Newborn Screening for Krabbe Disease for the 2022 RUSP Nomination

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Disease Course and Epidemiology

Krabbe Disease Overview

- Autosomal recessive lysosomal disorder
- Low functional levels of galactocerbrosidase (GALC)
  - GALC degrades galactolipids, including psychosine
  - Leads to death of myelin-producing oligodendrocytes and Schwann cells
  - Accumulation of globoid cells, which accumulate around areas of active demyelination
- Clinical findings due to white matter damage in the central nervous system (CNS) and peripheral nerve demyelination

Natural History

- Broad range of onset of clinical findings
- Untreated, the majority of cases will develop signs and symptoms by 36 months
- Earlier signs and symptoms associated with more severe illness and more rapid progression
  - Typically presenting signs in infancy are feeding problems and significant irritability
  - Without treatment, death in early childhood

Natural History

- Review of case reports and case series from 1982-2017 (n=248)

	Early Infantile (0-6 months)	Late infantile (7-36 months)	Juvenile/Adolescent (37-180 months)	Adult-Onset (>180 months)
Number (%)	98 (39.5%)	57 (23%)	46 (18.5%)	42 (16.9%)
Age of onset (median, range)	4 (3-5)	14 (10-24)	48 (48-72)	384 (165.9-516)
Survival	Median: 1.5 years	Median: 9.5 years	80% alive at 16 years	88% alive at 19 years

Komatsuzaki S, Zielonka M, Mountford WK, et al. Clinical characteristics of 248 patients with Krabbe disease: quantitative natural history modeling based on published cases. *Genet Med.* 2019;21:2208-2215.

Case Definition – Target for Newborn Screening

- Krabbe disease with expected onset of signs and symptoms by 36 months
  - Low GALC enzyme activity
  - Elevated psychosine concentration
  - *GALC* 30-Kb deletion or other pathogenic variants
  - Findings on neurophysiological studies and/or neurologic imaging tests

GALC Gene

- Chromosome 14, about 60-Kb with 17 exons
  - Most common variant associated with significant pathology: 30-Kb deletion, with an allele frequency of 1 per 2711; associated with many cases of infantile Krabbe disease (24%-66%)

Genome database	# GALC variants reported	# Pathogenic/ Likely Pathogenic	# Benign/ Likely Benign
Genome Aggregation Database [gnomAD]	>1400	62	179
ClinVar (curated database)	964	207	340

Birth Prevalence of Krabbe Disease

- Estimated Birth Prevalence using diagnosed cases

Country	Est. Live births (per 100,000)	95% Confidence Interval (CI)	Reference (1st au, year)
Finland	1.1	(0.23 – 3.1)	Knuutinen, 2021
Sweden	2.6	--	Hult, 2014
United Kingdom	0.5	--	Stellitano, 2016
United States *(*pediatric hospitalizations*)	0.3	--	Ghabash, 2022

- Estimated birth prevalence based on distribution of pathogenic variants, including those associated with adult onset
  - —As high as 8.3 per 100,000 per live births (Soderholm, 2020)

Newborn Screening and Diagnosis

Krabbe Disease Newborn Screening

- First-Tier Screening
  - **Low GALC enzyme activity on dried-blood spot**
    - MS/MS or fluorometry
    - MS/MS can be multiplexed with screening for other lysosomal storage disorders, but increases the incubation time
- Second-Tier Screening (or Reflex testing)
  - **Psychosine concentration on dried-blood spot**
    - Increases specificity
    - Sent to a referral laboratory
    - Available after 2015
  - ***GALC* molecular analysis**
    - 30-Kb deletion
    - Other variants
- Newborn screening programs have adopted various strategies of second-tier testing. The condition nomination specifies second-tier psychosine testing.

Krabbe Disease Newborn Screening to Diagnosis

- Krabbe disease has variable ages of onset.
- The ideal diagnostic process would not only diagnose whether an infant with a positive screen has Krabbe disease, but would predict age of onset to guide monitoring and treatment.

Expert Panel Recommendations For Follow-up After a Positive Newborn Screen

- Dried-blood spot psychosine levels
  - ≥2 nmol/L abnormal
    - ≥10 nmol/L strongly predictive of early infantile Krabbe disease (EIKD), follow-up is time critical
- Clinical follow-up pathways (3) suggested by experts
  1) EIKD: immediate referral for diagnostic evaluation and treatment
  2) "At-risk for late-onset Krabbe disease" (late infantile, childhood, juvenile, adult onset): follow-up in 2-4 weeks by a specialist or primary care provider in consultation with a specialist for further testing. Genotype can further stratify infants to:
     - *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
  3) Not expected to have Krabbe disease: no follow-up

Thompson-Stone, Ream, Gelb 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.

Diagnostic Evaluation

- GALC enzyme activity (clinical), psychosine concentration (clinical), molecular testing (if not previously done)
- Complete exam, neurophysiological studies, neurologic imaging, including:
  - MRI
  - Nerve conduction studies
  - Electroencephalogram (EEG)
  - Auditory and Visual Evoked Potentials
  - Cerebrospinal fluid (CSF) protein
- The timing of specific studies and imaging tests is based on risk classification.
- Staging systems have been developed to help synthesize the findings.

Krabbe Disease Newborn Screening in the US

- Ten newborn screening programs currently include Krabbe disease newborn screening
- Since the start of screening overall (2006) – reflecting all programs and all screening algorithms
  - 7.4 million infants screened
  - 28 infants with expected onset prior to 12 months of age (0.38 per 100,000 infants screened)

Krabbe Disease Newborn Screening in the US: Published Reports

State	Years	Second-Tier	Number Screened	Findings	Reference (1st au, year)
New York	2006 - 2015	Molecular Analysis	2.2 million	5 Early Infantile 55 at risk for later onset	Orsini, 2016a; Orsini, 2016b; Wasserstein, 2016
Missouri	2012 - 2015	Molecular Analysis	230,700	2 with disease-causing variants, asymptomatic	Orsini, 2016b
Illinois	2017 - 2020	Psychosine and Molecular Analysis	494,147	2 infantile onset, 6 suspected late-onset	Basheeruddin, 2021
Kentucky	Feb 2016– Feb 2017	Psychosine	55,161	1 infantile onset	Minter Baerg, 2018

Krabbe Disease Newborn Screening in the U.S.: Current Approaches

Newborn Screening Program	Year Screening Began	First-Tier GALC Enzyme Activity Testing	Second-Tier Psychosine Testing	Psychosine Cutoff	GALC 30-Kb deletion testing concurrent with psychosine testing	GALC Sequencing
Georgia	2021	In-house, MS/MS	Mayo Clinic	2.0	---	---
Illinois	2017	In-house, MS/MS	PerkinElmer	1.5	Yes	Yes
Indiana	2020	In-house, MS/MS	PerkinElmer	1.5	Yes	Yes
Kentucky	2016	Sent to Mayo Clinic	Mayo Clinic	2.0	Yes	Third-Tier
Missouri	2012	In-house, Fluorometric	Mayo Clinic	2.0	---	---
New Jersey	2019	In house, MS/MS	No	---	---	---
New York*	2006	In-house, MS/MS	Mayo Clinic since 2022*	2.0	Yes	Yes
Ohio	2016	In house, MS/MS	No	---	---	---
Pennsylvania	2021	Sent to PerkinElmer	PerkinElmer	1.5	Yes	Yes
Tennessee	2017	In-house, MS/MS	PerkinElmer	1.5	Yes	Yes

*Psychosine testing added later

Newborn Screening Outcomes

Newborn Screening Program	Screening Period	Number of Infants Screened	Referrals per 100,000 Screened	Krabbe Disease with Expected onset ≤12 mos per 100,000 Screened *[additional follow-up]*	At-Risk for Onset after 12 months per 100,000 Screened	Pending Classification, Declined Follow-up, Lost Referrals
Referral based on GALC Enzyme Activity Only						
Ohio	April 2020-Sept 2022	808,816	54.0	0.4 (n=3)*	1.2 (n=10)*	Pending: 20 Declined: 36 Lost: 1
New Jersey	July 2019-Sept 2022	312,158	28.9	0 (n=0)	2.2 (n=7)*	Pending: 8 Declined: 0 Lost: 4
Referral based on GALC Enzyme Activity Psychosine concentration, & GALC 30Kb Deletion						
Missouri	March 2020-Aug 2022	168,042	11.9	0.6 (n=1) [HSCT at 31 days]	1.2 (n=2)	Pending: 0 Declined: 0 Lost: 1
Tennessee	July 2017-Sept 2022	421,481	13.8	0.2 (n=1) [HSCT at 36 days]	0.5 (n=2) [Asymptomatic, no HSCT]	None
Referral based on GALC Enzyme Activity Psychosine concentration, &/OR GALC 30Kb Deletion						
Georgia	Sept 2021-Sept 2022	144,000	0.7	0.7 (n=1) [Family elected no HSCT]	0	None
Illinois	Oct. 2021-July 2022	98,721	8.1	0	2.0 (n=2)*	Pending: 2 Declined: 0 Lost: 0
Indiana	July 2020-Oct 2022	172,803	6.4	0	2.3 (n=4)*	None
Kentucky	Feb 2016-Sept 2022	330,555	0.6	0.6 (n=2) [HSCT at 24 and 30 days]	0	None
New York	March 2018-Sept 2022	985,726	7.3	0.2 (n=2) † [No HSCT based on psychosine and lack of symptoms]	2.5 (n=25)*	None
Pennsylvania	May 2021-Aug 2022	167,537	11.3	1.8 (n=3) [HSCT at 34 days, 101 days, 150 days]	0.6 (n=1)	Pending: 2 Declined: 0 Lost: 0

Newborn Screening Outcomes: Current Algorithms

- 3.6 million infants screened, since 2016
- Referrals
  - GALC only: 47.0 per 100,000
  - All others: 7.7 per 100,000
- Diagnoses
  - Krabbe disease with expected onset in the first 12 months: 13 (0.36 per 100,000)
  - Expected onset after 12 months: 15 (1.46 per 100,000)
  - 32 referrals pending classification, 36 declined follow-up, 6 lost to follow-up, most (77%) from a program which only screens using GALC enzyme activity
- One identified case refused HSCT
- Risk of misclassification in this table

Newborn Screening Program Cost of Krabbe Disease Screening

Cost of Krabbe Disease Newborn Screening

- Estimated cost from the program perspective, above and beyond the fixed cost of the existing newborn screening program: Between $2 and $7.
- Most of estimated costs reflect equipment, reagents, and added laboratory technician and laboratory scientist time for first-tier screening

Impact of Early Treatment

Hematopoietic Stem-Cell Transplant (HSCT)

- Initially described in 1998 (Krivit et al.)
- A case series from 2005 established the recommendation for treatment by around 6 weeks for those with early infantile Krabbe disease (Escolar et al.)
  - 11 subjects diagnosed prenatally or shortly after birth with early infantile Krabbe disease and received HSCT at a median age of 18.5 days when asymptomatic
  - 14 subjects diagnosed from 4-9 months of age and received HSCT from 142-352 days
  - Outcomes:
    - Survival: no deaths in asymptomatic group with a median follow-up of 36 months; 6 of the 14 infants in the symptomatic group survived for a median follow-up of 41 months
    - Motor Development: 10 in the asymptomatic group with follow-up; 1 with severe delays, 4 with mild-to-severe-delays, 2 with truncal weakness; symptomatic group who survived had "developmental level equivalent to that of a one-month-old."

Krivit W, Shapiro EG, Peters C, et al. Hematopoietic stem-cell transplantation in globoid-cell leukodystrophy. *N Engl J Med.* 1998;338:1119-1126.

Escolar ML, Poe MD, Provenzale JM, et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. *N Engl J Med.* 2005;352:2069-2081.

Clinical Practice Guidelines from the Hunter's Hope Leukodystrophy Care Network (2019)

- "HSCT does not offer benefit to infants with EIKD after symptoms have developed."
- Goal: HSCT by 4-6 weeks after birth of early infantile Krabbe disease

Page KM, Stenger EO, Connelly JA, et al. Hematopoietic Stem Cell Transplantation to Treat Leukodystrophies: Clinical Practice Guidelines from the Hunter's Hope Leukodystrophy Care Network. *Biol Blood Marrow Transplant.* 2019;25:e363-e374.

Experimental therapies in clinical trials

- Intrathecal delivery of a stem cell line derived from umbilical cord blood
- Gene therapies delivered by adeno-associated virus in Phase I/2 trials after FDA fast-track clearance for IND and human trials
  - FBX-101
  - PBKR03
- HSCT is the current recommended therapy targeted for Krabbe disease

Considerations before reviewing treatment studies

- Method of diagnosis could impact outcomes
  - Family history can lead to earlier delivery and expedite treatment
- Understanding of Krabbe disease and treatment has evolved over time
- Data points of interest for the purposes of making newborn screening recommendations are often not available
  - Pathway to diagnosis and method of categorizing phenotype
  - Genotype
  - Psychosine concentration, which was not available until after 2015
  - Standardized outcome measures at specific ages

Early Detection and Treatment Cases – Family History (n=6)‡

Classification	GALC/ Initial Psychosine Concentration*	Age at HSCT	Age at Follow-up, Status	Reference (1st Author Year)
Infantile	NR/NR	3.3 weeks	5 years, Kindergarten with an aide, able to run, talk in 5-word phrases, feed herself, ankle clonus, upgoing plantar responses, tendency to toe-walk	[50]Gelinas 2012
NP	NR/NR	4 weeks	5 years, spastic quadriparesis, need g-tube, some speech, "dependent for all cares"	[54†]Donoghue 2012
NP	NR/NR	5 weeks	5 years, neurologically abnormal, unable to walk, needs g-tube, some speech	[54†]Donoghue 2012
Infantile	NR/NR	6.5 weeks	7 years, requires wheelchair, not developmentally delayed	[55†]Donoghue 2016
Infantile	NR/NR	7 weeks	11 months, "doing well"	[55†]Donoghue 2016
Late Infantile	COMPHET30/NR	4.5 months	5 years, normal neurological exam	[51]Miśkiewicz-Migoń 2021

**GALC molecular analysis categorized as homozygous for the 30-Kb deletion (HOM30), compound heterozygous for the 30-Kb deletion with another variant present (COMPHET30), or whether the subject has other pathogenic variants (Other); for GALC and psychosine concentration
†Abstract from a meeting presentation; NR=not reported
‡Duplicated cases removed when possible.
Note: For NBS identified cases, early infantile and infantile classifications based on state reporting.

Early Detection/Treatment Cases – Newborn Screening (Infantile n=15)

State Newborn Screening Prog	Classification	GALC/ Initial Psychosine Concentration*	Age at HSCT	Age at Follow-up, Status	Reference (1st Author Year)
New York	Early Infantile	HOM30/NR	Family refused	18 months, died	[34]Wasserstein, 2016
New York	Early Infantile	HOMO30/NR	3.3 weeks	69 days, died	[34]Wasserstein, 2016
Kentucky	Early Infantile	NR/NR	3.3 weeks	9 months, "developing normally…but with some complications, attributed to the transplant itself."	[39]Minter Baerg, 2018
New York	Early Infantile	COMPHETERO30/NR	3.5 weeks	11 years, severely developmentally delayed, requires continuous care	[34]Wasserstein 2016 [49†]Wright 2017 [40]Kurtzberg 2023
Not New York	Infantile	COMPHET30/61	3-4 weeks	4.8 years, requires wheelchair, needs g-tube, developmentally delayed	[47]Page 2022
Not New York	Infantile	NR/NR	4 weeks	16 months, alive but no additional information	[40†]Kurtzberg 2023
Not New York	Infantile	Other/73	4-5 weeks	45 months, requires wheelchair, developmentally delayed	[47]Page 2022
Not New York	Infantile	HOMO30/56	4-5 weeks	52 months, requires wheelchair, developmentally delayed	[47]Page 2022
New York	Early Infantile	HOMO30/NR	4.5 weeks	84 days, died	[34]Wasserstein 2016
New York	Early Infantile	COMPHET30/N	4.5 weeks	15 years, requires wheelchair, attends school, uses upper extremities normally, eats and communicates orally and with an assistive device."	[34] Wasserstein 2016 [40†] Kurtzberg 2023
Not New York	Infantile	COMPHET30/38	5-6 weeks	36 months, requires wheelchair, needs g-tube, developmentally delayed	[47]Page 2022
Not New York	Infantile	COMPHET30/35	5-6 weeks	30 months, developmentally delayed	[47]Page 2022
Not New York	Infantile	COMPHET30/24	5-6 weeks	58 months, requires wheelchair, needs g-tube, developmentally delayed	[47]Page 2022
New York	Infantile	Other/2-10	18 months	5 years, "normal"	[40†]Kurtzberg 2023
New York	Infantile	Other/2-10	18 months	5 years, "normal"	[40†]Kurtzberg 2023

Early Detection and Treatment Cases – Newborn Screening (High Risk n=10)

State Newborn Screening Program	Classification	GALC/ Initial Psychosine Concentration*	Age at HSCT	Age at Follow-up, Status	Reference (1st Author Year)
New York	High risk	Other/NR		6 months	[34]Wasserstein 2016
New York	High risk	Other/NR		6 months	[34]Wasserstein 2016
New York	High risk	Other/NR		13 months	[34]Wasserstein 2016
New York	High risk	Other/NR		2 years	[34]Wasserstein 2016
New York	High Risk (retrospectively assigned as Onset in Late Infancy)	Other/1.2	Not offered prior to significant signs and symptoms	26 months, died	[32]Corre 2021
New York	High risk	Other/NR		4 years	[34]Wasserstein 2016
New York	High risk	Other/NR		4 years	[34]Wasserstein 2016
New York	High risk	Other/NR		5 years	[34]Wasserstein 2016
New York	High risk	Other/NR		7 years	[34]Wasserstein 2016
New York	High risk	Other/NR		8 years	[34]Wasserstein 2016

Early Detection & Treatment Cases – Not Otherwise Specified (n=15)

Classification	GALC/ Initial Psychosine Concentration*	Age at HSCT	Age at Follow-up, Status	Reference (1st Author Year)
Early Infantile	NR/NR	2.6 weeks	16.2 years, cannot walk, not toilet trained	[49] Allewelt 2017
Early Infantile	NR/NR	2.7 weeks	13.1 years, walks	[49] Allewelt 2017
Early Infantile	Other/NR	2.9 weeks	7.1 years, walks with assistive device	[49] Allewelt 2017
Early Infantile	NR/NR	3.1 weeks	6.29 years, died	[49] Allewelt 2017
Early Infantile	NR/NR	3.1 weeks	15 years, walks with assistive device	[49] Allewelt 2017
Early Infantile	NR/NR	3.3 weeks	11.2 years, walks with assistive device, not toilet trained	[49] Allewelt 2017
Early Infantile	NR/NR	3.6 weeks	11.3 years, walks	[49] Allewelt 2017
Early Infantile	NR/NR	3.7 weeks	12.3 years, walks with assistive device, needs g-tube	[49] Allewelt 2017
Early Infantile	NR/NR	4 weeks	10.2 years, walks with assistive device	[49] Allewelt 2017
Early Infantile	NR/NR	4.1 weeks	14.9 years, walks with assistive device	[49] Allewelt 2017
Early Infantile	COMPHET30/NR	4.7 weeks	8.6 years, cannot walk, not toilet trained	[49] Allewelt 2017
Early Infantile	NR/NR	5.1 weeks	13.8 years, walks with assistive device	[49] Allewelt 2017
Early Infantile	HOMO30/NR	5.3 weeks	15.4 years, died	[49] Allewelt 2017
Early Infantile	NR/NR	7 weeks	7.6 years, walks with assistive device, not toilet trained	[49] Allewelt 2017
NR	NR/NR	6 months	20 days after HSCT, died	[52]Wall 2010

Summary of Early Treatment Outcomes

- HSCT is the recommended treatment for individuals with Krabbe disease with expected onset of signs and symptoms by 36 months of life.
- For those with expected early infantile Krabbe disease (i.e., onset by 6 months of life), HSCT is recommended with a goal of treatment by 4 to 6 weeks after birth. Timely HSCT can reduce the risk of childhood mortality, but other outcomes are more variable and insufficient evidence is available to enable prediction of these other outcomes.

Summary of Early Treatment Outcomes (con't)

- For individuals with Krabbe disease with expected onset of signs and symptoms between 6 – 36 months, the available evidence suggests that treatment before the development of signs or symptoms reduces the risk of mortality and, although the evidence base is limited, there appears to be an association with improved cognitive, language, and fine motor development.

- The greatest risk of mortality following HSCT is around 100 days after treatment. Limited data suggest the risk is 11% in centers with expertise in HSCT for Krabbe disease. There is insufficient data about other potential long-term negative outcomes associated with HSCT for Krabbe disease.

Potential Benefits of Screening

Potential Benefits of Screening

- Krabbe disease newborn screening can eliminate the diagnostic odyssey. Infants with early infantile Krabbe disease develop feeding problems and extreme irritability. Natural history studies suggest that when there is no family history of Krabbe disease, the diagnosis of early infantile Krabbe disease is delayed beyond the recommended period of 4 to 6 weeks of age when HSCT would be an option.

- Detection of early infantile Krabbe disease through newborn screening allows families to decide whether to have their infant receive HSCT within the recommended period of 4 to 6 weeks of age.

- HSCT by 4 to 6 weeks of age for early infantile Krabbe disease is associated with decreased risk of childhood mortality.

Potential Benefits of Screening

- HSCT by 4 to 6 weeks of age for early infantile Krabbe disease is associated with improved functional outcomes, although outcomes can be variable and difficult to predict. A limitation of the evidence base is that these studies lack specific outcome measures at specific ages related to standardized health outcomes and quality of life. Similarly, the articles do not address the impact of Krabbe disease with or without HSCT on the family.

- A limited evidence base suggests that HSCT for late-infantile Krabbe disease (i.e., onset 6 – 36 months) early in the disease course is associated with decreased mortality and improved functional outcomes, with some variability.

Potential Harms of Screening

Potential Harms of Screening

- There are potential harms associated with all screening programs.

Potential Harms of Screening (con't)

- A false negative screen would be a harm because it could lead to false reassurance, potentially delaying diagnosis after signs or symptoms appear.
  - Although premature infants might have a higher likelihood of false negative first-tier screening with GALC enzyme activity, no missed cases have been reported.
  - The potential harm of false negative with second-tier psychosine testing is low. One case of infantile Krabbe disease with non-elevated psychosine concentration has been described (Corre et al., 2021) ; the study authors suggest this infant had a secondary condition.
- Treatment with HSCT when it is not required would be a harm. Using current diagnostic approaches (i.e., low GALC enzyme activity and elevated psychosine, known pathogenic *GALC* variants, complete neurological evaluation), the risk of HSCT being performed for Krabbe disease when it is not indicated is assumed to be low.

Potential Harms of Screening (con't)

- Krabbe disease newborn screening could lead to HSCT in centers with less experience than the small number of treatment centers that provide most of the outcome data included in this report, potentially leading to worse outcomes.
- Infants at risk for late onset Krabbe disease can require long-term clinical follow-up. Little is known about the impact of this follow-up on families.

Public Health System Impact

Adoption of Krabbe Disease Newborn Screening

- Ten programs have implemented Krabbe disease newborn screening
- Virginia has recently chosen not to implement Krabbe disease newborn screening (Schrier Vergano, 2022)
  - Not on the Recommended Uniform Screening Panel
  - Concerns about risk prediction
  - Challenges in providing HSCT by 30 days.
- Experts have emphasized that HSCT can be given up to 6 weeks for those with early infantile Krabbe disease

Potential for Implementing Krabbe Disease Newborn Screening

- Survey October 2022-December 2022 sent to 53 programs
- 34 of 44 programs (77%) responded that did not include Krabbe disease newborn screening at the time of the survey
- Expected time to implementation after a recommendation
  - <2 years: 36%
  - 2-3 years: 43%
  - 3-4 years: 12%
  - >4 years: 3%

Barriers and Facilitators Identified by PHSI Survey Respondents (n=34)

Possible Facilitators	Percent (%) indicating as Facilitator
Advocacy activities	27
Ability to multiplex screening	27
Expected clinical outcomes	21

Possible Barriers	Percent % indicating as Barrier
Availability of timely treatment	62
Other program activities	62
Increasing the newborn screening fee	47
Availability of GALC enzyme activity testing	47
Availability of specialists for diagnosis	41
Expected clinical outcomes	41
Administrative challenges	38
Availability of second-tier testing	24
Availability of staff for short-term follow-up	21

Treatment Center Availability

- Cannot be assessed by the Public Health System Impact Assessment
- 12 centers in the Leukodystrophy Care Network
- Hunter's Hope Krabbe Newborn Screening Advisory Council as resource for states, clinicians, families
- Experts willing to share expertise

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 & 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, confirmed Krabbe disease (KD), at risk for KD, other)
    - Cases: newborns who receive transplant, transplant outcomes
    - Mortality
  - Clinical Presentation (CLIN)
    - Identified cases of Krabbe disease: early infantile, later onset
    - Mortality

Projected Screening Results, # newborns (range)

	Newborn Screening	Clinical Presentation
Referred for clinical evaluation		
Infantile Krabbe disease		
At risk for Krabbe disease		
High risk		
Low risk		
Normal		
Pending diagnosis		
Received HSCT		

Assumptions (1)

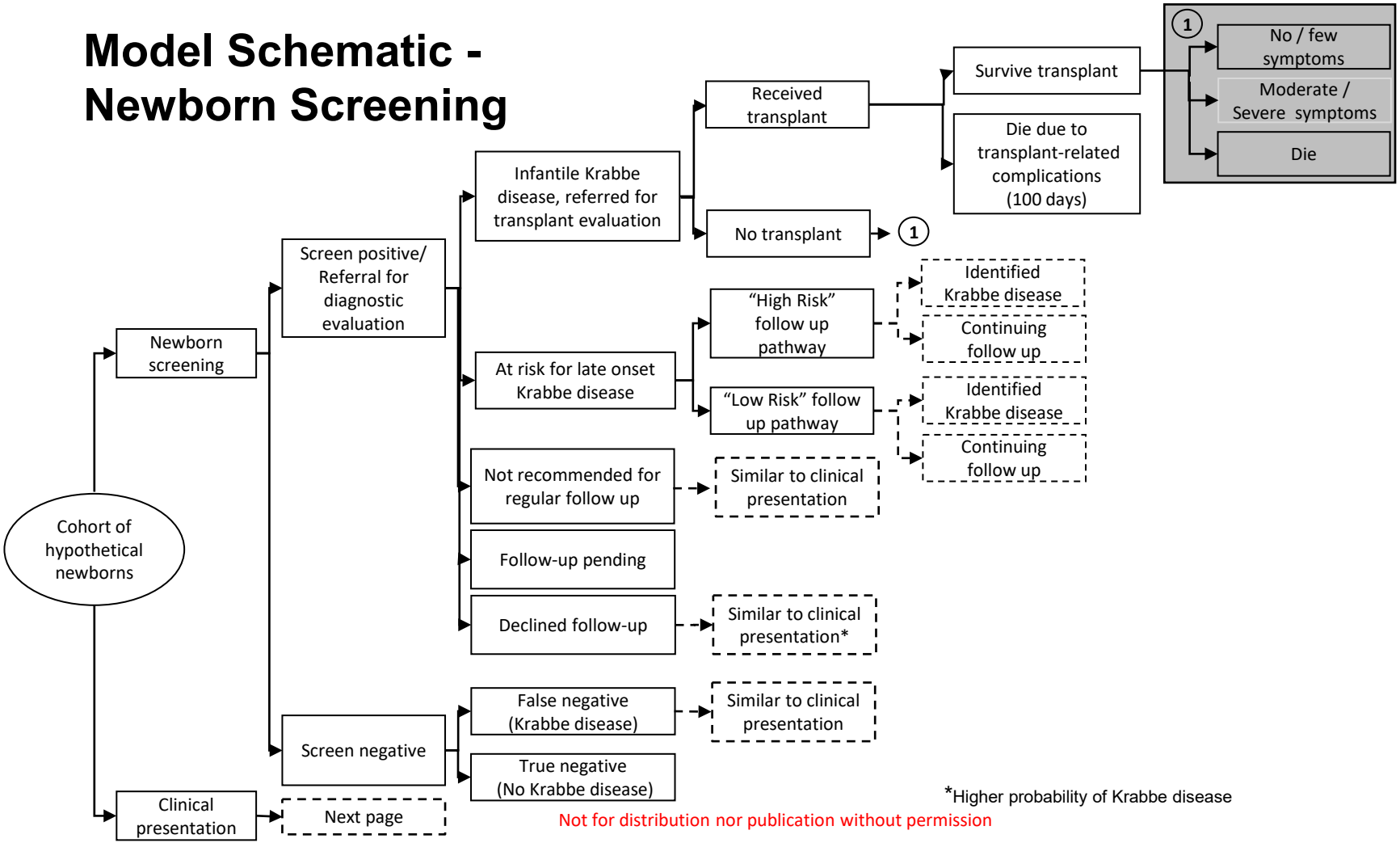
- Classification based in part on information available from state newborn screening programs
  - <12 months onset
  - 12+ months onset
- For NBS-identified newborns recommended for immediate treatment, transplant occurs before the development of overt symptoms
- Differences in outcomes for transplants occurring ≤ 30 days or >30 days are not included in the model (key assumption: differences in treatment effectiveness more likely due to other factors, such as severity of illness at time of HSCT, than a threshold of 30 days)

Assumptions, cont. (2)

- Newborns identified with markers suggesting Krabbe disease onset by 12 months are recommended for HSCT; most will be symptomatic at time of transplant
- Probability of mortality due to transplant-related complications within 100 days of transplant is the same for infants identified through NBS or clinical presentation
- HSCT-related morbidity >100 days post-transplant is typically not life threatening; not included in modeling

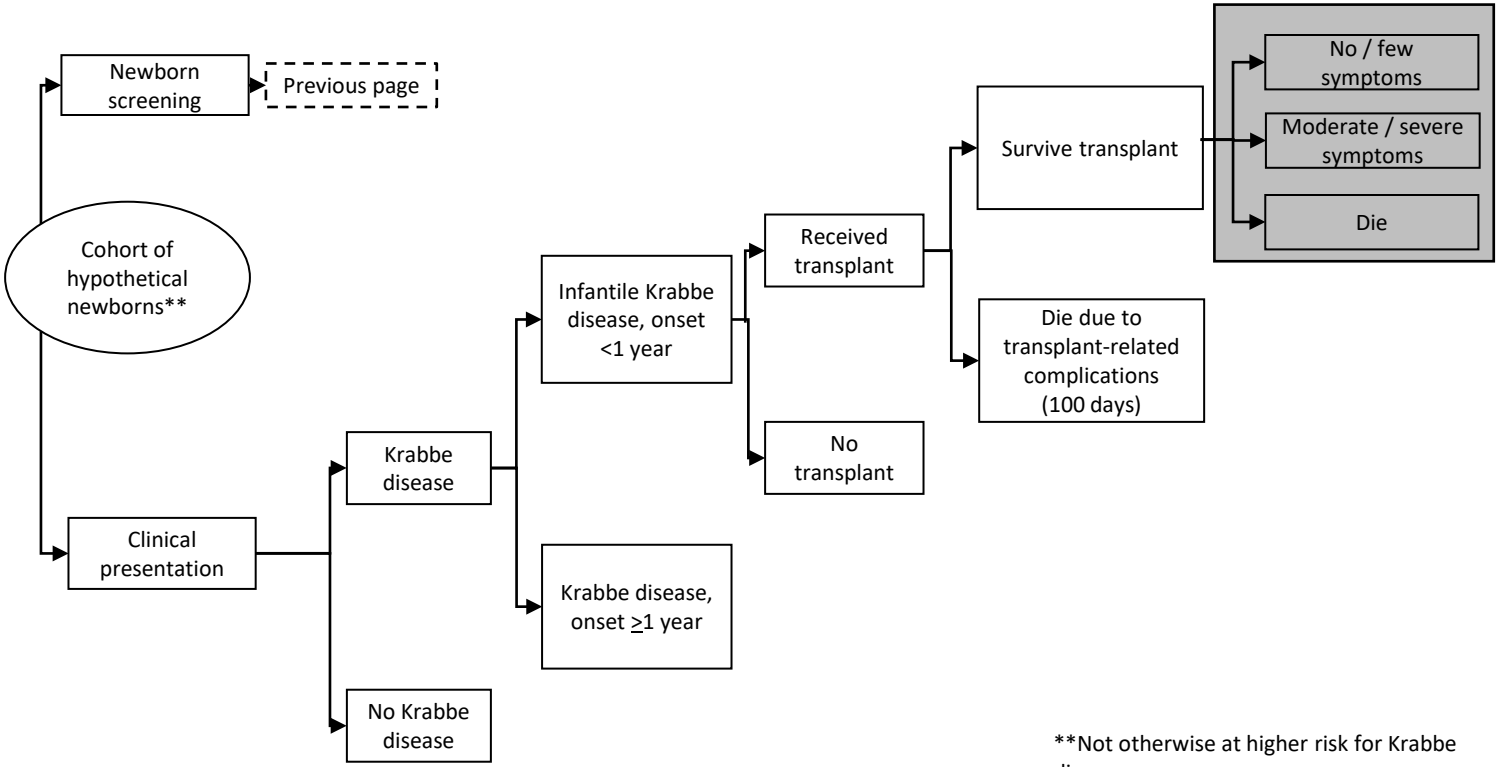
Model Structure

Model Schematic - Newborn Screening



*Higher probability of Krabbe disease

Model Schematic - Clinical Presentation



**Not otherwise at higher risk for Krabbe disease

Newborn screening program data, unadjusted*

	New York	Missouri	Kentucky	Tennessee	Illinois	Indiana	Pennsylvania	Georgia
Infants screened	985,726	168,042	330,555	421,481	98,721	172,803	167,537	144,000
Referred	72	21	2	58	8	11	19	1
Infantile Krabbe disease	2	1	2	1	0	0	3	1
At risk for Krabbe disease	25	2	0	2	2	4	1	0
Normal	45	17	0	55	4	7	13	0
Pending diagnosis	0	1	0	0	2	0	2	0

*Unadjusted, observed results from state NBS programs using psychosine to inform referrals in screening for Krabbe disease. Ohio and NJ NBS programs do not use psychosine in screening algorithm and not included in this table. A subsequent report suggests that the 2 cases of infantile Krabbe disease in New York had clinical onset >12 months

Newborn screening program data adjustments

- For modeling, state-reported data were adjusted to reflect a referral protocol based on low GALC enzyme level and high psychosine levels (screening protocol used by KY, GA)
- TN, MO: These states are currently referring based on GALC alone. Adjusted to exclude newborns with low GALC and normal psychosine levels from referrals
- PA, IL: These states are including carriers in their total number of referrals. Adjusted to exclude carriers from referrals
- NY, IN: Both adjustments

State newborn screening data, adjusted†

Possible Screening results	New York	Missouri	Kentucky	Tennessee	Illinois	Indiana	Pennsylvania	Georgia
Infants screened	985,726	168,042	330,555	421,481	98,721	172,803	167,537	144,000
Referred	27	3	2	3	4	7	4	1
Infantile Krabbe disease	2	1	2	1	0	0	3	1
At risk for Krabbe disease	25	2	0	2	2	4	1	0
Normal	0	0	0	0	0	3	0	0
Pending diagnosis*	0	0	0	0	2*	0	0	0

†adjusted or referrals based on low GALC and elevated psychosine levels
*Pending diagnoses not included in the model projections

Incidence rates derived from newborn screening program data, adjusted and unadjusted

	Unadjusted			Adjusted		
	Total newborns	Per 100k screened	Conditional probability given referral	Total newborns	Per 100k screened	Conditional probability given referral
Newborns screened	2,488,865	-	-	2,488,865	-	-
Screen positive/referral for diagnostic evaluation	191	7.67	-	51	2.05	-
Infantile Krabbe disease*	10	0.40	0.05	10	0.42	0.20
At risk for late onset Krabbe disease	36	1.45	0.19	37	1.50	0.73
Not recommended for regular follow up	140	5.63	0.73	3	0.13	0.06

*referred for transplant evaluation

Newborn Screening - Parameter Inputs

Parameter	Incidence	Conditional Probability	Range	Source
Screen positive/referral for diagnostic evaluation	2.05 per 100,000		1.53 - 2.69 per 100,000	Primary data from state newborn screening programs†
Infantile Krabbe disease* given positive screen	0.42 per 100,000	0.20	0.10 - 0.34	
At risk for late onset given positive screen	1.50 per 100,000	0.73	0.59 - 0.85	
Not recommended for regular follow up given positive screen	0.13 per 100,000	0.06	0.01 - 0.17	
Negative screen				
True negative	1	-	0.9999986 - 1	
False negative	0	-	0 - 0.0000015	

* Referred for transplant evaluation

† GA, IN, IL, KY, MO, PA, NY, and TN

Newborn Screening - Parameter Inputs (2)

Parameter	Probability	Range	Source
At risk for late onset Krabbe disease			
High risk follow up	0.40 (0.60 per 100,000)	0.21 - 0.61	Primary data from NYS newborn screening program (n=25)
Low risk follow up	0.60 (0.90 per 100,000)	0.39 - 0.79	
Identified with early infantile Krabbe disease			
Received transplant	0.88	0.62 - 0.98	Wasserstein 2016; Page 2022; state newborn screening data
No transplant	0.13	0.02 - 0.38	

Clinical Presentation - Parameter inputs

Parameter	Probability	Range	Source
Krabbe disease	1.1 per 100,000	0.76 - 1.6 per 100k	Wenger 2013
Infantile Krabbe disease, <12 mo	0.47	0.40 - 0.53	Komatsuzaki et al 2019
Post-infantile onset Krabbe disease, 12+m	0.53	0.47 - 0.60	Komatsuzaki et al 2019
Clinical presentation, <12 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	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	

Results: Projected Screening Outcomes, # newborns (range)

Annual cohort of 3.65 million newborns

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

Results: Projected Screening Outcomes, # newborns (range)

Annual cohort of 3.65 million newborns

Diagnosis	Clinical Presentation	Range
Krabbe disease	40.2	27.7 - 58.8
Infantile, <12 months	18.8	11.2 - 31.3
Post-infantile, 12+ months	21.4	16.5 - 27.5

Incidence of Krabbe disease: comparing NBS and to clinical presentation

Annual cohort of 3.65 million newborns

Diagnosis by Method of Detection	Base case	Range
Newborn screening		
Infantile Krabbe disease*	15.3	5.8 - 28.1
At risk for Krabbe disease – High Risk	22.0	13.2 - 28.0
Total	37.3	19.0 - 56.1
Clinical presentation		
Infantile onset, <12 mo	18.8	11.2 - 31.3
Post-infantile onset, 12+ mo	21.4	16.5 - 27.5
Total	40.2	27.7 - 58.8

* Referred for transplant evaluation

Diagnosis by Method of Detection	Incidence
Newborn screening	
Infantile Krabbe disease*	0.42 per 100,000
High risk follow up	0.60 per 100,000
Newborn Screening Total	1.02 per 100,000
Clinical presentation: Total	1.1 per 100,000

Results: Projected Screening Outcomes, # newborns (range)

Annual cohort of 3.65 million newborns

Potential Screening Outcomes	Newborn Screening	Clinical Presentation	Difference (NBS – CLIN)
Receive Transplant	13.4 (3.6 - 27.7)	1.9 (0 - 6.3)	11.5 (3.6-21.4)
Died from complications of transplant	1.4 (0.4 - 2.9)	0.2 (0 - 0.7)	1.2 (0.4-2.2)
Survive transplant	12.0 (3.2 - 24.8)	1.7 (0 - 5.6)	10.3 (3.2-19.2)
Did not Receive Transplant	1.9 (0.4 - 2.2)	16.9 (11.2 - 25.0)	-15.0 (-22.8- -10.8)
Died from Krabbe disease by 30 mo	1.5 (0.3 - 1.9)	13.0 (9.6 - 16.3)	-11.5 (-14.4 - -9.3)
TOTAL DIED (transplant + Krabbe disease) by age 30 mo	2.9 (2.3 - 3.2)	13.2 (9.6 - 17.0)	-10.3 (-13.8 - -7.3)

Summary of Model Prediction for the hypothetical 3.65 million infants born annually

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.

WITHOUT universal Krabbe disease newborn screening

- **18.8** (range: 11.2 – 31.3) infants would present before age 1 year
- **1.9** (range: 0 – 6.3) would be eligible for and receive HSCT
- **13.0** (range: 9.6 – 16.3) infants would be expected to die from Krabbe disease by age 2.5 years

Summary of Model Prediction for the hypothetical 3.65 million infants born annually

- Projected outcomes show differences in survival at 2.5 years of life for identification under newborn screening compared with clinical presentation
  - An additional ~10 babies would be alive at 2.5 years with newborn screening
- Evidence on treatment outcomes relating to quality of life are insufficient to model improvements in quality of life across cohorts

Questions