Recommendations to the ACHDNC for Newborn Screening of Krabbe Disease

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Revised Application, Expedited Review

- Infantile Krabbe disease is the disorder of interest
- Two-tiered dried-blood spot screening
    - First Tier: Low galactocerebrosidase (GALC) enzyme activity
    - Second Tier: Psychosine ≥10 nM

Revised Application, Expedited Review

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- Two-tiered dried-blood spot screening
    - First Tier: Low galactocerebrosidase (GALC) enzyme activity
    - Second Tier: Psychosine ≥10 nM

This psychosine cutoff is more specific for infantile Krabbe disease and reduces the number of “late-onset” cases with uncertain outcomes who need to be followed

Overall, the new 2-tier screening improves the net benefit of screening

Krabbe Disease

Characterization and epidemiology

- Autosomal recessive disorder due to deficiency of galactocerebrosidase (GALC) enzyme activity which leads to early injury to myelin and brain cells
  - Neurodegeneration is the hallmark of disease
  - Earlier age of onset associated with earlier mortality
- In infantile KD, infants may appear normal at birth, then within weeks to months, develop difficulty feeding accompanied by irritability, poor head control, and poor responsiveness
  - Clinical exams show increased muscle tone (stiffness) and abnormal reflexes
  - Death occurs early in childhood

Krabbe Disease

Treatment

- Hematopoietic stem cell transplant (HSCT) can improve survival and developmental outcomes in those with infantile KD who are treated presymptomatically (that is, without significant symptoms and signs)
  - HSCT procedures have associated morbidity and mortality
  - Since this is the only treatment offered to infantile KD patients, families who are appropriately counselled have refused treatment

Krabbe Disease

Screening and Diagnosis

- In reviewing data from state programs currently using incorporating psychosine in their KD screening, no infantile case was identified with dried blood spot psychosine of <10 nM
  - One infant (Corre et al., 2021) presenting with symptoms of infantile KD who died at 2 years of life had multiple psychosine levels < 2 nM
- Specificity is greatly improved using the psychosine cut-off of ≥10 nM
  - All cases of infantile KD identified by states currently screening for KD have had psychosine levels of ≥10 nM
- Confirmatory testing for IKD should include GALC genotyping, MRI, and nerve electrophysiology

Screening Program	Period	Number Screened	Positive First-Tier	Psychosine ≥10 nM	Infantile Krabbe Disease	Known or Suspected Later-Onset Cases not Detected with Psychosine ≥10 nM
GA	9/30/21-11/30/2023	329,661	63 (19.1 per 100,000 screened)	1 (1.6% of positive first-tier screens)	1 (3.0 per million screened)	0
IL*	12/1/2017-9/30/2023	848,000	600 (70.8 per 100,000 screened)	5 (0.8% of positive first-tier screens)	5 (5.9 per million screened)	12 (14.2 per million screened)
IN	7/2020-11/2023	272,077	148 (54.4 per 100,000 screened)	0	0	10 (36.8 per million screened)
KY	2/15/16-6/30/23	404,626	128 (31.6 per 100,000 screened)	2 (1.6% of positive first-tier screens)	2 (4.9 per million screened)	0
MO	3/20/2020-8/31/2023	232,721	401 (172.3 per 100,000 screened)	3 (0.7% of positive first-tier screens)	1 (4.3 per million screened)	1 (4.3 per million screened)
NY	1/1/2021-9/30/23	572,197	38 (6.6 per 100,000 screened)	0	0	2 (3.5 per million screened)
PA	5/21/2021-10/31/2023	316,918	43 (13.6 per 100,000 screened)	1 (2.3% of positive first-tier screens)	1 (3.2 per million screened)	3 (9.5 per million screened)
SC	5/15/2023-11/27/2023	29,748	16 (53.8 per 100,000 screened)	0	0	0
TN	7/1/2017-9/30/2023	545,085	68 (12.5 per 100,000 screened)	1 (1.5% of positive first-tier screens)	1 (1.8 per million screened)	5 (9.2 per million screened)
Total		3,551,033	1,505 (42.4 per 100,000 screened)	13 (0.9% of positive first-tier screens)	11 (3.1 per million screened)	33 (9.3 per million screened)

Outcomes of 11 Cases Identified by Screening

- 1/11 (9%) with no follow-up information available
- 3/10 (30%) declined HSCT
- 6/7 (86%) who received HSCT between 24 and 42 days are alive to at least 2 years (median 2.5 years, range 2-5 years)
    - 1 received an additional HSCT, 1 received gene therapy, 1 planning for gene therapy
- 1/7 (14%) died around 7 months due to graft vs. host disease

Krabbe Disease

Potential Harms

- Treatment
  - HSCT Morbidity and Mortality (~10%)
  - Equity concern around availability of appropriate donors for infants from under-represented minority populations

- Higher psychosine cutoff of of ≥10 nM, to date, appears to eliminate harms associated with indeterminate diagnoses (e.g., children with bi-allelic GALC variants and psychosine levels <10 nM)
  - These children are no longer “patients in waiting” and are no longer at risk for potentially unnecessary HSCT, but childhood onset disease will not be detected
  - It is possible that infantile KD cases may be missed using this cutoff, as suggested by the infant described by Corre et al.

Results: Projected outcomes using the revised nomination screening algorithm*

Annual cohort of 3.65 million newborns

Screening Outcome	Most Likely Number of Cases	Range
Screen positive/ referred for diagnostic evaluation	11.3	5.6 – 20.2
Infantile Krabbe disease†	11.3	5.6 – 20.2
Not infantile Krabbe disease	0	0 - 5.6
False negative	0	0 – 5.4

*Psychosine ≥10 nM referred for diagnostic evaluation
†Referred for transplant evaluation

Is there significant net benefit for compulsory, population-based Krabbe disease NBS?

Under the revised Krabbe disease screening algorithm that incorporates 2nd tier psychosine of ≥10 nM:

Summary of benefits

- Evident benefit in survival for those undergoing and surviving early HSCT
- Treatment data are limited, and there remain honest differences of opinion regarding value of treatment in infantile onset cases as evidenced by family decisions

Summary of harms

- Treatment related mortality

Decision Matrix for Nominated Conditions for the Recommended Uniform Screening Panel (RUSP)

NET BENEFIT/ CERTAINTY			READINESS: Ready	READINESS: Developmental	READINESS: Unprepared	FEASIBILITY: Feasibility	FEASIBILITY: HIGH or MODERATE	FEASIBILITY: LOW
SIGNIFICANT Benefit	Certainty	HIGH	**A1** Screening for the condition has a high certainty of significant net benefits, screening has high or moderate feasibility. Most public health departments are ready to screen.	**A2** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments have only developmental readiness.	**A3** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments are unprepared for screening.			
			A4 There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.					
		MOD	**B 1-4** There is moderate certainty that screening would have a significant benefit.			---		
Small to ZERO Benefit	Certainty	MOD/HIGH	**C 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a small to zero net benefit.			---		
NEG Benefit			**D 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a negative net benefit.			---		
---		LOW	**L 1-4** There is low certainty regarding the potential net benefit from screening.			---		

Newborn Screening for Infantile Krabbe Disease
Liaisons' Summary of Evidence for the ACHDNC

- For families that choose therapy there is a measurable improvement in the child's lifespan and neurodevelopmental course
- Some families do not find this improvement compelling enough to opt for HSCT
- If patients with psychosine values <10 are reported as high-risk by state NBS programs, balance of benefits and harms may be negatively impacted
- Newborn screening programs appear ready to enact screening for Krabbe
  - State labs are mostly able to implement in 2-3 years, with outliers due to funding and local response times to add new conditions
- The process of diagnosing and treating infantile Krabbe disease within 4 to 6 weeks will be challenging, with potential for errors and delays, unless state programs tightly coordinate NBS call-out, diagnostic testing, and HSCT referral

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Newborn Screening for Infantile Krabbe Disease

Liaisons' Guidance Based on Evidence Review

Infantile Krabbe disease as defined by low GALC enzyme activity AND psychosine ≥10 nM is NOT recommended for inclusion as a core condition on the RUSP

*NOTE: While this presentation did not recommend Krabbe disease for inclusion to the RUSP, the Committee ultimately voted to recommend to the Secretary to add Krabbe disease disease for inclusion to the RUSP. (2/5/2024)