WISCONSIN NEWBORN SCREENING (NBS) PROGRAM – CONDITION NOMINATION

Nomination of a Condition to the Wisconsin Newborn Screening Panel

Date of Nomination

April 28, 2014

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CO-SPONSORING ORGANIZATION #1 (as appropriate, additional sponsors may be included on page 5)	
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Condition	**STATEMENT**
Nominated Condition	Unrecognized Critical Congenital Heart Disease
Description of Disorder	Critical Congenital Heart Disease (CCHD) is usually described as those congenital cardiac malformations in which surgical or catheter-based therapy is necessary within the first months of life. In some circumstances, infants with CCHD may be asymptomatic and have a normal physical examination prior to routine hospital discharge or completion of home birth care.
Screening Method	Two site (right hand and one foot) pulse oximetry, preferably performed 24 hours or more after birth
Gene	N/A
OMIM or other names for condition	N/A
Case Definition	There are twelve lesions commonly considered as CCHD: Hypoplastic Left Heart Syndrome, Pulmonary Atresia, Tetralogy of Fallot, Total Anomalous Pulmonary Venous Return, Transposition of the Great Arteries, Tricuspid Atresia, Truncus Arteriosus, Coarctation of the Aorta, Double Outlet Right Ventricle, Ebstein's Anomaly, Single Ventricle/Hypoplastic Right Heart Syndrome, and Interrupted Aortic Arch.

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.* Unrecognized CCHD can result in death or disability shortly after hospital discharge. As the determination of disability is much more challenging, death due to unrecognized CCHD is the measure usually studied. In the Baltimore-Washington Infant Study, 62/76 (82%) of the infants who died due to unrecognized CCHD died within the first eight days after birth (Kuehl). In more recent data from Wisconsin, between 2002 and 2006 the median age at death due to unrecognized CCHD was 4.5 days (Ng).

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?* The incidence of one of the 12 CCHD lesions is 2.3/1,000 live births (Hoffman, Loffredo). Most of these infants are detected prenatally or by postnatal examination prior to circulatory collapse, but an important minority will become critically ill or die before the diagnosis of CCHD is recognized. A recent CDC analysis of 3746 infants with CCHD found that the diagnosis of CCHD was made at greater than three days of age in 29.5% of patients (Peterson).
Severity of Disease	*Morbidity, disability, mortality, spectrum of severity, natural history.* We reviewed the incidence of death or hospitalization due to unrecognized CCHD in Wisconsin from 2002 to 2006. This analysis was limited to events occuring within 14 days of birth and may underestimate the frequency of these events. Death due to unrecognized CCHD occurred in 1:38,397 Wisconsin births and death or rehospitalization occurred in 1:24,684 Wisconsin births before two weeks of age (Ng). The rate of missed or delayed diagnoses tends to be significantly higher in the European literature than in US literature and is not quoted. The incidence of a missed or delayed diagnosis of CCHD was reported to be 1:14,261 in New Jersey from 1999-2004 (Aamir). Although not indexed directly in the paper, up to 30 infants died of a missed or late diagnosis of CCHD over a period of time when the average birth rate was approximately 550,000 per year (California Department of Health, Chang) giving a rough incidence of 1:18,400.

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?* The primary adverse outcome of a missed diagnosis of CCHD is death. The effect of timely diagnosis on morbidity has been more difficult to ascertain. Limited data suggest that an earlier diagnosis of Transposition of the Great Arteries is associated with improved neurologic outcome (Calderon). Data on Texas infants with HLHS has shown that those infants born at a greater distance from a cardiac center had a higher presurgical mortality, suggesting that delays in diagnosis and definitive therapy adversely affect outcome (Morris).
Efficacy (Benefits)	*Extent of prevention of mortality, morbidity, disability. Treatment limitations, such as difficulty with acceptance or adherence.* Failure to identify any one of the 12 CCHD in a timely fashion may be lethal. Although late presentation of some of these lesions may occur, untreated hypoplastic left heart syndrome in particular is thought to be universally lethal in infancy. With current therapy, current expectations are that 70% of newborns with HLHS who are treated will reach adulthood (Feinstein).

Potential Harms	*Potential medical or other ill effects from treatment.* The primary treatment for the 12 CCHD lesions is cardiovascular surgery, although in some cases, the initial or even definitive therapy may be an interventional cardiac catheterization procedure. These procedures carry significant risk for morbidity and mortality. However, with improvements in mortality, a greater emphasis has been placed on the morbidity associated with these diseases and their treatments in order to define better methods of immediate and long term care (Marino).

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.* The primary treatment for the 12 CCHD lesions is cardiovascular surgery, although in some cases, the initial or even definitive therapy may be an interventional cardiac catheterization procedure. In many cases, infants can be stabilized by the initiation of prostaglandin E1 to reopen the ductus arteriosus. This action improves hemodynamic stability which allows for definitive diagnosis and treatment. These infants are usually transferred to a cardiovascular interventional center for their care after diagnosis and stabilization.
Availability	*Describe scope of availability and note any limitations.* Definitive diagnosis of CCHD is made using echocardiography, which is available at the place of birth to approximately 3/4 of babies born in Wisconsin. However, prostaglandin is on formularly in less than half of Wisconsin birth hospitals and may not be available until a neonatal transport team arrives. Definitive therapy is available at both the Children's Hospital of Wisconsin in Milwaukee and the American Family Children's Hospital in Madison. Approximately 14% of infants requiring advanced neonatal care will be sent to Minnesota for therapy. These results were reported by Beissel in a 2012 survey of Wisconsin hospitals (Beissel).

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.* As a point-of-care screening, the outcome of pulse oximetry screening must be determined prior to discharge from care. Infants who fail the pulse oximetry screening should undergo a "comprehensive evaluation for causes of hypoxemia. In the absence of other findings to explain hypoxemia, CCHD needs to be excluded on the basis of a diagnostic echocardiogram." (Kemper) The echocardiogram is considered the definitive diagnostic tool for the detection of CCHD. In light of a normal echocardiogram, a confident statement can be made on the absence of CCHD and no cardiology follow-up will be required. If other disease processes are identified, the response must be individualized to the clinical scenario.

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.* Point-of-care screening should be performed with a pulse oximeter which is FDA approved for use in infants.
Modality of Screening	*Dried blood spot, physical or physiologic assessment, other.* Pulse oximetry screening is ideally performed more than 24 hours after birth. Saturation measurements are taken in the right hand and one foot. An algorithm is used to determine if the newborn has passed, failed, or had an equivocal result which should be repeated in an hour. If a baby has not reached the criteria to pass by the thid attempt, they are considered to have failed the screening. (Kemper)

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.* If a newborn fails the screening protocol or cannot attain a passing criteria in three attempts, a comprehensive evaluation for causes of hypoxemia should be undertaken as outlined in criterion 5.
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 algorithm recommended by the US Secretary of Health and Human Services, the American Academy of Pediatrics, the American College of Cardiology, and the American Heart Association is based on a Swedish study of 39,821 newborns (Granelli). This study demonstrated a decrease in missed diagnoses and death due to unrecognized CCHD in the population undergoing pulse oximetry screening. The positive predictive value for CCHD was 21%, but 45% of those infants with a false positive result had a cardiac, pulmonary, or infectious diesease requiring therapy. The false positive rate was 0.17% in this study. the sensitivy was 62% and the specificity was 99.8%. A study of 72,694 infants from New Jersey demonstrated a false positive rate of 0.06% and a positive predictive value of 14.3% for CCHD. Other cardiac, pulmonary, or infectious concerns were found in 61% of infants failing their oximetry screening. 24.4% of babies failing their pulse oximetry screening were felt to be normal (Garg). Preliminary data from the Wisconsin SHINE project is being gathered to assess the performance of pulse oximetry screening in Wisconsin. Based on nearly 16,000 babies with SHINE data reported on their newborn screening card, the false positive rate is 0.082%. The positive predictive value is 23% for CCHD, but 46% of those babies with a false positive test for CCHD have a cardiac, pulmonary, or infectious disease requiring therapy other than CCHD. 31% of those babies failing the screening were felt to be healthy newborns. There are six known false negatives in the cohort. Tetralogy of Fallot (2) Coarctation of the Aorta with VSD Coarctation of the Aorta without VSD Total Anomalous Pulmonary Venous Return Complex Single Ventricle There were 19,745 births at hospitals enrolled in SHINE and attendend by SHINE-enrolled midwives and traditional birth attendants during the study period. Although the rate of screening cannot be determined, results of pulse oximetry screening were reported to SHINE for 16,168 (81.9%).
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.* When data collected in all manners is utilized, additional information is available on several more babies. With this additional data, the false positive rate is 0.1%. The positive predictive value is 19% for CCHD, but 44% of those babies with a false positive test for CCHD have a cardiac, pulmonary, or infectious disease requiring therapy other than CCHD. 38% of those babies failing the screening were felt to be healthy newborns. Although this results in minor variations of the statistics, the same pattern holds. Babies with diseases other than CCHD>healthy babies>babies with CCHD.

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?* The disease processes other than CCHD including cardiac disorders other than CCHD, pulmonary diseases, and infection will be treated at the discretion of attending medical care givers as part of routine medical care. • *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?* Pulse oximetry screening as a mechanism to detect unrecognized pulmonary disease and sepsis has not been studied.

Summary of Population-based Pilot Study(ies)

Location of Prospective Pilot	Wisconsin SHINE Project 1-1-13 to 1-31-14
Number of Newborns Screened	16,168
Number of Positive Results	*Positive by primary test versus 2nd tier test if applicable.* 13
False Positive Rate; False Negative Rate (if known)	*False positive by primary test versus 2nd tier test if applicable.* 0.082%
Number of Infants Confirmed with Diagnosis	*How is diagnosis confirmed [clinical, biochemical, molecular]?* Echocardiography

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.* The use of pulse oximetry screening to detect hypoxia has become the standard of care in Wisconsin hospitals and is utilized by 45 out-of-hospital midwives, traditional birth attendants, and public health nurses at the last analysis of the SHINE project. As a point-of-care screening, no additional systems are required to perform screenings outside the birth setting. The Wisconin SHINE project has created an extensive education system to support clinicians performing and interpreting pulse oximetry screening as well as those cardiac sonographers performing echocardiograms in response to failed oximetry (www.wisconsinshine.org). In order to provide quality assurance, results of the oximetry screening are currently voluntarily reported on the newborn screening card.

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.* Once a baby fails their pulse oximetry screening, an evaluation for causes of hypoxia is undertaken. If CCHD, or any other disease process is identified, routine clinical care is undertaken. The primary complication is the cost, inconvenience, and anxiety triggered by the failed screening and the necessary evaluation.
Is test FDA cleared/approved	*Include availability of information, sole source manufacturer, etc.* The US Secretary of Health and Human Services recommended that Critical Congenital Heart Disease be added to the recommended uniform screening panel in 2011.

List all CLIA or CAP certified labs offering testing in the US	*Link to GeneTests and Genetic Test Reference if applicable.* N/A
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 SHINE project has worked extensively with hospitals, midwives, and traditional birth attendants. As congenital heart disease is the most common serious birth defect, a plan for evaluation of the baby with suspect congenital heart disease is part of standard care in all birth settings. Should a child fail their pulse oximetry screening, the health care provider involved should utilize their available resources as they would if a child had other signs or symptoms of congenital heart disease.

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	A cost-effectiveness analysis performed at the CDC estimated a cost of $6.28 per infant attributable to pulse oximetry with incremental costs of $20,862 per newborn with CCHD identified and $40,385 per year of life gained (Peterson). The cost of pulse oximetry screening was estimated at $14 per infant in a review of New Jersey' s screening protocol (Garg). This cost could potentially be decreased by the use of re-usable rather than disposable pulse oximetry probes. A cost analysis of pulse oximetry screening for CCHD is part of the SHINE project and will be undertaken in the third year of the grant.
Confirmatory testing	Because of the low rate of screening failures the costs of echocardiography performed in infants with false-positive screening did not have a significant impact on the cost analyses in the CDC study (Peterson).
Treatment	The costs of treatment for infants with CCHD are considerable, but have not been previously included in any intent-to-treat assessment of CCHD that the authors have identified.
Counseling	Counseling regarding the presence or absence of CCHD must be provided by the bedside caregivers. Fortunately, echocardiography has the ability to definitively confirm or exclude CCHD in real time.
False positives	The costs of care for those infants with false positive screenings for CCHD who have other significant pulmonary, cardiac, or infectious disease processes indentified by oximetry screening fall in the context of routine clinical care. The evaluation of a newborn for congenital heart disease based on the presence of a heart murmur or other clinical suspicion is a common aspect of regular neonatal care and frequently is undertaken in infants who are cleared of these concerns. The management of those infants free of any disease process after failing their pulse oximetry screening represent a similar case.
Mechanism of funding	The cost of point-of-care pulse oximetry screening are shouldered by the local health care delivery systems and by patients. All Wisconsin hospitals have pulse oximetry hardware available in their newborn care facilities (Beissel) and oximeters have been provided to the majority of out-of-hospital birth providers through the Wisconsin SHINE project. The costs of echocardiography are part of routine neonatal care. The costs associated with data collection, analysis, and quality assurance have been paid for by the Wisconsin SHINE project. The HRSA demonstration grant funding the SHINE project runs through May, 2015.

Key References to support each criterion. Please list and attach as PDF(s). If mailing, include hard copies.	
#	**Criterion 1**
	Peterson C, Ailes E, Riehle-Colarusso T, Oster ME, Olney RS, Cassell CH, et al. Late Detection of Critical Congenital Heart Disease Among US Infants: Estimation of the Potential Impact of Proposed Universal Screening Using Pulse Oximetry. JAMA pediatrics. 2014;168:361-70.
	Kuehl KS, Loffredo CA, Ferencz C. Failure to diagnose congenital heart disease in infancy. Pediatrics. 1999;103:743-7. Ng B, Hokanson J. Missed congenital heart disease in neonates. Congenit Heart Dis. 2010;5:292-6.
	Criterion 2
	Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39:1890-900. Loffredo CA, Ferencz C, Wilson PD, Lurie IW. Interrupted aortic arch: an epidemiologic study. Teratology. 2000;61:368-75.
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	Criterion 3
	Calderon J, Angeard N, Moutier S, Plumet MH, Jambaque I, Bonnet D. Impact of prenatal diagnosis on neurocognitive outcomes in children with transposition of the great arteries. J Pediatr. 2012;161:94-8 e1. Morris SA, Ethen MK, Penny DJ, Canfield MA, Minard CG, Fixler DE, et al. Prenatal diagnosis, birth location, surgical center, and neonatal mortality in infants with hypoplastic left heart syndrome. Circulation. 2014;129:285-92.
	Feinstein JA, Benson DW, Dubin AM, Cohen MS, Maxey DM, Mahle WT, et al. Hypoplastic left heart syndrome: current considerations and expectations. J Am Coll Cardiol. 2012;59:S1-42. Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012;126:1143-72.
	Criterion 4
	Beissel D.J. Goetz EM, Hokanson J.S. Pulse Oximetry Screening For Congenital Heart Disease in Wisconsin. Congenit Heart Dis. 2011;6:521-2
	Criterion 5
	Kemper AR, Mahle WT, Martin GR, Cooley WC, Kumar P, Morrow WR, et al. Strategies for implementing screening for critical congenital heart disease. Pediatrics. 2011;128:e1259-67.
	Criterion 6
	Kemper AR, Mahle WT, Martin GR, Cooley WC, Kumar P, Morrow WR, et al. Strategies for implementing screening for critical congenital heart disease. Pediatrics. 2011;128:e1259-67.

	de-Wahl Granelli A, Wennergren M, Sandberg K, Mellander M, Bejlum C, Inganas L, et al. Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39,821 newborns. BMJ. 2009;338:a3037. Garg LF, Van Naarden Braun K, Knapp MM, Anderson TM, Koppel RI, Hirsch D, et al. Results from the New Jersey statewide critical congenital heart defects screening program. Pediatrics. 2013;132:e314-23.
	Criterion 7
	www.wisconsinshine.org
	Criterion 8
	Criterion 9
	Peterson C, Grosse SD, Oster ME, Olney RS, Cassell CH. Cost-effectiveness of routine screening for critical congenital heart disease in US newborns. Pediatrics. 2013;132:e595-603. Garg LF, Van Naarden Braun K, Knapp MM, Anderson TM, Koppel RI, Hirsch D, et al. Results from the New Jersey statewide critical congenital heart defects screening program. Pediatrics. 2013;132:e314-23.
	Beissel D.J. Goetz EM, Hokanson J.S. Pulse Oximetry Screening For Congenital Heart Disease in Wisconsin. Congenit Heart Dis. 2011;6:521-2

Additional Co-sponsoring Organizations

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

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Submit Nominations to: DHSWICongenitalDisorders@wisconsin.gov

Or mail to:

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