Curr Pediatr Rep (2016) 4:18–27
DOI 10.1007/s40124-016-0095-2

CARDIOLOGY (W LAI AND W ZUCKERMAN, SECTION EDITORS)

An Update on Critical Congenital Heart Disease Screening Using Pulse Oximetry

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Published online: 21 April 2016

Abstract This review paper places lessons learned from recent publications over the past 3 years into the larger context of newborn screening for critical congenital heart disease (CCHD) in the United States and internationally. Lessons learned from CCHD screening in previously unexamined populations and settings have helped refine the issues and eliminate preconceived barriers. Although the incidence of CCHD is relatively stable worldwide, the sensitivity of newborn screening and the impact on outcomes are greatly influenced by the healthcare resources available, type of facility, and the specific screening algorithm implemented, including timing and cut-off values. Screening in neonatal intensive care units, while feasible, may ultimately be of limited value, while screening home births and at altitude require further investigation. Defining goal targets and using standardized nomenclature are critical to being able to make comparisons and learn from emerging aggregate data sets as universal screening at the national level becomes a reality in additional countries.

This article is part of the Topical Collection on *Cardiology*.

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Keywords Pulse oximetry screening · Critical congenital heart disease screening · Newborn screening · Detection of critical congenital heart disease

Introduction

Congenital heart disease (CHD) is the most common birth defect, occurring in roughly 1 per 110 babies, with 25 % of these cases having critical CHD (CCHD) [1•]. Many cases of CCHD become clinically evident as the infant transitions from fetal to newborn circulation shortly after birth; however, some cases still escape timely detection. Late diagnosis is typically defined as CCHD diagnosis any time after discharge from the birth hospital. Late diagnosis may result in poorer outcomes such as heart failure, permanent cerebral and end-organ damage or death. Earlier CCHD diagnosis in a recent New Zealand study showed 16 % mortality compared to 27 % mortality for infants with CCHD who received a late diagnosis [2•].

Screening for CCHD using pulse oximetry in newborns is conducted to detect low oxygen saturation in the blood as a mechanism to identify infants who may have CCHD. In an effort to improve CCHD outcomes, CCHD screening was added to the United States Recommended Uniform Screening Panel (RUSP) in 2011. CCHD screening has been demonstrated to be an inexpensive, easy, and painless test that takes only a few minutes to perform. For infants with failed screens, a provider in the nursery assesses the infant and based on further evaluation determines whether CCHD or non-cardiac pathology may be the cause. The purpose of this article is to review the recent advances in the literature regarding CCHD screening, to describe trends in CCHD screening use, and to identify areas that require further study or consideration.

United States and Global Implementation

CCHD screening improves the detection of infants with CCHD who were not identified prenatally or from initial postnatal clinical assessment. These infants, who avoid the mortality and morbidity associated with late detection, are the greatest marker of success for this screening program. Unfortunately, to date in the United States, we are unable to quantify this success at the national level as only a few states have published outcome reports. Anecdotal reporting confirms that lives have been saved by early detection and intervention.

A major accomplishment in the U.S. has been the rate at which states have adopted mandatory newborn CCHD screening since 2011. Approximately, 98 % of births are potentially being screened based upon the number of births in states with mandates. The figure is even higher if one calculates births in states that are screening without a mandate into the total (Table 1). Debates related to whether screening should be implemented as the standard of care or added as part of a required newborn screening panel are largely resolved with 46 states plus the District of Columbia requiring the screen by law. As of February 2016, only four states (Wyoming, Vermont, Kansas and Idaho) do not have legislation or a regulation that require CCHD screening. Of those, Vermont and Kansas have fully implemented CCHD screening using pulse oximetry programs at birthing hospitals within their states. Universal screening for CCHD using pulse oximetry is nearly complete in the U.S. as states continue to tackle the challenges associated with the electronic data transfer of screening results, linking outcomes and diagnosis to birth defects registries and short- and long-term follow-up.

Global progress is also being made [3, 4•], adding to our understanding in areas of concern in the U.S. From parts of the world where there is a high percentage of out-of-hospital births and in areas where there is a trend toward earlier discharge prior to 24 h after birth [5], we are learning ways to maximize the effectiveness of screening in those contexts. Countries with national recommendations to screen are indicated in Table 2. The Nordic countries use the identical protocol as the U.S; the evidence used to support the U.S. recommendation came in part from a Swedish study. Sweden, Norway and Finland used a bottom-up approach to implementation and are now close to screening 100 % of births. Denmark and Iceland have significantly lower implementation rates overall, but enjoy high prenatal detection rates and some of the lowest infant mortality rates in Europe [6]. In China, a recent study showed that the use of pulse oximetry screening can increase the detection of CCHD from 77.4 % with clinical assessment alone to 93.2 % with clinical assessment plus pulse oximetry [7••].

The best method of achieving widespread implementation, particularly in middle and low income countries remains an open question. In some countries, a government mandate may be effective, whereas, in other countries the recommendation of a medical society may be the key to triggering implementation. An international CCHD expert work group met in 2013 [8•] and continues to meet to discuss strategies for developing a recommendation for implementation in Europe. Researchers in Malaysia and China investigating CCHD screening using pulse oximetry in middle-income countries found that it can also make a significant impact on detecting neonatal sepsis and respiratory diseases [9, 10]. Infrastructure development for point-of-care tests and collaborative strategies for low resource settings with limited access to pediatric cardiology will be important for successful implementation.

Cost Effectiveness

Recent publications addressing the issue of whether CCHD screening is cost-effective have concluded that screening is either reasonably cost-effective or cost-neutral. For example, in the U.S., Peterson et al. using a model-based analysis,

Table 1 Remaining states that do not have a law requiring CCHD pulse oximetryas of January 2016

States without a law	% of births out of total US births[a]	Raw number of births[a]
Kansas (screening without a law)	1 %	39,218
Wyoming	0.2 %	7683
Vermont (screening recommended not required)	0.2 %	6127
Idaho	0.6 %	22,871
Total	2 % screening not required	75,899
	0.8 % likely not screened	30,554

This table is a general estimate and does not account for variations in whether home births and special populations are screened or whether each facility required to screen by state law is fully compliant

Table created from [a]National Vital Statistics Reports, births: preliminary data for 2014, Table 5, page 11. http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_06.pdf

Table 2 Global CCHD pulse oximetry screening implementation as of January 2016

Over 90 % of births screened	Multi-center studies & pilot programs	Interest in screening
Finland	Australia	Argentina
Georgia	Azerbaijan	Austria
Norway[a]	Canada	Bangladesh
Sweden	Mexico	Bolivia
Switzerland[a]	China	Brazil
	Colombia	Chile
USA[a]	Costa Rica	Ecuador
	Denmark	Greece
	France	Iran
	Germany	Japan
	Guatemala	Kenya
	Honduras	Malaysia
	India	Morocco
	Indonesia	Nigeria
	Ireland[a]	Peru
	Israel	Philippines
	Italy	Singapore
	Kuwait	Saudi Arabia
	Netherlands	South Africa
	New Zealand	Sri Lanka[a]
	Malta	Zambia
	Paraguay	
	Poland[a]	
	Portugal	
	Qatar	
	Russia	
	Slovenia	
	Spain	
	Thailand	
	Turkey	
	UK	
	Uruguay	
	United Arab Emirates	
	Vietnam	

[a] National recommendation to screen

The category "Interest in screening" refers to countries with hospitals or centers that have requested toolkits or educational information from Children's National's CCHD Screening Program and from reports and personal emails sent in from researchers, physicians and CHD advocacy groups

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calculated a screening cost of $6.28 per newborn, an incremental cost of $0.50 per newborn (if using re-useable sensors) and an approximate cost of $40,385 per life-year gained [11••]. Using these calculations, if 1189 more newborns were found with CCHD annually in the U.S. and of those 20 newborn deaths are prevented by screening, it is cost effective to screen [11••]. New Jersey, the first state to publish their screening outcomes, described as a preliminary finding that CCHD incremental costs and resource utilization were not limiting factors. Compared to the cost of $20 for metabolic and $36–39 for hearing screening per newborn, CCHD screening per newborn was roughly only $14 (without factoring in the cost of intervention and additional diagnostics for failed screens) [12•]. A study from Minnesota, factoring in only nursing time to screen and the cost of supplies, arrived at a cost figure of $5.10 per newborn screened [13].

One of the biggest variables in costs between different centers is the choice of equipment, with disposable probes resulting in significantly higher costs than reusable probes [14]. An analysis of the Florida Birth Registry explored an additional benefit of implementing CCHD screening using pulse oximetry; a reduction in the costs associated with hospitalizations, re-admissions and in-patient stays for this population [15]. These studies did not consider the potential benefit of identifying children with important non-CCHD conditions, a benefit that could potentially make the use of pulse oximetry even more cost-effective.

Cost-effectiveness calculations balancing the number of infants with CCHD detected against the cost of intervention may conclude that it is less cost-effective to implement in regions where healthcare infrastructure is less developed. This is due to the high cost of intervention or transfer to facilities where intervention is possible [10]. While the cost of cardiac surgery or cardiac catheterization may be out of reach in low- to middle-income countries, there is the benefit of identifying and treating secondary conditions, or non-CCHD causes of a failed screen as well as the inherent value to parents and families of knowing about the presence of a CCHD in their newborn.

Impact on Specialties

While the interventions required for infants diagnosed with CCHD may be cost-prohibitive in developing countries, perhaps the biggest preconceived fears in the developed world were related to the cost of unnecessary transports for false positive screens, the additional referrals to pediatric cardiologists, and the increased number of echocardiograms required. Concerns over an increased burden on specialty services and unnecessary medical costs are not supported by recent literature. Any increased work load and transfers to centers for echocardiograms or pediatric cardiologists related to CCHD screening has been found to be minimal [12•, 16•]. An analysis from Australia went beyond costs and examined additional burdens on healthcare resources. The study concluded that concerns related to discharge delay, cross infection from equipment, increased workload for midwives and pediatric cardiology and increased equipment and staffing costs were also unfounded [16•]. CCHD screening using pulse oximetry has far fewer false positives than clinical assessment (2.7 % false positive rate versus 0.3 % for pulse oximetry) [7••]. Referrals for heart murmurs that turn out to be normal far outweigh the number of echocardiograms performed for false negatives from screening [17••].

Not every infant who fails the screen may require an echocardiogram. In fact, if non-cardiac reasons for a failed screen are ruled out, fewer than 1/3 of infants with positive screens may require an echocardiogram (when screening at around 7 h of life, which has a higher fail rate of 0.8 % than when screening at or around 24 h of life, as is common in the U.S.) [17••]. If a reversible cause of hypoxia is found and treated (such as infection or a respiratory illness), then an echocardiogram may not be necessary. This is particularly important in community or rural hospitals where pediatric echocardiographers or technicians are not in-house or easily available. Solutions for addressing transfers from areas without sub-specialty care include the use of telemedicine as well as providing additional training for local sonographers on pediatric cardiac assessment. These solutions have been explored by several programs in the U.S. as well as one in Abu Dhabi [18]. In Brazil, a telemedicine network implemented in a rural area allowed resources to be allocated more efficiently and resulted in the improved detection of congenital heart defects using CCHD screening [19]. When an echocardiogram is needed, the role of reading the echocardiograms can be given to specialists via telemedicine, thus addressing the problem of requiring a pediatric cardiologist immediately on-site. However, the problem remains if skilled echocardiography technicians are not readily available to obtain the images. In other parts of the world, specially trained neonatologists perform echocardiograms themselves.

Identification of Important Additional Non-cardiac Targets

In the U.S., the majority of states follow the American Academy of Pediatrics (AAP) guidelines which recommend screening babies for CCHD at >24 h of age [20••]. However, there is a recent trend, specifically in the United Kingdom and the Netherlands [17••, 21], towards screening earlier than 24–48 h of life. Any concern over a higher number of false positives is outweighed by the realization that by screening earlier, additional infants are detected prior to clinical symptoms appearing and that false positives are frequently important clinical conditions requiring treatment.

When screening occurs earlier than 24 h of life, the false positive rate can be close to 1 % (0.8 % at around 7 h on a study which screened 25,859 infants) [17••]. This is around ten times higher than the number of false positives when screening occurs around 24 h of life [17••]. However, the question of what is a "false positive" is an important one. In pure epidemiologic terms, any child who does not have a CCHD but has an abnormal pulse oximetry test is a "false positive." Traditionally, false positive results are to be avoided in medicine when possible. However, in CCHD screening using pulse oximetry, a "false positive" may indicate the presence of a serious clinical disease other than CCHD. In two recent studies, 47–75 % of false positives

had a significant clinical condition that required further intervention or monitoring, including congenital pneumonia, sepsis, persistent pulmonary hypertension, meconium aspiration, and pneumothorax [7••, 17••].

Given what we have learned about false positives from early CCHD screening using pulse oximetry, the timing of screening will likely be at around 24 h of age or earlier. A few studies looking at screening later, for example at discharge [22] and at 48–72 h of life [23], have not demonstrated any improvement over screening at the AAP recommended timeframe. The timing of screening is important also when screening special populations such as those born at altitude or in neonatal intensive care units (NICUs). Until there are more robust datasets on newborns born at higher altitudes, the possibility of whether the benefits of screening earlier may only extend to asymptomatic newborn nurseries around sea level remains untested.

Special Populations: NICUs, Home Births or at Altitude

Initial guidelines from the AAP focused on CCHD screening only in the well-baby nurseries [20••]. One recent challenge focuses on whether there is a role for CCHD screening using pulse oximetry in special care nurseries and NICUs. On one side, these babies are frequently monitored using pulse oximetry during their entire NICU stay which may be quite long, lasting several weeks or months. Many of them are on supportive respiratory therapies where oxygen and a ventilator render screening difficult to interpret. A large number of these babies receive echocardiograms. Yet, there remain anecdotal cases of infants who are missed and discharged from a NICU with undetected CCHD.

To date, there is not enough published data to provide an answer as to whether CCHD screening using pulse oximetry will help identify additional unknown cases in the NICU. We know that the pre- and post-ductal oxygen saturations are similar to the pulse oximetry saturations in late preterm and term infants and that CCHD screening using pulse oximetry can be implemented into NICUs [24]. There have been single center studies published which demonstrate feasibility but not a clear benefit from screening in NICU settings [25–27]. A study from India determined a case of CCHD which potentially may have been detected by pulse oximetry alone, a case of tetralogy of Fallot with pulmonary atresia, where the clinical assessment was negative [27]. A multi-center collaborative led by the New Jersey Department of Health is examining screening in NICUs and may be able to provide some insight as to the value of screening in special care nurseries as well as insight into eligibility criteria and timing refinements. Screening in special care and NICU nurseries will require modifications for those infants on oxygen or who receive echocardiograms [28].

Less debatable is the benefit of CCHD screening using pulse oximetry for out-of-hospital or home births. Screening is important in these settings, as this population may be subject to significantly higher missed or delayed diagnosis of CCHD [29•]. In the U.S., home births do not play a large role (less than 1 % of total births but slowly increasing), as most births occur in hospitals. The Netherlands has the highest percentage of home births in the developed countries and published a screening model as well as their 1-year outcomes based on a study conducted in the Leiden region (33 % of low risk births in the Netherlands are midwife supervised, 55 % of which occur in the home) [30•]. In this study, screening occurs early (typically after 1 h of life) and researchers have data showing that although it does result in more false positives, secondary conditions are identified earlier than they would have been without screening. This finding was similar to the out-of-hospital screening outcomes published out of Wisconsin, in which home birth or midwife-attended births (1.66 % of all births in the state) were screened at or around 24–48 h of life [29•]. One barrier that exists when screening out of hospital births is that of providing equipment for each midwife, rather than having a shared device as in a newborn nursery. Carefully examining a region's cost/benefit considerations are important when contemplating screening initiatives in low healthcare resource settings [31].

The scientific evidence required to recommend CCHD screenings as part of the RUSP in the U.S. was based upon studies mainly conducted at or around sea level. Infants born at altitude can experience a prolonged transition from fetal to newborn circulation. The lower partial pressure of oxygen at higher altitudes contributes to delayed pulmonary vasodilation resulting in a higher fail rate than when screening asymptomatic infants at sea level (1.1 % at moderate altitude vs. 0.2 % at sea level) [32•]. The issue of whether and how to screen for infants born at higher altitudes was explored by the Colorado legislature. In May 2015, after considering the evidence and with input from the Colorado School of Public Health, Colorado moved forward requiring newborn CCHD screening using pulse oximetry for all infants born in birthing facilities below 7000 feet [33].

For greater than 7000 feet, the fail rate for CCHD screening is considered too high to be beneficial as a screening tool. For infants screened at moderate altitude, a higher number of false positives are considered acceptable. Other adjustments to the AAP recommended algorithm when screening at moderate altitude [32•] include delaying screening to between 30 and 36 h of life to account for prolonged transition time and administering 26 % oxygen to infants who fail for 1 h prior to performing a repeat

CCHD screening to mimic sea level conditions [34]. Screening at moderate altitude is feasible, particularly with minor modifications to mitigate false positives.

Challenges that Remain

False Negatives and Quality Improvement

Since CCHD screening using pulse oximetry was first investigated as a screening tool, it was expected that not all infants with CCHD will be detected using pulse oximetry screening. Our knowledge of why infants are not detected has improved. It is well established that some infants with CCHD are missed as a result of their specific physiology, for example, non-cyanotic cardiac defects and infants that are still in the process of transitioning [35]. CCHD screening is particularly poor in detecting cases of coarctation of the aorta, with an estimated sensitivity of only 36 % for this defect. [36•]. What additional publications have provided is insight on infants with CCHD who are not detected as a result of technical errors including algorithm misinterpretation and process/work flow issues [12•, 37]. The likelihood of error in interpreting the AAP endorsed screening algorithm without a computer-based tool was quite high. In one study, the algorithm was only interpreted correctly 81.6 % of the time [37]. An initial review of screening data in Minnesota showed that 29 % of retesting was a result of misinterpretation of the algorithm; similar challenges with erroneous interpretation were reported in New Jersey [12•]. NICUs and special care nurseries may be the most prone to underreporting failed screens because of the high prevalence of other comorbidities [12•]. Quality improvement activities [38] and feedback to individual hospitals will continue to remain a critical component to creating and sustaining successful programs.

Algorithm Refinements

The recommended algorithm that has been endorsed nationally in the U.S. and is used in the majority of states is often referred to as the AAP algorithm [20••]. This algorithm has been endorsed by the AAP, Centers for Disease Control and Prevention (CDC), March of Dimes, American Heart Association and the American College of Cardiology. The workgroup commissioned by the United States Human Resource Service Administration's Secretary's Advisory Council on Heritable Disorders in Newborns and Children (SACHDNC) recommended use of the algorithm as one that maximized sensitivity while limiting the number of false positives. Compared to four other published CCHD screening algorithms, the AAP algorithm also has been found in one study to have the lowest re-test rate [39].

Two variations from the AAP algorithm are also used in the U.S. and are frequently referred to as the New Jersey algorithm [12•] and the Tennessee algorithm [40]. Figure 1 depicts differences between these and the AAP algorithm. The New Jersey algorithm results in additional cases of CCHD being identified at the expense of a slightly higher false positive rate, whereas the Tennessee algorithm involves an initial screen of only a foot and then defaults to the AAP protocol if re-testing based on the postductal saturation is required. An alternative algorithm that has been found to be effective and is used in the UK allows for (1) earlier screening (before 12 h of life) and (2) recommends retesting when there is a difference of greater than two between the hand and foot [17••]. Although the sensitivity is similar between using both pre and postductal readings versus only postductal, some infants with CCHD may be missed if only screening either foot [8•, 21]. The largest recent study examining oxygen saturation in newborns at or around 24 h of life found that the mean postductal saturation is higher than the preductal for asymptomatic newborns [41]. The difference is considered clinically insignificant but may inform how we approach or think about the algorithm [39] where we have very clearly learned that even minor modifications can have a big impact on screening sensitivity, false positives, and false negatives. In turn, small differences in these numbers have a tremendous impact on the work load and follow-up at the hospital and public health levels.

Regardless of which algorithm is chosen and where cut-offs values are placed, and notwithstanding quality improvement and process issues, some infants with CCHD will not be detected. Pediatricians and nursery clinical staff should not rely solely on CCHD screening using pulse oximetry to rule out CCHD [42]. When combined with prenatal detection and clinical assessment in the nursery, the addition of routine newborn CCHD screening provides the best method for detecting CCHD in newborns; however, not all babies will be detected and education of families on the signs and symptoms of CCHD remains important.

Public Health

In the U.S., public health departments at the state and federal level play a key role in providing infrastructure for surveillance, and can provide guidance, a coordinated way to identify technical barriers and disseminate best practices to implementing hospitals. Minimum data recommendations and considerations for the reporting of CCHD screening results were published in 2013 [43••]. However,

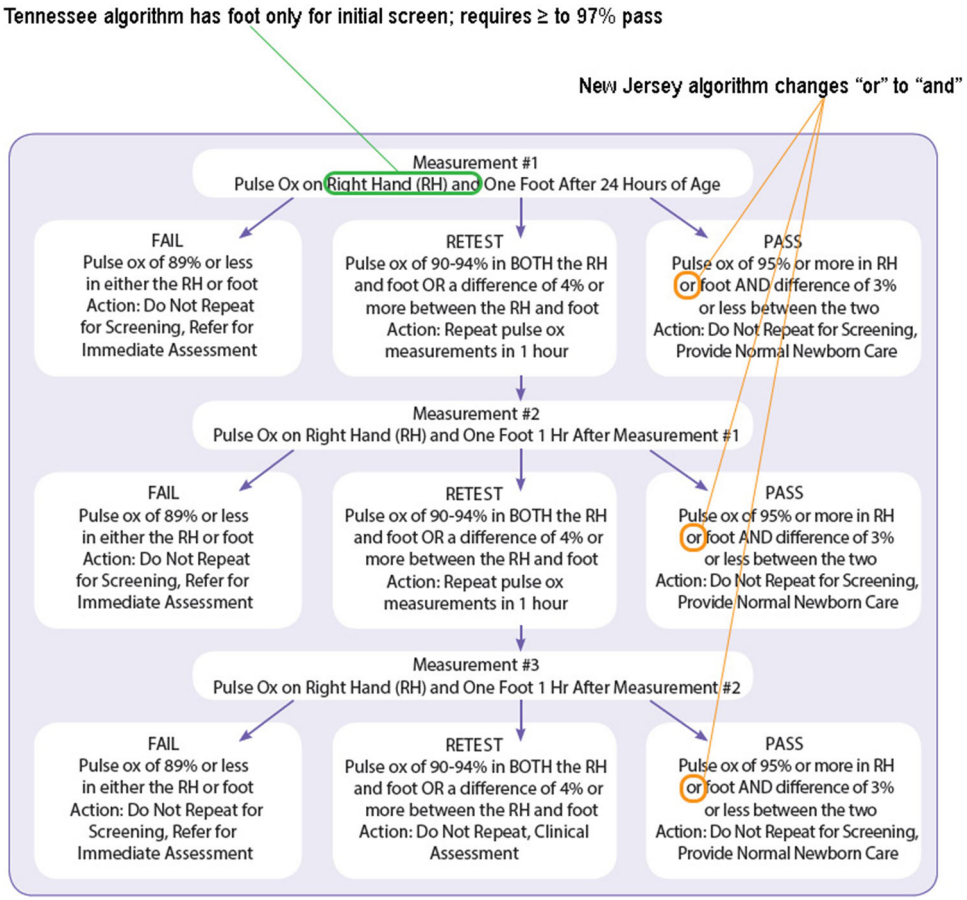

Fig. 1 AAP recommended CCHD screening algorithm and areas of variation. NJ algorithm: changes the 'OR' to an 'AND' for passing criteria. Tennessee algorithm: Foot only for the initial screen: requires ≥97 % pass. If the foot is 96 % or less, the right hand is also screened. Retest or fail is according to the AAP algorithm. Image of current AAP recommended algorithm From Children's National Medical Center. Congenital Heart Disease Screening Program Toolkit: A Toolkit for Implementing Screening. Washington, DC: Children's National Medical Center; 2013

requirements to collect data on newborn CCHD screening using pulse oximetry vary by state. While many regional birth defects registries exist and store data on CCHD, some birth defects surveillance programs do not have the capacity or authority to collect CCHD screening data [44]. Sensitivity is highly dependent on the types of CCHD included as targets; therefore, developing a standard nomenclature and consistent definitions is essential to be able to analyze data across state screening programs [44].

Using a model to analyze the impact on CCHD detection rates in the U.S. and applying the AAP algorithm, the number of additional babies detected through CCHD screening using pulse oximetry annually is close to the same number of babies with CCHD who will still be missed (factoring in babies who were detected prenatally) [36•]. The most commonly defined primary targets are the seven CCHD conditions most likely to be identified by screening: hypoplastic left heart syndrome, pulmonary atresia (with intact septum), tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, and truncus arteriosus. However, if the defined primary targets are expanded to fourteen CCHD targets (adding single ventricle, interrupted aortic arch, coarctation of the aorta, Ebstein's anomaly, double outlet right ventricle, critical aortic stenosis and critical pulmonary stenosis), then the calculated number of false negatives goes up, as these conditions may not be detected.

A recent expert panel convened by the AAP recommended that additional types of CCHD be considered targets of screening, and not just a select few [45••]. Analysis of existing large datasets by the AAP, CDC, and other national medical organizations will help improve the effectiveness of screening.

Eliminating Preventable Deaths Due to Undetected CCHD

The global end goal of newborn CCHD screening using pulse oximetry is to prevent deaths and morbidity due to undetected CCHD. The positive impact of CCHD screening using pulse oximetry will likely continue to be greatest in rural or community hospitals where prenatal diagnosis rates are lower than those at academic teaching institutions [31, 46]. Dectection rates continue to vary by region, can be center-specific, and are dependent on type of defect with coarctation and isolated CCHD (not associated with a syndrome or other congenital defects) the most difficult to

detect [47•, 48•, 49]. Currently, there is not enough evidence to know whether peripheral perfusion index (PPI) will play an important role in identifying defects related to left outflow tract obstructions.

Technological advances in pulse oximetry equipment including embedded algorithms, as well as electronic data transfer can further eliminate sources of error [37]. Small hand held devices and mobile device applications for pulse oximetry could improve access to CCHD screening for many. Quality, accuracy, and value will continue to be crucial drivers when selecting a pulse oximeter for screening. One study in India had significantly lower sensitivity than other centers (60 %) and the authors suggested a contributing factor may have been the use of oximeters that were calibrated for functional saturation only and were non-motion tolerant [50]. The cost of accurate screening equipment is most challenging in those countries with the fewest economic resources.

Conclusion

CCHD screening is spreading rapidly, with universal implementation nearly complete in the U.S., and in a small number of countries worldwide. Multicenter and regional projects continue to examine the remaining questions around definitions, algorithm specifications and special populations. There is a trend to screen earlier in Europe specifically in the UK and the Netherlands. Higher false positive rates may be deemed acceptable in favor of detecting additional non-cardiac diseases early. If so, ruling out respiratory or infectious causes of hypoxia will become increasingly essential as a way to minimize the number of echocardiograms ordered for babies who are false positives. Our ability to make recommendations around NICU screening, screening at altitudes >7000 feet and with different delivery models will improve as the data from additional unique settings become more robust. CCHD screening using pulse oximetry combined with other standard perinatal detection methods is an important tool for detecting CCHD. The detection and early identification of secondary conditions is where we may see the greatest impact in total number of lives saved as CCHD screening is implemented in the developing world. The effectiveness of screening will improve with technological advances in echocardiography, pulse oximetry devices, fetal ultrasound, and the availability of high-quality linked population level data sets for analysis and algorithm refinements.

Compliance with Ethics Guidelines

Disclosure Lisa A. Hom, Gerard R. Martin, and Matthew E. Oster declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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