Universal Pulse Oximetry Screening for Early Detection of Critical Congenital Heart Disease

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ABSTRACT: Critical congenital heart disease (CCHD) is a major cause of infant death and morbidity worldwide. An early diagnosis and timely intervention can significantly reduce the likelihood of an adverse outcome. However, studies from the United States and other developed countries have shown that as many as 30%–50% of infants with CCHD are discharged after birth without being identified. This diagnostic gap is likely to be even higher in low-resource countries. Several large randomized trials have shown that the use of universal pulse-oximetry screening (POS) at the time of discharge from birth hospital can help in early diagnosis of these infants. The objective of this review is to share data to show that the use of POS for early detection of CCHD meets the criteria necessary for inclusion to the universal newborn screening panel and could be adopted worldwide.

KEYWORDS: critical congenital heart disease, pulse-oximetry screening, newborn

Introduction

In September 2011, the United States Secretary of Health recommended that pulse-oximetry screening (POS) before discharge should be added to the universal newborn screening panel for early detection of critical congenital heart disease (CCHD) for all infants born in the US. Since then, nearly all states in the US have adopted this recommendation and require all birthing hospitals to screen newborns before discharge. However, POS is different from most other disorders on universal newborn screening panel. For metabolic and genetic disorders on universal newborn screening panel, a blood sample is collected before discharge, and the follow-up is usually done as an outpatient after discharge from the birthing hospital. In contrast, the result of POS is available immediately and since a positive result requires cardiology evaluation, it may cause a delay in discharge. The concerns about false-positive rates (FPRs) and the perception that this will place an undue burden on parents and limited health-care resources led to an intense debate about the appropriateness of adding POS to the universal newborn screening panel.

Newborn screening started with Guthrie when he described a screening test for phenylketonuria (PKU) in 1957, and by the end of the 1960s, newborn screening for PKU, as well as some other diseases, became a standard medical practice in hospitals across the USA. This rapid expansion of newborn screening made this a topic of growing importance and controversy. In 1968, World Health Organization (WHO) commissioned a report on newborn screening from James Maxwell Glover Wilson, then Principal Medical Officer at the Ministry of Health in London, England, and Gunner Jungner, then Chief of the Clinical Chemistry Department of Sahlgren’s Hospital in Gothenburg, Sweden. This WHO report, Principles and Practice of Screening for Disease, was published in 1968. Their guidelines have since then become the gold standard to determine if a disorder qualifies to be included for newborn screening. Wilson and Jungner described 10 important criteria to consider before a disease should become a candidate for universal screening (Table 1).

The objective of this review is to share data to show that the use of POS for early detection of CCHD meet the criteria for its inclusion to a universal newborn screening panel. In order to do that, this review will briefly discuss how frequent the problem is, and what is the impact of an early diagnosis on outcome, current options, and their limitations in timely diagnosis of CCHD, if POS can help in early detection of CCHD; and the current recommendations for screening.

Epidemiology of CHD and CCHD

Congenital heart disease (CHD) is one of the most common birth defects in the general population and is a major cause of death in infancy in the United States and other developed nations. It accounts for 6%–10% of all infant deaths and 30%–50% of all deaths from congenital malformations. The vast majority of these early deaths, particularly those...
occuring in the first two weeks of life, are primarily due to duct-dependent lesions. These lesions, although individually rare, form the bulk of the life-threatening heart conditions in the newborn period.

A systematic review, which included 114 papers and a total study population of over 24 million live births, described the birth prevalence of all CHDs from 1930 to 2010.\(^7\) Total CHD birth prevalence increased substantially over time, from 0.6 per 1,000 live births in 1930–1934 to 9.1 per 1,000 live births after 1995. Over the past 15 years, the prevalence rate of CHD has stabilized somewhat. Reported birth prevalence of CHD varies widely among studies worldwide. The estimate of 8 per 1,000 live births is generally accepted as the best approximation. Currently, approximately 1.35 million newborns are born worldwide with CHD every year. This increase in the prevalence of CHD is a result of an increase in true incidence as well as increase in our ability to detect and diagnose. The birth prevalence of certain lesions also depends on our ability to diagnose prenatally and maternal decision regarding termination of affected pregnancies. True increase in prevalence of CHD is attributed to various factors such as increase in maternal age; illnesses during pregnancy such as diabetes, infections, and PKU; increased exposure to drugs during pregnancy such as anticonvulsants, steroids, and alcohol; and environmental exposures such as organic solvent, dichlorodiphenyltrichloroethane (DDT), and other chemicals.\(^7\) Improved ability to diagnose is related to better health care and introduction of echocardiography in 1970s. The worldwide incidence of CHD in the coming decades will be influenced by improved prenatal diagnosis, termination of affected pregnancies, and improved access to care in the developing world.

A further review of the birth prevalence of the eight most common CHD subtypes from 1945 to 2010 demonstrated that the most dramatic increase in overall prevalence is secondary to the increase in the rates of ventricular septal defect, atrial septal defect, and patent ductus arteriosus, with much lower increase in the prevalence of other lesions and the prevalence of aortic stenosis appears to be lower now than before.\(^7\)

The incidence of CCHD varies from study to study, depending on the definition of CCHD and the number of different cardiac defects included in the study. The usage of the term CCHD is not uniform, and many different definitions have been used in different studies. CCHD broadly comprises cyanotic congenital heart defects and left-sided obstructive lesions, in which cyanosis may or may not be a predominant clinical presentation. However, it is important to note that all infants with these lesions may not require corrective surgery in early infancy based on the severity of lesion. The judgment as to whether a lesion is severe enough to need surgery before a certain age is frequently qualitative or subjective, especially in lesions such as Tetralogy of Fallot, which can present with a spectrum of severity (Tables 2 and 3). Based on the available data in 2006, Liske et al estimated the fraction of specific lesion either ductal dependent or requiring surgical or catheter intervention in the first month of life and are most likely to benefit from early detection by POS.\(^8\) Based on their estimates, prevalence of CCHD in US was 2.9 per 1,000 births but 1.65 infants per 1,000 live births were likely to benefit from early detection and treatment (Table 4). Since then, another large population-based study published in 2008 estimated that the overall prevalence of CHD in US was 8.14 infants/1,000 births, and the prevalence of CCHD was 2.2 infants/1,000 births.\(^9\) These estimates confirm that CCHD is an important health-care problem and meets the first Wilson and Jungner criteria for universal newborn screening.

### Table 1. Wilson and Jungner screening criteria.

| 1. | The condition sought should be an important health problem. |
| 2. | There should be an accepted treatment for patients with recognized disease. |
| 3. | Facilities for diagnosis and treatment should be available. |
| 4. | There should be a recognizable latent or early symptomatic stage. |
| 5. | There should be a suitable test or examination. |
| 6. | The test should be acceptable to the population. |
| 7. | The natural history of the condition, including development from latent to declared disease, should be adequately understood. |
| 8. | There should be an agreed policy on whom to treat as patients. |
| 9. | The cost of case-finding should be economically balanced in relation to possible expenditure on medical care as a whole. |
| 10. | Case-finding should be a continuing process and not a “once and for all” project. |

### Table 2. Estimate of birth prevalence of critical cyanotic congenital heart lesion.

| LESION                      | NATIONAL MEAN OF ALL CASES (PER 1000 LIVE BIRTHS) | ESTIMATED PREVALENCE OF CRITICAL CASES (PER 1000 LIVE BIRTHS) |
|-----------------------------|---------------------------------------------------|-------------------------------------------------------------|
| Tetrology of fallot         | 0.42                                              | 1/8                                                         |
| Transposition of great arteries | 0.32                                           | 7/8                                                         |
| Hypoplastic right heart     | 0.22                                              | All                                                        |
| Tricuspid atresia           | 0.08                                              | 3/4                                                         |
| Ebstein’s anomaly           | 0.11                                              | 1/8                                                         |
| Pulmonary atresia           | 0.13                                              | 7/8                                                         |
| Truncus arteriosus          | 0.11                                              | All                                                        |
| Double outlet right ventricle | 0.16                                           | 1/2                                                         |
| Single ventricle            | 0.11                                              | 3/4                                                         |
| Total anomalous pulmonary venous return | 0.09                                      | All                                                        |
| Total                       | 1.75                                              | 1.1                                                         |

Note: Data from Liske et al.\(^8\)
Benefits of Early Diagnosis

Several studies have been done to evaluate the impact of prenatal diagnosis on outcome in infants with CCHD. Preoperative and postoperative morbidity and mortality were compared in 68 neonates with prenatal diagnosis and in 250 neonates with a postnatal diagnosis of Transposition of great arteries (TGA) over a period of 10 years.\textsuperscript{10} Prenatally diagnosed infants were admitted soon after birth (the interval between birth and admission was 2 ± 2.8 hours), while infants with a postnatal diagnosis were admitted at about 3 days of age (73 ± 21 hours). Clinical condition at arrival, including metabolic acidosis and multiorgan failure, was worse in the postnatal group (P < 0.01). Preoperative mortality was 6% in the postnatal group and 0 in the prenatal group (P < 0.05). Postoperative morbidity was not different (25 of 235 versus 6 of 68), but hospital stay was longer in the postnatal group (30 ± 17 versus 24 ± 11 days, P < 0.01). In addition, postoperative mortality was significantly higher in the postnatal group (20 of 235 versus 0 of 68, P < 0.01), although the risk factors for operative mortality were identical in the two groups.

Similar benefits were observed in infants with hypoplastic left heart syndrome (HLHS) and coarctation of the aorta. In a study of 88 patients with HLHS, 33 with prenatal and 55 with postnatal diagnosis, all patients who were prenatally diagnosed and underwent surgery survived, whereas only 25 of 38 postnatally diagnosed patients survived (P = 0.009).\textsuperscript{11} Patients diagnosed prenatally had a lower incidence of preoperative acidosis (P = 0.02), tricuspid regurgitation (P = 0.001), and ventricular dysfunction (P = 0.004). They were also less likely to need preoperative inotropic medications or bicarbonate (P = 0.005). Preoperative factors correlating with early mortality included postnatal diagnosis (P = 0.009), more severe acidosis (P = 0.03), need for bicarbonate or inotropes (P = 0.008 and P = 0.04), and ventricular dysfunction (P = 0.05).\textsuperscript{11}

Another retrospective review of infants with coarctation of the aorta reported that hemodynamic instability, circulatory collapse, and death were more common in the infants diagnosed after birth.\textsuperscript{12} The authors concluded that antenatal diagnosis of coarctation of the aorta is associated with improved survival and preoperative clinical condition.

There has been an increasing recognition over the years that a significant proportion of neonates and infants requiring cardiac surgery have adverse neurodevelopmental outcomes.\textsuperscript{13,14} Although it is likely that the early detection and treatment of CCHD will decrease neurological injury by providing a more stable perioperative status, the studies published so far have not specifically evaluated the impact of early detection of CCHD on long-term neurodevelopmental outcome of these infants.

Opportunities for Timely Diagnosis

These studies demonstrate that a timely diagnosis of life-threatening forms of CCHD helps to improve survival and reduce morbidity. It will be ideal to identify these cases before they are born, as it will allow these mothers to deliver at a center equipped to initiate appropriate treatment promptly. However, studies have shown that as many as 30%–50% of infants with CCHD are discharged after birth without being identified. Prior to the introduction of POS, detection of CCHD primarily relied on prenatal screening and physical examination after birth.

Prenatal diagnosis. Antenatal detection of most cardiac anomalies usually occurs via sonographic screening at 18–20 weeks. Although this technology continues to evolve, it is still prone to operator error, and 100% detection of cardiac anomalies is unlikely. The prenatal detection rate ranges from 8% to 48% but is on average 25%–30% in most studies. In a study from Western US, 99% of CCHD infants requiring surgical or catheter intervention in the first six months of life had prenatal ultrasounds but only 28% were prenatally diagnosed.\textsuperscript{15} Using the population-based data, prenatal detection rate for CCHD was reported to be 35% in UK and 39% in US.\textsuperscript{16}

Two most important factors influencing prenatal detection of CCHD were the type of lesion and the type of medical practice performing the screening ultrasound. Prenatal detection at university-based practices was 71%–100% but ranged from 0% to 39% at non-university-based practices. Anomalous pulmonary venous return (0%), transposition of the great arteries (19%), and left obstructive lesions (23%) had the
Diagnostic Gap in Early Detection of CCHD

Diagnostic gap describes the proportion of infants with CCHD who are discharged from their birth hospital without a diagnosis. A retrospective review from UK of all potentially lifethreatening cardiovascular malformations reported that nearly 30% of these infants were diagnosed after discharge from their birth hospital and that diagnosis of CCHD was made in 5% after death. They estimated that delayed or missed diagnosis of CCHD accounted for 0.14 deaths per 1,000 live births. Based on CCHD prevalence rate of 1–2 per 1,000 live births, it will mean that nearly 10% of all infants with CCHD die before a timely diagnosis is made. Although only limited data are available, it is estimated that as many as 30%–50% of all cases with CCHD leave the hospital undiagnosed in US. This diagnostic gap is likely to be even higher in low-resource countries.

Role of POS in Early Detection of CCHD

In 2009, the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) reviewed the evidence to decide if universal POS should be recommended. Ten studies with a total of 123,846 infants were included in the analysis. This meta-analysis reported a FPR of 0.87% but the FPR was 0.035% if screening was done after 24 hours. A FPR of 0.035% means that approximately 3–4 infants out of every 10,000 screened infants will have a false-positive screen.

Subsequently, four large multicenter prospective studies have been reported from Europe. Although all these studies evaluated the role of POS in early detection of CCHD, there were some differences in the study design and the definitions of CCHD. Table 5 summarizes these differences and their findings. The low sensitivity of POS in these studies was primarily due to its inability to detect a cyanotic left heart obstructive lesions such as coarctation of the aorta. The sensitivity for detecting pulmonary duct-dependent lesions and TGA was almost 100%. The high FPR in Norway and the UK studies was probably related to earlier age at screening compared with the other two studies. Overall, nearly 50% of all infants with a false-positive screen had some other underlying medical condition that could explain the abnormal pulse oximetry values.

In 2012, Thangaratinam et al completed a meta-analysis that included 13 studies and nearly 230,000 infants. They reported a specificity of 99.9% and a FPR of 0.05% (5 false positive cases per 10,000 screened infants; Table 6). Based on the findings of these studies, it is estimated that the use of POS can reduce the diagnostic gap from 30% to 5%–10%. After excluding prenatally detected infants, it is estimated that nearly 50%–70% of infants born with undiagnosed CCHD can be detected by POS. A large majority of cases missed by POS are duct-dependent systemic circulation such as coarctation of the aorta, severe aortic stenosis. In contrast, about half of all the missed cases on examination are cyanotic.
Early detection of critical congenital heart disease

Cost-effectiveness. Studies from US and Europe have shown that POS is a cost-effective intervention and unlikely to place significant burdens on the existing manpower and resources. Based on a cohort model with a time horizon of infancy to estimate the inpatient medical costs and health benefits of CCHD screening, screening was estimated to incur an additional cost of $6.28 per newborn, with incremental costs of $20,862 per newborn with CCHD detected at birth hospitals and $40,385 per life-year gained in 2011 US dollars. Sensitivity analyses suggested screening to be cost-effective under a range of plausible circumstances. A cost survey and time and motion study from New Jersey observed that the mean screening time per newborn was 9.1 minutes and the total mean estimated cost per newborn screened was $14.19 ($7.36 in labor costs and $6.83 in equipment and supply costs. It was also noted that the cost of POS for early detection of CCHD is lower than the cost estimates of some of the existing newborn screening tests (for example, estimated cost of $20 per newborn for laboratory metabolic screening and about $36–$39 per newborn for hearing screening). These studies have also noted that the equipment cost of screening can be substantially reduced if reusable screening sensors were to be used for POS, an acceptable and safe option. It is important to note that the cost-effective analyses for each country will vary depending on the diagnostic gap in that population, which will depend on access to prenatal care, rates of prenatal detection, quality of postnatal care, and local costs for labor and equipment. POS is likely to be more cost-effective in regions of the world with high diagnostic gap such as low-resource countries and less cost-effective in countries with lower rates of diagnostic gaps.

Limitations of POS. The primary limitation of POS is its relatively low sensitivity in most studies, ranging from 62% to 78% (Table 5). It is important for health-care providers and parents to understand that a normal screen at birth does not eliminate the possibility of CCHD. As noted earlier, the large majority of false negatives are cases of duct-dependent systemic circulation such as coarctation of the aorta, severe aortic stenosis. A robust follow-up program to identify the magnitude of false-negative cases in the setting of universal screening may allow opportunities to make improvements to the screening algorithm. It has also been reported that human errors in following the protocol and misinterpretation of the algorithm can lead to false negatives with serious consequences. Enhanced education efforts, electronic interpretation of data, and quality controls can help in identifying and correcting these issues.

Gaps in knowledge. The current screening guidelines are for asymptomatic newborns in normal newborn nursery,

| COUNTRY | GERMANY | NORWAY | SWEDEN | UK |
|---------|---------|--------|--------|----|
| Total infants | 41,445 | 50,008 | 39,821 | 20,055 |
| Study period | 2006–2008 | 2005–2006 | 2004–2007 | 2008–2009 |
| Age at screening | 24–72 hrs | 1–21 hrs | 1–406 hrs | Before discharge |
| Pulse oximetry site | Postductal | Postductal | Pre and postductal | Pre and postductal |
| Oxygen saturation cutoff | ≥96% | ≥95% | ≥95% | ≥95% |
| Pre – post ductal oxygen saturation difference | Not applicable | Not applicable | >3% | >2% |
| Number of retest | 1, after 1 hr | 1, after 2–3 hr | 2, 1 hr apart | 1, after 1–2 hr |
| Screening staff | Routine care providers | Routine care providers | Routine care providers | Routine care providers |
| Equipment | variable | Standardized | Standardized | Standardized |
| Sensitivity | 77.8 | 77.1 | 62.07 | 75 |
| Specificity | 99.9 | 99.4 | 99.82 | 99.12 |
| Positive predictive value | 25.9 | 8.3 | 20.69 | 9.23 |
| Negative predictive value | 99.99 | 99.98 | 99.97 | 99.97 |
| False positive rate | 0.10 | 0.6 | 0.17 | 0.8 |

Note: Data from Thangaratinam et al.

Table 6. Summary of a meta-analysis on the use of pulse-oximetry for the detection of CCHD.

| | Total number of studies | Total number of infants | Sensitivity | Specificity | False positive rate |
|---|---|---|---|---|---|
| | 13 | 229,421 | 76.5% (67.7–83.5) | 99.8% (99.7–99.9) | 0.14% (0.06–0.33) |
| | | | | | 0.05% (0.02–0.12) |
| Note: Data from Thangaratinam et al. | | | | | |

heart diseases such as TGA and Total anomalous pulmonary venous return (TAPVR).

Table 5. Summary of four large randomized trials on the use of pulse-oximetry for detection of CCHD.
and evidence-based guidelines for screening infants in neonatal intensive care setting are lacking. There is also a lack of clarity and consensus on appropriate oxygen saturation cutoffs to be used at higher elevations because baseline oxygen saturations in healthy infants born at high altitude are lower. Studies are currently underway to answer these questions.

**Current guidelines.** The US Health and Human Services Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children formed a work group in collaboration with the AAP, AHA, and the American College of Cardiology Foundation to review the evidence on the use of POS for early detection of CCHD. The work group published their recommendations in 2011, which were subsequently endorsed by AAP, AHA, and other organizations.36

These guidelines recommend that all infants in newborn nursery should receive POS preferably after 24 hours of life, or as close to discharge as possible. Screening should be performed by measuring oxygen saturations in the right hand (preductal saturation) and one foot (postductal saturation) either concurrently or one immediately after the other. An oxygen saturation of \( \geq 95\% \) in the right hand or foot and \( \leq 3\% \) difference between right hand and foot is considered negative or a pass and require no further evaluations before discharge.36

A screen is considered positive or a fail if measurement of oxygen saturation is below 90\%, below 95\% in both extremities after three measurements (one hour apart), or if there is a difference of more than 3\% in oxygen saturation between preductal and postductal saturations after three measurements. Infants with a failed screening should receive diagnostic echocardiogram and evaluation by a physician/pediatric cardiologist.36 Not all infants with a positive screen will have CCHD. In addition to CCHD, infants with other conditions associated with hypoxemia such as certain hemoglobinopathies and persistent pulmonary hypertension may also have a positive screen.36

**Summary**

In conclusion, POS for early detection of CCHD is a simple, noninvasive, and inexpensive test, which meets the necessary criteria for inclusion to universal newborn screening panel. Wider acceptance and adoption can significantly decrease morbidity and mortality in infants with CCHD. The reduction in morbidity and mortality in these infants is likely to be more pronounced in low-resource settings where most of these infants are born without a prenatal diagnosis.

**Author Contributions**

Conceived and designed the experiments: PK. Analyzed the data: PK. Wrote the first draft of the manuscript: PK. Contributed to the writing of the manuscript: PK. Agree with manuscript results and conclusions: PK. Developed the structure and arguments for the paper: PK. Made critical revisions and approved final version: PK. The author reviewed and approved of the final manuscript.

**REFERENCES**

1. Sebelius K. Secretary of Health & Human Services letter to the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children (SACH-DNC). 2011. Available at: http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendations/coronaryheartscreen09212011.pdf. Accessed September 21, 2011.

2. Guthrie R, Suss A. Simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. Pediatrics. 1963;32:338–43.

3. Wilson JM, Jungner YG. Principles and practice of mass screening for disease. Bull Oficina Sanit Panam. 1968;65:281–393.

4. Botto LD, Correa A, Erickson JD. Racial and temporal variations in the prevalence of heart defects. Pediatrics. 2001;107(3):E32.

5. Mele MP, Smith BL. Deaths: leading causes for 2003. Natl Vital Stat Rep. 2007;55(10):1–92.

6. Rosano A, Botto LD, Botting B, Mastroiacovo P. Infant mortality and congenital anomalies from 1950 to 1994: an international perspective. J Epidemiol Community Health. 2006;59(4):461–66.

7. van der Linde D, Konings F, Wiegman MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol. 2011;58(21):2241–7.

8. Liske MR, Greeley CS, Law D, et al; Tennessee Task Force on Screening Newborn Infants for Critical Congenital Heart Disease. Report of the Tennessee task force on screening newborn infants for critical congenital heart disease. Pediatrics. 2006;118(4):e1250–6.

9. Reller MD, Strickland MJ, Riehle-Clarosuato T, Mahle WT, Correa A. Prevalence of congenital heart defects in metropolitan Atlanta, 1998–2005. J Pediatr. 2008;153(6):807–12.

10. Bonnet D, Coltri A, Butera G, et al. Detection of transposition of the great arteries in fetuses reduces neonatal morbidity and mortality. Circulation. 1999;99(7):916–8.

11. Tworetzky W, McElhinney DB, Reddy VM, Munsey FL, Silverman NH. Improved surgical outcome after fetal diagnosis of hypoplastic left heart syndrome. Circulation. 2001;103(9):1269–73.

12. Franklin O, Burch M, Manning N, Sheenan K, Gould S, Archer N. Prenatal diagnosis of coarctation of the aorta improves survival and reduces morbidity. Heart. 2002;87(1):67–9.

13. Gaynor JW, Stopp C, Wypij D, et al; International Cardiac Collaborative on Neurodevelopment (IICON) Investigators. Neurodevelopmental outcomes after cardiac surgery in infancy. Pediatrics. 2015;135(5):816–25.

14. Goldberg CS, Lu M, Slepper LA, et al; Pediatric Heart Network Investigators. Factors associated with neurodevelopment for children with single ventricle lesions. J Pediatr. 2014;165(3):490–e6.e.

15. Frazier MK, Silverman NH, Moon-Grady AJ, et al. Prenatal detection of congenital heart disease. J Pediatr. 2009;155(1):26–31.

16. Brown KL, Sullivan ID. Prenatal detection for major congenital heart disease: a key process measure for congenital heart networks. Heart. 2014;100(5):359–60.

17. Bahtiyar MO, Copel JA. Improving detection of fetal cardiac anomalies: a fetal echocardiogram for every fetus? J Ultrasound Med. 2007;26(12):1639–41.

18. Comnes JH Jr, Botelso S. The unreliability of cyanosis in the recognition of arterial anoxemia. Am J Med Sci. 1947;124(1):1–6.

19. Gardiner HM, Voracevic A, van der Heijden LB, et al. Prenatal screening for major congenital heart disease: assessing performance by combining national cardiac audit with maternity data. Heart. 2014;100(5):375–82.

20. O’Donnell CP, Karlin CO, Davis PG, Carlin JB, Morley CJ. Clinical assessment of infant colour at delivery. Arch Dis Child Fetal Neonatal Ed. 2007;92(6):F465–7.

21. Wren C, Reinhardt Z, Khawaja K. Twenty-year trends in diagnosis of life-threatening neonatal cardiovascular malformations. Arch Dis Child Fetal Neonatal Ed. 2008;93(1):F33–5.

22. Kueil KS, Loffredo CA, Ference C. Failure to diagnose congenital heart disease in infancy. Pediatrics. 1999;103(4 pt 1):743–7.

23. Hoffman JL. It is time for routine neonatal screening by pulse oximetry. Neonatology. 2011;99(1):1–9.

24. Mahle WT, Newburger JW, Matherne GP, et al; American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, and Interdisciplinary Council on Quality of Care and Outcomes Research; American Academy of Pediatrics Section on Cardiology and Cardiac Surgery; Committee on Fetus and Newborn. Role of pulse oximetry in examining newborns for congenital heart disease: a scientific statement from the AHA and AAP. Pediatrics. 2009;124(2):823–36.

25. Koppel RI, Druschel CM, Carter T, et al. Effectiveness of pulse oximetry screening for congenital heart disease in asymptomatic newborns. Pediatrics. 2003;111(3):451–5.
26. de-Wahl Granelli A, Wennergren M, Sandberg K, 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.

27. Riede FT, Wiener C, Dahnert I, Möckel A, Kostella M, Schneider P. Effectiveness of neonatal pulse oximetry screening for detection of critical congenital heart disease in daily clinical routine – results from a prospective multiscenter study. *Eur J Pediatr*. 2010;169(8):975–81.

28. Meberg A, Brügmann-Pieper S, Due R Jr, et al. First day of life pulse oximetry screening to detect congenital heart defects. *J Pediatr*. 2008;152(6):761–5.

29. Ewer AK, Middleton LJ, Furmston AT, et al; PulseOx Study Group. Pulse oximetry screening for congenital heart defects in newborn infants (PulseOx): a test accuracy study. *Lancet*. 2011;378(9793):785–94.

30. Thangaratinam S, Brown K, Zamora J, Khan KS, Ewer AK. Pulse oximetry screening for critical congenital heart defects in asymptomatic newborn babies: a systematic review and meta-analysis. *Lancet*. 2012;379(9835):2459–64.

31. 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(3):e595–603.

32. Peterson C, Grosse SD, Glidewell J, et al. A public health economic assessment of hospitals’ cost to screen newborns for critical congenital heart disease. *Public Health Rep*. 2014;129(1):86–93.

33. Roberts TE, Barton PM, Auguste PE, Middleton LJ, Furmston AT, Ewer AK. Pulse oximetry as a screening test for congenital heart defects in newborn infants: a cost-effectiveness analysis. *Arch Dis Child*. 2012;97(3):221–6.

34. Peterson C, Dawson A, Grosse SD, et al. Hospitalizations, costs, and mortality among infants with critical congenital heart disease: how important is timely detection? *Birth Defects Res A Clin Mol Teratol*. 2013;97(10):664–72.

35. Kochilas LK, Lohr JL, Brubin E, et al. Implementation of critical congenital heart disease screening in Minnesota. *Pediatrics*. 2013;132(3):e587–94.

36. Kemper AR, Mahle WT, Martin GR, et al. Strategies for implementing screening for critical congenital heart disease. *Pediatrics*. 2011;128(5):e1259–67.