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Evidence and Recommendation for Infantile Krabbe Disease Newborn Screening

Margie A. Ream, MD, PhD¹, Wendy K. K. Lam, PhD², Scott D. Grosse, PhD³, Jelili Ojodu, MPH⁴, Elizabeth Jones, MPH⁴, Lisa A. Prosser, PhD⁵, Angela M. Rose, MPH⁵, Anne Marie Comeau, PhD⁶, Susan Tanksley, PhD⁷, Katie P. DiCostanzo, BA⁸, Alex R. Kemper, MD, MPH, MS⁸

¹Division of Child Neurology, Nationwide Children's Hospital, Columbus, Ohio

²Duke Clinical and Translational Science Institute, Duke University School of Medicine, Durham, North Carolina

³National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia

⁴Association of Public Health Laboratories, Bethesda, Maryland

⁵Susan B. Meister Child Health Evaluation and Research Center, Department of Pediatrics, University of Michigan, Ann Arbor, Michigan

⁶New England Newborn Screening Program, Department of Pediatrics, UMass Chan Medical School, Worcester, Massachusetts

⁷Texas Department of State Health Services, Public Health Laboratory Division, Austin, Texas

⁸Division of Primary Care Pediatrics, Nationwide Children's Hospital, Columbus, Ohio

Abstract

Krabbe disease (KD), which affects 0.3–2.6 per 100 000 live births, is an autosomal recessive lysosomal disorder caused by variants in the *GALC* gene that reduce galactosylceramidase (GALC) activity, leading to psychosine accumulation, cerebral white matter degeneration, and peripheral neuropathy. The most common form, infantile KD (IKD), has onset by 12 months with irritability, feeding difficulty, neurologic regression, and, when untreated, death in early childhood. Hematopoietic stem cell transplantation (HSCT) for IKD approximately 1 month after birth can improve long-term survival but has about a 10% risk of mortality within 100 days, and affected individuals can still have significant functional impairment. Newborn screening for KD is based on low GALC levels in dried-blood spots. Second-tier testing to assess whether

Address Correspondence to: Margie A. Ream, MD, PhD, 700 Children's Dr, Columbus, OH 43205-2664. Margie.Ream@nationwidechildrens.org.

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an elevated psychosine concentration is present in the same dried-blood spot improves the specificity of screening for IKD. Without newborn screening, diagnosis of IKD is generally made after significant clinical symptoms develop, past when HSCT can be effective. The benefit of newborn detection of later-onset phenotypes of KD is uncertain. In 2024, the US Secretary of Health and Human Services added IKD to the Recommended Uniform Screening Panel after a recommendation by the Advisory Committee on Heritable Disorders in Newborns and Children. For IKD newborn screening to be as effective as possible, it is important to have systems in place to support families in making challenging decisions soon after diagnosis about whether to pursue HSCT and to ensure rapid access to HSCT if chosen.

INTRODUCTION

In the United States, state governments determine which conditions to include in their state's newborn screening panel. To help support these decisions, the US Secretary of Health and Human Services maintains the Recommended Uniform Screening Panel (RUSP), a list of conditions that benefit from early detection and can feasibly be identified through screening soon after birth. The RUSP contains a list of core conditions for which the expected benefits of early detection through newborn screening exceed the potential harms. It also contains a list of secondary conditions that can be detected in screening for core conditions. Twelve states (Arizona, California, Florida, Georgia, Iowa, Maryland, Mississippi, North Carolina, Ohio, Pennsylvania, Tennessee, and Texas) are required by law to screen for all core conditions included on the RUSP within a prespecified time period (eg, 1 or 2 years).

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) helps inform which core conditions are on the RUSP by evaluating nominated conditions. Considerations for recommending a condition for the RUSP include screening accuracy, expected outcomes from early detection compared with usual case identification, and the ability of states to provide comprehensive population-based screening.¹

Krabbe disease (KD) is a lysosomal disorder with variable severity associated with severe, progressive neurologic impairment. The ACHDNC recommended against adding KD to the RUSP in 2010 and again in 2023.^{2,3} The 2023 recommendation cited gaps regarding treatment benefit for infantile Krabbe disease (IKD), the most severe phenotype; lack of information regarding the benefits and harms of identifying later-onset KD; and concerns about the lack of screening specificity for IKD.³ However, additional information, including a screening approach that targets IKD, and the potential benefit of allowing families to choose disease-modifying therapy for IKD in early infancy led the ACHDNC in 2024 to recommend adding IKD to the RUSP.⁴ This recommendation was subsequently accepted by the US Secretary of Health and Human Services. This report summarizes the key elements leading to this recommendation. The full evidence review report, the letter from the ACHDNC to the US Secretary of Health and Human Services, and the response from the US Secretary of Health and Human Services are available at the ACHDNC's website (<https://www.hrsa.gov/advisory-committees/heritable-disorders/recommendations-reports>).

OVERVIEW OF KD

KD is an autosomal recessive lysosomal disorder resulting from pathogenic variants in the *GALC* gene, which encodes the enzyme galactosylceramidase (GALC) (chromosome 14q31; OMIM: #245200).⁵ GALC degrades glycolipids, including the compound psychosine, in neuronal myelin sheaths. GALC deficiency leads to accumulation of psychosine, which is neurotoxic and results in progressive damage to the white matter of the brain and myelinated peripheral nerves.^{5,6} Age of onset and rapidity of symptom progression correlate with the degree of psychosine accumulation.^{7,8}

Based on clinical case detection in other countries, the overall prevalence of KD is estimated to be from 0.3 to 2.6 per 100 000 live births.^{9,10} The proportion identified by newborn screening in the United States could be different. Subtypes of KD are classified by age of onset, with earlier onset of signs and symptoms being associated with more severe disease. Because of the rarity of the condition, the estimate of the proportion who present in the first 6 months after birth is wide, ranging from 30% to 70% of affected infants.¹¹ When untreated, these infants have a median survival of 1.5 years.¹¹ Typically, affected infants will have severe irritability and feeding problems followed by rapid loss of neurologic function. In contrast, children with KD onset between 12 and 36 months, when untreated, have a median survival of 9.5 years.¹¹ Juvenile or adolescent KD presents by 15 years of age, and adult KD presents after mid-adolescence. Overall, disease onset before 12 months of age is classified as IKD. Later-onset forms account for 15% to 20% of known cases. The overall increased risk of mortality for those with later-onset forms is not well described, in part because the lower severity and rarity make epidemiologic studies difficult.

KD GENETICS

There are more than 1250 variants of the *GALC* gene, of which more than 300 are known to be pathogenic or likely pathogenic.¹² Some variants are associated with reduced protein function in vitro but not with disease. This is referred to as pseudodeficiency, in which individuals have abnormal functional enzyme assay results but do not develop clinical findings or accumulation of psychosine.⁸ Allele frequency varies by genetic ancestry. The most common variant associated with IKD in individuals of European ancestry is a specific 30-kb deletion (ClinVar allele ID 1675125), with an allele frequency of approximately 1 per 1089.¹³ In European studies before newborn screening, the frequency of the 30-kb deletion (homozygous or with another variant) in individuals with IKD ranged from 24% to 66%.^{14–16} Other variants leading to severe loss of enzyme function are increasingly recognized, including the missense variants, p.T529M and p.Y4567S, which together with the 30-kb deletion accounted for 62% of alleles in a group of 29 patients with KD in Denmark, of whom 75% had symptom onset by 6 months of age.¹⁵ In contrast, in a case series of 18 patients with KD in Korea, of whom 28% had IKD, the 30-kb deletion was not found, and the most frequent variants were p.Asn228_Ser232delinsThrPro and p.Leu634Ser, accounting for 46% of alleles.¹⁷ Phenotype is difficult to predict when an individual carries 1 variant associated with IKD and 1 variant either associated with later-onset disease or of uncertain significance. To help clinicians quickly follow up after a positive newborn screen for KD, the American College of Medical Genetics and Genomics has developed information sheets

and algorithms to distinguish among IKD, later-onset phenotypes of KD, and false-positive newborn screens.¹⁸

KD NEWBORN SCREENING

Infants with KD can be identified through newborn screening by measuring GALC enzyme activity in dried-blood spots. This measurement can be done with tandem mass spectrometry and can be multiplexed with screening for other lysosomal disorders.¹⁹ The Missouri newborn screening program, an early adopter of KD newborn screening, has used a spectrophotometric assay to measure GALC enzyme activity.¹⁹ Dried-blood spots with low enzyme activity can undergo second-tier testing for psychosine concentration to improve the specificity of screening, reducing the false-positive rate.²⁰ The only other condition known to be associated with elevated psychosine concentration is saposin A deficiency, an ultrarare condition clinically similar to IKD that is diagnosed through identification of pathogenic variants in the *PSAP* gene or, in the absence of definitive findings in the *PSAP* gene, low GALC enzyme activity and only benign or likely benign variants in the *GALC* gene.²¹ Measuring psychosine concentration requires a complex assay that is available from a limited number of laboratories. Psychosine concentrations of 10 nM or greater are highly specific for IKD, with a low risk for missing a case.^{7,8,20} Psychosine concentrations of 2 to 10 nM identify less severe phenotypes.^{7,8,20}

KD TREATMENT

The only specific disease-modifying treatment currently available for IKD is hematopoietic stem cell transplant (HSCT), which can increase the available functional GALC.^{22–24} To be effective, HSCT for IKD must be completed before 4 to 6 weeks after birth, before significant disease involvement and earlier than clinical identification usually occurs.^{22–24} The risk of death due to HSCT-related complications within 100 days of the transplant is approximately 10%.²⁵

Limited data are available regarding long-term outcomes after HSCT for IKD. One study of 6 patients with IKD who were consecutively identified through newborn screening, treated with HSCT, and survived the procedure found that all were alive after 30 to 58 months of follow-up (median, 47.5 months).²³ Additional follow-up information was presented at a 2024 conference for 5 of these infants (1 was lost to follow-up) and an additional infant subsequently identified by newborn screening who received transplant approximately 1 month after birth.²⁴ By 30 months of age, all infants were alive, which is significantly different than the expected mortality without HSCT. Cross-sectional function was evaluated with the Vineland Adaptive Behavior Scales, third edition (Vineland-3), at 2.2 to 7.1 years of age.²⁴ All 6 had moderately low or low composite scores and had markedly low gross motor scores. Although other domains (eg, social, emotional) were higher, they were still lower than normative controls.

Insufficient information is available at this time to assess the impact of HSCT on later-onset phenotypes, regardless of the timing of treatment.

Parents of children with IKD diagnosed presymptomatically must weigh the upfront risk of HSCT against the greater probability of survival after HSCT and other potential functional benefits. Owing to the need for HSCT to be done within roughly 1 month after birth, parents must make a rapid decision after diagnosis about whether to proceed with this intervention. Because of the limited number of centers with experience with HSCT for IKD, infants may need to be transferred out of state, as has happened in the past, leading to additional burdens for families and challenges related to care coordination and payment for the services (eg, Medicaid coverage for out-of-state care).

KD NEWBORN SCREENING AND SCREENING OUTCOMES IN THE UNITED STATES

By 2023, 11 states were screening for KD. Of these, 9 included second-tier dried-blood spot psychosine concentration testing using a cutoff of 1.5 to 2 nM.²⁶ Although setting the threshold for psychosine concentration to 10 nM or greater is expected to be specific to IKD, the lower thresholds used by states at the time of the report increase the risk of false positives and identify phenotypes other than IKD.

For this report, which focused on the nominated condition of IKD, we assessed outcomes for second-tier psychosine concentration testing, assuming a threshold of at least 10 nM to specifically target detection of IKD. Based on information for more than 3.55 million infants screened by the 9 newborn screening programs that included second-tier psychosine concentration testing, 42.4 per 100 000 (n = 1505) had a positive first-tier screen result (ie, low GALC enzyme concentration), and 13 had a psychosine concentration of 10 nM or greater.²⁶ A laboratory error resulted in falsely elevated psychosine concentrations in 2 infants, and the remaining 11 infants were diagnosed with IKD.

Of the 11 infants identified as having IKD through newborn screening using psychosine measurement as a second-tier screen, all had psychosine concentrations of 10 nM or greater, and 1 was lost to follow-up. Of the remaining 10, 3 (30%) families declined HSCT. The other 7 received HSCT between 24 and 42 days after birth. One infant (14%) died at 7 months because of graft-vs-host disease, and the other 6 (86%) were alive to at least 2 years (median, 2.5 years; range, 2–5 years).²⁶

EXPECTED OUTCOMES OF IKD NEWBORN SCREENING

Based on the experience of these newborn screening programs and the epidemiology of IKD, screening all 3.65 million infants born each year in the United States annually for IKD, using simulation modeling, would be expected to identify 11.3 infants (range, 5.6–20.2) annually.²⁶ Of these, 9.9 (range, 3.5–19.9) would be expected to receive HSCT. Of the infants who received HSCT, 1.0 (range, 0.3–1.2) would be projected to die from HSCT complications within 100 days, and all others would be projected to be alive at 2.5 years. In contrast, without IKD newborn screening, 11.3 infants (range, 4.0–23.0) infants would be expected to present before 1 year of age, of whom 1.1 (range, 0–4.0) would be eligible for and receive HSCT. Of the remaining 10.2, 7.8 (range, 3.5–10.6) infants would be expected to die from IKD by 2.5 years of age. Evidence regarding other outcomes, including

quality of life or neurologic status, and for outcomes beyond 2.5 years was insufficient for modeling. The model does not assess the impacts of KD identification and treatment outcome on family members or society.

IDENTIFICATION OF KD WITH ONSET AFTER 12 MONTHS

In 2023, all 9 newborn screening programs in the United States that screened for KD with second-tier psychosine testing used a cutoff of 1.5 to 2 nM, which would identify infants who are at risk of developing KD after their first year.²⁰ Timing of disease onset is difficult to predict in these patients. There is an expert consensus regarding longitudinal follow-up and timing of diagnostic tests that can help identify early disease symptoms (eg, magnetic resonance imaging, nerve conduction studies, cerebral spinal fluid analysis), the results of which can guide treatment.²⁷ There is insufficient evidence regarding the impact of early identification on these infants.

FINAL RECOMMENDATION

In 2024, the ACHDNC recommended newborn screening for IKD, recognizing the severity of IKD, the ability to accurately and specifically identify IKD using a psychosine concentration of 10 nM or greater as a second-tier test, and the brief window for providing HSCT. No recommendation was made for newborn screening for later-onset phenotypes of KD. Almost 6 months later, the US Secretary of Health and Human Services “accept[ed] the Committee’s recommendation to expand the RUSP to include infantile Krabbe disease (low GALC and psychosine $\geq 10\text{nM}$).”⁴

Newborn screening programs that choose to screen for KD without second-tier psychosine concentration testing or to report all cases, regardless of psychosine concentration, will identify later-onset phenotypes.^{8,20} Given the uncertainty of benefits of newborn screen-based identification of later-onset KD, these programs should prepare clinicians and families for the potential to identify later-onset KD and have systems in place for follow-up care after identification.

Individuals with IKD and their families require high-quality supportive services, regardless of whether the condition was identified through newborn screening. Because of the risk of HSCT-related mortality and the risk of long-term functional impairment, it is important that families work with medical professionals to weigh the pros and cons of HSCT and choose what they consider to be best for their child and situation. Systems are needed to ensure timely HSCT for those families that opt for this treatment. Based on the experience of KD newborn screening in the United States thus far, perhaps 30% of families with a newborn who has IKD may refuse HSCT.

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or policy of, nor should any endorsements be inferred by, the Health Resources and Services Administration, US Department of Health and Human Services, or US Government.

ABBREVIATIONS

ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children
FDA	Food and Drug Administration
GALC	galactosylceramidase
HSCT	hematopoietic stem cell transplant
KD	Krabbe disease
IKD	infantile Krabbe disease
RUSP	Recommended Uniform Screening Panel
Vineland-3	Vineland Adaptive Behavior Scales, third edition

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