ACHDNC
Advisory Committee on Heritable Disorders in Newborns and Children

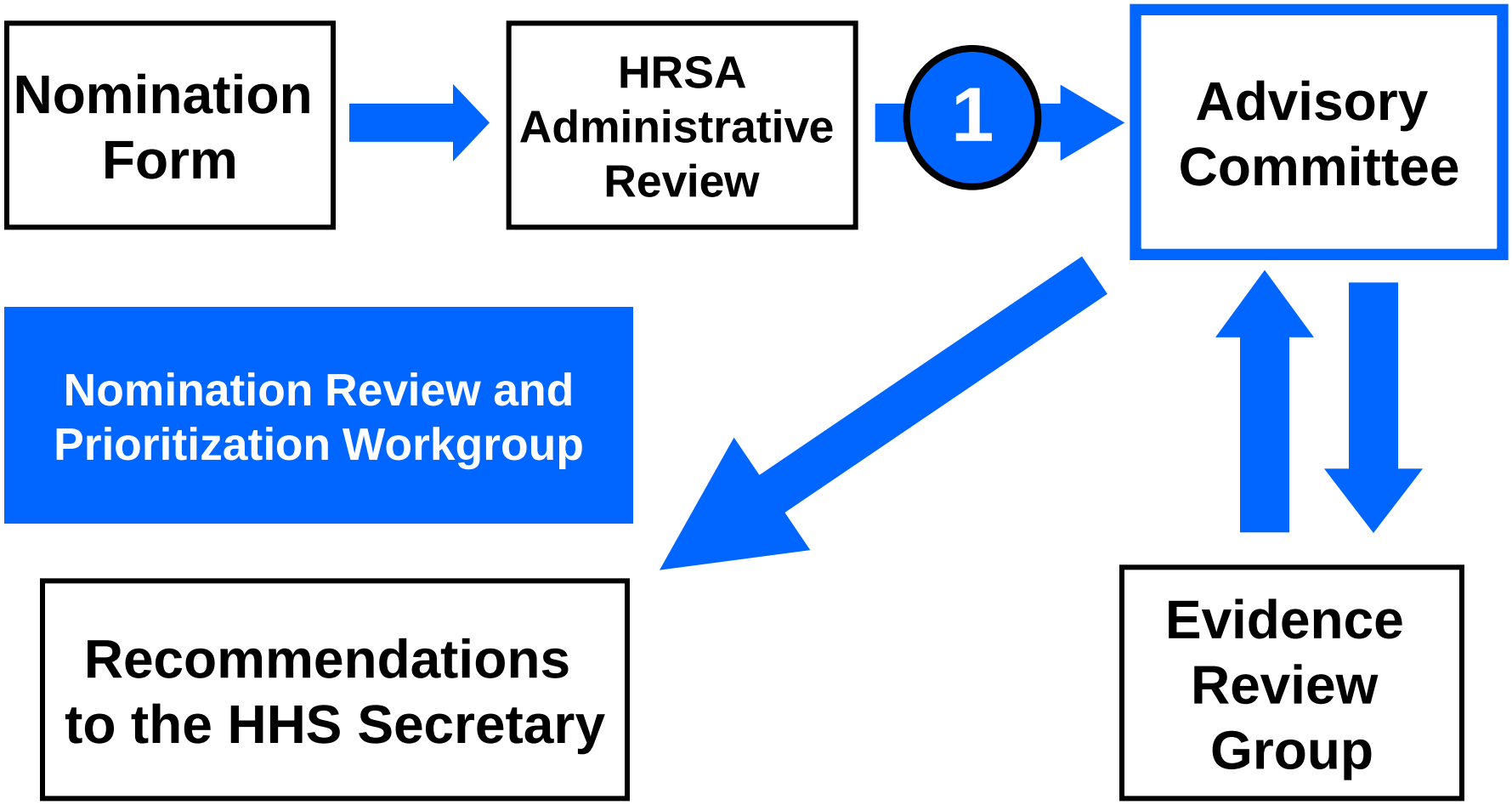
Meeting of the Advisory Committee on Heritable Disorders in Newborns and Children

Tab 6
Presentation

Reports from the Nomination and Prioritization Workgroup

- Hyperbilirubinemia
- Critical Congenital Heart Disease

Process for Addition of New Conditions to the Uniform Panel



Nomination Review and Prioritization Workgroup

- **Six members**
- **Makes recommendation to Adv Comm on**
  - **Appropriateness of submission to ERG (Y/N)**
  - **Order of submission of nominations to ERG**

Summary of Review

1. **The nominated condition(s) is medically serious.**
2. **Prospective pilot data (U.S. and/or international) from population-based assessment are available for this disorder.**
3. **The spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based screening.**
4. **The characteristics of the screening test(s) are reasonable for the newborn screening system (among other aspects, a low rate of false negatives).**
5. **If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky.**
6. **Defined treatment protocols, FDA approved drugs (if applicable), and treatment are all available.**

Overall recommendations to the Advisory Committee

Bilirubin Encephalopathy (ABE) & Kernicterus

NOMINATION REVIEW AND PRIORITIZATION WORKGROUP - FORM Summary
NOMINATED CONDITION: Universal Pre-Discharge Bilirubin Screening to prevent acute bilirubin encephalopathy (ABE) and kernicterus. **Date of review:** November 2, 2009

1) The nominated condition(s) is medically serious. Both acute bilirubin encephalopathy (ABE) and kernicterus.are serious conditions that may cause permanent damage to the CNS.

2) Prospective pilot data (U.S. and/or international) from population-based assessment are available for this disorder. This screening is performed at the birth site, either by a serum test or using one of commercially available non-invasive devices. Prospective studies have been conducted both in the US and elsewhere, outcome studies suggest a lower incidence of re-admissions. The University of Pennsylvania Health System (Reference # 1) and hospitals in Utah (Reference # 6) and in Israel (Reference # 2) have adapted the practice of obtaining a pre-discharge bilirubin level on all infants in an effort to identify those at high risk of extreme hyperbillirubinemia and all report a lower incidence of re-admissions for this problem since instituting this practice.

3) The spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based screening. Hyperbilirubinemia is an extremely heterogenous spectrum of clinical manifestations. It is likely that many identified newborns will not receive treatment on the basis of their evaluation following a first abnormal result (according to the Buthani protocol). However, there is a widely used nomogram (see Reference 1, Figure 2 that predicts the risk of extreme hyperbilirubinemia based on the bilirubin concentration at specified hours of age.

4) The characteristics of the screening test(s) are reasonable for the newborn screening system (among other aspects, a low rate of false negatives). The tests to measure serum bilirubin or transcutaneous bilirubin are widely used and presumably well standardized if used in hospital labs that must pass CAP inspections, so they should be reasonable tests to use for newborn screening. However, it is uncertain why CAP laboratory accreditation should constitute a blanket of assurance on this matter. Ref 1 implies a FPR of approximately 2%.
The nomogram referred to in Reference 1 is used throughout the world to calculate the predicted risk of a given bilirubin level and is considered the gold standard for plotting age of baby and bilirubin rise, along with rate of rise of serum bilirubin.

5) If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky. There are clearly risk factors for extreme hyperbilirubinemia (early jaundice, African American, male sex, prematurity, exclusive breast feeding, G6PD deficiency, etc.) that can alert physicians to check for elevated bilirubin levels while the infant is in the hospital. However, the practice of early discharge, i.e. after 1 to 2 days, makes it difficult to perceive these risk factors. Therefore, the infant most likely to benefit is one whose risk factors were not perceived during the short hospital stay and who did not have a bilirubin level measured.

6) Defined treatment protocols, FDA approved drugs (if applicable) and treatment are all available. These are already widely employed and include phototherapy and/or exchange transfusion—both accepted practices.

Overall recommendation to the Advisory Committee: The gravity and ability to prevent ABR and kernicterus are compelling reasons to screen in the newborn period. The *Internal Nomination and Prioritization Workgroup* recommends forwarding the nomination package for Universal Pre-Discharge Bilirubin Screening to prevent acute bilirubin encephalopathy (ABE) and kernicterus to the Evidence Review Workgroup.

1 The nominated condition(s) is medically serious

- **Both acute bilirubin encephalopathy (ABE) and kernicterus are serious conditions that may cause permanent damage to the CNS**

2 Prospective pilot data (U.S. and/or international) from population-based assessment are available for this disorder

- **This screening is performed at the birth site, either by a serum test or using one of commercially available non-invasive devices**
- **Prospective studies have been conducted both in the US and elsewhere, outcome studies suggest a lower incidence of re-admissions**
- **The University of Pennsylvania Health System (Reference # 1) and hospitals in Utah (Reference # 6) and in Israel (Reference # 2) have adapted the practice of obtaining a pre-discharge bilirubin level on all infants in an effort to identify those at high risk of extreme hyperbilirubinemia. All report a lower incidence of re-admissions for this problem since instituting this practice**

Ref 1 - Pediatrics 1999;103:6

Predictive Ability of a Predischarge Hour-specific Serum Bilirubin for Subsequent Significant Hyperbilirubinemia in Healthy Term and Near-term Newborns

Vinod K. Bhutani, MD; Lois Johnson, MD; and Emidio M. Sivieri, MS

Ref 6 - Pediatrics 2006;117:e855

The Effect of Instituting a Prehospital-Discharge Newborn Bilirubin Screening Program in an 18-Hospital Health System

Larry D. Eggert, MD[a], Susan E. Wiedmeier, MD[a,b], Janie Wilson, RN, MS[a], Robert D. Christensen, MD[a]

[a]NICU Development Team, Intermountain Health Care, Salt Lake City, Utah; [b]Department of Pediatrics, Division of Neonatology, University of Utah, Salt Lake City, Utah

Ref 2 - Pediatrics 2000;105:533

Predischarge Bilirubin Screening in Glucose-6-Phosphate Dehydrogenase-Deficient Neonates

Michael Kaplan, MB, ChB*‡; Cathy Hammerman, MD*‡; Roselyn Feldman, RN, MPA*; and Rachel Brisk, MSc§

3 The spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based screening

- **Hyperbilirubinemia is an extremely heterogenous spectrum of clinical manifestations. It is likely that many identified newborns will not receive treatment on the basis of their evaluation following a first abnormal result (according to the Buthani protocol)**
- **However, there is a widely used nomogram (see Reference 1, Figure 2) that predicts the risk of extreme hyperbilirubinemia based on the bilirubin concentration at specified hours of age**

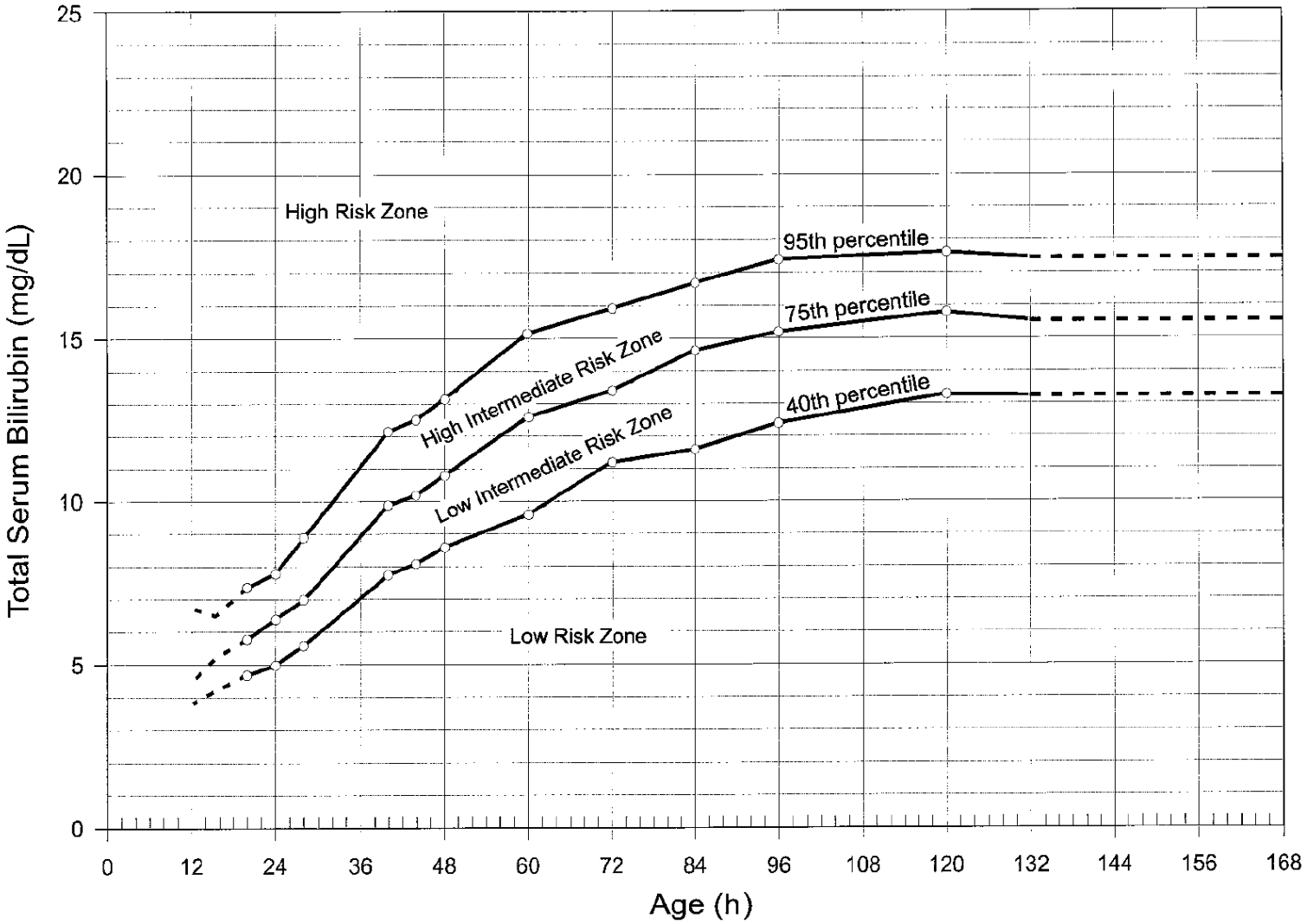


Fig 2. Risk designation of term and near-term well newborns based on their hour-specific serum bilirubin values. The high-risk zone is designated by the 95th percentile track. The intermediate-risk zone is subdivided to upper- and lower-risk zones by the 75th percentile track. The low-risk zone has been electively and statistically defined by the 40th percentile track. (Dotted extensions are based on <300 TSB values/epoch).

Ref 1 - Pediatrics 1999;103:6

4 The characteristics of the screening test(s) are reasonable for the newborn screening system (among other aspects, a low rate of false negatives)

- **The tests to measure serum bilirubin or transcutaneous bilirubin are widely used and presumably well standardized if used in hospital labs that must pass CAP inspections, so they should be reasonable tests to use for newborn screening. However, it is uncertain why CAP laboratory accreditation should constitute a blanket of assurance on this matter**
- **Ref 1 implies a FPR of approximately 2%**
- **The nomogram referred to in Ref 1 is used throughout the world to calculate the predicted risk of a given bilirubin level and is considered the gold standard for plotting age of baby and bilirubin rise, along with rate of rise of serum bilirubin**

5 If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky

- **There are clearly risk factors for extreme hyper-bilirubinemia (early jaundice, African American, male sex, prematurity, exclusive breast feeding, G6PD deficiency, etc) that can alert physicians to check for elevated bilirubin levels while the infant is in the hospital**
- **However, the practice of early discharge, i.e. after 1 to 2 days, makes it difficult to perceive these risk factors. Therefore, the infant most likely to benefit is one whose risk factors were not perceived during the short hospital stay and who did not have a bilirubin level measured**

6

Defined treatment protocols, FDA approved drugs (if applicable), and treatment are all available

- **These are already widely employed and include phototherapy and/or exchange transfusion—both accepted practices**

Overall recommendations to the Advisory Committee

- **The gravity and ability to prevent ABR and kernicterus are compelling reasons to screen in the newborn period. The Internal Nomination and Prioritization Workgroup recommends forwarding the nomination package for Universal Pre-Discharge Bilirubin Screening to prevent acute bilirubin encephalopathy (ABE) and kernicterus to the Evidence Review Workgroup**

Critical Congenital Heart Diseases (CCHD)

NOMINATION REVIEW AND PRIORITIZATION– SUMMARY
The information is derived primarily from the Nomination Form. Submitted supporting references and other publicly available data may also inform this review.

NOMINATED CONDITION: Critical Congenital Heart Diseases Date of review: 12/28/2009

1) The nominated condition(s) is medically serious.
Yes. Failure to recognize Critical cyanotic Congenital Heart Diseases (CCHD) can result in hypoxic-ischemic encephalopathy, multi-organ injury and death. Many cases (25%) are missed at birth and the infant is discharged only to return with these serious complications (see reference #3). Congenital heart disease is still the most common cause of death in the first year of life. According to Botto et al (CDC), the combined prevalence of coarctation and hypopolastic left heart is approx 3 per 10,000 births.

2) Prospective pilot data (U.S. and/or international) from population-based assessment are available for this disorder.
Several pilot studies for feasibility of screening have been performed at multiple international sites over the past 10 years. A recent consensus report in Pediatrics (reference # 6) summarizes the American Heart Association analysis of screening of 123,846 infants. This document recommends performing pulse oximetry after 24 hours of life. The recommended cut-off value is <95% saturation (see reference # 7)

3) The spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based screening.
There are multiple CCHD that can lead to hypoxic-ischemic encephalopathy, multi-organ injury and death if they are not recognized. These are all well-recognized conditions with appropriate treatments available. The most common CCHD that were missed were hypoplastic left heart syndrome (HLHS) and coarctation of the aorta (see reference # 5).

4) The characteristics of the screening test(s) are reasonable for the newborn screening system (among other aspects, a low rate of false negatives).
The proposed screening test is pulse oximetry. Pulse oximetry is not universally currently performed on all neonates. It is a non-invasive test that can be performed by a nurse so does not require an expert. It should be performed with one lead pre-ductal (R hand) and one post-ductal (either leg). The most common cause of a low PO2 is transient tachypnea of the newborn. However, neonatal nurses are taught to perform a hyperoxia test if a low PO2 is detected: if blow-by O2 corrects the low PO2, it is not a CCHD. Done with these caveats, pulse oximetry reportedly has a specificity of 99.9%, a sensitivity of 69.6%, a positive predictive value of 47% and a false positive rate of 0.035 according to a recent report in Pediatrics (reference # 6). The cost of the test should be less than for newborn hearing screening, which requires a trained audiologist. The cost would be primarily that of nurse time and the probes, which if cleaned properly, can be reused.

5) If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky.
Yes, if the screening test is positive, the confirmatory test is echocardiography which is capable of definitively diagnosing all forms of CCHD. Echocardiography is now very widely available in community hospitals where technicians are qualified to perform this on adults but not always in young infants for CCHD. However, telemedicine consultation with major teaching centers is available at most such hospitals, and a technician can be taught how to screen for these over the telephone. Thus, there should not be a significant lag time between detection of an abnormal pulse oximetry reading and performance of echocardiography. This should reduce parental anxiety, about the only negative to finding an abnormal pulse oximetry test result.

6) Defined treatment protocols, FDA approved drugs (if applicable) and treatment are all available.
Yes. It is either surgery or catheter intervention. Procedure related risks are inherent in the management of CCHD.

Overall recommendations to the Advisory Committee: Recommend that this condition be approved to be sent to the Evidence Review Committee.

1 The nominated condition(s) is medically serious

- **Yes. Failure to recognize Critical cyanotic Congenital Heart Diseases (CCHD) can result in hypoxic-ischemic encephalopathy, multi-organ injury and death. Many cases (25%) are missed at birth and the infant is discharged only to return with these serious complications (see reference #3).**
- **Congenital heart disease is still the most common cause of death in the first year of life. According to Botto et al (CDC), the combined prevalence of coarctation and hypopolastic left heart is approx 3 per 10,000 births.**

2 Prospective pilot data (U.S. and/or international) from population-based assessment are available for this disorder

- **Several pilot studies for feasibility of screening have been performed at multiple international sites over the past 10 years.**
- **A recent consensus report in Pediatrics (reference # 6) summarizes the American Heart Association analysis of screening of 123,846 infants. This document recommends performing pulse oximetry after 24 hours of life. The recommended cut-off value is <95% saturation (see reference # 7)**

3 The spectrum of this disorder is well described, to help predict the phenotypic range of those children who will be identified based on population-based screening

- **There are multiple CCHD that can lead to hypoxic-ischemic encephalopathy, multi-organ injury and death if they are not recognized. These are all well-recognized conditions with appropriate treatments available. The most common CCHD that were missed were hypoplastic left heart syndrome (HLHS) and coarctation of the aorta (see reference # 5).**

TABLE 2 CCHD Lesions and Associated Clinical Characteristics

Lesion	Prevalence[a]	Hypoxemia	Ductus Arteriosus Dependent
Outflow tract defects			
Tetralogy of Fallot	6.1	Most	Uncommon
D-transposition of the great arteries	4.0	All	Uncommon
Double-outlet right ventricle	1.7	Some	Some
Truncus arteriosus	1.0	All	None
TAPVC	1.2	All	None
Ebstein anomaly	0.6	Some	Some
Right obstructive defects			
Tricuspid atresia	0.5	All	Some
Pulmonary atresia, intact septum	0.8	All	All
Pulmonic stenosis, atresia	6.3	Some	Some
Left obstructive defects			
Hypoplastic left heart	3.3	All	All
Coarctation of the aorta	4.7	Some	Some
Aortic arch atresia or hypoplasia	1.0	Some	All
Aortic valve stenosis (critical)	1.6	Uncommon	Some
Other major heart defects	12.4	Some	Some

TAPVC indicates total anomalous pulmonary venous connection.

[a] Per 10 000 livebirths. Data are derived from the Metropolitan Atlanta Congenital Defects Program.[1]

Ref 5 - Pediatrics 2009;124:823

4a

The characteristics of the screening test(s) are reasonable for the newborn screening system (among other aspects, a low rate of false negatives)

- **The proposed screening test is pulse oximetry. Currently, pulse oximetry is not performed on all neonates. It is a non-invasive test that can be performed by a nurse so does not require an expert. It should be performed with one lead pre-ductal (R hand) and one post-ductal (either leg)**
- **The most common cause of a low PO2 is transient tachypnea of the newborn. However, neonatal nurses are taught to perform a hyperoxia test if a low PO2 is detected: if blow-by O2 corrects the low PO2, it is not a CCHD**

4b

The characteristics of the screening test(s) are reasonable for the newborn screening system (among other aspects, a low rate of false negatives)

- **Done with these caveats, pulse oximetry reportedly has a specificity of 99.9%, a sensitivity of 69.6%, a positive predictive value of 47% and a false positive rate of 0.035 according to a recent report in Pediatrics (ref # 6)**
- **The cost of the test should be less than for newborn hearing screening, which requires a trained audiologist. The cost would be primarily that of nurse time and the probes, which if cleaned properly, can be reused**

5a

If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky

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5b

If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky

- **Thus, there should not be a significant lag time between detection of an abnormal pulse oximetry reading and performance of echocardiography. This should reduce parental anxiety, about the only negative consequence to finding an abnormal pulse oximetry test result.**

6

Defined treatment protocols, FDA approved drugs (if applicable), and treatment are all available

- **Yes. It is either surgery or catheter intervention**
- **Procedure-related risks are inherent in the management of CCHD**

Overall recommendations to the Advisory Committee

- **Recommend that this condition be approved to be sent to the Evidence Review Committee**

Meeting of the Advisory Committee on Heritable Disorders in Newborns and Children

Advisory Committee Next Steps

- **Decision whether to send or not to ERG**
- **Order of submission to ERG if both nominations are approved**