WISCONSIN NEWBORN SCREENING (NBS) PROGRAM – CONDITION NOMINATION

Nomination of a Condition to the Wisconsin Newborn Screening Panel

Date of Nomination
March 9, 2020

NOMINATOR

Name	Organization
Kevin Cushman	Parent

Affiliation (i.e., health professional, researcher, clinician, advocate)
Advocate

Address
[redacted]

Email Address	Phone Number
[redacted]	[redacted]

CO-SPONSORING ORGANIZATION #1 (as appropriate, additional sponsors may be included on page 5)

Name	Organization
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Affiliation (i.e., health professional, researcher, clinician, advocate)
Health professional, researcher, clinician

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Condition	STATEMENT
Nominated Condition	Globoid leukodystrophy (Krabbe Disease)
Description of Disorder	an inherited disorder that destroys the protective coating (myelin) of nerve cells in the brain and throughout the nervous system, resulting in permanent damage to the nerve cells, severe progressive neurologic impairment and death. The early infantile form is fatal in infancy and early childhood if not treated in the first month of life.
Screening Method	Blood, newborn blood spot, enzyme activity and psychosine
Gene	Mutations in the GAL-C gene (galactocerebrosidase gene)
OMIM or other names for condition	globoid cell leukodystrophy
Case Definition	

NOTE: Please reference each statement/answer with the corresponding reference number listed in **Key References**.

CRITERION

Criterion 1: Mandated testing should be limited to conditions that cause serious health risks in childhood that are unlikely to be detected and prevented in the absence of newborn screening.

Timing of Clinical Onset	*Relevance of the timing of newborn screening to onset of clinical manifestations. Must cause serious health risks in childhood that are unlikely to be detected and prevented in the absence of newborn screening.* Hematopoietic stem cell transplantation extends life and improves functional outcomes in infants with the early onset and infantile forms of the disease bif treatment begins BEFORE the onset of symptoms — that is, when a diagnosis results from a newborn screening test.

Criterion 2: For each condition, there should be information about the incidence, morbidity and mortality, and the natural history of the disorder.	
Incidence	*Determined by what method(s): pilot screening or clinical identification?* Initially estimated at 1:100,000, but may be lower. In NY, it appears to be closer to 1:400,000.

Severity of Disease	*Morbidity, disability, mortality, spectrum of severity, natural history.* terminal, progressive worsen into vegetative state. Most die by age 2.

Criterion 3: Conditions identified by newborn screening should be linked with interventions that have been shown in well-designed studies to be safe and effective in preventing serious health consequences.	
Urgency	*How soon after birth must treatment be initiated to be effective?* For early infantile Krabbe Disease (EIKD), the diagnosis must be confirmed within 5-14 days of birth. Ideally the diagnosis should be made in the first few days of life. This can be accomplished within 5-7 days if screen + reflex psychosine testing is performed on the NBS.
Efficacy (Benefits)	*Extent of prevention of mortality, morbidity, disability. Treatment limitations, such as difficulty with acceptance or adherence.* Presymptomatic infants receiving a stem cell transplant have had significant extension of life (current data shows into the 2-3 decade of life or longer). slows disease progression, but these children still experience varying, but often, significant difficulties with speech, walking and other motor skills. Children with later onset infantile Krabbe disease can be identified and treated before disease onset and can live a relatively normal life. Diagnosis and early therapy greatly improves the family‘s and child’s comfort level as well as quality of life and enables genetic counselling for potential future children in the family and other family members. Without diagnosis, EIKD babies become sick with extreme irritability, poor feeding, failure to thrive, severe spasticity, and generally undergo months of testing enhancing suffering of the baby and family before a diagnosis is determined. At that time, it is too late for any disease altering treatment.
Potential Harms	*Potential medical or other ill effects from treatment.* Mortality associated with hematopoietic stem cell transplantation is 5%, worst side effects would be host vs graft disease. The incidence of these events are relatively low and justified since the alternative is extreme suffering of the family and baby with 100% mortality early in life.

Criterion 4: The interventions should be reasonably available to affected newborns.	
Modality	*Drug(s), diet, replacement therapy, transplant, surgery, other. Include information regarding regulatory status of treatment.* Hematopoietic stem cell transplantation has been shown to dramatically improve the course of babies with early and late onset Krabbe disease as well as in children with juvenile and adults with adult onset Krabbe disease. The procedure is performed in transplant programs, which are located in over 180 tertiary care medical centers in the USA. For infants and children, HSCT is available at nearly 100 transplant centers in the USA. There are also over 10 expert pediatric centers in the USA with prior experience transplanting infants with Krabbe disease. HSCT is standard of care and approved by private and public healthcare providers. Public umbilical cord blood donors, which are banked and readily available to all patients, are typically utilized. Transplant centers will accept EIKD patients emergently and are equipped to assist with referrals, third party payer approvals, evaluation and workup, donor procurement and all associated procedures. It is likely that in the next few years, gene therapy will also be available for selected patients with infantile Krabbe disease. This will emerge as experimental and covered by sponsors at first, but if effective and safe, will become SOC, possibly in combination with HSCT in the next 3-7 years.
Availability	*Describe scope of availability and note any limitations.* as above. HSCT is available to all eligible babies and older patients with Krabbe disease in the USA. Emergent referral for newborns with EIKD is essential. Older babies and patients with later onset forms of Krabbe disease need to be followed for signs of disease onset and referred at that time.

Criterion 5: Appropriate follow-up should be available for newborns that have a false positive newborn screen.	
Follow-up for False Positives	*Define the follow-up process.* If NB screen is positive, reflex testing with psychosine must be done. The NBS lab can contract with one of 4 labs in the USA performing this test (Mayo, NY State NBS lab, Nationwide, Perkin Elmer) for reflex testing on the original NBS bloodspot. If the psychosine is very high, (>20), this result is diagnostic for EIKD. This only occurs in ~1:400,000 newborns. If the psychosine is normal (<2), the newborn is NOT affected with Krabbe disease and further testing or referrals can be accomplished over the first few months of life, if necessary. If the psychosine is intermediate (>2-<20), the baby needs further workup starting with mutation analysis. Once results of mutation analysis are reviewed, a plan for clinical follow up can be established with the baby's pediatrician and, if required, neurologist/other consultants. The addition of psychosine testing has greatly simplified the diagnostic testing algorithm for newborns who screen positive for Krabbe disease. The estimates are that <20 newborns will be diagnosed with EIKD in the USA annually and that 30-50 babies with be at risk for the development of later onset Krabbe disease annually in the USA each year. Thus resources for follow up and the numbers of families at risk will be minimal.

Criterion 6: The characteristics of mandated tests in the newborn population should be known, including specificity, sensitivity, and predictive value.	
Screening test(s) to be used	*Description of the high volume method, instrumentation and if available as part of multi-analyte platform.* Measurement of galactocerebrocidase enzyme activity by tandem mass spectrometry on DBS. Reflex Psychosine testing can be performed on the NB Dried Blood Spot.
Modality of Screening	*Dried blood spot, physical or physiologic assessment, other.* tandem mass spectrometry
Does the screening algorithm include a second tier test? If so, what type of test and availability?	*Dried blood spot, physical or physiologic assessment, other.* Psychosine is the second tier test and can be referred to 1 of 4 labs in the USA (Mayo, Nationwide, NY State NBS lab, Perkin Elmer).
Clinical Validation	*Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation, positive predictive value, false positive rate, analytical specificity, sensitivity.*
Analytic Validation	*Limit of detection/quantitation, detection rate, reportable range of test results, reference range. Include regulatory status of test, information about reference samples and controls required for testing and availability of or potential for external quality assurance system, e.g., QC and PT for both screening and confirmatory tests.*

Potential Secondary Findings	*May other disorders be identified by the screening test for the nominated condition?* ☐ Yes ☒ No ***If yes:*** • *How should that identification be handled—should those screening results be disclosed to the physicians or parents?* • *Would that disorder(s) meet the outlined criteria?* ☐ Yes ☐ No o *If yes, please prepare a separate nomination form for the secondary disorder(s)* o *If no, what criteria does it not meet?*

Summary of Population-based Pilot Study(ies)

Location of Prospective Pilot	NB screening for Krabbe disease was piloted in New York State for the past 13 years. Screening has been added by several other states including Ohio, IL, PA, NJ, TN, MI in the past 4-5 years.
Number of Newborns Screened	Since 2006, there have been more than 3,200,000 infants screened for KD in New York State. Six infants (including 2 siblings) screened positive for EIKD, plus 2 (twins) with later onset infantile Krabbe Disease to date. In addition, 28 patients form the NY cohort are being followed because they are at risk for later onset (juvenile or adult) Krabbe Disease. Of the 7 novel cases (excluding the 1 sibling), 4 are alive after transplant from 1-12 years later. Since that time, additional states have added Krabbe Disease to their NBS panels. As a result, 6 babies have been identified with EIKD in the past 4 years. All were transplanted and all are surviving and doing well. An additional 2 babies were diagnosed with EIKD where their families decided not to proceed to transplant and to pursue palliative care options instead.
Number of Positive Results	*Positive by primary test versus 2nd tier test if applicable.* see above
False Positive Rate; False Negative Rate (if known)	*False positive by primary test versus 2nd tier test if applicable.* see above
Number of Infants Confirmed with Diagnosis	*How is diagnosis confirmed [clinical, biochemical, molecular]?* After a positive screen, psychosine is performed to assess risk for EIKD. In NY state, the GAL-C gene is also sequenced within ~48 hours of a positive test. In some other states, there is a screen for the 30KB deletion, but this does not pick up all cases of EIKD. The current consensus is that enzyme screen, followed by reflex Psychosine testing is the optimal screening method.

Criterion 7: If a new sample collection system is needed to add a disorder, reliability and timeliness of sample collection must be demonstrated.	
Is this a new sample collection system?	*If yes, demonstrate reliability and timeliness of sample collection process, including data collection, analysis, and reporting of new results.* No, not new.

Criterion 8: Before a test is added to the panel, the details of reporting, follow-up, and management must be completely delineated, including development of standard instructions, identification of consultants, and identification of appropriate referral centers throughout the state/region.	
Considerations of Screening and Diagnostic Testing	*False positives, carrier detection, invasiveness of method, other.* Those that screen positive are sent for DNA testing to determine if they have a mutation in the GALC gene. Finally, those with positive blood spot results and positive DNA analysis are analyzed for galactocerebrosidase activity. Based on the level of galactocerebrosidase activity, they are then categorized as being at high, medium or low risk of actually developing the disease. Those with the lowest levels are at highest risk of becoming symptomatic, while those with higher levels of enzyme activity are at lower risk.
Is test FDA cleared/approved	*Include availability of information, sole source manufacturer, etc.* Yes

List all CLIA or CAP certified labs offering testing in the US	*Link to GeneTests and Genetic Test Reference if applicable.* NY, KY, Missouri, Ohio, Mayo, IL. http://www.cdc.gov/nbslabbulletin/bulletin.html
Follow-up and management process	*Development of standard instructions, identification of consultants, identification of appropriate referral centers throughout the state/region, follow-up for results, management of ongoing care, education and outreach.* The rare newborn who screens positive for EIKD (+ screen and high psychosine) should be immediately referred to a pre identified transplant center. Other screen positive newborns at risk for LOKD, should be referred to a geneticist/neurologist for mutation testing (or have this done through their pediatrician). Once those results are back, the LOKD follow up guidelines (soon to be published) should be followed. Babies at low risk for LOKD will be followed clinically. Babies at high risk for LOKD, will be followed by a pediatrician and neurologist and may need additional testing.

Criterion 9: Recommendations and decisions should include consideration of the costs of the screening test, confirmatory testing, accompanying treatment, counseling, and the consequences of false positives. The mechanism of funding those costs should be identified. Expertise in economic factors should be available to those responsible for recommendations and decisions.	
Screening test	Over the time period from August 2006 through July 2010, the total cost of the program was estimated to cost an average of $3,002,607. This translates into an annual average cost of $750,652
Confirmatory testing	The average cost to families was $2700, some of which was covered by insurance. They estimated that the total cost of testing was $500,000 and $750,000 per case of disease diagnosed.
Treatment	The stem cell transplantation itself may be free if enrolled in a study. However the long term cost of supportive care of a handicapped child is very hard to estimate -- frequent doctor visits, hospitalizations, physical- occupational- speech therapy, special equipments, time away from work, etc…
Counseling	and the psychological impact on the family!
False positives	
Mechanism of funding	NBS fee. The recently estimated cost for Pompe screening is $10 per infant. Since other lysosomal disorders, like Krabbe, can be added as a part of a multiplex assay, the laboratory cost is estimated at approximately $4 for each additional screening test.

Key References to support each criterion. Please list and attach as PDF(s). If mailing, include hard copies.	
#	**Criterion 1**
1	http://www.ninds.nih.gov/disorders/krabbe/krabbe.htm
2	http://www.mayoclinic.org/diseases-conditions/krabbe-disease/basics/risk-factors/con-20029450
	Criterion 2
	http://www.mayoclinic.org/diseases-conditions/krabbe-disease/basics/definition/con-20029450
	Criterion 3
	the above plus http://www.ninds.nih.gov/find_people/voluntary_orgs/volorg155.htm
	Criterion 4
1	http://www.huntershope.org/site/DocServer/Clinical_Trial_for_Newly_Diagnosed_Krabbe_Patients.pdf?docID=16861 is just ONE of many examples
2	http://www.huntershope.org/site/PageServer?pagename=hjkri_landing
	Criterion 5
	http://www.huntershope.org/site/PageNavigator/4.%20Newborn%20Screening/unbs_krabbe_newborn_screening.html
	Criterion 6
	http://www.pedneur.com/article/S0887-8994(08)00618-8/pdf Alas, I don't have access to this article, but it may answer many of the questions in this criteria
	http://academiccommons.columbia.edu/catalog/ac:132317 this shows data from New York
	Criterion 7
	http://www.wadsworth.org/newborn/krabbe.htm
	Criterion 8
	http://www.wadsworth.org/newborn/krabbe.htm
	http://www.huntershope.org/site/PageServer?pagename=hjkri_centerforkrabbedisease
	Criterion 9
	http://www.wadsworth.org/newborn/krabbe.htm
	https://clinicaltrials.gov/ct2/results?cond=%22krabbe%20disease%22

Additional Co-sponsoring Organizations

CO-SPONSORING ORGANIZATION #2	
Name	Organization None
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Phone Number

CO-SPONSORING ORGANIZATION #3	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Phone Number

CO-SPONSORING ORGANIZATION #4	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Phone Number

CO-SPONSORING ORGANIZATION #5	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Phone Number

Submission Checklist	
☒	Nomination form
☐	Conflict of Interest Forms completed by Nominator and all Co-Sponsoring Organizations
☐	PDF(s) or hard copies of references

Contact information of Nominator:

Submit Nominations to: DHSWICongenitalDisorders@wisconsin.gov

Or mail to:

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