Nomination and Prioritization Workgroup Report: *Krabbe Disease*

Advisory Committee on Heritable Disorders in Newborns and Children

Presented by: Cynthia M. Powell, MD, MS, FACMG, FAAP

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N&P WG: Kyle Brothers, Carla Cuthbert,
Shawn McCandless, Cynthia Powell, Scott Shone

Condition Information

Krabbe disease is an autosomal recessive lysosomal storage disease caused by homozygous or compound heterozygous pathogenic variants in the gene coding for the enzyme galactocerebrosidase (GALC)

It is also known as globoid cell leukodystrophy

The most severe form is the **infantile form (IKD)** and that is the intended target for newborn screening

- Develop symptoms in first 2-12 months of life
- Irritability, feeding difficulties, failure to thrive, spasticity, vision loss, seizures, aspiration pneumonias, loss of fine and gross motor skills, and communication skills
- Most children die by 2 years of age

Other forms:

- Late infantile KD (LIKD) with onset 1-3 years of age
- Juvenile KD (JKD) with onset 4-17 years of age
- Adult KD (AKD) with onset >18 years of age

Condition Information

Nominators:

NAME OF NOMINATOR AND ORGANIZATION (include professional degrees)	**INDICATE AFFILIATION** (i.e., Health Professional, Subject Matter Expert, Researcher, Clinician, Advocate, etc.)
Hunter's Hope Foundation	Krabbe Disease Advocacy Organization
CO-SPONSORING ORGANIZATIONS (include professional degrees)	**INDICATE AFFILIATION** (i.e., Health Professional, Subject Matter Expert, Researcher, Clinician, Advocate, etc.)
Joanne Kurtzberg, MD	Krabbe Disease Expert, Clinician, Researcher
Dietrich Matern, MD, PhD	Researcher, Subject Matter Expert
Michael Gelb, PhD	Researcher
Maria Escolar, MD, MS	Health Professional, Clinician, Researcher
David Wenger, PhD	Researcher
Barbara Burton, MD	Health Professional, Clinician

Key Question 1

Is there prospective pilot data (U.S. and/or international) from population-based assessment available for this disorder?

Yes

- NY, MO, IL, KY, NJ, TN, OH, IN, PA are currently screening for Krabbe disease
- According to nomination form: 5,753,100 babies have been screened for KD by 8 NBS programs in the USA. A total of 15 babies were identified with IKD through NBS and 2 more have been diagnosed in the second year of life with LIKD for an estimated incidence of 1:338,418.

Key Question 2

Does the screening test have established analytic validation?

Yes

- FIA-MS/MS; LC-MS/MS; fluorometry (LDT)
  - FDA-approved kit for 6 LSDs using MS/MS
- First tier population screening utilizes measurement of GALC activity (NY/IL: 0.035% and 0.058% below cutoff) also detects carriers and those with pseudodeficiencies
- This has low specificity
- CLIR suggested to decrease percent positive screens: in NY it decreased need for repeat GALC analysis from 0.44% to 0.09%, and the need for second-tier testing from 0.035% to 0.005%
- The workgroup has concerns about availability of CLIR for all state NBS labs

Key Question 2

Does the screening test have established analytic validation? (continued)

- Second tier psychosine (PSY) measurement is needed
  - PSY is a substrate for GALC
  - IL 0.06% required second tier PSY
  - LDT
  - ~ $100/sample
  - Availability of PSY? Need to send to referral testing lab

Key Question 2

Does the screening test have established analytic validation? (continued)

- Gene sequencing also suggested as second/third tier
  - 30 kb deletion homozygosity and other severe pathogenic variants in trans indicative of IKD
  - Can help detect pseudodeficiency alleles

Table 2

Assignment of diagnosis after receiving second-tier testing results for KD (n = 288).

GALC * Activity	*N*	% Send Out	PSY Levels (nM) **		Mutations Detected	Diagnosis	Follow Up
			<2 nM	>2–<3 nM			
≤13%	178	62	178	0	Pseudodeficiency alleles	Negative [1]	No
≤13%	35	12	30	5	VUS □	VUS [2]	No
≤13%	67	23	60	7	One pathogenic allele or heterozygous 30-kb deletion	Carrier [3]	No
<12%	6	2	See Table 3		Two pathogenic mutations	Late onset	Yes
<11%	2	0.7	See Table 3		Two pathogenic mutations	IKD #	Yes

Basheerudin et al. PMID: 34065072 Illinois experience 2021

Suspected Late on-Set Krabbe (Age #)	PSY (nM)	Mutations *
Case 1 (38)	6	Heterozygous pathogenic c1671G>A; VUS c.235C>T; PD C.1685T>C
Case 2 (32)	2	Heterozygous pathogenic c.430delA and c.1901T>C; 2 heterozygous PD c.550C>T; c.1685T>C
Case 3 (28)	3	Homozygous pathogenic c.349A>G
Case 4 (13)	3	Heterozygous VUS c.334A>G; c.977C>T; heterozygous PD c.1685T>C
Case 5 (12)	3	Heterozygous VUS c.334A>G; c.977C>T; heterozygous PD c.1685T>C
Case 6 (8)	5	Homozygous pathogenic c.956A>G
IKD- transplanted		
Case 1 (32)	10	Heterozygous pathogenic alleles: c.1171_1175het_delCATTCinsA and c.749T>C
Case 2 (25)	35	Heterozygous likely pathogenic alleles: c.1723_1724insT and c.1913G>T

Basheerudin et al. PMID: 34065072 Illinois experience 2021

Key Question 3

Is there a widely available and CLIA and/or FDA approved confirmatory test/ diagnostic process?

Yes

- Measurements of GALC activity in leukocytes, preferably using a high-sensitivity assay
- Psychosine analysis in another DBS specimen or erythrocytes
- Molecular genetic analysis of the *GALC* gene
  - 30 kb deletion
  - sequencing

Condition information 1

The nominated condition(s) is medically serious.

Yes

Condition information 2

A case definition and the spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based screening.

Unclear

- Case definition is available
- Psychosine measurement aids in identification of those with IKD
- Some genotype-phenotype correlation with alleles known to be associated with IKD (30 kb del, truncating)
- Some IKD cases may be difficult to identify or differentiate from LIKD
- See tables submitted in response to request and Page et al. paper

4. In table format, please provide the following information on all known patients with Krabbe disease from both published and unpublished sources:
    a. Number screened positive
    b. Number true positive
    c. Number false negative
    d. Number with IKD and how they were identified as having IKD (e.g., variants utilized, second tier testing with psychosine)
    e. Number undergoing HSCT and location
    f. Transplant outcomes

State	Pop'n screened	Presumptive Positive	True Positive[1]	Number receiving transplant	% False Positive(b)	False Negative
KY*	315K	1 Plus 1 on 1/1/22	1-IKD Plus 1 on 1/1/22	1(patient has neurodevelopmental delays but is a "happy camper" and parents are glad there was NBS for KD when he was born)	0%	0
IL***	610K	216 (30 psy+)	5-IKD 7 -likely LOKD 1 pending	4 - All transplanted babies are doing well except with mild development delays One family declined HSCT	94%; 60% using psy + only	0
NY**	2.68 mil	519	7-IKD 1-LOKD (symp) 29-likely LOKD	7 transplanted. Outcomes of first four patients wer previously described (Wasserstein et al). Two cases were late infantile, patients are	92.9%	0

				4 years old and in school. Developing quite normally. Gross motor function is normal. Talking normally, off all meds. The LOKD patient was transplanted, is doing well cognitively, but is having GVH related problems. Both have normal brain MRIs.		
NY***	993K	19 (13 psy+)	2-IKD 10- likely LOKD	1 was transplanted, no updates available.	37%; 7.7% using psy+ only	0
MO	557K	197	2-IKD	2 received successful transplants, both have developmental delays	99.0%	0
MO*	57K	0	0		0%	0
NJ	135K	52	2-likely LOKD		96.2%	0
OH	590K	233	2-IKD 5-likely LOKD	Ohio cannot collect info. after STFU, they think 2 IKDs were transplanted and 1 LOKD possibly transplanted	97.0%	0
TN***	311K	40 (2 psy+)	1-likely LOKD	0	50%	0
Totals	6.24 million	1,278	71 total: 17 IKD, 1 LOKD (symp) 53 likely LOKD	15 transplanted, another 3 from OH possibly transplanted	0-97% High FP in states without full implementation of psychosine	0

(a) states that have not fully implemented second tier psychosine testing.
(b) True positives based on psychosine and/or genotypes and subsequent diagnostic evaluation.

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Notes:

[1] "Likely LOKD" cases are followed but have remained asymptomatic.

*GALC activity with psychosine as second-tier test; **GALC activity with genotyping as second-tier test; *** GALC genotyping and psychosine used for second-tier.

Note: The second-tier cutoff for psychosine is currently set at 2nM (9). Congruency between laboratories measuring psychosine in DBS and adoption of same cutoffs was not established until 2020 (24) which likely accounts for some earlier false positive cases despite use of psychosine.

Table 1. Results of Newborn Screening, Confirmatory Testing and Pre-transplant Studies.

Study or Testing	Patient (normal values)					
	1	2	3	4	5	6
GALC enzyme activity assayed on DBS sample, in nmol/ml/hour	0.11 (>0.55)	0.1 (>0.4)	0.01 (>0.4)	0.03 (>0.55)	0.15 (>0.4)	10% (>13% of daily mean value)
GALC enzyme activity in leukocytes, in nmol/ml/mg protein	0.05 (>0.15)	0.03 (>0.15)	0.01 (>0.15)	0.34 (≥1.2)	0.09 (>0.15)	0.61 (>1.2)
Psychosine assayed on DBS sample, in nmol/L	24 (<2)	61 (<2)	56 (<3)	73 (<2)	38 (<3)	35 (<2)
Protein, CSF in mg/dL	117	386	348	332	444	446
Mutation analysis	c.379C>T (p.R127X); Del30kb	c.1884dupA (p.Trp629fs); del exon 8 (entire)-exon 9 (portion)	Del30kb; Del30kb	c.387C>G (p.Tyr129Ter)	c.1270C>T, (p.Gln424Ter); Del30kb	c.1723_1724insT (p.G575Vfs*10); c.1913G (p.G638V)
MRI	Abnormal	Normal	Abnormal	Normal	Normal	Abnormal
NCS	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	Not Done
BAER	Abnormal	Abnormal	Abnormal	Abnormal	Abnormal	Not Done
VEP	Abnormal	Abnormal	Normal	Normal	Normal	Not Done
EEG*	ESTs	Normal	ESTs	ESTs	Normal	ESTs
Total number of abnormal studies	4	3	3	2	2	1

GALC, galactocerebrosidase; DBS, dried blood spot; PCR, polymerase chain reaction; MRI, magnetic resonance imaging; NCS, nerve conduction studies; BAER, brainstem auditory-evoked responses; VEP, visual evoked potentials; EEG, electroencephalogram; EST, excessive sharp transients; *ESTs were not considered abnormal for this purpose.

Page et al. 2022 PMID: 35042231

Condition information 3

The characteristics of the screening test(s) are reasonable for the newborn screening system (among other aspects, a low rate of false negatives).

Yes

- No known false negatives
- Psychosine testing is a reasonable second tier test and cost is on par with other types of second tier testing such as DBS GAGs for MPS

Condition information 4

If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky.

Yes

- IKD cases (most/all?) can be identified with second tier and confirmatory PSY and genetic testing
- There are a number of patients who had slightly elevated psychosine with VUS alleles and are being followed
- HSCT needs to be done within first 30 days of life for those with IKD

Condition information 5

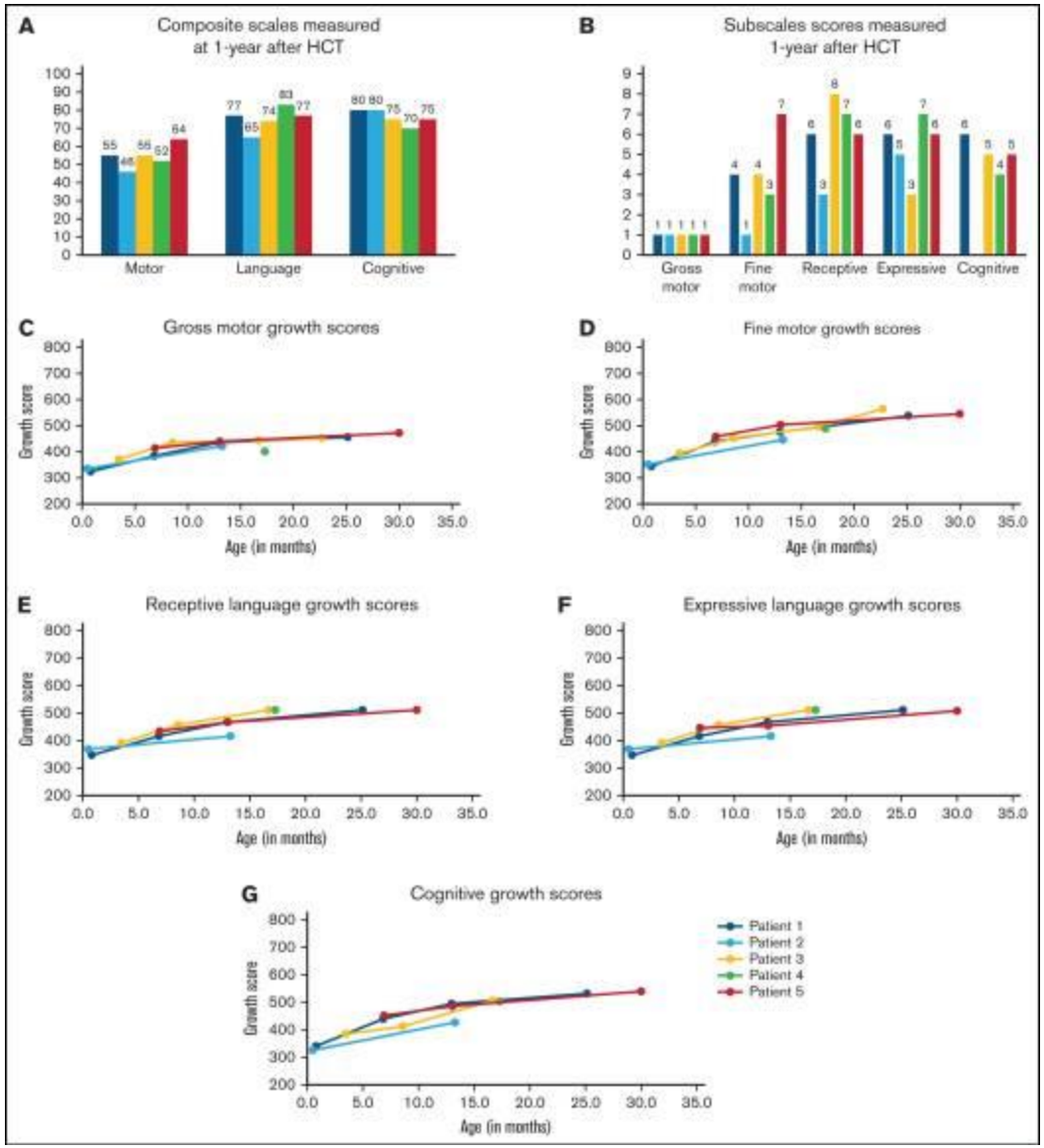
Defined treatment protocols, FDA approved drugs (if applicable) and treatment are all available.

Unclear

- Over 100 pediatric centers in U.S. for HSCT but only 9 have been doing LSD tx
- Not all with experience with KD
- Experts at other centers can help those with inexperience
- Logistical problems for those states without in-state centers (Vergano et al. PMID: 35229104)

Benefits

- Benefit of treatment within first 30 days of life?
- See tables
- Only 1 of the 6 patients reported in the Page et al. paper received transplant prior to 30 days
- Neurodevelopmental composite and subscale scores reported only for 1 year post transplant, with growth scores reported beyond this age
- Only descriptions given for longer term follow-up in the 6 recently published cases
- Other cases identified through NBS with IKD with results published are the NY cases, others were reported as “doing well” and “happy camper” by nominators without specifics
- Gross motor skills most impacted due to peripheral neuropathy and ?, better receptive language



Page et al. 2022 PMID: 35042231

Supplemental Table 1. Clinical results at most recent follow-up.

	Patient (current age in months)					
	1	**2**	**3**	**4**	**5**	**6**
Current age/age at most recent follow-up (in months)	**58/53**	**57/52**	**52/44**	**43/45**	**36/35**	**30/24**
Height, weight, head circumference (in percentiles)	< 1%, < 1%, 76%	< 1%, < 1%, 3%	67%, 97%, 87% (HC at 29mo)	10%, 40%, 50%	3%, 10%, 99%	1%, 2%
Method of Nutrition	By mouth; G-tube supplemental feeds	Primarily G-tube, purees by mouth	By mouth	By mouth	By mouth; supplemental G-tube	By mouth
Fine motor	Drinks from cup; Self feeds crackers (pincer); Stacks 5 blocks; Scribbles; Plays on tablet	Drinks from cup; Holds toys with both hands & puts into container/take out; Plays on tablet	Drinks from cup; Self feeds: crackers (pincer) & utensils; Scribbles, Plays on tablet	Drinks from cup; Self feeds crackers (pincer) & utensils; Scribbles; Plays on tablet	Drinks from cup; Self feeds crackers (pincer); Stacks 2 blocks; Scribbles; Turns pages;	Waving bye; Reaches & holds toys with both hands; self-feeds
Speech/Language	Follows 2-3 step directions, learning colors; 1-2-words phrases, signs, ACC;	Approximates words; follows commands; nods & gestures;	Speaking 2-3 word sentences; uses 75 signs	Uses signs & gestures; limited words. Strong receptive, ACC	3 verbal words plus several signs; follows commands;	Saying several words, pointing to body parts
Ambulation	Wheelchair; limited walking with gait-trainer;	Wheelchair;	Self -propel wheelchair; Ride tricycle; Sits unsupported	Limited walking with gait-trainer; Sits unsupported; Crawling	Self -propel wheelchair; Crawls, but not pull up to stand	Walking independently, climbing
Tone	Central hypotonia; UE & LE hypertonia	Central hypotonia; LE hypertonia	Mild central & UE hypotonia; LE hypertonia	Central hypotonia; LE hypertonia	Low tone in trunk, increased in legs	Increased tone LE, no clonus
Spasticity management	Baclofen, braces, PT	Baclofen, braces, PT, surgery*, botulinum toxin	Baclofen, PT, braces	Baclofen, botulinum toxin, braces, PT	Braces	PT

GALC, galactocerebrosidase; G-tube, gastrostomy tube; AAC, augmentative and alternative communication; LE, lower extremities; UE, upper extremities; PT, physical therapy. *Patient underwent bilateral intertrochanteric ostomy and hip adductor lengthening.

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Nomination and Prioritization Workgroup Recommendation

Yes: send forward to condition review process for evidence review and public health impact analysis