Recommendations to the ACHDNC for Newborn Screening of Krabbe Disease

Jennifer Kwon, MD

Shawn E. McCandless MD

Committee Representatives to the Condition Review Workgroup

ACHDNC Meeting

February 9, 2023

Decision Matrix

- Understanding the level of certainty of net benefits of newborn screening for identification of infants affected by Krabbe disease in the population

- States' readiness to implement newborn screening for Krabbe disease

- Feasibility of newborn screening for Krabbe disease, including
  - High-throughput screening procedures that can be completed by public health laboratories
  - A clear approach to diagnostic confirmation
  - Acceptable treatment plan with an established approach to long-term follow-up

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

NET BENEFIT/ CERTAINTY			READINESS			FEASIBILITY	
			Ready	Developmental	Unprepared		
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.	Feasibility	HIGH or MODERATE
			A4 There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.				LOW
		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.			---	

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
  - Onset 0-6 months with median age of death by age 2 years
  - Onset 6 months to 3 years with death during childhood
- Significant disability and burden of condition for affected individuals and families

Krabbe Disease

Findings and symptoms

- Psychosine accumulates in Krabbe disease (KD)
  - Thought to be directly toxic to neurons and myelin-producing cells, and
  - Is a marker of severity of disease
- 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
- MRI shows abnormal white matter findings and nerve electrophysiology is abnormal

Krabbe Disease

Screening and Diagnosis

- All programs currently screening for KD use GALC enzyme activity from dried blood spots (DBS) as their first-tier test
- Screening by GALC activity alone leads to unacceptably high call-out rates
- Most states reduce referral rates and false positive screening results using
  - Psychosine from DBS, and/or
  - *GALC* molecular testing from DBS
- It has become clear that screening with psychosine is required to make the referral rate (call-out rate) and the false positive rate acceptable
- Confirmatory testing—repeat GALC enzyme activity, psychosine levels and molecular testing—and other markers of disease may further reduce the number of infants needing urgent evaluation for treatment or close clinical follow-up

KD Treatment

- Hematopoietic stem cell transplant (HSCT) is currently the only available therapy recommended to begin before significant symptoms and signs are seen
  - Symptomatic treatment with HSCT is not recommended
- Evidence regarding efficacy HSCT is challenging to interpret
  - Challenges with case definition in literature (“comparing apples to apples”)
- Equally concerning are particular HSCT risks for very young infants
  - Centers experienced with KD HSCT still have morbidity and mortality associated with this procedure
  - Since this is the only treatment offered to infantile KD patients, families who are appropriately counselled have refused treatment
- With treatment, the most severe cases (i.e., early infantile onset) appear to have prolonged life with variable neurological disability
- Later onset cases may have greater benefit from HSCT in terms of prolonged life and improved quality of life, however, data are lacking to say this with confidence

Krabbe Disease

Net Benefit/Certainty

- The peer reviewed evidence base contains several case reports, but data are still very challenging to interpret with confidence
- Much of the assessment of the value of NBS relies on expert opinion
- Overall, NBS and early treatment benefits those with early onset of disease (less than 6 months of age) by improving survival
  - Advocacy groups report that families feel strongly that this is valuable to them
- It is possible that later onset cases, while less common, may have more significant benefit from HSCT
  - For later onset cases, comparison of outcomes of NBS cases and those diagnosed clinically is difficult because of limited data

Annual Projected Outcomes for Newborn Screening for Krabbe in the U.S (~3.6 M births)

Screening Outcome	Newborn Screening	Range
Screen positive/ referred for diagnostic evaluation (#)	74.8	55.8 - 98.2
Infantile Krabbe disease* (#)	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

* Referred for transplant evaluation

Benefit to affected infants/children

WITH universal Krabbe disease newborn screening

- **15.3** (range: 5.8 – 28.1) infants annually would be referred for evaluation for HSCT
- **13.4** (range: 3.6 – 27.7) infants would receive 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.

- Infants with expected onset of symptoms before 6 months, current data suggest
  - ~80% would benefit from therapy
  - ~20% would not benefit
    - ~10% mortality from transplant
    - ~10% would not opt for transplant
- 3-4 times as many would not be diagnosed with early onset and would enter follow up protocols
  - Many of these would likely benefit from NBS, but data are not available to assess this assertion
  - No data exist on the effects of repeated clinical visits and diagnostic procedures in those with indeterminate status

Benefit to affected infants/children

Reasonable assertions based on challenging data for “early” onset cases

- Increased lifespan
- More achievement of developmental milestones (some with substantial disability)
- Treatment associated mortality (minority of cases undergoing HSCT)

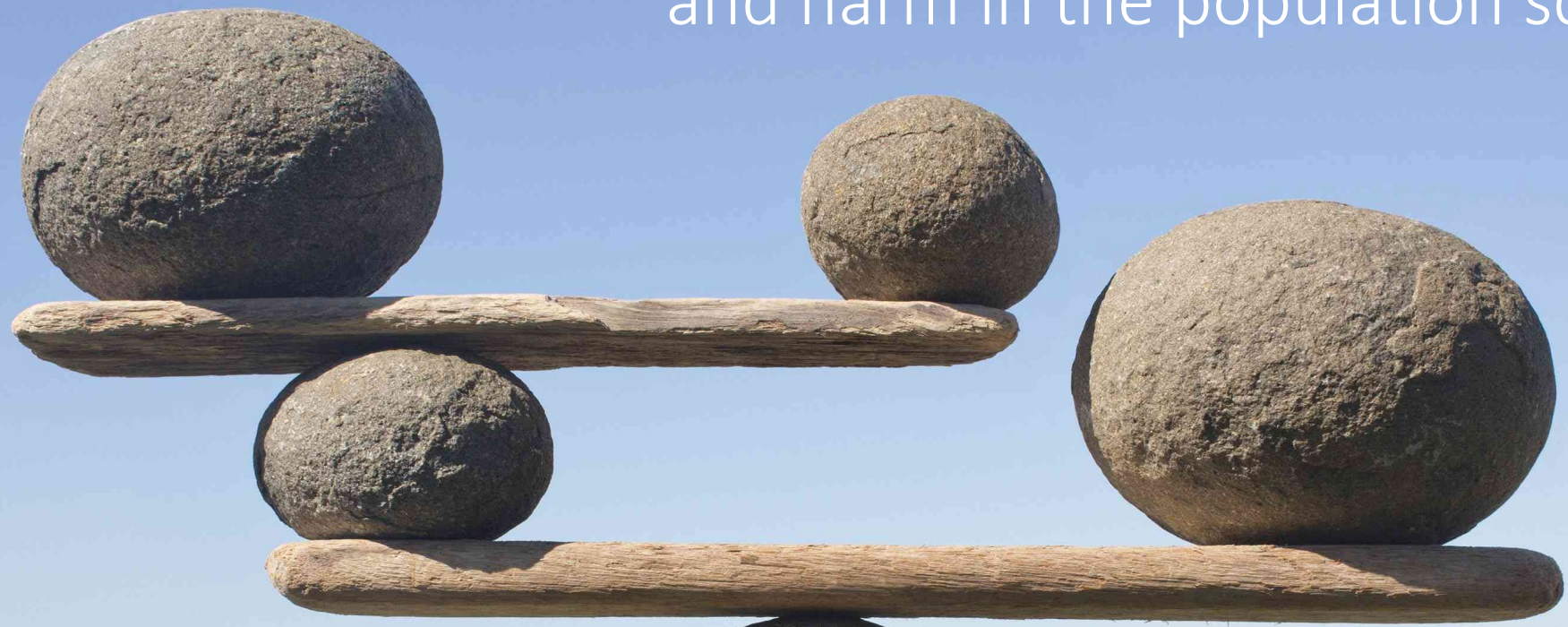
Potential Harms

- Potential harms of the NBS process
  - Death resulting from early HSCT (~10%)
  - False-positive results (especially likely without 2nd tier psychosine testing):
    - Low GALC activity may be due to pseudodeficiency alleles
    - *GALC* sequencing may result in VUS and indeterminate genotyping results
  - Compressed time frame for complex diagnostic process and therapy planning increases risk of treating unnecessarily
- False negative results – one case report suggests that reliance on psychosine alone may not accurately classify an infant as having early onset disease
- Potential for psychological and financial burdens for families after false positive and indeterminate diagnostic testing, particularly for those requiring on-going follow-up
  - Costs of repeated visits and testing are monetary and for time lost from work or other responsibilities
  - Lowered quality of life from parental anxiety and stress
  - “Lost to follow-up” likely reflects parental dissatisfaction with the process

Net Benefit is the balance of benefit and harm in the population screened

Getty Image

Net Benefit is the balance of benefit and harm in the population screened



Benefit and Harm accrue to different individuals in the population

Is there any reason to think that different groups will be affected differently by benefits or harms? (Justice)

Getty Image

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

Summary of benefits

- Moderate to significant benefit to most confirmed infantile onset cases
- Potential benefit for uncertain diagnoses and later onset cases

Summary of harms

- Treatment related mortality
- Potential mis-classification of disease onset leading to inappropriate treatment
- Relatively high number of individuals that cannot be clearly classified early
- Potential harms for uncertain diagnosis and later onset cases
- Diagnosis before symptom onset may not be possible with current follow-up protocols

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

NET BENEFIT/ CERTAINTY			READINESS			FEASIBILITY	
			Ready	Developmental	Unprepared		
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.	Feasibility	HIGH or MODERATE
			A4 There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.				LOW
		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 Krabbe
Recommendation to the ACHDNC

- Newborn Screening for Krabbe disease meets criteria for net benefit of screening
  - Moderate to significant benefit to confirmed infantile onset cases
  - Harm from intervention for infantile onset cases
  - Potential benefit for uncertain diagnosis and later onset cases
  - Potential harms for uncertain diagnosis and later onset cases
- 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
  - Unclear if all states will incorporate psychosine testing within the NBS lab
- There is limited evidence to address the of feasibility of screening, testing and treatment in states' newborn screening systems
  - Screening – likely that states will be able to implement screening
  - Approach to diagnosis and follow up – less clear given the complexities of HSCT delivery
  - 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

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		MOD/HIGH	**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.			---		

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		MOD/HIGH	**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 Krabbe Disease
Recommendation to the ACHDNC

- Newborn Screening for KD meets criteria for matrix category

C1

- Ability for newborn screening programs to enact screening is

"Ready"

- There is Moderate to Low evidence of feasibility of screening, testing and treatment in States' newborn screening systems

Newborn Screening for Krabbe Disease
Recommendation to the ACHDNC

- Newborn Screening for KD meets criteria for matrix category

C1

- Ability for newborn screening programs to enact screening is

"Ready"

- There is Moderate to Low evidence of feasibility of screening, testing and treatment in States' newborn screening systems

RECOMMENDATION

Krabbe Disease does not meet the threshold for addition to the RUSP as a core condition at this time