow-up, two had severe fine motor delays. Those in the symptomatic group who survived were severely impaired.
- Cognitive Function and Language: Of the 10 of 11 in the asymptomatic group with follow-up, all were reported to gain cognitive skills at a normal rate, one had below normal receptive language ability, and two had below average expressive language, associated with motor involvement. Those who survived in the symptomatic group had significantly abnormal cognitive function and language ability.

These and other similar findings[43] support the goal of pre- or early symptomatic treatment, which may be up to 6 weeks after birth for those with early infantile Krabbe disease.

A 2019 guideline from the Hunter's Hope Leukodystrophy Care Network described the approach to allogenic HSCT for individuals with a leukodystrophy, including Krabbe disease.[44] The first consideration is whether the potential benefit of HSCT is expected to outweigh the potential risks. Contraindications include airway instability, uncontrolled seizures, coma, and need for

mechanical ventilation. The guideline states "In the early infantile form [defined as: expected symptoms before 6 months of age] of Krabbe disease (EIKD), HSCT is beneficial if performed in newborns in the first month of life who are clinically presymptomatic."[44] This guideline also states that "HSCT does not offer benefit to infants with EIKD after symptoms have developed." To help assess benefit, the guideline outlines four stages to describe the severity of signs and symptoms in patients with early infantile or late infantile Krabbe disease. Only newborns or those at stage 1 (defined as 2 or fewer of the following: mild thumb clasp, hypotonia of the shoulder girdle, weak feeding, or gastroesophageal reflux) are expected to have greater benefit than risk of transplant. The hierarchy of the best donor for HSCT is from an HLA-matched noncarrier sibling, followed by cord blood, then unrelated bone marrow. Infants should receive myeloablative conditioning and not total body irradiation.

Potential Future Treatment Options

A novel approach to HSCT that includes intrathecal delivery of a stem cell line derived from umbilical cord blood is under investigation.[45,46] Gene therapy for Krabbe disease is an active area of investigation. FBX-101 (Forge Biologics, Inc.) and PBKR03 (Passage Bio, Inc) are gene therapies using adeno-associated virus for delivery that have FDA fast-track designation. Trials of FBX-101 focus on intravenous delivery after HSCT (RESKUE, ClinicalTrials.gov identifier NCT04693598). The ongoing study of PBKR03 excludes subjects with prior HSCT and the drug is injected into the cisterna magna (GALax-C, ClinicalTrials.gov identifier NCT04771416). Novel therapies not available for routine treatment are not considered further in this report.

Reports of Treatment Outcome Since the Previous ACHDNC Evidence Review

For this report, we separately describe treatment outcomes for cases identified through newborn screening compared to cases identified based on the development of symptoms or resulting from a high index of suspicion due to family history. Cases identified through newborn screening provide information regarding expected outcomes with the full complexity of the newborn screening process. In addition, some infants diagnosed prenatally are delivered early to minimize potential *in utero* harm. Outcomes from these late preterm infants might be different than full-term infants diagnosed through newborn screening.

It is not possible to conduct a meta-analysis of the effectiveness of HSCT because of the many factors related to timing of diagnosis and treatment, expected phenotype, and approach to HSCT. The effectiveness of HSCT might have also improved over time with greater clinical experience.

As identified by the nominators, the risk of HSCT include "infection related to immunosuppression, toxicity of the condition agent…, and graft-versus host disease…there are also risks of late effects of HSCT in skeletal growth and dentition,[and] infertility." The nominators point out that HSCT regimens have improved and that there are medical treatments for late effects. Harms directly related to HSCT from the studies included in this review are described. This review focused only on HSCT for Krabbe disease and so does not comment on potential harms identified related to HSCT for other indications.

Outcomes following Newborn Screening

Two published reports described outcomes of treatment from diagnosis through newborn screening. One study described outcomes from 14 cases identified by Krabbe disease screening

in New York from August 2006 to August 2014.[34] Five subjects were classified as having early infantile Krabbe disease based on a point system developed to predict the risk of onset by 6 months. Four underwent HSCT. Nine infants were identified as at high risk, but not early infantile Krabbe disease. The following information was provided about the 14 infants with positive screens and referred for treatment and follow up (note that this report is before the availability of psychosine testing):

- Subject 1: Received HSCT at 32 days after birth, developed autoimmune hemolytic anemia and steroid-related hypertrophic cardiomyopathy, and was reported to have significant developmental delays and unable to walk independently at 8 years. This subject had the 30-kb deletion on one allele and a second suspected pathogenic variant on the other allele. A recent meeting abstract states that the subject at 15 years of age "uses a wheelchair, attends school, is bilingual, uses upper extremities normally, eats and communicates orally and with an assistive device."[40]
- Subject 2: Received HSCT at 31 days after birth and died at 84 days from HSCT-related complications. This subject was homozygous for the 30-kb deletion.
- Subject 3: Parents decided against HSCT, died at 18 months. This subject was ! homozygous for the 30-kb deletion.
- Subject 4: Received HSCT at 41 days after birth, had graft versus host disease, and is reported at five years to be severely developmentally delayed and failing to thrive. This subject had the 30-kb deletion on one allele and a second pathogenic variant on the other allele. A recent meeting abstract states that this subject is 11 years of age and "requires continuous care."[40]
- Subject 5: Received HSCT at 24 days after birth and died at 69 days after birth of progressive pulmonary hypertension. This subject was homozygous for the 30-kb deletion.
- Subject 6: At high risk, with normal findings at 8 years.
- Subject 7: At high risk, with normal findings at 6 years, 7 months.
- Subject 8: At high risk, incomplete follow-up with last contact at 4 years.
- Subject 9: At high risk, with normal findings at 6 months
- Subject 10: At high risk, incomplete follow-up with last contact at 5 years.
- Subject 11: At high risk, incomplete follow-up with last contact at 4 years.
- Subject 12: At high risk, incomplete follow-up with last contact at 6 months.
- Subject 13: Initially considered for HSCT based on an abnormal myelination pattern on MRI. Family refused HSCT and subsequent MRI showed improvement in myelination and was no longer a candidate for HSCT. Normal neurologic examination at 26 months. With changes in treatment criteria, one member of the TEP stated that this subject would not have been considered for HSCT.
- Subject 14: Initially considered for HSCT based on an abnormal myelination pattern on MRI. Family refused HSCT and subsequent MRI showed improvement in myelination and was no longer a candidate for HSCT. Normal neurologic examination at 13 months. With changes in treatment criteria, one member of the TEP stated that this subject would not have been considered for HSCT.

Another report describes six subjects born between January 2016 and February 2019 identified with infantile Krabbe disease through newborn screening outside of New York.[47] According to the authors, the report includes all newborns identified with infantile Krabbe disease through

newborn screening during this time period outside of New York. All infants had low GALC enzyme activity and the range of initial psychosine levels was 24–73 nmol/L. One subject was homozygous for the 30-kb deletion and two subjects were heterozygous for the 30-kb deletion. The other variants *GALC* variants found in the subjects were expected to be disease-causing. The median age at HSCT was 36 days of age (range: 24–40 days) and all subjects survived. The median period of follow-up was 47.5 months (range: 30–58 months).

Of the 6 subjects, 5 had follow-up at 1 year after HSCT; one was lost to follow-up for neurocognitive testing. In general, motor skills lagged behind cognitive and expressive skills. The following summarizes the Bayley Scales of Infant and Toddler Development, third edition, range one year after HSCT (mean standard score = 100, standard deviation =15),:

- Cognitive: 75–80
- Language: 65–83
- Motor: 46–77

At 30–58 months of age, all subjects still had normal GALC enzyme activity. Three had elevated psychosine level in dried-blood spots (range: 3.7–16.2 nmol), two had no detectable psychosine, and psychosine level was not available for one. All subjects continued to have neurodevelopmental delay and some degree of lower extremity spasticity and weakness. One subject was able to walk independently and climb. All subjects could sit unsupported. Three subjects did not require gastric-tube feeds.

Other Outcome Studies

Seven reports described outcomes following HSCT for Krabbe disease in young children but did not distinguish outcomes by whether they were diagnosed through newborn screening, family history, or clinical suspicion.

One study reported outcomes of 18 subjects who survived >5 years after HSCT for Krabbe disease with treatment before 2 years of age.[48] No information was provided about *GALC* genotype and this was before psychosine testing was available. These subjects were identified from a single center and received HSCT between September 1993 to August 2008. The process leading to the diagnosis of Krabbe diagnosis was not described. This report described on a total population of 102 subjects who underwent HSCT for a variety of indications and did not consistently separate those whose indication was Krabbe disease. One subject with Krabbe disease died after "a reaction to ketamine after surgical tendon release."[48] Another subject with Krabbe disease developed "disease-unrelated cardiac disfunction…[and]…underwent surgical correction of a subaortic stenosis with ventricular hypertrophy."[48]

Another report described 19 subjects with Krabbe disease who underwent HSCT by 2 months of age and compared outcomes for treatment before versus after 30 days after birth.[43] Most (17) received HSCT at the study center and all subjects received follow-up at the study center. No information was provided regarding *GALC* genotype and this study was also before psychosine testing was available. All subjects received HSCT between December 1996 to July 2010 and received care at a single center, although two received HSCT at a different center. Of the 19 subjects, 3 were identified by newborn screening and 16 by family history. Prior to HSCT, all had low GALC enzyme activity and a known pathogenic *GALC* variant. The median age at HSCT was 27 days (range: 19–61 days) and the median follow-up was 11.2 years (0.1–18.8

years). Three subjects died from HSCT-related complications within 1-2 months of treatment. There were an additional 2 deaths, one due to progressive disease at 15.5 years and another due to "idiopathic and fatal reaction to ketamine after surgical tendon release 6.3 years post-transplant"[43] (likely the same case as previously described[48]). Survival to 5 years post-HSCT (84.2%; 95% CI: 58.7%–94.6%) and 10 years post-HSCT (78.6%, 95% CI: 52.5%–91.4%) did not differ based on transplant <30 days (n=10) or ≥30 days–2 months (n=6); (p=0.95, p=0.65). However, earlier treatment was associated with a lower likelihood of requiring a wheelchair for mobility at 5 years (10% vs. 83.3%; p=0.02) and a greater likelihood of normal verbal communication (80% vs. 16.7%; p=0.02). At the most recent follow-up, those with earlier transplant still had a lower likelihood of requiring a wheelchair for mobility (10% vs. 83.3%; p=0.01) and greater likelihood of normal communication (80% vs. 16%; p=0.02). Although there was no statistical difference in feeding by mouth independently at 5 years (70% vs. 33.3%; p=0.29), statistical differences emerged by the most recent follow-up (90% vs. 1.7%; p<0.01).

One report described long-term outcomes in subjects with Krabbe disease following HSCT in the first 7 weeks after birth.[49] Of the 18 subjects referred to a single center from January 2000 to September 2011, three were identified by newborn screening. All had low GALC enzyme activity prior to transplant. *GALC* genotype information was available for five subjects, of whom 2 were homozygous for the 30-Kb deletion and 2 were compound heterozygotes for the 30-Kb deletion and another likely pathogenic variant. Psychosine testing was not available at this time.

Overall, 3 died after HSCT, 1 died of a "surgical complication unrelated to Krabbe disease" six years after HSCT, and one died of progressive Krabbe disease 15 years after transplant. Of the 15 who survived after HSCT, the follow-up period was 11.3 years (range: 5.4–16.2 years). Development was variable. For example, 7 of the 13 subjects with follow-up information had receptive language development in the normal range. However, most had articulation difficulties and two required communication devices. Three were able to walk independently, 7 required assistive devices, and 5 were unable to walk. Two of 11 subjects with EEG follow-up required anti-seizure medication, although one was able to wean off the medication.

One case report published in 2012 compared an infant who received HSCT for infantile-onset Krabbe disease at 24 days to an older sibling with infantile-onset Krabbe disease that presented at 6 months with irritability and developmental regression, did not receive HSCT and died at 22 months of age.[50] Psychosine testing was not available. The younger sibling was heterozygous for the 30-Kb deletion (the other allele had the variant c.1538 C>T). Over time, the younger sibling had normal receptive language but delayed expressive language. The younger sibling could ambulate at 5 years and at that time could talk in 5-word phrases.

A case report from Poland published in 2021 described a 4.5 month old child diagnosed with late-infantile Krabbe disease after the diagnosis of an older sibling at 16 months.[51] Neither the psychosine concentration nor the *GALC* genotype was provided. It is unclear if such testing was available. The infant was described as not having normal neurologic development at 5 years.

One report of the safety of HSCT for various indications involving 24 subjects described one subject with Krabbe disease transplanted at 0.6 years who died from pneumonia 20 days after treatment.[52]

One report of subjects with late infantile Krabbe disease, defined as expected to develop symptoms between 6 to 36 months, compared 19 subjects with HSCT from 1997–2020[53] to subjects who did not receive HSCT who had been previously reported in a natural history study.[6] The 19 subjects were referred to the study center for treatment, and the process leading to diagnosis was not described. Of the 19, 5 were asymptomatic prior to HSCT. For the asymptomatic subjects, the median GALC enzyme activity prior to HSCT was 0.04 nmol/h/mg (range: 0–0.08 nmol/h/mg) and after, the median GALC enzyme activity was 2.4 nmol/h/mg (range: 1.8–6.1 nmol/h/mg). Among the symptomatic subjects, the median GALC enzyme activity prior to HSCT was 0.03 mol/h/mg (range: 0–0.13 nmol/h/mg) and after, the median GALC enzyme activity was 1.85 nmol/h/mg (range: 0.32–4.5 nmol/h/mg). Psychosine concentration over time was available for a subset of patients in a figure without sufficient information to link specific values to specific subjects. *GALC* genotype information was available for 1 of the five asymptomatic subjects and 5 of the 14 who were symptomatic. Of the 6 with genotype available, 4 carried two pathogenic or likely pathogenic alleles in *trans*, based on an updated search of pathogenicity on Clinvar. Four of the 6 carried at least one pseudodeficiency allele in combination with at least one pathogenic/likely pathogenic allele.

Two subjects died related to complications of HSCT, one died from a varicella infection 1.2 years after HSCT, one died after "losing his graft" 2.7 years after HSCT, and one died with disease progression 5.6 years after HSCT. The survival to 11 years of age among the subjects treated asymptomatically was 100% compared to 79% for those who had developed symptoms and 13% for those who were untreated. Overall survival to 25 years for subjects treated with HSCT is 72.5%.

All 5 subjects treated when asymptomatic were reported to have normal cognitive, receptive language, and expressive language development. All also had normal or near-normal fine motor development. Three of the asymptomatic subjects had normal gross motor development, one was delayed, and one plateaued at 1.5 years thought to be related to steroid myopathy. Four of the asymptomatic subjects had normal adaptive development and one, who also had delayed gross motor development also had delayed adaptive development.

An abstract accepted for publication describes fraternal twins born in New York with late infantile onset Krabbe disease identified through newborn screening, both of whom received HSCT at 16 months are described as normal at 5 years of age, and another infant born outside of New York who received HSCT around 1 month of age.[40] One author provided additional information about these three subjects, as described below.

Table 5 summarizes individual cases and outcomes from these reports and other relevant meeting presentations based on published abstracts. Several studies provided aggregate information about cases and therefore do not appear in this summary table.[43,48,53] Where possible, individual cases with more than one report were grouped together. Note that this table is not comprehensive of all cases and it is possible that the same case appears more than once or are inappropriately grouped. For each case, this table provides the method of identification if

provided (i.e., newborn screening [with state and year of identification, if provided], family history, not specified), phenotypic classification as described in the study, *GALC* gene information and initial psychosine concentration (if provided in the report), age at HSCT if treated as provided in the report, the age at last follow-up as provided in the report, and a summary of the clinical status as provided in the report. The table is organized by method of detection (family history, newborn screening, not specified) and from youngest to oldest at HSCT, with those identified with an infantile phenotype who did not receive HSCT listed first. For cases identified by newborn screening, any information about the state newborn screening program is provided. Only one of the reports provided the specific year that newborn screening led to identification of the case (Kentucky, 2016).[39]

There are several important considerations when interpreting Table 5. There have been advancements in diagnosis and treatment, so that earlier cases might not reflect outcomes that would be expected with the current delivery of care. *GALC* information is also missing for many of the earlier reports. Similarly, psychosine testing was not generally available until 2015. Most of the descriptions do not have standard neurologic evaluations at specific ages and instead have qualitative assessments. For example, although irritability is a common feature of untreated Krabbe disease, the studies do not describe or measure irritability.

Table 5. Individual cases of Krabbe disease and outcomes from peer-reviewed publications included in this review

State Newborn Screening Program	Classification	*GALC*/ Initial Psychosine Concentration*	Age at HSCT	Age at Follow-up, Status	Reference (Year)
Family History					
	Infantile	NP/NP	3.3 weeks	5 years, Kindergarten with an aide, able to run, talk in 5-word phrases, feed herself, ankle clonus, upgoing plantar responses, tendency to toe-walk	[50](2012)
	NP	NP/NP	4 weeks	5 years, spastic quadriparesis, need g-tube, some speech, "dependent for all cares"	[54†](2012)
	NP	NP/NP	5 weeks	5 years, neurologically abnormal, unable to walk, needs g-tube, some speech	[54†](2012)
	Infantile	NP/NP	6.5 weeks	7 years, requires wheelchair, not developmentally delayed	[55†](2016)
	Infantile	NP/NP	7 weeks	11 months, "doing well"	[55†](2016)
	Late Infantile	COMPHET30/ NP	4.5 months	5 years, normal neurological exam	[51](2021)

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Newborn Screening					
New York	Early Infantile	HOM30/NP	Family refused	18 months, died	[34](2016)
New York	Early Infantile	HOMO30/NP	3.3 weeks	69 days, died	[34](2016)
Kentucky	Early Infantile	NP/NP	3.3 weeks	9 months, "developing normally…but with some complications, attributed to the transplant itself."	[39](2018)
New York	Early Infantile	COMPHETERO30/NP	3.5 weeks	11 years, severely developmentally delayed, requires continuous care	[34,40,49†] (2016, 2017, 2023)
Not New York	Infantile	COMPHET30/61	3-4 weeks	4.8 years, requires wheelchair, needs g-tube, developmentally delayed	[47](2022)
Not New York	Infantile	NP/NP	4 weeks	16 months, alive but no additional information	[40†](2023)
Not New York	Infantile	Other/73	4-5 weeks	45 months, requires wheelchair, developmentally delayed	[47](2022)
Not New York	Infantile	HOMO30/56	4-5 weeks	52 months, requires wheelchair, developmentally delayed	[47](2022)
New York	Early Infantile	HOMO30/NP	4.5 weeks	84 days, died	[34](2016)
New York	Early Infantile	COMPHET30/NP	4.5 weeks	15 years, requires wheelchair, attends school, uses upper extremities normally, eats and communicates orally and with an assistive device."	[34,40†] (2016, 2023)
Not New York	Infantile	COMPHET30/38	5-6 weeks	36 months, requires wheelchair, needs g-tube, developmentally delayed	[47](2022)
Not New York	Infantile	COMPHET30/35	5-6 weeks	30 months, developmentally delayed	[47](2022)
Not New York	Infantile	COMPHET30/24	5-6 weeks	58 months, requires wheelchair, needs g-tube, developmentally delayed	[47](2022)
New York	Infantile	Other/2-10	18 months	5 years, "normal"	[40†](2023)
New York	Infantile	Other/2-10	18 months	5 years, "normal"	[40†](2023)
New York	High risk	Other/NP		6 months	[34](2016)
New York	High risk	Other/NP		6 months	[34](2016)
New York	High risk	Other/NP		13 months	[34](2016)
New York	High risk	Other/NP		2 years	[34](2016)
New York	High Risk (retrospectively assigned as Onset in Late Infancy)	Other/1.2	Not offered prior to significant signs and symptoms	26 months, died	[32](2021)
New York	High risk	Other/NP		4 years	[34](2016)
New York	High risk	Other/NP		4 years	[34](2016)
New York	High risk	Other/NP		5 years	[34](2016)
New York	High risk	Other/NP		7 years	[34](2016)
New York	High risk	Other/NP		8 years	[34](2016)

Continued

Continued

Not Specified					
	Early Infantile	NP/NP	2.6 weeks	16.2 years, cannot walk, not toilet trained	[49](2017)
	Early Infantile	NP/NP	2.7 weeks	13.1 years, walks	[49](2017)
	Early Infantile	Other/NP	2.9 weeks	7.1 years, walks with assistive device	[49](2017)
	Early Infantile	NP/NP	3.1 weeks	6.29 years, died	[49](2017)
	Early Infantile	NP/NP	3.1 weeks	15 years, walks with assistive device	[49](2017)
	Early Infantile	NP/NP	3.3 weeks	11.2 years, walks with assistive device, not toilet trained	[49](2017)
	Early Infantile	NP/NP	3.6 weeks	11.3 years, walks	[49] (2017)
	Early Infantile	NP/NP	3.7 weeks	12.3 years, walks with assistive device, needs g-tube	[49](2017)
	Early Infantile	NP/NP	4 weeks	10.2 years, walks with assistive device	[49](2017)
	Early Infantile	NP/NP	4.1 weeks	14.9 years, walks with assistive device	[49](2017)
	Early Infantile	COMPHET30/ NP	4.7 weeks	8.6 years, cannot walk, not toilet trained	[49](2017)
	Early Infantile	NP/NP	5.1 weeks	13.8 years, walks with assistive device	[49](2017)
	Early Infantile	HOMO30/NP	5.3 weeks	15.4 years, died	[49](2017)
	Early Infantile	NP/NP	7 weeks	7.6 years, walks with assistive device, not toilet trained	[49](2017)
	NP	NP/NP	6 months	20 days after HSCT, died	[52](2010)

*_GALC_ molecular analysis categorized as homozygous for the 30-Kb deletion (HOM30), compound heterozygous for the 30-Kb deletion with another variant present (COMPHET30), or whether the subject has other pathogenic variants (Other); for _GALC_ and psychosine concentration, not presented (NP) is for when the information was not presented in the report.
†Abstract from a meeting presentation

The outcome studies included in this review do not have standardized neurodevelopmental testing results at specific ages. Such an approach would allow for a clearer assessment of the impact of HSCT on functional outcomes and quality of life. Although irritability is a common feature of early infantile and infantile Krabbe disease, the outcome studies do not specifically comment on the impact of treatment on irritability.

Treatment Summary

- HSCT is the recommended treatment for individuals with Krabbe disease with expected onset of signs and symptoms by 36 months of life.
- For those with expected early infantile Krabbe disease (i.e., onset by 6 months of life), HSCT is recommended with a goal of treatment by 4 to 6 weeks after birth. There are many factors that influence outcomes (e.g., gestational age, genotype). Timely HSCT

can reduce the risk of childhood mortality, but other outcomes are more variable and insufficient evidence is available to enable prediction of these other outcomes.

- For individuals with Krabbe disease with expected onset of signs and symptoms by from 6 – 36 months, the available evidence suggests that treatment before the development of signs or symptoms reduces the risk of mortality and, although the evidence base is limited, there is also an association with improved cognitive, language, and fine motor development.
- The greatest risk of mortality following HSCT is around 100 days after treatment. Limited data suggest the risk is 11% in centers with expertise in HSCT for Krabbe disease. There is insufficient data about other potential long-term negative outcomes associated with HSCT for Krabbe disease.

Potential Benefits of Screening

- Krabbe disease newborn screening can eliminate the diagnostic odyssey. Infants with early infantile Krabbe disease develop feeding problems and extreme irritability. This leads to a significant burden for families as they seek diagnosis and effective treatment. Incorrect diagnoses (e.g., colic) can be made during this process. The evidence review did not identify any studies addressing the diagnostic odyssey. However, the natural history studies suggest that when there is no family history of Krabbe disease, the diagnosis of early infantile Krabbe disease can take months after the onset of signs and symptoms, beyond the recommended period of 4 to 6 weeks of age when HSCT would be an option.
- Detection of early infantile Krabbe disease through newborn screening allows families to decide whether to have their infant receive HSCT within the recommended period of 4 to 6 weeks of age.
- HSCT by 4 to 6 weeks of age for early infantile Krabbe disease is associated with decreased risk of childhood mortality. Insufficient evidence is available to compare overall life expectancy of those who receive HSCT because HSCT has been available as a treatment for early infantile Krabbe disease, a rare disease, for less than 20 years.
- HSCT by 4 to 6 weeks of age for early infantile Krabbe disease is associated with improved functional outcomes, although outcomes can be variable and difficult to predict. Cases were identified of children who were reported to be "normal" and cases who required various supports (e.g., assistive device for walking, wheelchair, g-tube support for feeding) and with a wide range of neurodevelopmental function. None of the case reports or case series identified in the review described the subjects as being irritable after HSCT, although irritability was not listed as a measured outcome. A limitation of the evidence base is that these studies lack specific outcome measures at specific ages related to standardized health outcomes and quality of life. Similarly, the articles do not address the impact of Krabbe disease with or without HSCT on the family. Such information would inform the overall impact of Krabbe disease newborn screening and provide additional insight into additional interventions that could improve outcomes.
- A limited evidence base suggests that HSCT for late-infantile Krabbe disease (i.e., onset 6 – 36 months) early in the disease course is associated with decreased mortality and improved functional outcomes, with some variability.

Potential Harms of Screening

There are potential harms associated with any screening program.

- A false negative screen would be a harm because it could lead to false reassurance, potentially delaying diagnosis after signs or symptoms appear. Although premature infants might have a higher likelihood of false negative first-tier screening with GALC enzyme activity, no missed cases have been reported. The potential harm of false negative with second-tier psychosine testing is low. One case of infantile Krabbe disease with non-elevated psychosine concentration has been described; however, although this case also had pathogenic *GALC* variants, it is possible that this infant had a secondary condition.
- Treatment with HSCT when it is not required would be a harm. Using current diagnostic approaches (i.e., low GALC enzyme activity and elevated psychosine, known pathogenic *GALC* variants, complete neurological evaluation), the risk of HSCT being performed for Krabbe disease when it is not indicated is assumed to be low.
- Krabbe disease newborn screening could lead to HSCT in centers with less experience than the small number of treatment centers that provide most of the outcome data included in this report, potentially leading to worse outcomes.
- Infants at risk for late onset Krabbe disease can require long-term clinical follow-up. Little is known about the impact of this follow-up on families.

3. ESTIMATED POPULATION IMPACT OF KRABBE DISEASE NEWBORN SCREENING

This component of the report addresses the question, "What would be the impact at the population level of Krabbe disease newborn screening if adopted by all newborn screening programs in the US compared to clinical case detection in the absence of Krabbe disease newborn screening?"

Overview

In April 2011, an Evidence Evaluation and Methods Workgroup met to consider the methods and used by the external Evidence-based Review Group (ERG) for the Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC). One of the recommendations from this group was to incorporate the application of decision analysis into the evidence review process. An April 2012 publication coauthored by some of the workgroup members noted that a decision analytic model "could provide an estimate of the range of cases prevented, deaths prevented, and/or number of children requiring treatment, as well as other health outcomes, for universal screening compared to clinical ascertainment."[56] Since the recommendations were made, decision analytic modeling has been used as part of the evidence review process for hyperbilirubinemia, Pompe disease, mucopolysaccharidosis type I disease, X-linked adrenoleukodystrophy, spinal muscular atrophy, mucopolysaccharidosis type II disease, and guanidinoacetate methyltransferase deficiency. Krabbe disease is the eighth condition to incorporate decision analytic modeling into the evidence review process.

Objectives of Decision Analysis

Decision analysis is a systematic approach to decision making under conditions of uncertainty that has been applied to clinical and public health problems.[57] Decision analytic models can be used to simulate randomized clinical trials for new health interventions, to project beyond the clinical trial time frame, or to compare treatment protocols not directly compared in head-to-head trials. The decision analytic approach allows the decision maker to identify which alternative is expected to yield the most health benefit. It can also allow researchers to characterize the uncertainty associated with projections of clinical and economic outcomes over the long-term,[57] which is important given the lack of long-term outcomes data for most conditions considered for newborn screening.

A decision analytic model (or decision tree) defines the set of alternatives and short- and long-term outcomes associated with each alternative. In the application to screening for Krabbe disease, this approach was anticipated to aid in the estimation of the range of screening outcomes that could be expected for universal newborn screening of Krabbe disease compared with clinical identification.

Applying Decision Analysis to Krabbe Disease Newborn Screening

Published literature for rare disorders such as Krabbe disease is limited with respect to data for prevalence, natural history, and response to treatment. For this review, we used data from state newborn screening programs together with published and unpublished data. Through modeling,

we aim to supplement the evidence base identified through the evidence review by providing projections of key screening outcomes at the population level for newborn screening compared with clinical identification. This approach focused on the condition as nominated (i.e., Krabbe disease with expected onset of signs and symptoms by 36 months of life).

Expert Panel Input

Clinical and scientific experts in the screening and treatment of Krabbe disease were identified and invited to serve on the Technical Expert Panel (see Table 1). TEP members were asked to provide input on the design and assumptions of the decision analysis model. A series of three TEP meetings (see Table 6) were conducted to identify sources for input probabilities for each outcome in the model; to provide feedback on the structure of the initial and revised decision analytic models, including the relevant timeframe for key outcomes; and to develop assumptions where little or no data were available. All meetings were conducted via webinar.

Table 6. Timeline of Decision Analytic Modeling for Krabbe Disease Screening

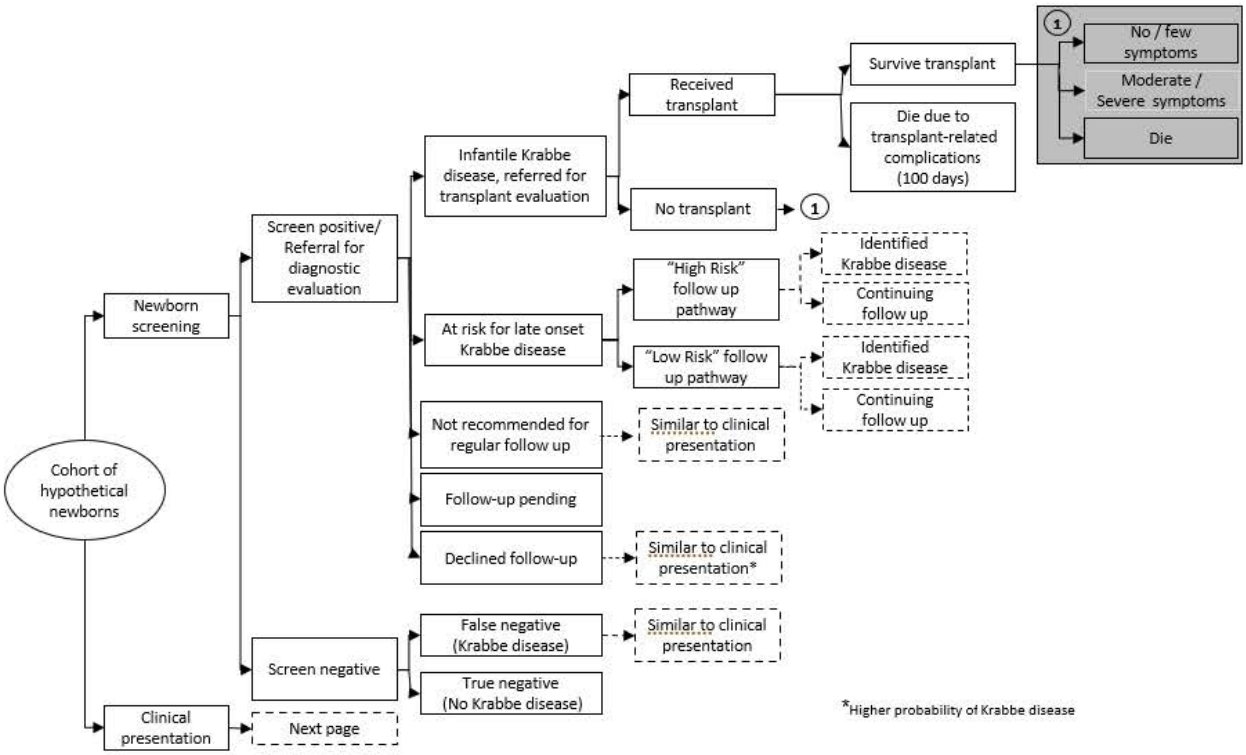
Date	Milestone
May 2022	Krabbe disease nominated for addition to uniform newborn screening panel; referred to external ERG
August 2022	TEP meeting #1
August 2022	Initial development of decision analytic model to evaluate newborn screening for Krabbe disease
September 2022	TEP meeting #2 – review model structure and preliminary evidence review summary
January 2023	TEP meeting #3 – review revised model structure and input assumptions
February 2023	Final Krabbe disease evidence review report and decision analysis findings presented to ACHDNC

Methods

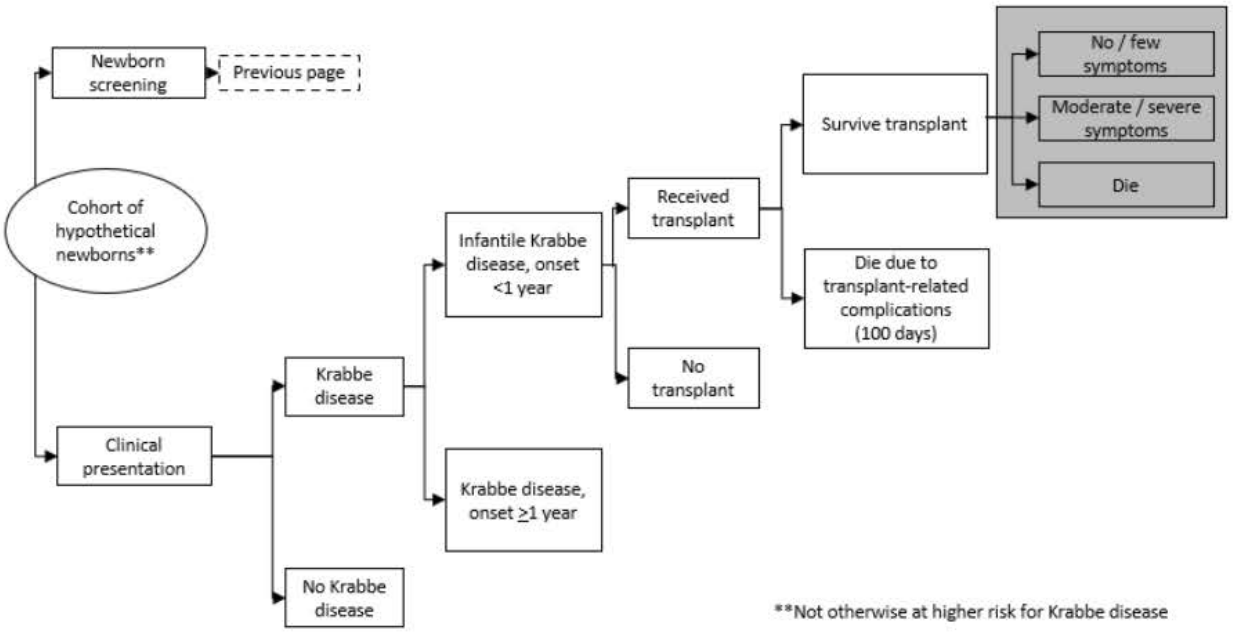
An initial decision analysis model was developed concurrently with the evidence review process. The initial model structure was reviewed with the expert panel in September 2022. A schematic of the final Krabbe disease newborn screening decision model is shown in Figure 1.

Figure 1. Model Schematic

a. Newborn screening



b. **Clinical presentation**



Key Assumptions

The scope of the modeling analysis is as follows. The target population reflect the annual newborn cohort for the US (i.e., 3.65 million newborns) not otherwise at known to be at high risk for Krabbe disease. Strategies included in the model were universal newborn screening for Krabbe disease compared with diagnosis of 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 number of positive screens, number of confirmed cases of Krabbe disease, number of cases at risk for Krabbe disease, and number of false positives. Clinical presentation outcomes include the number of cases of Krabbe disease identified <1 year of age and the number identified ≥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. The model structure and parameter estimates were revised following each TEP meeting based on additional data sources identified and supplemented by expert opinion in cases where no data were available.

Overall approach

The model estimates outcomes for two identical cohorts of newborns for Krabbe disease, one cohort that receives newborn screening for 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 based on data from the state newborn screening programs with some adjustments. Since individual state newborn screening programs use different algorithms for determining which newborns are referred for diagnostic follow-up, we adjusted to reflect a referral protocol based on low GALC enzyme activity and elevated psychosine levels, consistent with the screening protocol used by Kentucky and Georgia. Tennessee and Missouri will make referrals based on GALC enzyme activity even if the psychosine level is not elevated. For these two states, data were adjusted to exclude newborns with non-elevated psychosine levels from the referrals. We also excluded referrals from other state newborn screening programs for low GALC enzyme activity and *GALC* molecular analysis alone. Ranges for the parameter inputs were derived assuming a binomial distribution (Tables 7 and 8).

Probabilities related to the cases of Krabbe disease identified through screening, including the phenotype (expected signs and symptoms <1 year vs. ≥1 year), 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 8). State reported data may have some misclassification. For example, the 2 cases classified as <1 year were described in another report as being ≥1 year. Relevant probabilities for the clinical presentation cohort were derived from the literature and expert assumption (Table 9 and 10).

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.

Table 7. Adjusted state newborn screening data

	NY‡	MO*	KY	TN*	IL†	IN‡	PA†	GA
Infants screened	985,726	168,042	330,555	421,481	98,721	172,803	167,537	144,000
Referred	27	3	2	3	4	7	4	1
Infantile Krabbe disease	2	1	2	1	0	0	3	1
At risk for Krabbe disease	25	2	0	2	2	4	1	0
Normal	0	0	0	0	0	3	0	0
Pending diagnosis	0	0	0	0	2§	0	0	0

*States referring based on GALC alone. Adjusted to exclude newborns with low GALC and normal psychosine levels from referrals.

† States are including carriers in their total number of referrals. Adjusted to exclude carriers from referrals

‡ States are currently referring based on GALC alone and including carriers in the total number of referrals. Adjusted to exclude newborns with low GALC and normal psychosine and carriers from referrals

§ Pending diagnoses not included in the model projections

Table 8. Newborn screening parameters

Parameter	Most likely value	Range	Source
Screen positive/referral for diagnostic evaluation	2.05 per 100,000	1.53 – 2.69 per 100,000	Primary data from state newborn screening programs*
Infantile Krabbe disease/referral for diagnostic evaluation given positive screen	0.20 (0.42 per 100,000)*	0.10 – 0.34	
At risk for late onset Krabbe disease given positive screen	0.73 (1.5 per 100,000)*	0.59 – 0.85	
High risk follow up	0.40 (0.60 per 100,000)*	0.21 – 0.61	Primary data from New York newborn screening program
Low risk follow up	0.60 (0.90 per 100,000)*	0.39 – 0.79	
Not recommended for regular follow up given positive screen	0.06 (0.13 per 100,000)*	0.01 – 0.17	Primary data from state newborn screening programs*
Negative screen			
True negative	1	0.9999986 - 1	
False negative	0	0 – 0.0000014	
Identified with early infantile Krabbe disease			
Received HSCT	0.88	0.62 – 0.98	[34,47]; state newborn screening data
No HSCT	0.13	0.02 – 0.38	
Received HSCT			
Survive HSCT	0.89	0.67 – 0.99	[53]
Died due to HSCT-related complications within 100 days	0.11	0.01 – 0.33	
Survival at 30 months			
HSCT	1	0.59 – 1	[34,47]
No HSCT	0.23	0.14 – 0.35	[58]

*Incidence at the population level as an alternative representation of this value

Table 9. Clinical presentation parameter inputs

Description	**Most Likely**	Range **(min-max)**	**Source**
Krabbe disease	1.1 per 100,000	0.76 – 1.6 per 100,000	[2]
Infantile Krabbe disease, <1 year	0.47	0.40 – 0.53	[3]
Krabbe disease, ≥1 year	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	[53]
Died due to HSCT-related complications within 100 days	0.11	0.01 – 0.33	
Survival at 30 months			
Survival given infant has received HSCT	1	0.59 - 1	[34,47]
Die given infant has received HSCT	0	0 – 0.41	
Survival given infant has not received HSCT	0.23	0.14 – 0.35	[58]
Die given infant has not received HSCT	0.77	0.65 – 0.86	

Results

Under a policy of Krabbe disease newborn screening, 74.8 infants (range: 55.8 – 98.2) are estimated for referral for diagnostic testing due to a positive screen annually assuming an annual newborn cohort of 3.65 million newborns. Of these, 15.3 infants (range: 5.8 – 28.1) are projected to be identified with likely infantile Krabbe disease with expected onset <1 year (Table 10a) and referred for HSCT of whom 13.4 (range: 3.6 – 27.7) would be expected to receive HCST and 2 (range: 0 – 2) would not receive HSCT (either due to ineligibility based on disease status or declined by family). Of those infants receiving HSCT, 1.9 (range: 0.4 -2.2) would be expected to die from complications within 100 days of transplant. By 30 months of age, 12.4 infants would be alive and 2.9 (range: 2.3 – 3.2) would be expected to have died (1.4 from HSCT and 1.5 from Krabbe disease). (Table 10c)

An additional 54.9 screened infants (range: 33.1 – 70.1) would be identified as at risk for later onset Krabbe disease (i.e., onset ≥1 year), of whom 22.0 (range: 13.2 – 28.0) would be recommended for a high-risk follow-up pathway and 33 (range: 20 - 42) would be recommended

for a low risk follow up pathway. The remaining 4.6 infants (range: 0.0 -17.0) would not be recommended for regular follow up (Table 10a).

Under a policy of clinical presentation in the absence of newborn screening, 40.2 infants (range 27.7–58.8) would be identified with Krabbe disease. Of these, 18.8 (range: 11.2–31.3) would be expected to present with symptoms in the first year of life and 21.4 (range: 16.5–27.5) would be expected to present later (Table 10b). 1.9 clinically identified infants (range: 0.0–6.3) would be expected to receive HSCT. By 30 months of age, 13.2 (range 9.6-17.0) would be expected to have died either from HSCT complications or Krabbe disease progression (Table 10c).

This model finds that the expected number of cases of Krabbe detected with newborn screening annually among the 3.65 million infants born in the United States (about 1.02 per 100,000) is similar to what would happen with clinical presentation only (about 1.1 per 100,000). Differences in timing of identification leads to the expected differences in outcomes.

Table 10. Projected outcomes for an annual cohort of 3.65 million newborns

a. With Krabbe disease newborn screening

	Most Likely Number of Cases (range)
Screen positive/ referral for diagnostic evaluation given positive screen	74.8 (55.8 – 98.2)
Infantile Krabbe disease/referral for diagnostic evaluation given positive screen	15.3 (5.8 – 28.1)
At risk for late onset Krabbe disease	54.9 (33.1 – 70.1)
High risk follow up	22.0 (13.2 – 28.0)
Low risk follow up	33.0 (19.8 – 42.0)
Not recommended for regular follow up	4.6 (0 – 17.0)
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	40.2 (27.7 – 58.8)
<1 year	18.8 (11.2 – 31.3)
≥1 year	21.4 (16.5 – 27.5)

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	13.4 (3.6 – 27.7)	1.9 (0 – 6.3)	11.5 (3.6 – 21.4)
Died from complications of HSCT	1.4 (0.4 – 2.9)	0.2 (0- 0.7)	1.2 (0.4 – 2.2)
Survive HSCT	12.0 (3.2 – 24.8)	1.7 (0 – 5.6)	10.3 (3.2 – 19.2)
Did not receive HSCT by1 year	1.9 (0.4 - 2.2)	16.9 (11.2 - 25.0)	-15 (-22.8 – -10.8)
Died from Krabbe disease by 30 months	1.5 (0.3 – 1.9)	13.0 (9.6 – 16.3)	-11.5 (-14.4 – -9.3)
Total who died by age 30 months	2.9 (2.3 – 3.2)	13.2 (9.6 – 17.0)	-10.3 (-13.8 – -7.3)

Table 11. Projected cases of Krabbe disease, comparing newborn screening with clinical identification

	Most Likely	Range
Newborn screening		
Krabbe disease referred for HSCT in newborn period	15.3	5.8 - 28.1
At risk for Krabbe disease – High Risk	22.0	13.2 - 28.0
Total	37.3	19.0 - 56.1
Clinical presentation		
<1 year	18.8	11.2 - 31.3
≥1 year	21.4	16.5 - 27.5
Total	40.2	27.7 - 58.8

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 Krabbe disease newborn screening, this analysis predicts that 15.3 (range: 5.8 – 28.1) infants annually would be referred for evaluation for HSCT. Of these, 13.4 (range: 3.6 – 27.7) infants would receive HSCT. Of the infants who received HSCT, 1.4 (range: 0.4–2.9) would die from complications of HSCT within 100 days and all others would be alive at 2.5 years. An additional 22.0 (range: 13.2 – 28.0) infants would be identified at high risk for Krabbe disease and require close clinical follow-up.

Without universal Krabbe disease newborn screening, relying on clinical presentation, 18.8 (range: 11.2 – 31.3) infants would present before age 1 year, of whom 1.9 (range: 0 – 6.3) would be eligible for and receive HSCT. Of the remaining 16.9, 13.0 (range: 9.6 – 16.3) infants would be expected to die from Krabbe disease by age 2.5 years.

4. ASSESSMENT OF THE PUBLIC HEALTH IMPACT OF KRABBE DISEASE NEWBORN SCREENING

A recent report described that Virginia chose not to implement Krabbe disease newborn screening primarily because Krabbe disease is not included on the RUSP, concerns about risk prediction, and concerns about providing HSCT by 30 days after birth (e.g., lack of HSCT centers in Virginia, difficulty with obtaining Medicaid approval for out-of-state HSCT).[59] The focus on the need to provide HSCT by 30 days is more restrictive than the 6 weeks currently recommended by experts. Ten other state newborn screening programs have implemented Krabbe disease newborn screening. The process and reported outcomes of screening from these ten programs is described in Section 3.

In partnership with the ERG, the Association of Public Health Laboratories (APHL) evaluated state newborn screening programs' ability to screen for Krabbe disease, including readiness and feasibility. Readiness refers to the ability to adopt Krabbe disease NBS onto the program's existing panel and is classified as ready (could implement within one year), developmentally ready (could implement within 1 to 3 years), and unprepared (would take more than 3 years). Feasibility is based on the degree to which there is an established and available screening test, a clear approach to diagnostic confirmation, an acceptable treatment plan, and an established approach to long-term follow-up.

The public health system impact assessment focuses on the activities involved and time it takes to implement Krabbe disease newborn screening. This evaluation does not consider other factors that may be involved prior to implementing a disorder. Examples of these other factors include, but are not limited to, getting funds to screen, obtaining a legislative agreement, or procuring new technology for screening. These pre-implementation activities can add several years to the process. NBS programs vary with regards to their activities and requirements to add new conditions.

Methods

Survey of Programs Not Screening for Krabbe Disease

APHL conducted a survey of newborn screening programs that did not screen all newborns for Krabbe disease. APHL developed a fact sheet prepared before evidence review and based on expert opinion solicited by APHL (see Appendix C) to provide baseline knowledge about Krabbe disease newborn screening. APHL hosted a webinar in October 2022 to discuss Krabbe disease and prepare respondents for the survey. The screening outcomes included on the factsheet were what was known at the time of the webinar. Programs provided subsequent updates that were included elsewhere in this report.

A web-based survey approved by the Office of Management and Budget, designed to assess readiness and feasibility of implementing Krabbe disease newborn screening (see Appendix C) was administered to the 53 US public health programs via email from October 20, 2022, to December 12, 2022. The survey focused on activities directly related to public health programs and not personal medical care services. The email with the survey link emphasized the importance of working collaboratively with stakeholders in the state (e.g., laboratory experts, follow-up staff, medical specialists, Title V directors, advocates, public health commissioners) to

complete the survey. All survey results were submitted directly to APHL for analysis. In December, reminders were sent to survey non-respondents.

Interviews of Programs with Krabbe Disease Newborn Screening

APHL interviewed representatives from 7 of the 10 newborn screening programs (Indiana, Kentucky, New Jersey, New York, Ohio, Pennsylvania, Tennessee) that include Krabbe Disease newborn screening. These interviews gathered information regarding state implementation processes, algorithms and methods, follow-up and confirmatory protocols, and challenges and facilitators to screening for Krabbe Disease (see Appendix C).

Summary of Survey Results

The full summary of survey appears in Appendix C.

Overall, 34 of the 44 programs that do not include Krabbe disease newborn screening (77%) responded to the survey. Overall, 36% reported that it would take less than 2 years to implement Krabbe disease newborn screening if it were recommended, 47% reported that it would take 2 to 3 years, 12% that it would take 3 to 4 years and 3% that it would take more than 4 years.

Major barriers to implementing Krabbe disease newborn screening included:

- Availability of timely treatment: 62%
- Other ongoing newborn screening program activities: 62%
- Increasing the newborn screening fee: 47%
- Availability of GALC enzyme activity testing: 47%
- Availability of specialists for the diagnostic evaluation: 41%
- Expected clinical outcomes following newborn screening: 41%
- Administrative challenges: 38%
- Availability of second-tier testing: 24%
- Availability of staff for short-term follow-up: 21%

Major facilitators of implementing Krabbe disease newborn screening included:

- Advocacy activities: 27%
- The ability to multiplex screening: 27%
- Expected clinical outcomes: 21%

Availability of Treatment Centers

The public health system impact assessment survey cannot evaluate the availability of centers with experience in HSCT for Krabbe disease. There are currently 12 centers in the Leukodystrophy Care Network. According to the TEP, these centers are willing to share their expertise with other centers that provide HSCT. Those newborn screening programs that implement Krabbe disease newborn screening will need to develop partnerships with treatment centers. This might include referral out-of-state, which can be a challenge for payment and a travel burden for families.

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APPENDIX A: EVIDENCE REVIEW TECHNICAL METHODS

Literature Search

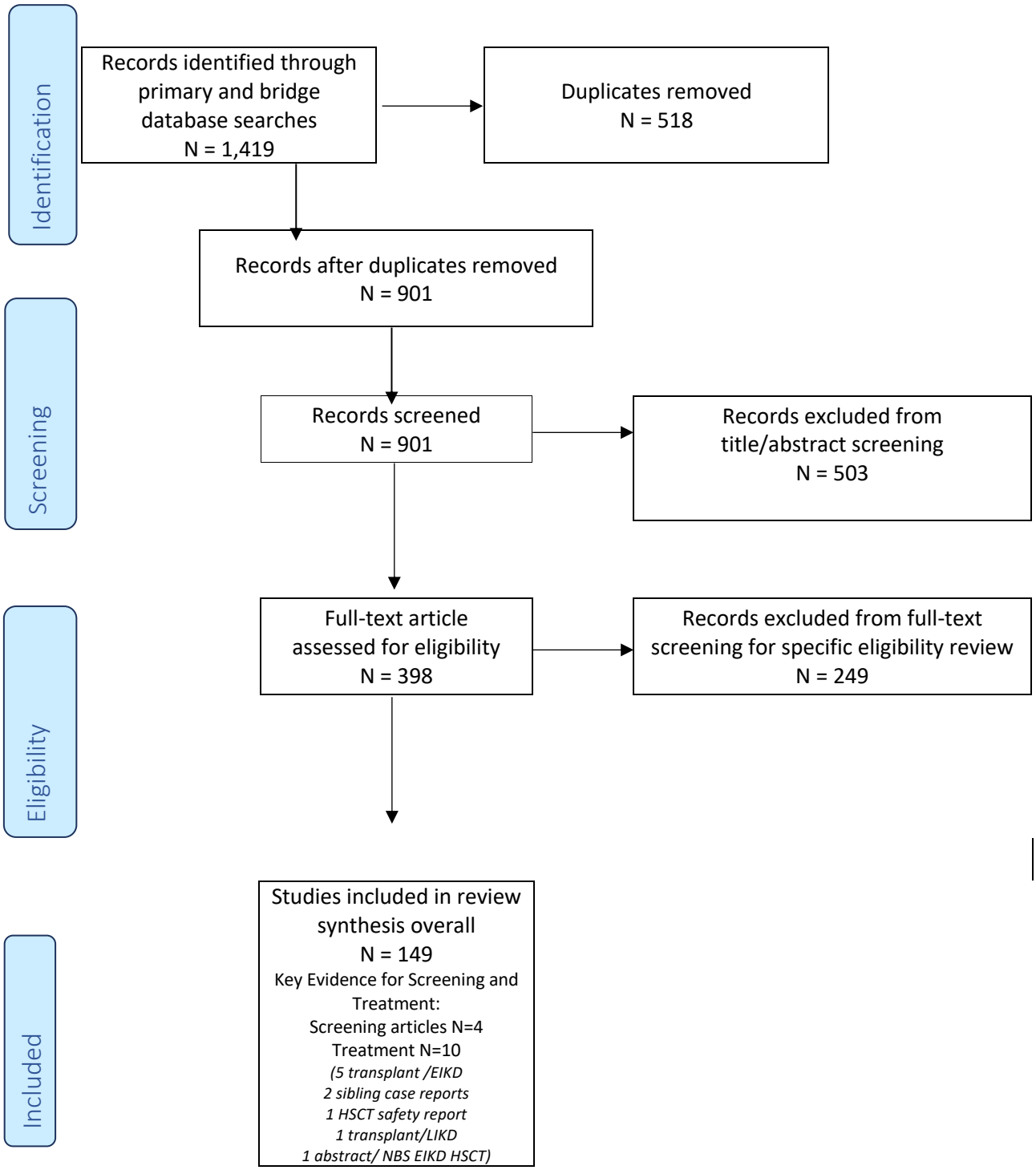
The following table lists the search terms for each of the four databases that were queried to identify articles for the systematic evidence review. The initial literature search was conducted for references published from January 1, 2010, to July 1, 2022, and a bridge search was conducted to update the references with publications from July 1, 2022, through January 10, 2023 (publications through January 10, 2023).

Table 12. Summary of initial literature search results by database for Krabbe disease search terms, and number of articles identified from primary literature search (1/1/2010 – 7/1/2022) and bridge search (7/1/2022 – 1/10/2023)

Database	Search Terms	Primary search (1/1/10-7/1/22) (# articles identified)	Bridge search (7/1/22-1/10/23) (# articles identified)
PubMED	("Leukodystrophy, Globoid Cell"[Mesh] OR "Globoid Cell Leukodystrophy"[tw] OR "krabbe disease"[tw] OR "krabbe's disease"[tw]) Filters: English, Humans, 2010-present	347	35
CINAHL	(MH "Leukodystrophy, Globoid Cell") OR "globoid cell leukodystrophy" OR "krabbe disease" OR "krabbe's disease" Limiters: English, Humans, Publication Date: 01/01/2010 to present Expanders - Apply equivalent subjects Search modes - Find all my search terms	20	6
EMBASE	(‘'globoid cell leukodystrophy'/exp OR "Globoid Cell Leukodystrophy" OR "krabbe disease" OR "krabbe's disease") AND Limiters English, Humans, 2010-present)	943	64
Cochrane	(MeSH descriptor: [Leukodystrophy, Globoid Cell] explode all trees) OR ("krabbe disease" OR "krabbe's disease" OR "globoid cell leukodystrophy"):ti,ab,kw with Publication Year from 2010 to present, with Cochrane Library publication date Jan 2010 to present, in Trials	4	0
All databases	**---**	**1,314**	**105**
All databases and search periods	**Total results = 1314 + 105**	**1,419**	

The figure below describes the process leading to the articles included in this review, following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[1]

Figure 2. Identification of Studies Via Screening and Review



Quality Assessment of Screening and Treatment Reports

Following the methods for developing reports for the ACHDNC, the risk of bias was assessed for published reports of Krabbe disease newborn screening in the United States and for published reports of early treatment of infantile Krabbe disease.

Screening Studies

Risk of bias was assessed related to newborn selection, standard use of a screening test, standard application of a reference standard, and the appropriate flow and timing of screening. The following studies met the criteria for risk of bias assessment:

Table 13. Risk of Bias Ratings: Screening Studies

		Patient Selection		Newborn Screening Test		
Reference	**Global publication rating**	**Risk of Bias**	**Applicability**	**Conduct and Interpretation of Test**	**Reference Standard**	**Flow and Timing**
Orsini 2016[2]	Low Risk	Low	Low Risk	Low Risk	Low Risk	Low Risk
Orsini 2016[3]	Low Risk	Low	Low Risk	Low Risk	Low Risk	Low Risk
Minter Baerg 2018[4]	Low Risk	Low	Low Risk	Low Risk	Unclear	Low Risk
Basheeruddin 2021[5]	Low Risk	Low	Low Risk	Low Risk	Unclear	Low Risk

All of the screening studies were considered to have a low risk of bias. For two of the studies, the specific reference standard for diagnosing Krabbe disease was unclear, but enough information was provided to suggest that the overall impact on bias in the reports is low.

Treatment Studies

No treatment study met the criteria for formal risk-of-bias assessment. The treatment studies were based on case series and case reports (siblings), which have significant risk of bias related to selective identification, measurement bias because assessment is often not blinded and the lack of pre-specified standard outcome measures, and confounding bias because of the many factors related to treatment and outcomes that were often not reported (e.g., gestational age, psychosine concentration, method of identification).

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APPENDIX B: *GALC* VARIANTS CLASSIFIED BY THE NEW YORK NEWBORN SCREENING PROGRAM

The New York newborn screening program has categorized variants based on whether they are expected to be pathogenic but without respect to expected phenotypic severity (Table 3) . Note that variant nomenclature has changed over time and there are different approaches to describing these specific variants because of changes in the coding DNA reference. For this report, coding DNA reference nomenclature is described and, when possible, the interpretation reported in specific studies is provided. Throughout this report variants from published and unpublished studies are listed as described in the studies, along with any interpretation of the variant provided by the authors. Please note that any variants described in this report should not be used to guide health care delivery. For clinical application, it would be prudent for variants to be interpreted in accordance with Standards and Guidelines for the interpretation of sequence variants as recommended by the American College of Medical Genetics and Genomics and making use of reliable resources such as the Genome Aggregation Database and the National Library of Medicine ClinVar data archive.

Table 14. Classification of variants from the New York newborn screening program

Pathogenic	Likely Pathogenic	Variant of Uncertain Significance	Likely Benign	Benign	Pseudodeficiency
c.1901T>C	c.1851del	c.2041G>A	c.-80_-75del	c.1921G>A	c.1685T>C
c.1712dup	c.1700A>C	c.1418G>A		c.1834+5G>C	c.742G>A
c.1586C>T	c.1450C>T	c.1174T>C		c.1698T>A	c.550C>T
c.1472del	c.868C>T	c.973A>G		c.1620G>A	
c.1158_1161+6del	c.2036_2040delTTCTT	c.956A>G		c.1350C>T	
c.908+1G>A	c.560A>T	c.334A>G		c.1162-4del	
c.857G>A		c.266C>T		c.1072C>T	
c.658C>T		c.206G>A		c.984G>A	
c.628A>T		c.1861C>T		c.397T>C	
c.583-1G>C		c.442+5G>A		c.96G>T	
c.388G>A		c.680A>G		c.75C>A	
c.379C>T				c.61G>C	
c.349A>G				c.42G>C	
c.328+1G>T					
c.195G>C					
del30kb					

APPENDIX C: PUBLIC HEALTH SYSTEM IMPACT ASSESSMENT

This appendix provides the fact sheet developed by APHL to provide baseline information to state newborn screening programs about Krabbe disease newborn screening, the web-based survey, and a detailed assessment of survey responses. Please refer to the main report for an overview of the process and a synthesis of the key findings.

Survey Results

Overall, 34 of 44 newborn screening programs (77%) that do not include Krabbe disease screening responded to the survey. Among the survey respondents, 20 were from the public health or newborn screening laboratory, nine from programs that contract newborn screening laboratory services regionally, three came from laboratory where there was a state university laboratory for which there is an intra-state agency agreement, one from a program that contracts newborn screening laboratory services commercially, and one had an "other" designation.

Figure 3. Reported Barriers to Krabbe Disease Newborn Screening (n = 34)

Potential Barriers to Krabbe Disease Newborn Screening	Not a Challenge	Minor Challenge	Major Challenge
Availability of timely treatment for infants born in your state with Krabbe Disease	3%	35%	62%
Increasing your NBS fee	15%	38%	47%
Availability of first-tier validated screening test	35%	18%	47%
Identifying specialists in your state who are confident in the diagnostic evaluation of Krabbe Disease	38%	21%	41%
Addressing administrative challenges	18%	44%	38%
Availability of second-tier validated screening test	21%	56%	24%
Availability of staff to report and track infants with out-of-range results through to diagnosis or resolution	21%	59%	21%

Forty-five percent of the newborn screening program respondents reported not being able to conduct second-tier psychosine testing for Krabbe Disease within one year. Additionally, NBS programs noted difficulties getting LIMS capacity within a year, as well as treatment centers for expected Krabbe Disease caseload. NBS programs that conduct their own screening, were less concerned with getting specialists, as well as laboratory expertise for Krabbe Disease screening. For the 14 NBS programs that contract services, 50%-79% indicated that in one year, they would not have treatment centers for expected Krabbe Disease caseload, specialists and genetic counselors, and the availability of a first-tier screening test with the contracted entity [

Figure 4. Resources Needed for Own State's Public Health or NBS Laboratory (n = 20) and Figure 5. Resources Needed for Contracted or State University Laboratories with Intrastate Agreement (n = 14)].

Figure 4. Resources Needed for Own State's Public Health or NBS Laboratory (n = 20)

Resources for Krabbe disease Newborn Screening – State Public Health or NBS Laboratory	**Have Already**	**Don't have but can get within 1 year**	**Cannot get within 1 year**
Second-tier psychosine screening for Krabbe Disease	5%	50%	45%
LIMS capacity and instrumentation interface	10%	50%	40%
Treatment centers for expected Krabbe Disease caseload	35%	25%	40%
First-tier screening method for Krabbe Disease	30%	35%	35%
Genetic counselors to cover expected caseload	45%	20%	35%
Sufficient number of technical staff to screen for Krabbe Disease	20%	50%	30%
Sufficient number of NBS staff to notify and track NBS results	25%	55%	20%
Laboratory technical expertise to screen for Krabbe Disease	55%	25%	20%
Specialists to cover expected Krbbe Disease caseload	55%	25%	20%
Follow-up protocols for Krabbe Disease	0%	85%	15%
Access to appropriate diagnostic services after an abnormal or out-of-range screening result is reported	50%	35%	15%

Figure 5. Resources Needed for Contracted or State University Laboratories with Intrastate Agreement (n = 14)

Resources for Krabbe Disease Newborn Screening – Outside Contracted Laboratory Agreements	Have Already	Do not have but can get within 1 year	Cannot get within one year
Treatment centers for expected Krabbe Disease caseload	7%	14%	79%
Specialists to cover expected Krabbe Disease caseload	14%	21%	64%
Genetic counselors to cover expected Krabbe Disease caseload	14%	36%	50%
Availability of the first-tier screening test with contracted entitity	29%	21%	50%
Availability of the secont-tier screening test at a contracted laboratory	21%	43%	36%
Follow-up protocols for Krabbe Disease	14%	57%	29%
Sufficient number of NBS staff to notify and track NBS results	29%	43%	29%
Access to appropriate diagnostic services after an abnormal result is reported	36%	36%	29%
LIMS capacity and instrumentation interface	14%	71%	14%

Approximately 74% of respondents stated that they would perform first-tier GALC activity followed by second-tier psychosine, 12%, were unsure, 9% selected “other” and 6% planned to conduct GALC enzyme screening only. Please see Figure 6. Second-Tier Screening for Krabbe Disease (n = 34) for more details. Among those that planned to include psychosine as part of their algorithm, 64% planned to contract this testing to an outside laboratory, 20% were unsure, and 16% planned to perform psychosine testing in-house. The majority of respondents (59%) were unsure whether they would conduct molecular testing for Krabbe Disease; 29% stated they would not; 12% indicated they would include it.

Figure 6. Second-Tier Screening for Krabbe Disease (n = 34)

Possible Second-Tier Screening for Krabbe Disease	NBS programs reporting potential second-tier screening activities (%)
First-tier GALC followed by second-tier psychosine	74%
First-tier GALC enzyme only	6%
Unsure	12%
Other	9%

Figure 7. Molecular Testing for Krabbe Disease (n = 34)

Potential use of molecular testing for Krabbe disease	NBS programs reporting potential use of molecular testing in Krabbe disease screening (%)
Yes	12%
No	29%
Unsure	59%

Most newborn screening programs reported the following facilitators for screening: existing advocacy and the ability to multiplex testing with other lysosomal storage disorders. Eighty-nine percent of NBS programs stated that other NBS activities were a major or minor barrier to adding Krabbe Disease. Although it was not a focus of this report, many programs have indicated that they cannot add this condition until they begin screening for other conditions that have been added on the RUSP. Other frequently cited barriers included expected cost per specimen for screening and predicted run time for screening. Barriers and facilitators are summarized in Figure 8. Barriers and Facilitators for Krabbe Disease (n = 34).

Figure 8. Barriers and Facilitators for Krabbe Disease (n = 34)

Possible Barriers and Facilitators for Krabbe disease	Not Applicable	Major Barrier	Minor Barrier	Minor Facilitator	Major Facilitator	Major + Minor
Predicted run time to screen for Krabbe Disease as it relates to other workload	24%	24%	44%	3%	6%	9%
Other ongoing NBS program activities	3%	62%	27%	6%	3%	9%
Estimated cost of treatment for newborns diagnosed with Krabbe Disease	27%	53%	12%	3%	6%	9%
Estimated cost per specimen to conduct screening	12%	29%	47%	6%	6%	12%
Other non-NBS public health priorities within your state	29%	12%	47%	9%	3%	12%
Expected cost-benefit of screening in your state	24%	38%	15%	15%	9%	24%
Expected clinical outcomees of newborns identified by screening	9%	41%	15%	15%	21%	36%
Extent to which the screening test for Krabbe Disease can be multiplexed	9%	15%	15%	35%	27%	62%
Advocacy for screening for Krabbe Disease	18%	6%	12%	38%	27%	65%

Among open-ended responses, the most significant barriers to screening include concerns with the effectiveness of treatment, timely treatment, as well as obtaining funding and staff/resources for screening. The most significant facilitator for adding Krabbe Disease is better treatment options that lead to improved outcomes. Other facilitators that were frequently cited included the addition of the disorder on the RUSP, funding/fee increases, and an effective screening test.

Nearly half of the newborn screening programs not currently screening reported that it would take 2 to 3 years to implement Krabbe Disease newborn screening. Thirty-eight percent reported being able to implement faster than 2 years and 15% reported implementing slower than 3 years. Please see Figure 9. Estimated Time it Would Take to Implement Krabbe Disease Screening in Your State (n=34) for additional details. The majority of respondents indicated that it would take more than a year (in tandem) to complete each of the following activities: obtain authorization to screen, get funds available, hire staff, select and validate the test, develop protocols, and set up their LIMS.

Figure 9. Estimated Time it Would Take to Implement Krabbe Disease Screening in Your State (n=34)

Possible time to implement Krabbe disease screening	Time estimated by NBS programs (%)
12 months or less	9%
13 to 24 months	29%
25 to 36 months	47%
37 to 48 months	12%
More than 48 months	3%

Readiness

Approximately half of NBS programs not currently screening reported that it would take between 2 and 3 years to implement Krabbe Disease which would make them developmentally ready for implementation. Readiness varies greatly across the country, with 38% percent reporting being able to implement faster than 2 years and 15% reported implementing slower than 3 years.

Feasibility

Krabbe disease newborn screening can be multiplexed with other LSDs when using MS/MS; however, the up to 18-hour incubation time is a challenge, and has resulted in at least one NBS program extending its work week. The introduction of psychosine has substantially reduced false postives and uncessary referrals. The NBS programs screening contract psychosine testing to improve timeliness and efficiency. Six out of the 10 programs screening include a molecular component (30 kb deletion and/or sequencing) to their algorithms which assists with making timely referrals. This service is generally contracted to an outside laboratory and performed simultaneous with psychosine. Sixty-percent of NBS programs that are not screening were unsure whether they would conduct molecular testing. More guidance is needed in this area. Additionally, laboratory information systems will likely need to be updated with the addition of Krabbe Disease.

Limitations

Information from the surveys is hypothetical and subjective, however, it was counterbalanced by some of the real-world experience gathered from the ten states currently screening for Krabbe Disease.

Fact Sheet

Public Health Impact Assessment Fact Sheet for Krabbe Disease Newborn Screening

This fact sheet provides newborn screening programs with background information on Krabbe Disease (KD) so they can complete a public health impact assessment survey that evaluates their program's readiness and feasibility to add Krabbe Disease onto their newborn screening panels. The factsheet discusses background information pertaining to the condition, screening methods, resources/materials, personnel requirements, screening results, costs, short-term follow up, and treatment for Krabbe Disease. Contact Jelili Ojodu (jelili.ojodu@aphl.org) for more information.

Condition	Krabbe Disease
Description	Krabbe disease (KD) is an autosomal recessive disorder caused by mutations in the *GALC* gene. It is considered a lysosomal storage disorder and leukodystrophy. KD is characterized by a deficiency in the lysosomal enzyme glactocerebrosidase (GALC) which is necessary for myelin turnover. Low GALC enzyme activity can lead to elevated psychosine levels, which is toxic to cells. Some infants develop KD in the first few years of life, known as infantile KD. Newborn screening can lead to earlier hematopoietic stem cell transplant, which can extend life and improve other outcomes. Without screening, infantile KD typically presents in the first year of life with irritability, feeding difficulties, seizures, and progressive spasticity. Infantile KD can progress quickly, with progressive neurologic decline leading to death.
Expected Incidence	Based on clinical detection, about 1/100,000 live births have infantile KD.

First-Tier Screening Methods	
Screening Strategy and Markers	The first-tier screen is to measure GALC enzyme activity using either tandem mass spectrometry (MS/MS) or fluorometry. Both tests have been multiplexed with other lysosomal storage disorders.

Second-Tier Screening Methods	
Screening Strategy and Markers	Psychosine concentrations in dried-blood spots can be measured as a second-tier test to reduce false-positive results and assist with assessing risk (e.g., > 10 nmol/L high-risk for infantile KD, 2-10 nmol/L "at risk" for late onset KD and need for follow-up). Psychosine concentration can be measured in-house or by a contracted laboratory. This testing is offered by the Mayo Clinic, Nationwide Children's Hospital, and PerkinElmer. Some NBS programs also routinely conduct molecular testing after an initial positive screen. The supplemental information can be helpful for referrals and clinical follow-up, but is not necessary for screening.

Resources and Materials	
Minimum Instrumentation, Equipment and Requirements Necessary to Process 100,000 Specimens Annually	First-tier GALC enzyme activity screening MS/MS or fluorometry. Second-tier psychosine concentration testing in-house or as a send-out.
Equipment Suppliers and Availability of Kits, Reagents and Consumables	Reagents are available as an FDA approved kit from PerkinElmer for MS/MS. Some NBS programs originally used the analyte specific reagents from PerkinElmer and then converted to NeoLSD. Other NBS programs that rely on fluorometry use reagents from Baebies.

Workstation Resources and Capacity	
Instrument Time	NBS programs that screen for other LSDs can analyze results using existing instrumentation since the GALC enzyme activity is multiplexed.
Maximum Number of Specimens to Be Analyzed at One Workstation In A Day	NBS programs that screen for other LSDs can analyze the same number of samples that they currently analyze each day since the test is multiplexed.
Minimum Space Requirements	If a NBS program is screening for other LSDs, no additional space is required since this test can be multiplexed.

Personnel Requirements	
FTE Needed to Process 100,000 Specimens Annually	The laboratory may not require additional FTEs assuming that the assay is multiplexed with existing assays and incorporated into the workflow. Additional FTEs for follow-up may be minimal.

Other Considerations	
LIMs Adjustments	Variable (dependent on vendor). LIMs revisions for new conditions may require additional staff time and cost for initial set up.
Availability of Quality Control Materials	CDC has QC materials available.

Screening and Diagnostic Results Among Nine States Screening for KD After the Introduction of Psychosine to Some Algorithms [2016-2022]	
Rate of Referrals	With psychosine second-tier testing: 0.6-13.8 per 100,000 live births. *Some of the newborn screening programs refer based on GALC enzyme activity before second-tier test results are available, increasing referral rates.* Without psychosine second-tier testing: 28.8-54.0 per 100,000 live births.
Range of Infantile KD	0-1.8 per 100,000 live births
Range of Infants "At Risk" For Late-Onset KD	0-2.3 per 100,000 live births
Age At Hematopoietic Stem Cell Transplant (HSCT) for Infantile KD	Age to transplant collected for 8 babies identified with infantile KD from states using psychosine as second-tier test (n=5): 5 infants received HSCT between 24-36 days after birth, 2 between 101-150 days after birth, and the family of one infant elected not to have HSCT. *Transplants did not all occur in state where baby was identified.*

Estimated Costs from Two NBS Programs	
Estimated Total Program Costs	▪ Annually $430,000-$693,224 ▪ One-time costs $30,730
Estimated Cost of Equipment	▪ MS/MS: $582,874 ▪ Biotek fluorimeter provided through reagent rental ➢ Integra Viaflo = $20,450 ➢ Integra Viaflo maintenance agreement = $2,970 ➢ Ultra-low freezer = $9,650 ➢ Microplate shaker = $630
Estimated Cost of Consumables and Disposable Supplies	▪ MS/MS: $9,000/yr. ▪ Fluorometry: $34,000/yr
Estimated Cost of Reagents	▪ MS/MS: Included in reagent rental ▪ Fluorometry: $320,000/yr
Estimated 2nd Tier Testing Costs	▪ Avg 8.7 samples/month @ $60each +$60 shipping = $1041.82/month or $12,500/yr ▪ Avg. 10 samples/year @ $99each+$9.17 shipping= $1081/yr
Estimated Personnel Cost	▪ 0.73-1.0 FTE for Krabbe testing, labor cost (salary + fringe) = $53,000/yr -$57,000/yr ▪ 0.05-.17 FTE is used for Krabbe follow-up, labor cost = $3,000/yr-$17,852/yr
Other Cost Considerations for Implementation	▪ $5,000 - $10,000 per year in contracts with genetic specialty centers

*High range of cost estimate includes Krabbe Disease screening and 4 other LSDs.
*Costs estimates come from one state using MS/MS and another using fluorometry.

Short-Term Follow-Up	
Description	A clinician will perform KD confirmatory testing including measuring GALC enzyme activity and psychosine concentration in a new sample of blood, and additional neurologic testing. Molecular testing of the *GALC* gene will be done if not completed previously.
Case Definition	The case definition of early-onset Krabbe disease includes: GALC enzyme activity in peripheral blood leukocytes AND either ▪ 30-kb deletion in both alleles of the GALC ▪ Elevated psychosine level
Diagnostic Method & Criteria	Enzyme activity, psychosine level, mutations, neurodiagnostic/clinical abnormalities.

Current Treatment	
Description and Current Treatment Guidelines with Clinical Identification	Hematopoietic stem cell transplantation (HSCT) is recommended for infantile KD. Infants with the most severe form, early infantile KD, may require HSCT within 30 days after birth for best outcomes. Gene therapy trials are underway but not widely available. Some infants will be identified with KD that does not require HSCT before 3 years but does require frequent clinical follow-up. KD screening and clinical follow-up can also identify infants with Saposin A Deficiency, a very rare neurodegenerative lysosomal storage disorder that has similar laboratory findings and clinical presentation as KD.

Survey

Public Burden Statement: An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this project is 0906-0014. Public reporting burden for this collection of information is estimated to average 10 hours per response, including the time for reviewing instructions, searching existing data sources, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to HRSA Reports Clearance Officer, 5600 Fishers Lane, Room 10C-03I, Rockville, Maryland, 20857.

The purpose of this survey is to inform the Advisory Committee on Heritable Disorders in Newborns and Children (Committee) about states' ability to add newborn screening (NBS) for Krabbe Disease using information gathered from most of the state and territorial NBS programs in the U.S. Your input will provide valuable information and aid the deliberations of the Committee.

Please refer to the Krabbe Disease screening factsheet to help you answer the following questions about the ability of your state or territory to add screening for Krabbe Disease to your NBS program**.** Please consult with others, as needed, including laboratory and follow-up staff, medical professionals and specialists, to complete the survey. When unsure about a response, please provide your best estimate. If you were to answer every question, we estimate it will take an average of 10 hours to complete this form.

1. Has your state: (*check all that apply)*
    - Included Krabbe Disease as part of the routine NBS panel? (*end survey*)
    - Planned, implemented, or completed any type of pilot study or pilot evaluation for Krabbe Disease? (*end survey*)
    - Issued a mandate or state-level decision to start screening for Krabbe Disease? *(end survey)*
    - None of the above (*go to question 2*)

2. Which of the following entities provide the majority of the NBS laboratory services for your state's NBS program? (multiple choice*)*
    - Your own state's public health or NBS laboratory
    - A state university laboratory for which there is an intra-state agency agreement
    - A contracted regional NBS laboratory (e.g., another state laboratory)
    - A contracted commercial laboratory
    - Other – please specify: _____

NBS programs consider many factors when deciding to add a condition to their NBS panel. The following question asks you to consider, in general, how much the following factors would be an issue when considering adding Krabbe Disease to your NBS panel.

3. Please indicate if the following implementation factors for Krabbe Disease would present a major challenge, a minor challenge, or would not be a challenge, given the current status of the NBS Program in your state.

4. Factor	1. Major Challenge	2. Minor Challenge	3. Not a Challenge	Comments
Availability of a first-tier validated screening test (in-house or contracted)				
Availability of staff to report and track infants with out-of- range results through to diagnosis or resolution				
Identifying specialists in your state (or region) who are confident in the diagnostic evaluation of Krabbe Disease				
Availability of timely treatment for infants born in your state with Krabbe disease (e.g. in-state treatment centers or funds for travel and out of state treatment)				
Increasing your NBS fee				
Addressing administrative challenges (e.g., obtain authorization); please specify in comments section				

4. Please describe any additional overarching challenges.

_____

For questions 5-7 please assume that Krabbe Disease has been authorized for addition to your state's panel and funds for laboratory testing and follow-up have been made available.

5. The following question considers the various resources needed (e.g. human resources, facilities, etc.) by your NBS program in order to implement screening for Krabbe Disease.

5.a. Please complete the following table if you answered "your own state's public health or NBS laboratory" on question #2. If your answer on question #2 was any of the other options, please skip to 5.b.

5.a. Resources Needed	Have Already	Do not have but can get within 1 year	Cannot get within 1 year	Comments
Screening method for GAMT deficiency: MS/MS using a derivatized or non-derivatized assay				
First-tier screening method for Krabbe (MS/MS or fluorometry)				
Second-tier psychosine screening for Krabbe				
Quantity and type of laboratory equipment needed to screen for Krabbe Disease				
Laboratory technical expertise to screen for Krabbe Disease				
Sufficient number of technical staff to screen for Krabbe Disease				
LIMS capacity and instrumentation interface				
Sufficient number of NBS staff to notify and track NBS results				
Access to appropriate diagnostic services after an abnormal or out of range screening result is reported (e.g., diagnostic testing, clinical evaluations)				
Genetic counselors, or other staff with the necessary expertise, to cover the expected caseload				
Specialists to cover expected Krabbe Disease caseload				
Treatment centers for expected Krabbe Disease caseload				
Follow-up protocols for Krabbe Disease				

SKIP PATTERN (respondents fill out either 5.a.or 5.b., but not both)

5.b. Please complete the following table if you answered “a state university laboratory for which there is an intra-state agency agreement”, “a contracted regional NBS laboratory”, “a contracted commercial laboratory”, or “other – please specify” on question #2.

5.b. Resources Needed	Have Already	Do not have but can get within 1 year	Cannot get within 1 year	Comments
Availability of the screening test in the state university laboratory for which there is an intra-state agency agreement, or contracted regional laboratory, or commercial laboratory				
Availability of the second-tier screening test at a contracted laboratory				
LIMS capacity and instrumentation interface				
Sufficient number of NBS staff to notify and track NBS results				
Access to appropriate diagnostic services after an abnormal or out of range screening result is reported (e.g., diagnostic testing, clinical evaluations)				
Specialists to cover expected Krabbe Disease caseload				
Treatment centers for expected Krabbe Disease caseload				
Follow-up protocols for Krabbe Disease cases				

6. Please indicate the degree to which these factors impede or facilitate your ability to adopt screening for Krabbe Disease in your state.

Factor	Major Barrier	Minor Barrier	Minor Facilitator	Major Facilitator	Not Applicable
Predicted run time to screen for Krabbe Disease as it relates to other workload					
Extent to which the screening test for Krabbe Disease can be multiplexed with screening for other conditions					
Other ongoing NBS program activities (e.g., addition of other conditions, other quality improvements)					
Estimated cost per specimen to conduct screening (personnel, equipment, reagents)					

Factor	Major Barrier	Minor Barrier	Minor Facilitator	Major Facilitator	Not Applicable
Estimated cost of treatment for newborns diagnosed with Krabbe Disease					
Expected clinical outcomes of newborns identified by screening					
Expected cost-benefit of screening in your state					
Advocacy for screening for Krabbe Disease					
Other non-NBS public health priorities within your state					

**Major barrier- Will prevent testing from being implemented effectively and/or timely.*
**Minor barrier- May compromise testing so it is not performed effectively and/or timely.*
**Minor facilitator- May allow testing to be done effectively and/or timely.*
**Major facilitator- Will allow testing to be done effectively and/or timely.*

7. Please describe any additional factors that impede or facilitate adoption of screening for Krabbe Disease in your state.

_____

8a. What are the most significant barrier(s) to screening for Krabbe Disease in your state?

8b. What would most facilitate screening for Krabbe Disease in your state?

9. Please estimate the time it would take your NBS program to initiate screening for Krabbe Disease in your state (i.e. get authority and funds to screen for Krabbe Disease, go through administrative processes, meet with your state NBS committees and complete all activities needed to implement and commence screening for all newborns in your state)?

- 12 months or less
- 13 to 24 months
- 25 to 36 months
- 37 to 48 months
- More than 48 months

10. The question above related to the overall timeline. We recognize some of the activities happen in tandem and some cannot begin until a previous activity has been completed. Please

estimate the total time needed, in general, for each individual activity listed below within your NBS program. If needed, please consult with laboratory and follow-up staff, medical professionals and specialists, prior to completing the survey.

Please complete the following table if you answered "your own state's public health or NBS laboratory" on question #2. If your answer on question #2 was any of the other options, please skip to 10.b.

10a.
SKIP PATTERN (respondents fill out either 10.a.or 10.b., but not both)

Activity	12 months or less	13 – 24 months	25 – 36 months	37 to 48 months	> 48 months	N/A	Comment
Obtain authorization to screen for Krabbe Disease							
Availability of funds to implement screening for Krabbe Disease							
Meet with Advisory committees and other stakeholders							
Obtain and procure equipment for screening for Krabbe Disease							
Hire necessary laboratory and follow-up staff							
Select, develop, and validate the screening test within your laboratory							
Develop a screening algorithm, follow-up protocols, and train follow up staff							
Set up reporting and results systems for added condition (e.g., LIMS)							
Collaborate with specialists and clinicians in the community to determine which diagnostic tests will be recommended upon identification of an out of range NBS result							
Add the screening test to the existing outside laboratory contract							
Conduct an internal validation study for Krabbe Disease							
Pilot test the screening process within your state, after validation has taken place							
Implement statewide screening for all newborns, including full reporting and follow-up of abnormal screens after validation and pilot testing							

10b.

16. Activity	12 months or less	13 – 24 months	25 – 36 months	37 to 48 months	> 48 months	Not Applicable	Comment
Obtain authorization to screen for Krabbe Disease							
Availability of funds to implement screening for Krabbe Disease							
Meet with Advisory committees and other stakeholders							
Develop follow-up protocols, and train follow up staff							
Set up reporting and results systems for Krabbe Disease (e.g., LIMS)							
Collaborate with specialists and clinicians in the community to determine the approach for identification of an out-of-range NBS result							
Add the screening test to the existing outside laboratory contract							
Implement statewide screening once validation and pilot testing is complete							

11. a. Which of the following best describes the screening approach your program would most likely choose for Krabbe Disease:

- First-tier GALC enzyme only (jump to 11c)
- First-tier GALC activity followed by second-tier psychosine testing (jump to 11b)
- Other; specify _____
- Unsure

11. b. What is your plan for psychosine testing? (all go to 11c)

- In-house
- Contract to outside laboratory
- Unsure

11.c. Would your program rely on molecular testing in-house as part of your *newborn screening algorithm*?

- Yes
- No
- Unsure

12. Are there any special considerations regarding Krabbe Disease that need to be taken into account when assessing the impact on the public health system (e.g. variants of unknown significance, age of onset, access to specialists, access to treatment, cost of treatment, etc)? Please describe:

_____

13. Please share any additional information regarding implementation of NBS for Krabbe Disease.

_____

14. Please provide information about the respondent:
    Name:
    Phone number:
    Email address:
    Job title:

15. Who did you consult with to answer these questions? *Please check all that apply*.
    - State NBS laboratory experts
    - Other NBS program staff
    - State NBS advisory board
    - State Title V Director
    - Krabbe Disease Specialists
    - Primary care providers
    - Advocates within your state for Krabbe Disease screening
    - Others- please specify: _____
    - None of the above

Thank you for completing the survey!