Overview of Newborn Screening for Krabbe Disease for the 2022 RUSP Nomination

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Objective

- Overview
- Current Progress
- Next Steps

Krabbe Disease

- Lysosomal storage disorder and leukodystrophy
- Low galactocerebrosidase (GALC) enzyme activity (also referred to as “galactosylceramidase”)
- Chromosome 14 (>200 mutations)
- ~1 per 100,000 (based on registry data, ~75% infantile)

Phenotypes, Based on Natural History

Escolar ML, Kiely BT, Shawgo, et al. Psychosine, a marker of Krabbe phenotype and treatment effect. *Mol Genet Metab.* 2017;121:271-278.

- Infantile: Onset before 12 months, death before 2 years on average
  - Irritability, spasticity, blindness, seizures, failure to thrive, aspiration pneumonia
  - Focus of newborn screening
- Late Infantile: Progressive symptoms from 1-3 years
- Juvenile: Progressive symptoms from 4-17 years
- Adult: Progressive symptoms after 17 years

Krabbe Disease Newborn Screening

- Georgia
- Illinois
- Indiana
- Kentucky
- New York
- New Jersey
- Missouri
- Ohio
- Pennsylvania
- Tennessee

Diagnoses Following Newborn Screening (Unconfirmed)*

State	Year Began	Number Screened	Early Infantile Krabbe Disease	Late-Onset Krabbe Disease
New York	2006	3,700,000	7	3
Missouri	2012	682,000	3	2
Ohio	2016	766,631	2	5
Kentucky	2016	330,000	2	0
Tennessee	2017	311,000	0	2
Illinois	2017	660,630	5	7
New Jersey	2019	135,000	1	0
Indiana	2020	88,899	0	0
Georgia	2021			
Pennsylvania	2021	99,387	1	0
Total		**6,773,547**	**21**	**19**

*https://krabbeconnect.org

Approach to Screening

- Tier 1: GALC enzyme activity in dried-blood spots (DBS)
- Tier 2: Psychosine in DBS to reduce false positives and help stratify expected phenotype
  - Galactolipid formed in the production of myelin; toxic
  - Not used by all newborn screening programs

Diagnostic Tools after a positive screen

- Low GALC enzyme activity
- Elevated psychosine helpful but not definitive
- Additional neurologic evaluations (supportive but not specific)
  - MRI
  - Nerve conduction studies
  - Electroencephalogram (EEG)
  - Auditory and Visual Evoked Potentials
  - Cerebrospinal fluid (CSF) protein
- Molecular genetic testing is supportive

Expert Panel Recommendations For Follow-up After Newborn Screening

Thompson-Stone R, Ream MA, Gelb M, et al. Consensus recommendations for the classification and long-term follow up of infants who screen positive for Krabbe disease. *Mol Genet Metab*. 2021;134:53-59.

- Dried-blood spot psychosine levels
  - ≥2 nmol/L abnormal
    - ≥10 nmol/L consistent with infantile Krabbe disease
- Three pathways
  - Infantile: **immediate** referral for diagnostic evaluation and treatment
  - "At-risk for late-onset Krabbe disease": seen in 2-4 weeks by a specialist or primary care provider in consultation with a specialist for further testing; based on genotype, classified into
    - High risk: Specialty visits every 2-3 months for 24 months, every 6 months until 3 years, annually until 12 years, 2-5 years until adulthood
    - Low risk: Specialty visits every 6 months for 24 months, annually until 12 years, 2-5 years until adulthood
  - Unaffected: no follow-up

Targeted Treatment

Thompson-Stone R, Ream MA, Gelb M, et al. Consensus recommendations for the classification and long-term follow up of infants who screen positive for Krabbe disease. *Mol Genet Metab*. 2021;134:53-59.
Kwon JM, Matern D, Kurtzberg et al. Concensus guidelines for newborn screening, diagnosis and treatment of infantile Krabbe disease. *Orph J Rare Diseases*. 2018;13:30.

- Current treatment recommendation: Hematopoietic stem cell transplantation (HSCT)
  - For infantile phenotype, by 30 days (even earlier is better) and 45 days might be too late, depending on degree of involvement
  - A focus of the review, including stratifying by expected phenotype at the time of screening (psychosine and genotype)
- Gene therapy in development

Contextual Questions

1. What is the current approach to establish the diagnosis of infantile-onset Krabbe disease after a positive screen?
2. What clinical practice guidelines are available for diagnosis and treatment? What is the evidence base for these recommendations?
3. How accessible is care for infantile-onset Krabbe disease? What is the uptake of this care?
4. What are the barriers and facilitators of newborn screening for Krabbe disease?

Systematic Review Questions

1. What is the analytic and clinical validity of NBS strategies to screen for infantile-onset Krabbe disease?
2. What is the impact of NBS for infantile-onset Krabbe disease compared with usual case detection on the timing of diagnosis and the timing of treatment? What is the impact on mortality and on development?
3. What are the negative consequences of newborn screening for Krabbe disease?

Progress

- TEP Call #1: August 8
- Evidence Review: Underway, focusing on the past 10 years
- Modeling: Pending evidence review, will be the focus of TEP Call #2
- PHSI: Surveys to start in October

Questions