WISCONSIN NEWBORN SCREENING (NBS) PROGRAM – CONDITION NOMINATION

Nomination of a Condition to the Wisconsin Newborn Screening Panel

Date of Nomination

April 9, 2015

NOMINATOR	
Name Thu-Thao Trinh, MD	Organization Marshfield Clinic, Marshfield
Affiliation (i.e., health professional, researcher, clinician, advocate) Pediatrician	
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CO-SPONSORING ORGANIZATION #1 (as appropriate, additional sponsors may be included on page 5)	
Name None	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate) Please note that I am NOT actively involved in any of the research on Krabbe's. I am a pediatrician who is taking care of a patient with Krabbe	
Address	
Email Address	Phone Number

Condition	**STATEMENT**
Nominated Condition	Krabbe's and other leukodystrophy
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
Screening Method	blood test
Gene	look for GALC gene mutation
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.* Stem cell transplantation may improve outcomes in infants if 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?* 1 in 100,000

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?* ASAP before symptoms occurs in order to PREVENT the loss of nerve function
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 slower disease progression, but these children still experience significant difficulties with speech, walking and other motor skills. Therapy would greatly improe the child's comfort level as well as quality of life. (and of course the family also)
Potential Harms	*Potential medical or other ill effects from treatment*. Mortality associated with transplantation is 5%, worst side effects would be host vs graft disease. However I would say these are relative since the alternative is early death.

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.* stem cell transplantation is only available at large Children's medical centers
Availability	*Describe scope of availability and note any limitations.* as above. Also there are several clinical trials throughout the country that the newborn can be enrolled in. Most of these are at no cost to the family.

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, the newborn will need confirmatory test via several ways: genetic testing, biopsy, cerebrospinal fluid studies, brain MRI

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.*
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.* Unfortunately, I do not run the test and not sure the answer to these questions. I cannnot really find the answer online either
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	New York was the first state who ran NB screen for Krabbe's
Number of Newborns Screened	Since 2006, there have been more than 1,000,000 infants screened for KD in New York State. Using the data from the State annual reports of 9 positive KD screening results, sensitivity was calculated at 100%, specificity was 99%, positive predictive value was 5%, negative predictive value was 100% and prevalence was 1/100,000 births.
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]?* the screening has identified four infants with the early infantile form of the disease, mainly via molecular

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 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.* those newborns who are screened positive should see their primary physicians right away, who then can refer the next step to either a geneticist or a pediatric neurologist to workup the confimation test.

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	research, insurance, fundraising

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: trinh.thu-thao@marshfieldclinic.org

Submit Nominations to: DHSWICongenitalDisorders@wisconsin.gov

Or mail to:
WI Division of Public Health
Newborn Screening Program
1 West Wilson Street – Room 233
Madison, WI 53703