Newborn Screening for Krabbe Disease Expedited Evidence-Based Review

January 30, 2024

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Nomination

Nominated Condition

- Infantile Krabbe Disease
  - Significant and progressive neurologic impairment by 12 months after birth with death in early childhood without targeted treatment
    - Later-onset – development of signs or symptoms 12 months after birth or later
  - Two-tiered dried-blood spot screening
    - First Tier: Low galactocerebrosidase (GALC) enzyme activity
    - Second Tier: Psychosine ≥10 nM
- Currently, there is variation in newborn screening for Krabbe disease
  - Use of molecular testing
  - Use of psychosine as a second-tier test
  - Threshold for a positive psychosine, when used as second-tier test is 1-2 nM

Summary of Sources of New Evidence

New Evidence Included in This Expedited Review

- Information from the state newborn screening programs that include dried-blood spot psychosine as a second-tier test (collected by the ERG)
  - Sensitivity and specificity of the proposed screening algorithm
  - Prevalence of infantile Krabbe disease with dried-blood spot psychosine ≥10 nM
- A published survey of families regarding attitudes about Krabbe disease newborn screening[2]
- A published study of health disparities related to Krabbe disease identification[3]
- An abstract to be presented at an international meeting related to outcomes for infantile Krabbe disease with HSCT around 1 month of age[6]

Newborn Screening Clinical Validity

Sensitivity of Dried-Blood Spot Psychosine ≥10 nM

- Many cases of infantile Krabbe disease in the newborn period have psychosine levels far above 10 nM
- Very low risk of infantile Krabbe disease with newborn dried-blood spot psychosine <10 nM
  - Reports of psychosine <10 nM in residual dried blood spots could reflect lack of stability of psychosine[7,9-10]
  - One case with an initial dried-blood spot psychosine concentration of 1.2 nM later diagnosed with infantile Krabbe disease. However, the atypical course raises concern about whether this subject met the clinical criteria for infantile Krabbe disease[11]
  - No case of infantile Krabbe disease with psychosine <10 nM has been identified by the newborn screening programs

Specificity of Dried-Blood Spot Psychosine ≥10 nM

- Low risk of identifying later-onset Krabbe disease with newborn dried-blood spot psychosine ≥10 nM
  - One article described 11 cases of late-onset Krabbe disease (9 from newborn screening, 2 based on symptoms). Of these, one had dried-blood spot psychosine ≥10 nM (12 nM, at 460 days). The others had psychosine concentrations from 2.1-9.7 nM[7]
  - No case of later-onset Krabbe disease with psychosine ≥10 nM has been identified by the newborn screening programs

Findings from State Newborn Screening Programs

- Currently, some variation in first-tier screening and the use of molecular testing
- Two state newborn screening programs do not include psychosine as a second-tier test
- Nine state newborn screening programs include psychosine as a second-tier screening test, with a threshold ranging from 1-2 nM
  - 11 cases of infantile Krabbe disease have been identified by these newborn screening programs, all with psychosine ≥10 nM

Screening Program	Period	Number Screened	Positive First-Tier
GA	9/30/21-11/30/2023	329,661	63 (19.1 per 100,000 screened)
IL*	12/1/2017-9/30/2023	848,000	600 (70.8 per 100,000 screened)
IN	7/2020-11/2023	272,077	148 (54.4 per 100,000 screened)
KY	2/15/16-6/30/23	404,626	128 (31.6 per 100,000 screened)
MO	3/20/2020-8/31/2023	232,721	401 (172.3 per 100,000 screened)
NY	1/1/2021-9/30/23	572,197	38 (6.6 per 100,000 screened)
PA	5/21/2021-10/31/2023	316,918	43 (13.6 per 100,000 screened)
SC	5/15/2023-11/27/2023	29,748	16 (53.8 per 100,000 screened)
TN	7/1/2017-9/30/2023	545,085	68 (12.5 per 100,000 screened)
Total		3,551,033	1,505 (42.4 per 100,000 screened)

Screening Program	Period	Number Screened	Positive First-Tier	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)
IL*	12/1/2017-9/30/2023	848,000	600 (70.8 per 100,000 screened)	5 (0.8% of positive first-tier screens)
IN	7/2020-11/2023	272,077	148 (54.4 per 100,000 screened)	0
KY	2/15/16-6/30/23	404,626	128 (31.6 per 100,000 screened)	2 (1.6% of positive first-tier screens)
MO	3/20/2020-8/31/2023	232,721	401 (172.3 per 100,000 screened)	3 (0.7% of positive first-tier screens)
NY	1/1/2021-9/30/23	572,197	38 (6.6 per 100,000 screened)	0
PA	5/21/2021-10/31/2023	316,918	43 (13.6 per 100,000 screened)	1 (2.3% of positive first-tier screens)
SC	5/15/2023-11/27/2023	29,748	16 (53.8 per 100,000 screened)	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)
Total		3,551,033	1,505 (42.4 per 100,000 screened)	13 (0.9% of positive first-tier screens)

Screening Program	Period	Number Screened	Positive First-Tier	Psychosine ≥10 nM	Infantile Krabbe Disease
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)
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)
IN	7/2020-11/2023	272,077	148 (54.4 per 100,000 screened)	0	0
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)
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)
NY	1/1/2021-9/30/23	572,197	38 (6.6 per 100,000 screened)	0	0
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)
SC	5/15/2023-11/27/2023	29,748	16 (53.8 per 100,000 screened)	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)
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)

*No information available directly from the IL newborn screening program about the cases of infantile Krabbe disease

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)

Summary from the Nine Newborn Screening Programs that include Second-Tier Psychosine Testing

- Infantile Krabbe Disease case detection with second-tier psychosine ≥10 nM
  - 3.1 cases per million infants screened
- False Positive Second-Tier Tests
  - Two simultaneously submitted samples with low GALC enzyme activity contaminated with psychosine standard. Repeat psychosine at another laboratory was normal.
  - Led to a change in laboratory process
- False Negative Second-Tier Tests
  - No newborn screening program reported that a case would have been missed with psychosine concentration ≥10 nM
  - One state reported twins with psychosine concentrations of 4.9 and 5.2 nM who received HSCT around 100 days after birth but not classified as having infantile Krabbe disease

Summary from the Nine Newborn Screening Programs that include Second-Tier Psychosine Testing

- No case of later-onset Krabbe disease would have been identified by the state newborn screening programs with psychosine ≥10 nM
- Moving the threshold for second-tier psychosine to ≥10 nM for diagnostic referral would eliminate detection of about 9.3 cases of later-onset Krabbe disease (i.e., signs or symptoms at 12 months of age or later) per million infants screened

Impact of Detection by Newborn Screening Compared with Usual Case Detection

Summary from the Nine Newborn Screening Programs that include Second-Tier Psychosine Testing

- 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

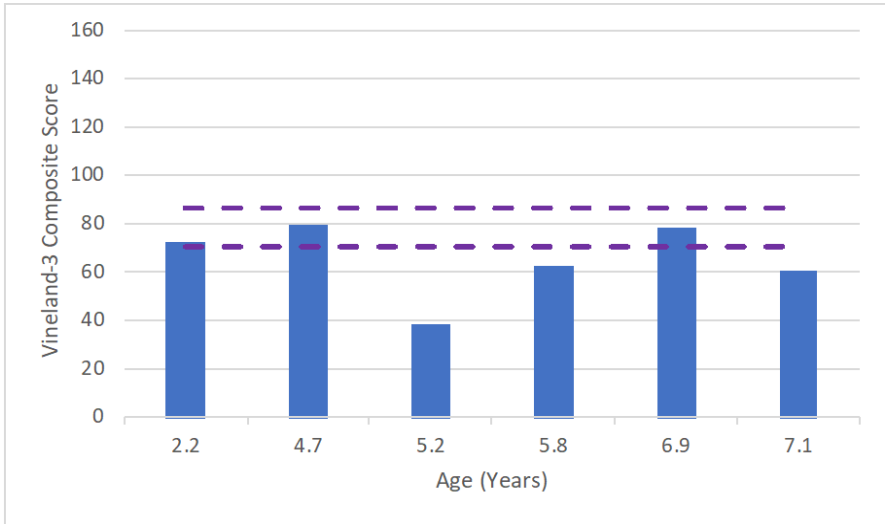
Point-in-Time Outcomes of 6 Cases

- Abstract describing 6 cases of infantile Krabbe disease past 2 years of age who received HSCT at 3-6 weeks of age[6]
  - Includes 5 out of 6 cases reported in an article included in the previous evidence review, recruited 2016-2019[13]
  - 1 additional case
  - Consecutively identified
  - Includes 2 of the 11 cases reported by the nine state newborn screening programs that include second-tier psychosine testing
- Outcomes
  - Vineland Adaptive Behavior Scales, third edition (Vineland-3)
    - 4 adaptive domains (communication, daily living skills, socialization, motor skills) and an overall adaptive behavior composite) – population mean 100, standard deviation 15
  - Pediatric Quality of Life Inventory
    - Physical and psychosocial subscales, and overall score with a population mean 100, standard deviation 15

Point-in-Time Outcomes of 6 Cases[6]

Psychosine (nM)	Age at HSCT (days)	Age at Neurodevelopmental Assessment (years)
70	32	2.2
35	40	4.7
38	28	5.2
83	31	5.8
61	24	6.9
24	39	7.1

Point-in-Time Outcomes of 6 Cases[6]

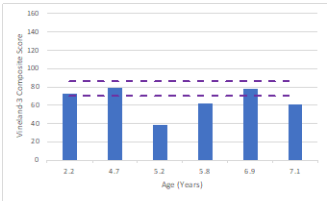


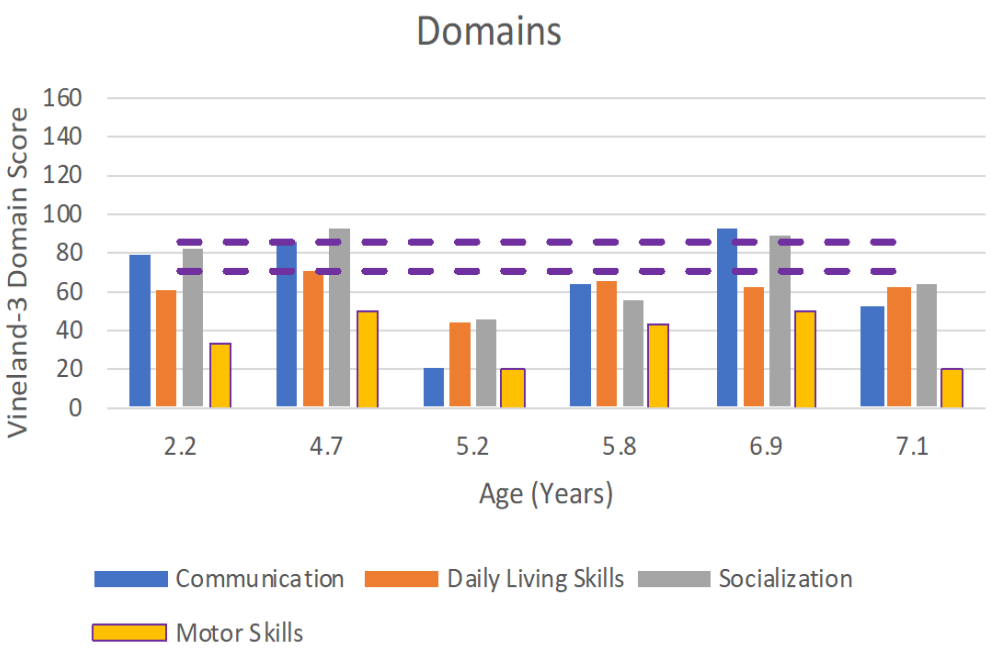
Adequate or above

Moderately Low

Low

Point-in-Time Outcomes of 6 Cases[6]



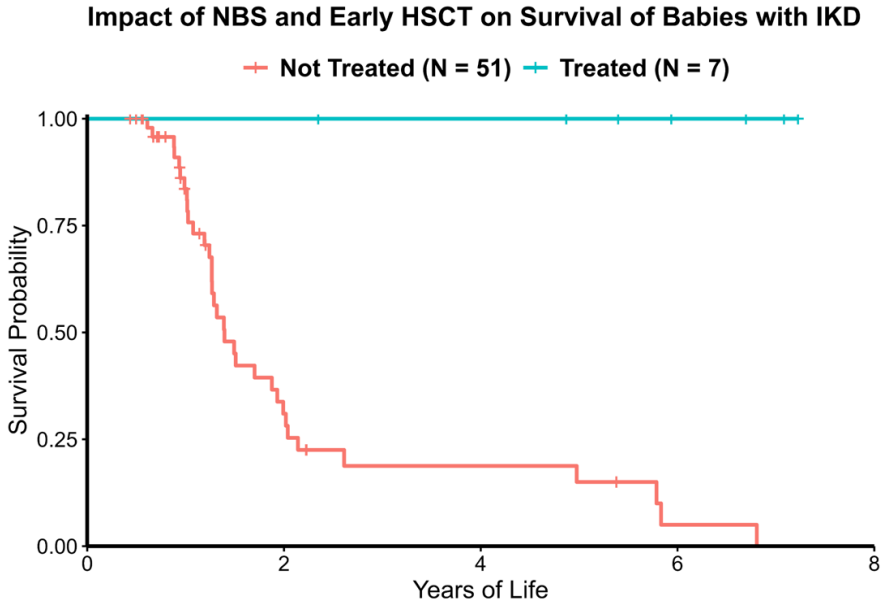


Adequate or above

Moderately Low

Low

Survival of 7 Cases Identified by Newborn Screening and Successfully treated with HSCT Around 1 month of age Compared with Outcomes without Newborn Screening[6]



- 2/7 (29%) cases of those described previously from the state newborn screening are included here
- Among the cases from the 9 programs with second-tier psychosine testing
  - 3/10 refused HSCT
  - 1/7 who received HSCT died

- 51 cases of infantile Krabbe disease from states without newborn screening who did not qualify for HSCT based on disease status

Family Perspective

Family Perspectives

- Online survey of 170 respondents impacted by Krabbe disease[2]
  - Nearly all (97%) "feel that KD NS should be implemented in every state"
  - Does not address perspectives of those not directly impacted by Krabbe disease
  - Unclear response rate

Health Disparities

Health Disparities

- Recent publication[3] suggests that Krabbe disease newborn screening can reduce disparities by race and ethnicity in detection and treatment
- Significant Methodological Limitations
  - Does not focus on infantile Krabbe disease
  - Excludes major Krabbe disease treatment centers
  - Risk of misclassification of race and ethnicity
  - Determining the timing of symptom onset and diagnosis not possible from administrative claims data only

Projecting Population Health Outcomes

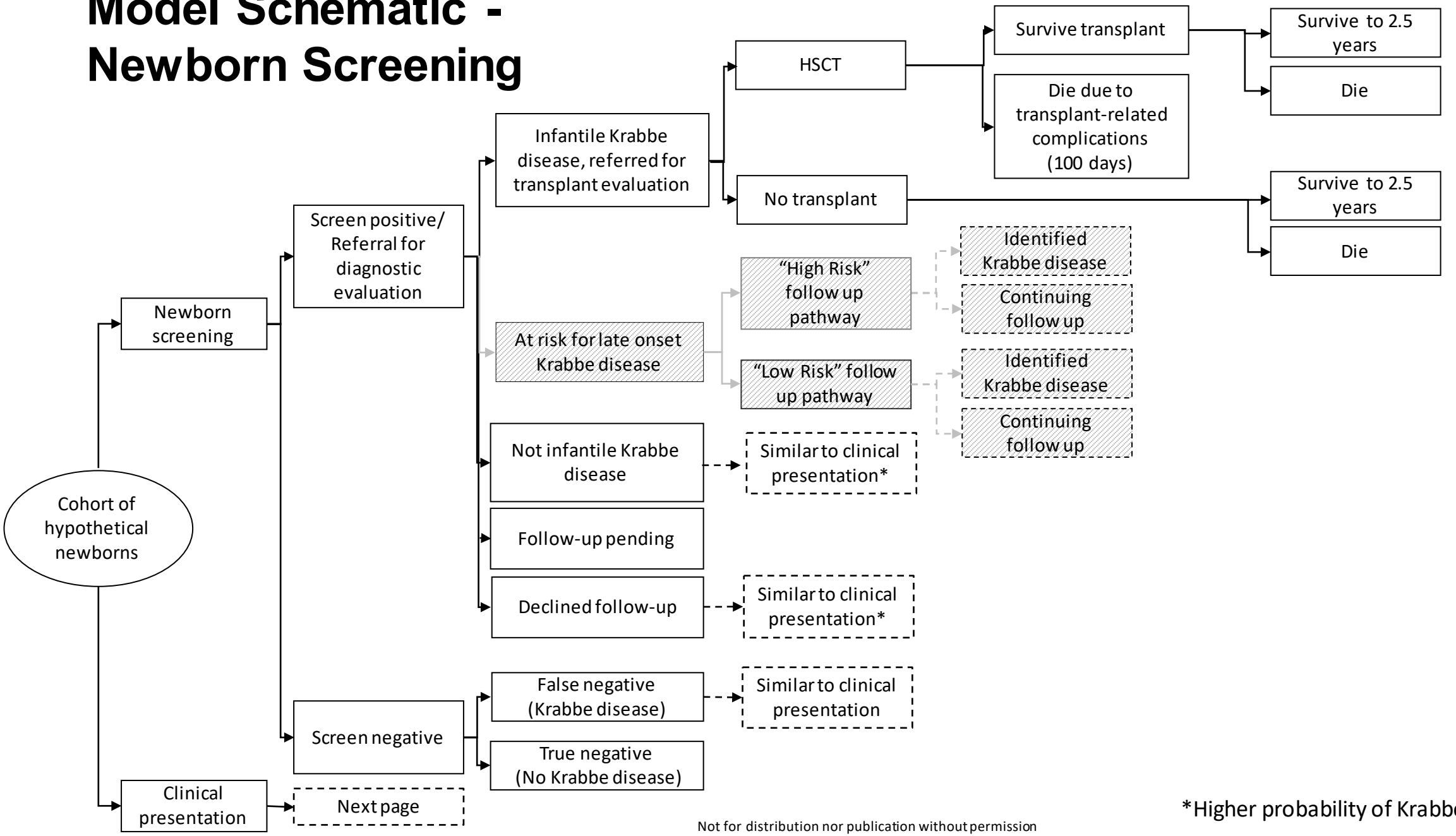
Methodological Approach - Decision Analysis

- Systematic approach to decision making under conditions of uncertainty
- Project ***ranges*** of short-term outcomes
- Allows decision maker to identify which alternative is expected to yield the most health benefit
- Identify key parameters and assumptions

Using modeling, objective is to project population-level health outcomes

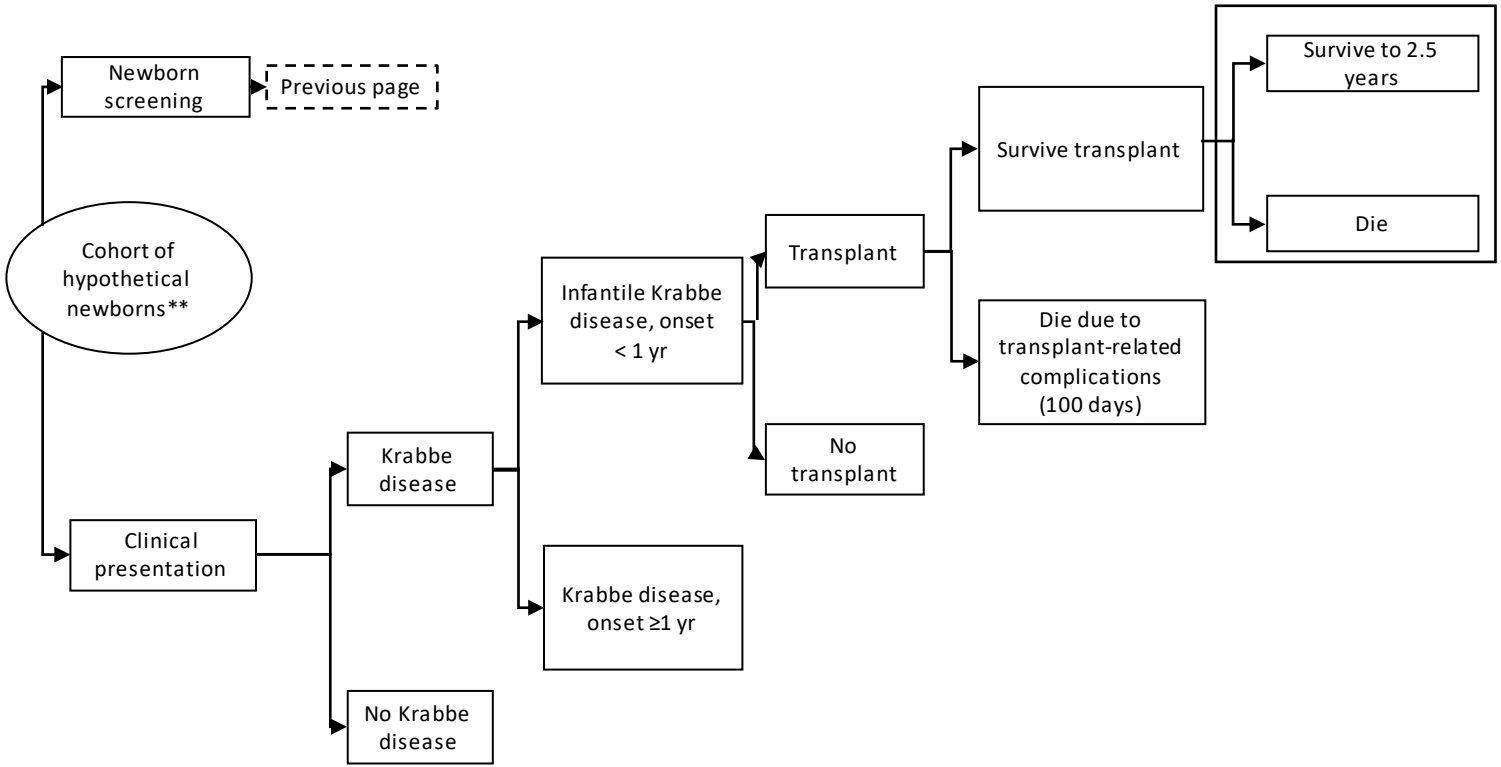
- Annual US newborn cohort of 3.65 million
- Health outcomes
  - Newborn screening (NBS)
    - Screening outcomes (positive screens)
    - Identified cases of Krabbe disease (KD): infantile, later-onset
    - Receipt of HSCT and transplant outcomes
    - Mortality
  - Clinical Presentation (CLIN)
    - Identified cases of Krabbe disease (KD): infantile, later-onset
    - Receipt of HSCT and transplant outcomes
    - Mortality

Model Schematic - Newborn Screening



*Higher probability of Krabbe disease

Model Schematic - Clinical Presentation



**Not otherwise at higher risk for Krabbe disease

Newborn Screening Parameters

Parameter	Most likely value	Range	Source
Screen positive/referral for diagnostic evaluation*	0.30977 per 100,000	0.15464 – 0.55426 per 100,000	Primary data (updated) from state newborn screening programs
Infantile Krabbe disease/referral for diagnostic evaluation given positive screen	1 (0.30977 per 100,000)†	0.72 – 1	
Not infantile Krabbe disease given positive screen	0	0 - 0.28	
Negative screen			
True negative	1	0.9999986 - 1	
False negative	0	0 – 0.0000014	
Identified with infantile Krabbe disease			
Received HSCT	0.88	0.62 – 0.98	Wasserstein 2016; Page 2022; primary data from state newborn screening programs (from previous analysis)
No HSCT	0.13	0.02 – 0.38	
Received HSCT			
Survive HSCT	0.89	0.67 – 0.99	Yoon 2021
Died due to HSCT-related complications within 100 days	0.11	0.01 – 0.33	
Survival at 30 months			
HSCT, survived 100 days	1	0.59 – 1	Wasserstein 2016; Page 2022
No HSCT	0.23	0.14 – 0.35	Duffner 2012

* Using the revised nomination screening algorithm: psychosine ≥10 nM referred for diagnostic evaluation.
†Incidence at the population level as an alternative representation of this value

Clinical Presentation - Parameter inputs

Parameter	Probability	Range	Source
Krabbe disease	0.662 per 100,000	0.236 - 1.18 per 100,000	Primary data (updated) from state newborn screening programs, Wenger 2013
Infantile Krabbe disease, 0-11 mo	0.47	0.40 - 0.53	Primary data from state newborn screening programs, Komatsuzaki et al 2019
Not infantile-onset Krabbe disease, 12+m	0.53	0.47 - 0.60	
Infantile Krabbe disease, 0-11 mo			
Received transplant	0.1	0 - 0.2	Assumption
No transplant	0.9	0.8 - 1	Assumption

Survival- Newborn Screening and Clinical Presentation

Parameter	Probability	Range	Source
Transplant outcomes			
Survive transplant	0.89	0.67 - 0.99	Yoon 2021
Died due to transplant-related complications within 100 days	0.11	0.01 - 0.33	
Survival at 30 months			
Survival given infant has received transplant and survived 100 days	1	0.59 - 1	Wasserstein 2016; Page 2022
Died given infant has received transplant	0	0 - 0.41	
Survival with no transplant			
Survival given infant has not received transplant	0.23	0.14 - 0.35	Duffner 2012
Died given infant has not received transplant	0.77	0.65 - 0.86	

Note: Input parameters unchanged from previous evidence review, based on published evidence.

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

Results: Projected clinical identification outcomes, # newborns (range)

Annual cohort of 3.65 million newborns

Diagnosis	Clinical Presentation	Range
Krabbe disease	24.2	8.6 - 43.3
Infantile, 0-11 months	11.3	4.0 – 23.0
Post-infantile, 12+ months	12.9	4.6 – 20.2

Projected cases of Krabbe disease, comparing newborn screening using the revised nomination screening algorithm* with clinical identification

Diagnosis by Method of Detection	Most Likely	Range
Newborn screening		
Infantile Krabbe disease*	11.3	5.6 - 20.3
Clinical presentation		
<1 year	11.3	4.0 - 23.0
≥1 year	12.9	4.6 - 20.2
Krabbe disease, total	24.2	8.6 - 43.4

*Psychosine ≥10 nM referred for diagnostic evaluation

Results: Projected outcomes at 2.5 years of age for newborn screening using the revised nomination screening algorithm* compared with clinical presentation

Potential Screening Outcomes	Newborn Screening	Clinical Presentation	Difference (NBS – CLIN)
Receive HSCT by 1 year	9.9 (3.5 – 19.9)	1.1 (0 – 4.0)	8.8 (3.3 - 16.6)
Died from complications of HSCT	1.0 (0.1 – 4.1)	0.1 (0 – 0.4)	0.9 (0.1 – 4.1)
Survive HSCT	8.9 (2.3 – 19.7)	1.0 (0 – 4.0)	7.8 (2.3 – 15.7)
Did not Receive HSCT by 1 year	1.4 (0.1 – 7.8)	10.2 (2.8 – 23.0)	-8.8 (-15.9, - 1.9)
Died from Krabbe disease by age 30 months	1.1 (0 – 10.1)	7.8 (1.8 – 19.7)	-6.7 (-11.7, - 0.7)
Total who died by age 30 months	2.1 (0.1 – 14.2)	7.9 (1.8 – 19.7)	-5.8 (-10.4 – 0.5)

*Psychosine ≥10 nM referred for diagnostic evaluation

References

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Questions