WISCONSIN NEWBORN SCREENING (NBS) PROGRAM – CONDITION NOMINATION

Nomination of a Condition to the Wisconsin Newborn Screening Panel

Date of Nomination

4/6/2017

NOMINATOR	
Name Khoon Ghee Queenie TAN and Patrice HELD	Organization Wisconsin State Laboratory of Hygiene
Affiliation (i.e., health professional, researcher, clinician, advocate) Clinician and Newborn Screening Laboratory Co-Director	
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CO-SPONSORING ORGANIZATION #1 (as appropriate, additional sponsors may be included on page 5)	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Telephone Number

Condition	**STATEMENT**
Nominated Condition	Carnitine Palmitoyltransferase IA
Description of Disorder	Carntine palmitoyltransferase IA (CPT IA) deficiency is a fatty acid oxidation disorder associated with hypoketotic hypoglycemia and liver failure. Children with CPTI present with hypoglycemia, liver dysfunction and encephalopathy, cholestatic jaundice and hepatomegaly, as well as renal dysfunction manifesting as renal tubular acidosis, when viral illness or prolonged fasting occurs (1, 2). Prior to the episodes of metabolic crisis, they typically have normal growth and development. Studies have also found evidence for an association between infant mortality associated with infectious disease and homozygosity for CPT IA mutations (1).
Screening Method	Tandem Mass Spectrometry on Dried Blood Spots
Gene	CPT1A
OMIM or other names for condition	CPT IA, CPT I liver, CPT1. OMIM 600528
Case Definition	None

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.* Studies have found evidence for an association between infant mortality associated with infectious disease, and homozygosity for CPT IA mutations (1). With viral illnesses or with prolonged fasting, children present in metabolic crisis with hypoglycemia, liver dysfunction and encephalopathy, cholestatic jaundice and hepatomegaly, as well as renal dysfunction manifesting as renal tubular acidosis (2). Children can have normal development and growth before episodes of metabolic crises. Initiation of treatment, prior to the metabolic crisis, is critical for preventing adverse outcomes. Newborn screening affords the opportunity for early detection, as there are no clinical symptoms that can be observed, indicating a child's risk for CPT IA.
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?* Incidence: It has been reported that the incidence of CPT IA for non-Inuit diagnoses is estimated to be 1/500,000 to 1/1000000 newborns (Region 4 Stork (R4S) collaborative, Pierro Rinaldo, personal communication). The incidence is higher in Inuit populations, with 1.3/1000 incidence of births with homozygosity for the p.Pro479Leu pathogenic variant in the native Alaskan population (2). There is also an increased carrier rate (1:16) for the pathogenic p.Gly710Glu variant in the Hutterite population (3).
Severity of Disease	*Morbidity, disability, mortality, spectrum of severity, natural history.* Morbidity associated with CPT IA typically results after periods of illnesses (even mild viral illnesses) or prolonged fasting, and clinical symptoms include seizures, liver failure, kidney dysfunction, coma, and respiratory arrest and in some cases necessitate invasive life-saving procedures such as mechanical ventilation (4). Residual neurological deficits such as developmental delays and epilepsy can be seen, as well as continued liver and kidney dysfunction.

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? Dietary and sick day management should be initiated right after birth in order to avoid metabolic decompensation.
Efficacy (Benefits)	Extent of prevention of mortality, morbidity, disability. Treatment limitations, such as difficulty with acceptance or adherence. Children demonstrate catch up growth after starting treatment (5, 6) and are able to tolerate viral infections without major decompensation (5).
Potential Harms	Potential medical or other ill effects from treatment. Dietary treatment is relatively easy and not known to be harmful, but does involve parental awareness and vigilance, and ability and willingness to seek treatment when the child is ill. A study of management and outcome in 75 individuals with long chain fatty acid oxidation defects (with similar dietary management as CPT IA) showed optimal adherence to treatment in about 74% of patients (7).
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.* Treatment for CPT IA includes high carbohydrate and low fat diet or heart-healthy diet, medium chain triglyceride (MCT) oil supplementation, frequent feedings for infants, restriction of fasting time and emergency treatment plans.
Availability	*Describe scope of availability and note any limitations.* The treatment should be readily available to all patients.
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.* The follow-up process will be initiatied by the laboratory calling out positive screening results to the primary care physician and the metabolic physician. Dietary recommendations and emergency care protocols will be provided by the metabolic physician to the primary care physician, who will evaluate the patient, as well as discuss the disease, confirmatory testing, and treatment with the family. Follow up laboratory studies will be obtained. If these studies are suggestive of CPT IA (true positive), the patient will be followed by a metabolic physician for further discussion, diagnosis, and management. If follow-up studies are suggestive of false positive results, the metabolic team will contact the primary care physician to report these results.
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.* Screening for CPT IA will be performed by tandem mass spectrometry as part of the multi-analyte platform currently being used for acylcarnitines and amino acids.
Modality of Screening	*Dried blood spot, physical or physiologic assessment, other* Dried blood spot
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* No
Clinical Validation	*Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation, positive predictive value, false positive rate, analytical specificity, sensitivity.* The Wisconsin State Laboratory of Hygiene Newborn Screening Laboratory has conducted a pilot study of 50,731 infants with no cases identified using proposed cutoff values, during an eleven month period (January to Nov 2016). A case from Montana was identified by newborn screening in 2015 in the Wisconsin State Laboratory using the same platform.

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.* The established analytes for detection of CPT IA are free carnitine (C0) and the ratio of free carnitine to palmitoyl plus stearoyl carnitine (C0/(C16 + C18)). The analytes (C0, C16, and C18) have been previously validated and are currently in use to detect other fatty acid oxidation defects. To identify CPT IA, the ratio (C0/(C16+C18) will be added to the panel. Addition of the ratio does not require validation. Normal patient ranges for the ratio and the one identified true case of CPT IA were used to set cutoffs. Analytical validation for each analyte (C0, C16, C18) are assessed quarterly using CDC quality control and proficiency testing samples.
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	Newborn Screening Laboratory in the Wisconsin State Laboratory of Hygiene
Number of Newborns Screened	50,731
Number of Positive Results	*Positive by primary test versus 2nd tier test if applicable.* 0
False Positive Rate; False Negative Rate (if known)	*False positive by primary test versus 2nd tier test if applicable.* 0
Number of Infants Confirmed with Diagnosis	*How are diagnosis confirmed [clinical, biochemical, molecular]?* not applicable
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
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* Using the proposed cutoff values, there was no false positive result in the pilot study. This test will be performed as part of an existing testing platform for other metabolic disorders such as medium chain acyl-CoA dehydrogenase deficiency (MCADD) and very long chain acyl-CoA dehydrogenase deficiency (VLCADD).
Is test FDA cleared/approved	*Include availability of information, sole source manufacturer, etc.* No. This is a laboratory developed test that has been validated and used for screening since 2000.

List all CLIA or CAP certified labs offering testing in the US	*Link to GeneTests, and Genetic Test Reference if applicable.* CPT IA is screened universally in 28 states and District of Columbia. It is recommended on the Uniform Screening Panel as a Secondary Condition by the Advisory Committee on Heritable Disorders in Newborns and Children. It is recommended for addition to the Wisconsin newborn screening panel by the Metabolic Subcommittee after discussion during the meeting on 1/27/17.
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.* A positive screen will be communicated with the patient's primary care provider, as well as a metabolic physician (Children's Hospital of Milwaukee Genetics program or the University of Wisconsin-Madison division of Pediatric Genetics and Metabolism). The metabolic physician will contact the primary care physician for discussion about follow-up of results and management of ongoing-care.
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	Tandem mass spectrometry
Confirmatory testing	Plasma acylcarnitine profile will be evaluated. Confirmatory testing may also include molecular genetic testing or enzyme activity on cultured skin fibroblasts
Treatment	Heart-healthy diet or low fat diet, MCT oil supplementation, frequent feedings for infants, emergency protocols for patients
Counseling	Provided by metabolic physicians
False positives	The metabolic physician will review all follow-up testing results. If follow up testing indicates false positive results, the primary care physician and patient will be informed.
Mechanism of funding	No additional costs

Key References to support each criterion. Please list and attach as PDF(s). If mailing, include hard copies.	
#	**Criterion 1**
1	Gessner BD, Wood T, Johnson MA et al. Evidence for an association between infant mortality and homozygosity for the artic variant of carnitine palmitoyltransferase 1A. Genet Med 2016 18:933
2	Bennett MJ and Santani AB. Carnitine Palmitoyltransferase 1A Deficiency. Pagon RA, Adam MP, Ardinger HH et al. editors. GeneReviews. Seattle (WA): University of Washington, Seattle 1993-2016
	Criterion 2
3	Prasad C, Johnson JP, Bonnefont JP et al. Hepatic carnitine palmitoyl transferase 1 (CPT1A) deficiency in North American Hutterites (Canadian and American): evidence for a founder effect and results of a pilot study on a DNA-based newborn screening program Molec Gen and Metab 2001 73:55
4	Lee BH, Kim Y-M, Kim JH et al. Atypical manifestation of carnitine palmitoyltransferase 1A deficiency: hepatomegaly and nephromegaly. J Ped Gastroenterology Nutri 2015 60:e19
	Criterion 3
5	Falik-Borenstein ZC, Jordan SC, Saudubray J-M et al. Brief report: renal tubular acidosis in carnitine palmitoyltransferase type 1 deficiency. New Engl J Med 1992 327:24
6	Choi JS, Yoo HW, Lee KJ et al. Novel mutations in the CPT1A gene identified in the patient presenting jaundice as the first manifestation of carnitine palmitoyltransferase 1A deficiency. Ped Gastroenterol,Hepatol and Nutr 2016 19:76
	Criterion 4
7	Spiekerkoetter U, Lindner M, Santer R et al. Management and outcome in 75 individuals with long-chain fatty acid oxidation defects: results from a workshop. J. Inher Metab Dis 2009 32:488
	Criterion 5
	Criterion 6
	Criterion 7
	Criterion 8
	Criterion 9

Additional Co-sponsoring Organizations

CO-SPONSORING ORGANIZATION #2	
Name	Organization
Affiliation (i.e., health professional, researcher, clinician, advocate)	
Address	
Email Address	Telephone Number

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

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

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

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Or mail to:

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