Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

Summary of 23rd Meeting

January 27–28, 2011

Washington, DC

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children was convened for its 23rd meeting at 8:30 a.m. on Thursday, January 27, 2011, at the Renaissance Washington Dupont Circle Hotel in Washington, DC. The meeting was adjourned at 2:30 p.m. on Friday, January 28, 2011. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments.

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I. COMMITTEE BUSINESS

Thursday, January 27, 2011

R. Rodney Howell, M.D.
(Committee Chairperson)
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Dr. Rodney Howell welcomed Dr. Vindod Bhutani and Dr. Lois Johnson-Hamerman, who will join the meeting by telephone for the committee discussion on hyperbilirubinemia screening. Ms. Diane Zook and Dr. Mathew Park will join the meeting on Friday for the committee discussion on screening for critical congenital cyanotic heart disease.

Dr. Joseph Bocchini moved to approve the September 2010 committee meeting minutes and Dr. Tracy Trotter seconded the motion. The minutes were approved unanimously, with five members absent (Dr. Alan Guttmacher, Ms. Jana Monaco, Dr. Kwaku Ohene-Frempong, Dr. Michael Skeels, and Dr. Peter van Dyck).

Dr. Rodney Howell reviewed the correspondence received by the committee and related research that has occurred since the last meeting.

- In a letter dated September 23, 2010, the Secretary of Health and Human Services, Kathleen Sebelius, responded to the white paper on health care reform submitted to her by this committee. She recognized the need for the health care reform to align efforts to improve the care and outcomes for the vulnerable population of newborns and children with heritable disorders, and she adopted the first three recommendations. On December 14, 2010, the Secretary responded to the fourth recommendation (medical foods), acknowledging the value of the information provided by this committee to inform the Secretary's decision. She will wait, however, until she has the results of the Department of Labor survey and the Institute of Medicine recommendations to make determinations about particular benefits. She assures the committee that she will give serious consideration to the issues raised.

- Other letters from Secretary Sebelius include two interim responses that acknowledge receipt of the committee's recent letters and assurance of her response after careful review. On September 17, 2010, she responded to the letter about coordinating newborn screening emergency preparedness activities (CON Plan). On November 26, 2010, she responded to a letter on recommendations on residual blood specimens, critical congenital cyanotic heart disease, and sickle cell disease.

- The committee sent letters to the Secretary about revision to the sickle cell traits and disease screening of NCAA athletes (sent October 11, 2010), the retention and use of residual blood spots (sent October 13, 2010), and critical congenital cyanotic heart disease (sent October 15, 2010).

- The committee received a letter, dated November 29, 2010, from Dr. Janet Corrigan of the National Quality Forum thanking the committee for its support and encouraging participation in the NQF's consensus development process. Dr. Sara Copeland will be referencing this letter in her presentation later today.

- The thumb drive distributed to each committee member as a supplement to the briefing book includes the committee's response letter providing comments on the CLIAC report and recommendations on biochemical laboratory practices for genetic testing and newborn screening. It also contains a response from Drs. Frieden, Hamburg, and Berwick concerning the committee's recommendations. Dr. Coleen Boyle will share the MMRW paper with the committee via HRSA.

II. UPDATE ON NQF MEASURES

Sara Copeland, M.D.
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Dr. Howell introduced Dr. Sara Copeland, who provided an update on National Quality Forum (NQF) measures. At the previous meeting, Dr. Alan Zuckerman presented the measures that have been submitted to the NQF. Dr. Copeland will provide an update on the progress of those submissions.

- By way of describing its role, Dr. Copeland explained that the NQF is tasked with managing a set of standardized quality measurements. NQF-endorsed measures set the stage for standardization and public reporting. They are the measures of first choice for federal government and private purchasers. In 2009, in conjunction with the Department of Health and Human Services, the NQF began to establish a portfolio of quality and efficiency measures for use in reporting on and improving health care quality.

- The NQF consensus process has nine steps: call for intent to submit candidate standards, call for nominations, call for candidate standards, candidate consensus standard review, public and member comment, member vote, approval committee decision, board ratification, and appeals. This committee's nomination is currently at the fourth step, candidate consensus standard review. HRSA and NCQA have each submitted one measure, and the CDC has submitted eight.

- The HRSA measure, on the percentage of infants who receive newborn blood spot screening, has been recommended for endorsement in a time-limited manner (it lacked sufficient data). The number of infants born will come from state birth certificates and hospital discharge records. State mandates on the screening will define which infants may be excluded.

- The NCQA measure, regarding the percentage of children who turned 6 months of age during the measurement year and who had documentation of newborn metabolic screening by that age, was not recommended for endorsement.

- Of the eight hearing screening measures submitted by the CDC, four were recommended for endorsement.

    - One measure assesses the proportion of newborn infants who have been screened for hearing loss prior to hospital discharge.

- Another measure assesses the proportion of newborn infants who did not complete a hearing screen prior to discharge, but who went on to receive an outpatient screen before 31 days of age. This one was given a time limited recommended endorsement.

- The next measure assesses the percentage of newborn infants who did not pass the hearing screening and had an audiological evaluation no later than 3 months of age.

- The final measure recommended assessing the proportion of infants with permanent hearing loss who have been referred to intervention services by 6 months of age.

- The next step in the process for these measures is public and member comments. A draft report has been posted on the NQF website for review and comment.

- The result of being endorsed is that the measure is deemed scientifically acceptable and thus suitable for public reporting. It can also affect payment decisions made by payers.

  - In answer to a question from Dr. Howell regarding the practical outcomes of an endorsement for a health care provider, Dr. Denise Dougherty noted that following the recommendation is strictly voluntary. Dr. Robert Ostrander, of the New York State Academy of Family Physicians, related that when the NQF endorsed screening for aortic aneurysm in men over the age of 65 with a history of smoking, the practice was increasingly adopted as a medical standard and insurance was willing to cover the screening test as a medically necessary service. Dr. Alan Fleischman explained that the NQF endorsed five perinatal-related measures that were then adopted by the Joint Commission and added to their standard package of measures. The NQF is highly respected, and it vets measures thoroughly. Dr. Christopher Kus noted that such endorsements also affect state reporting mechanisms and that they are sometimes used for determining pay-for-performance by managed care organizations in New York.

  - Ms. Kathryn McLaughlin (HRSA) added that CMS uses NQF-endorsed measures for their physician quality reporting initiative, for which physicians can report measures which may give them a bump in their payment rate, depending on how good their reported measures are. So it can lead to higher payments from Medicare and Medicaid.

- In response to a question from Dr. Howell regarding the composition of the board that reviews the nominations, Dr. Dougherty explained that it is a voluntary board comprising a broad constituency from the private sector, professional societies, and payers. Dr. Fleischman added that it is chaired by Mr. William Roper and has liaisons from federal agencies such as the CDC and CMS.

III. EVIDENCE REVIEW WORKGROUP REPORT: PRELIMINARY REPORT ON THE CANDIDATE NOMINATION HYPERBILIRUBINEMIA

James M. Perrin, M.D.
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Dr. Howell introduced Dr. James Perrin, joining us in Boston by telephone, who reported on the preliminary systematic evidence review the published literature on neonatal screening for hyperbilirubinemia. Workgroup members Dr. Vinod Bhutani and Dr. Lois Johnson-Hamerman also joined the meeting by telephone for this report. A full written report of the evidence review is included in this meeting's briefing book. The report is also available on the meeting's website.

- Neonatal hyperbilirubinemia is an elevated total bilirubin level in a newborn. It arises from a variety of etiologies and is a detectable risk factor for acute bilirubin encephalopathy (ABE) and kernicterus. The primary concern is its potential for neurotoxic effects of severe hyperbilirubinemia.

- In the conceptual framework, there is a continuum from neonatal jaundice to hyperbilirubinemia and on to acute and then chronic encephalopathic results. Treatment takes place to address hyperbilirubinemia, aimed at reducing the incidence of ABE or kernicterus.

- Hyperbilirubinemia indirectly can lead to permanent damage to the central nervous system and death. The conditions can be serious with major implications for the baby and the family. Early identification of risk factors, leading to intervention, may lead to a lower risk of kernicterus, the end problem. Measurement of hyperbilirubinemia (TcB - cutaneous and TSB-blood) is widely available, as is treatment.

- At the request of the advisory committee, three conditions were reviewed: neonatal hyperbilirubinemia, acute bilirubin encephalopathy (ABE), and chronic bilirubin encephalopathy (kernicterus). It was difficult to develop a single case definition for these conditions, so the review team developed three definitions for the committee's consideration. In the literature, the definition for ABE is the least consistent. It is important to note that hyperbilirubinemia has been associated with other long-term neurologic dysfunction, especially auditory dysfunction.

    - Neonatal hyperbilirubinemia — Clinically significant hyperbilirubinemia in the neonatal period as indicated by TSB (total serum bilirubin) levels >95th percentile for age in hours, per measurement algorithms, which may require follow up and treatment.

    - ABE—Variable acute manifestations of bilirubin toxicity present in the first weeks of life. Symptoms include neurological manifestations, somnolence, hypotonia, loss of the Moro reflex, followed by an irreversible stage characterized by hypertonia of the extensor muscle groups. Fever or a high-pitched cry may be present.

    - Kernicterus—Chronic and permanent brain damage caused by bilirubin toxicity and characterized by four clinical manifestations: movement disorder (athetosis, dystonia, spasticity, hypotonia), auditory dysfunction, oculomotor impairment, and dental enamel hypoplasia.

- The literature review comprised a systematic search of MEDLINE for relevant screening studies published over a 20-year period (January 1990–September 2010). References from the nomination form and bibliographies of review papers were also reviewed, as were abstracts and a subset of independently abstracted articles. Originally, 2,742 abstracts were selected, and 172 articles were selected for in-depth review. Ninety-nine articles met all inclusion criteria for abstraction. The large number reflects the fact that neonatal hyperbilirubinemia is a relatively common disorder with substantial literature. The vast majority of the studies are case studies, and by way of grading the evidence, they are not high level.

- Incidence rates, as reported in the literature, of hyperbilirubinemia show that newborn jaundice is common (10–15%), while cases of elevated bilirubin quickly become increasingly rare (above 25 is 0.14% and above 29 is 0.01%). The rate of incidence of kernicterus in newborns is rare (0.001–0.002%). There is some evidence of changing incidence rates, both in jaundice and readmission rates for jaundice. Although the review team did not locate evidence to show association, the changing incidence rate is possibly related to changing patterns of screening methods for hyperbilirubinemia.

- Risk factors for hyperbilirubinemia are prematurity, Asian race, isoimmunization, hemolytic disease, and low birth weight. Risk factors for kernicterus are prematurity, Asian race, early discharge, and glucose-6-phosphate dehydrogenase deficiency. The early discharge risk factor for kernicterus is of interest for thinking of strategies for following children over time.

- The severity spectrum has been described in a number of studies that are summarized in table 5 of the larger report. Although a reasonable spectrum of manifestations is described, the differences in design studies limit comparison of the data in a meta-analytic fashion.

- Acute manifestations occur in the first few weeks of life and typically include behavioral changes in the newborn, some symptoms of nervous system involvement, and abnormal MRI, VEP, and BAEP findings. Some studies show an association between the severity of symptoms with TSB levels. Table 5 in the larger report provides more information.

- As for chronic manifestations, seven studies show a significantly increased risk of abnormal neurodevelopment, and six studies suggest resolved or minor effects on neurodevelopment outcomes. None of studies are large and there are concerns about the quality of the evidence. Auditory problems are better described and indicate a direct relationship between elevated TSB levels and a risk of developing long-term auditory disorders.

- The evidence on kernicterus is predominantly retrospective. The Pilot USA Kernicterus Registry indicates this is a serious condition. There is no clear evidence that one has to reach a certain level of bilirubin to lead to kernicterus. Kernicterus has been reported in apparently healthy babies, although the majority of cases are infants with high bilirubin levels.

- Dr. Coleen Boyle asked if the team had found sufficient evidence on the relationship between ABE and chronic or long-lasting outcomes. Dr. Perrin answered that they found evidence on persistent neurodevelopmental and auditory outcomes, but that it is not extremely good evidence. There is some evidence that supports the association of hyperbilirubinemia and longer neurodevelopmental outcomes other than kernicterus.

- In response to a comment from Dr. Boyle regarding the case definitions, Dr. Perrin said that, now that the literature review is complete, it is apparent that the definition of chronic bilirubin encephalopathy may need to be expanded to include other neurodevelopmental findings.

- There are three major screening methods to estimate the level of a newborn's bilirubin: visual assessment, noninvasive transcutaneous bilirubin (TcB), and total serum bilirubin (TSB). The evidence on visual assessment indicates it is not a reliable strategy for accurately determining total serum level for bilirubin and, so, will not be addressed closely in this review.

- In determining whether TSB screening is useful for detecting subsequent significant hyperbilirubinemia, a comparison of studies done with healthy term infants shows that the sensitivity in almost all cases is good (the one exception involves a study that used a different cut-off measure, which may explain the sensitivity difference). Specificity is high throughout. Positive predictive values are in the teens to twenties, and negative predictive values are very high. This provides strong evidence that early TSB screening is predictive of subsequent significant hyperbilirubinemia. The negative results are reassuring of the lack of likelihood of developing significant hyperbilirubinemia.

- To consider whether there is good association of TcB bilirubin measurement with concurrent TSB bilirubin values, the review team looked at three studies of healthy term infants and two studies of preterm infants. The basic question being addressed is whether TcB is an accurate measure of TSB. The studies used differing cut-off measures, and the TSB comparison values are somewhat comparable to TcB levels in these cut-off values. Sensitivity is extremely high except in one of the studies in premature infants, and specificity is generally quite good, with the exception of the same prematurity study.

- The studies reported on vary on the definition of hyperbilirubinemia. The review team's definition of significant hyperbilirubinemia is bilirubin greater than 95% for age.

- Using two large studies, the review team looked at whether TcB screening is useful for detecting subsequent significant hyperbilirubinemia (in these cases defined as ≥17 mg/dl at >72 hours of age). Sensitivity levels are good, and specificity levels are comparable to the studies that used TSB instead of TcB. The negative predictive value is extremely high, and the positive predictive value varies from 24.8 to 67.9.

    - Dr. Ned Calonge asked for clarification on how many of the 461 newborns in this study met the definition, because that number would provide a better sense of the variation and confidence intervals. Dr. Perrin assured him that the information will be researched. Dr. Calonge also warned that laboratory variation is an issue that would affect the stability of the PPV.

- The screening risk nomogram brings together a series of data and develops curves that are predictive of infants having an increased likelihood of developing severe hyperbilirubinemia. At 95% level for age, the sensitivity is 54% and the specificity 96.2%. The nomogram has curves for the 95th, 75th, and 40th percentiles. The use of the nomogram is associated with good prediction of hyperbilirubinemia.

- To summarize screening, the literature confirms that using a visual assessment is not an optimal method for finding hyperbilirubinemia. TcB screening is useful to rule out subsequent hyperbilirubinemia in infants, when compared with TSB,. With an hour-specific bilirubin nomogram based on TSB or TcB values, it is possible to interpret risk of subsequent hyperbilirubinemia. Finally, multi-hospital universal bilirubin screening was associated with a significantly lower incidence of hyperbilirubinemia and lower rates of hospital readmission due to bilirubin levels.

- Dr. Frederick Chen concurred that this screening differs from others considered by this Committee in that it is already common practice in newborn care. It seems that a critical consideration for this Committee is moving it from usual practice to universal screening. He asked if the decrease in incidence is a result of more infants being screened or is it a result of infants receiving treatment after screening identifies them. Dr. Perrin responded that the studies reviewed suggest that the increased identification and treatment of identified children

has lowered the levels of bilirubin and diminished the readmission rate to hospitals for high bilirubin levels. He added that the review team did not find studies comparing the three screening strategies on rates of readmission. Dr. Howell commented that this is an important finding, noting that certain institutions have systematic screening programs.

- Dr. Joseph Bocchini wondered about the role of outpatient treatment and home phototherapy treatment in the decreased readmission rates. Dr. Perrin noted that a problem with looking systematically at the evidence is making a clear connection between an intervention and a particular outcome.

- Dr. Christopher Kus requested that the final report provide information on how many newborns currently receive at least one bilirubin test. Dr. Bhutani believes there may be such data on institutions that have adopted universal screening; the number that have not adopted universal screening is about 40–50% based on anecdotal observation.

- There are two major forms of treatment for hyperbilirubinemia: phototherapy and exchange transfusion (EcT).

    - The evidence clearly and strongly supports the effectiveness of phototherapy in decreasing levels of TSB in the neonatal period. The effectiveness varies to a degree depending on age, gender, and gestational age; confirmation on the strength of those factors is needed. Indirect evidence indicates phototherapy is widely available. There are some physical complications associated with phototherapy, the two most common being skin rash and diarrhea. There is no evidence of disruption of mother-child bonding.

    - Today, exchange transfusion is limited to a small population of children who commonly have other medical conditions in addition to hyperbilirubinemia. Most of the evidence available on EcT as treatment for hyperbilirubinemia is from older studies.

- The level of evidence on outcomes of treatment is not extremely good, due in part to the fact that the studies are not large. There are mixed results regarding whether treatment is associated with neurological and developmental symptoms. (These refer to chronic rather than acute hyperbilirubinemia.) Evidence on long-term outcomes is limited.

- Dr. Johnson commented that, although actual data available to show that is very limited, the duration of exposure to dangerous levels of bilirubin in relation to the time of treatment makes a difference in the reversal of clear evidence of ABE. Some of those cases were mentioned in the kernicterus registry. In Dr. Boggs' work at the University of Pennsylvania, there is clear evidence of phototherapy reversing ABE and at 4- and 7-year follow ups having none of the characteristic sequelae of kernicterus or minor manifestations.

- Dr. Alan Fleischman would like the review team to address whether phototherapy prevents exchange transfusion. Dr. Perrin suspects there is no direct evidence of cause and effect, but there is substantial temporal evidence that the use of phototherapy replaced EcT dramatically. The review team can try to address the question and provide evidence. Dr. Fleischman said the relevant point is that if there isn't early intervention for an acutely symptomatic child, the likelihood of the child receiving exchange transfusion treatment increases, so screening for hyperbilirubinemia could potentially cause earlier intervention and treatment for these children.

- Dr. Howell assumes that every birthing center in the United States has ready access to phototherapy, but believes that should be verified as the case moves forward.

- As for the economics of screening for hyperbilirubinemia, the reviewers found only one good study of the cost effectiveness in the literature. That study looked at the cost per case of kernicterus prevented (over $5 million per case). There are some issues with it in defining what the real costs of kernicterus are. The review team will ask its group of experts for more evidence on reported costs of screening treatment.

- Key Findings

  - High total bilirubin concentration leads to acute clinical manifestations. The evidence shows that, when compared to controls, neonates with increased TSB experience increased acute clinical manifestations. This is based on a series of case studies, and strength of the evidence is fair.

  - TcB has additional sensitivity over visual assessment for hyperbilirubinemia. TcB detects most cases of neonatal hyperbilirubinemia that may necessitate further assessment. Adding TcB to visual assessment increased the sensitivity of predicting TSB levels of 12.1–15 mg/dL from 5.7% to 30.8%. Evidence suggests that TcB leads to less subsequent TSB blood draws and a greater number of newborns identified at and above the higher risk 75th percentile.

  - Specificity is moderate and sensitivity is high for risk assessment and predischarge screening prediction. The specificity of the predischarge screening and risk assessment nomogram for at and above the 75th risk percentile is high (84.7% for TSB,≥79% for TcB). The sensitivity at and above the 75th risk percentile is also high (90.5% for TSB, >82% for TcB). At and above the 40th percentile, the specificity is 64.7% (TSB) or 38.4% (TcB) and the sensitivity is 100% (TSB) or 94.1% (TcB). The evidence does not address whether this prediction assessment decreased the incidence of kernicterus.

  - There is no good evidence that screening for hyperbilirubinemia prevents kernicterus.

  - Early intervention for hyperbilirubinemia effectively improves outcomes. There is indirect evidence that early intervention is associated with improved outcomes for those with neonatal hyperbilirubinemia. The evidence indicates that treatment lowers elevated bilirubin concentration levels, and lower bilirubin level is associated with less acute clinical manifestations.

- Remaining Questions on Condition

  - What evidence is available regarding the relationship between severe neonatal hyperbilirubinemia and kernicterus?

  - When does kernicterus appear clinically?

- Remaining Questions on Screening

  - What is the optimal approach for newborn screening for hyperbilirubinemia?

  - Do risk factor assessments improve prediction of developing hyperbilirubinemia leading to kernicterus?

  - What follow-up practices should be in place for newborns found to have an intermediate risk level by bilirubin screening?

- Do outpatient facilities have the capacity to handle follow-up visits for screen positive infants?
- What are the potential harms or risks associated with screening?
- Has there been population-based pilot screening?
- What would be the effect of taking bilirubin screening in its current form to state-mandated newborn screening?
- What proportion of cases of kernicterus would be prevented by screening?

- Remaining Questions on Treatment
  - Does treating neonatal hyperbilirubinemia prevent kernicterus?
  - What is the availability of treatment?
- Remaining Questions on Economics
  - What are the costs associated with the screening test and follow up for newborns found to have an intermediate risk level by bilirubin screening?
  - What are the costs associated with confirmatory testing, and the failure to find at-risk newborns in the presymptomatic period?
  - What are the costs associated with treatment?
  - What is the cost-effectiveness of newborn screening for neonatal hyperbilirubinemia?
- The next step is to put together a panel of experts to contact for more information. The review team welcomes suggestions of individuals to add to their list from the committee.
- Dr. Jeffrey Botkin mentioned that he has not heard or seen much in the report about the heritable conditions and wants to confirm that those conditions are off the table for general discussion here. Those conditions might be worth a brief comment as part of the spectrum. He had a more general query regarding the disease modeling. It sounds as if the assumption is that, irrespective of the etiology of hyperbilirubinemia, high bilirubin is the direct cause of the adverse effects about which we are concerned. With the variety of etiologies with hyperbilirubinemia, it may well be that it is the primary etiology that is the problem and not the bilirubin per se. The primary etiology is what we need to understand and treat. He wonders if there might be a targeted screening approach that would identify hemolytic disease or intracranial hemorrhages or some other primary etiology for hyperbilirubinemia and adverse outcomes that would get us most of the way to reducing the adverse consequences without the universal screening approach.
  - Dr. Perrin explained that the best evidence for what might cause kernicterus comes from the kernicterus registry data and its ability to look back on children's neonatal records. It documents that there were a variety of risk factors associated with these children's diseases in most, but not all, cases. It also includes the fact that some children did not have high bilirubin levels. In the literature, nothing was found that would address whether a targeted screening would be more beneficial.

- Dr. Johnson-Hamerman does not think a targeted screening approach could be done at this point. The things learned from the kernicterus registry were learned after the fact. They would not have been identified prior to discharge. On another note, she would like to add information about how many of the predischarge screenings were multiple (more than one TSB level). In the bilirubin nomogram, there were no values included after phototherapy was instituted, nor for babies in who jaundice was noted early or for some reason a TSB was thought necessary. If the bilirubin level was worrisome at that point, a repeat was done to determine a rate of rise for bilirubin for that particular baby. On the basis of that rate, if it was determined necessary to treat, the baby had phototherapy or, if needed, EcT. That small number of babies does not appear in the nomogram.

- Dr. Chen would like to know the effects of taking bilirubin screening from its current form to state-mandated newborn screening. How many children in the kernicterus registry were not screened at all? What is the potential for improvement?

  - Dr. Johnson-Hamerman reported that, in that paper, many babies were sent home early with no evaluation, but the bilirubin levels must have been high based on their levels when the mother returned with the baby to the hospital. That is retrospective data, but it is predictable because bilirubin tends to rise at a regular rate. A large number of babies could have been identified as needing evaluation and not discharged. There was no estimate of a risk of jaundice done before. That happened much more in babies sent home within 24 hours of birth. This is the main reason for saying we need universal screening.

- Dr. Boyle requested clarification on who the independent external review panel was for this report. It was Janine Cody, Celia Kaye, Harvey Cohen, and Robert Davis.

- Dr. Jane Getchell wants to know more about how, when, and why the cutaneous test is preformed and how much it costs. Dr. Perrin assured her that these questions will be answered in the next step. She also hopes the committee considers testing for hyperbilirubinemia as a standard of practice, not necessarily as a public health program. Dr. Perrin said that decision is the advisory committee's to make, but he welcomes suggestions on the evidence needed to help the committee discuss it.

When the final report is presented in May, the review team will have updated the literature review and will have consulted with appropriate experts and consumers. Where relevant unpublished data has been defined, it will be summarized for the committee.

IV. NEWBORN SCREENING FOR SEVERE COMBINED IMMUNODEFICIENCY (SCID): STATE STATUS

Jelili Ojodu, M.P.H.
Session Leader
Director of the Newborn Screening and Genetics Program
Association of Public Health Laboratories
Silver Spring, Maryland

Dr. Howell introduced session leader Mr. Jelili Ojodu, and explained that in response to the committee's letter on SCID, the Secretary requested a report on state implementation of the recommendation to add

SCID as a core condition. The report needs to go to the Secretary by May 2011. This session presented various activities already underway in state implementation.

Mr. Ojodu briefly introduced each of the four session speakers. Dr. Carla Cuthbert, who gave the laboratory update, presented algorithms from states currently doing newborn SCID screening and also provided an update on the newborn screening quality assurance program as it relates to QC and PT material. Dr. Christine Seroogy gave an update on follow-up activities and treatment protocols in Wisconsin. President and founder of the Immune Deficiency Foundation, Ms. Marcia Boyle, talked about SCID advocacy activities and education materials that have been developed. Dr. Michael Watson updated the committee on the newborn screening translational research network as it relates to the coordinated activities for the funding that came from NICHD to expand SCID testing in the states.

A. LABORATORY UPDATE

Carla Cuthbert, Ph.D., F.C.C.M.G., F.A.C.M.G.
Chief of Newborn Screening and Molecular Biology
Division of Laboratory Sciences
Centers for Disease Control and Prevention

Dr. Carla Cuthbert presented updates on the SCID newborn screening experiences of Wisconsin, Massachusetts, California, and New York laboratories. Today, all states that perform SCID screening have adopted use of the T cell receptor excision circles (TREC) assay. These four states perform this assay in-house.

- Wisconsin rolled out its program in January 2007 with funding from the Jeffrey Modell Foundation, the Wisconsin State Laboratory of Hygiene, and the Childrens' Hospital of Wisconsin. In January 2008, Wisconsin launched routine newborn screening for SCID and subsequently demonstrated the efficacy of TREC assay to detect SCID. In October 2008, the state garnered a 3-year CDC grant in support of the activities.
    - Wisconsin has screened over 200,000 newborns for SCID. Of those, 10% were premature. There were 160 abnormal results, of which 93 were premature and 67 full term. Inconclusive results were received in 288 (a significant number of those were premature). The final results (3 years) came back with five cases of severe lymphopenia.
    - The sensitivity of the TREC assay on full-term babies was 100% with a specificity of >99% and a positive predictive value of 40%.
- Massachusetts began working on its program in March 2007, and began statewide screening for SCID in February 2009. The program is supported by a 3-year CDC award, received in October 2008. Since September 2010, it has been correlating samples for the incipient Texas screening program.
    - Massachusetts has screened over 143,000 initial specimens, resulting in nearly 140,000 valid specimens used for the SCID program. Of the valid screens, 29 were abnormal and referred to flow cytometry, and 18 of those had abnormal flow results.
    - The sensitivity is 100%.
- California, with funding from the NIH and the Jeffrey Modell Foundation, began its pilot screening in August 2010. Working with the Perkin Elmer staff at the Genetic Disease Laboratory facility, it uses the lab within a laboratory model. Originally conservatively set at 60, the cut-off level was dropped to 25 in September of 2010.

- In 4½ months, California screened over 217,500 newborns, of which 12 were positive and four were positive for SCID. Of the 229 inconclusive results, the 10 positives were rescreened with one resultant SCID. Of all screened newborns, 26 were referred to flow cytometry.

- New York received regulatory approval in September 2010 to perform statewide mandated screening for SCID using the TREC assay. The program receives funding from the New York State Department of Health, the Jeffrey Modell Foundation, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

  - In 3 months, 76,250 New York newborns were screened. Of those, 223 full-term and 85 premature infants had abnormal results. Of the 109 referrals for testing, one baby had leukemia and 18 were very ill and 6 or those 18 had DiGeorge syndrome, CHARGE syndrome, idiopathic T-cell leukopenia, or adenosine deaminase deficiency.

- The CDC continues to provide reference materials for these states and any others interested in materials for the TREC assay. Materials are available for the screen normal, screen negative, and indeterminate samples. There are many dry blood spots ready for anyone who would like to use them. There are monthly send-outs available to interested groups, and five blinded reference dry blood spot are sent out. There are currently seven enrolled participants included the four states discussed in this presentation.

- Dr. Cuthbert's PowerPoint presentation lists a number of relevant publications.

B. FOLLOW-UP AND TREATMENT UPDATE

Christine Seroogy, M.D.
Associate Professor of Pediatric Allergy, Immunology, and Rheumatology
University of Wisconsin
Madison, Wisconsin

Dr. Christine Seroogy presented two SCID screening cases managed by the hospital over the past 7 months. The cases exemplify the successes and challenges of screening programs as well as the spectrum of SCID disease.

- In the first case, the infant was a male born at 40 weeks. The delivery was uncomplicated and the parents were unrelated. His newborn screen was drawn on the first day of life, and he left the hospital the next day. When he was 8 days old, Dr. Seroogy was contacted by the Wisconsin State Laboratory of Hygiene with his abnormal SCID screen results.

  - Because the initial TREC assay value was undetectable at 0, arrangements were made for flow cytometry that day. It demonstrated profound lymphopenia with very low T cell and B cell numbers; the NK cell numbers were normal. There were very few T cells of the naïve phenotype. The filter card was repeated, and again the TREC value was 0. The findings were consistent or highly suggestive of a T-B-NK+ form of SCID.

  - The infant was admitted to American Family Children's Hospital and put into protective isolation. Antimicrobial prophylaxis and intravenous gamma globulin were initiated. Breastfeeding was suspended while continued diagnostic testing ensued.

- Diagnostic testing utilized genetic sequencing by commercial and research laboratories, commercial and research-based radiosensitivity testing, functional studies of T cells, FISH for evidence of maternal engraftment, and biochemical testing for ADA (normal).

- The gene sequencing was done as rapidly as possible. Data was returned in 4–5 weeks indicating there were no deleterious mutations for the genes commonly associated with SCID.

- The fibroblast was analyzed by two laboratories. The analysis showed that the infant was radiosensitive, but not as severely affected as an artemis or ligase IV form of SCID. These data were not available until the infant was 10 weeks old.

- While waiting for the diagnostic testing to become available, serial flow cytometry was done to ascertain that this was a stable phenotype of T-B-NK+ SCID. The patient had persistently profoundly diminished T and B cell numbers with maintenance of normal NK cell numbers.

- Multiple considerations went into deciding on a curative approach. Data shows that timing of a transplant is very important. It is best done under 3 months of age because the infant is less likely to have pre-existing conditions. The donor source is also important. The best donor would be a matched sibling (not an option in this case); other sources include a parent, an unrelated match, or umbilical cord blood. Another consideration is the need for conditioning the patient to prepare for transplant. For this infant, a good cord blood match was found in the donor marrow registries. At 8 weeks of age, a reduced intensity conditioning regimen of busulfan and fludarabine was used with GVHD prophylaxis.

- To demonstrate engraftment over time, engraftment studies at the molecular level were conducted. Flow cytometry was monitored to look at immune cell number normalization. At 180 days out from transplant, the flow cytometry demonstrates normal immune cell numbers, including normal naïve T cell numbers.

- In summary, the infant tolerated the transplantation procedure well at 77 days of age. He was discharged home at 107 days of age, and at 6 months since transplant continues to be clinically stable with normalization of immune cell numbers. The molecular diagnosis is still unknown. This case provides evidence that TREC analysis can identify a patient early for successful transplantation patients while minimizing morbidity and mortality.

- In the second case, the infant's family had a history of SCID (this information was blinded to the state lab). Cord blood was drawn in the delivery room, and the filter card was obtained shortly after the newborn period and sent to the state lab.

  - His initial blood count showed profound lymphopenia with almost absent T, B, and NK cell numbers. The dry blood spot TREC value was 0. Based on the family history, the concern was that it was an ADA form of SCID. Cord blood was sent for biochemical testing, and confirmation was received within 48 hours.

  - The patient was sent home in protective isolation and started on enzyme replacement (PEG-ADA) and antimicrobial prophylaxis and intravenous gamma globulin. The infant was able to continue breastfeeding.

  - When monitoring the therapeutic effects of the enzyme replacement therapy, the data showed the enzyme working and decreasing the toxic metabolites. The serial flow

cytometry showed that the enzyme replacement improved this infant's lymphocyte numbers. He is still, though, profoundly immune compromised.

    - This baby continues to grow and thrive and remains infection-free. The baby will proceed to gene therapy at NIH when he reaches 10 kg.

- These two cases span the spectrum of SCID patients. The first has a form of molecular SCID rarely seen in this country, one that represents about 5% of SCID cases. He was initially evaluated and worked up in the hospital. In contrast, the second patient had a rapid metabolic test to screen for the genetic defect ADA, which allowed quick identification. He was sent home in isolation and given enzyme replacement, which decreased the toxic metabolites and improved immune function.

- These two cases exemplify the success of this program and highlight some of the challenges.

    - It is important to quickly follow genetically undefinable forms of SCID to ensure phenotype and move to curative approaches. A TREC value of 0 seems to be a robust indicator that this is a classical form of SCID.

    - A rapid radiosensitivity test needs to be developed, as it affects the approach to a cure.

    - Donor selection and approach to transplant is an ongoing investigation challenge.

C. PARENT ADVOCACY/EDUCATIONAL MATERIAL DEVELOPMENT

Marcia Boyle
President and Founder
Immune Deficiency Foundation

Immune Deficiency Foundation (IDF) representative Ms. Marcia Boyle explained that the mission of the organization is to improve the diagnosis, treatment, and quality of life of persons with primary immunodeficiency diseases through advocacy, education, and research. Supporting newborn screening for SCID is one of their initiatives. Their website is www.primaryimmune.org.

- The results of a 2009 survey conducted amongst SCID families were published in *Clinical Immunology*. The article is included in the briefing book for this meeting. IDF uses the findings (summarized immediately below) from the survey in its advocacy.

    - Morbidity, delayed diagnosis, increased medical costs, and death might have been prevented had a universal newborn screening test for SCID been in place.

    - Approximately half of the deaths among infants with SCID may be missed in the statistics arising from referral centers.

- Once the Secretary approved SCID for the newborn screening panel, IDF launched its campaign. The campaign goal is, through advocacy and education, to get SCID included in newborn screening protocols in all 50 states and territories.

- States and territories currently screening for SCID include California, Louisiana, Massachusetts, New York, Puerto Rico, Texas (limited pilot program in select hospitals), and Wisconsin. States where newborn screening advisory committees have voted to recommend the addition of SCID include Colorado, Delaware, Iowa, Michigan, Minnesota, North Carolina, and Rhode Island.

- In the summer of 2010, an IDF intern surveyed all state health departments regarding their processes for adding a condition to their screening panel. With that information, IDF developed a better understanding of how to approach each state to advocate for SCID to be added. IDF has met with state health departments, providing them with resources regarding cost analysis and recommendations of expert immunologists in the state for follow-up. IDF is active in 30 states and has formed alliances with other advocates in the states to collaborate on newborn screening (e.g., March of Dimes in Georgia, Pennsylvania Medical Society).

    - Five advisory committees have voted to recommend SCID based on IDF's efforts—Delaware, Michigan, Minnesota, North Carolina, and Rhode Island.

    - IDF staff and volunteers have given presentations, participated in advisory committees, provided data and resources, and held discussions with department of health staff members in Connecticut, Florida, Georgia, Illinois, Maryland, New Jersey, Ohio, Oregon, Pennsylvania, Utah, Virginia, and Washington.

- IDF's education activities include the following:

    - The website provides access to many of IDF's efforts. https://www.primaryimmune.org/advocacy_center/scid/scid_newborn_screening_initiative.asp

    - The IDF SCID Newborn Screening Advocacy Toolkit is used in educating policymakers.

    - The IDF blog on SCID newborn screening is very active and is kept up-to-date on relevant activities around the country.

    - IDF created and distributed a brochure on the live rotavirus to alert providers to the dangers of administering the vaccine to infants with SCID.

    - IDF produced two videos featuring SCID parents to provide a human perspective on the importance of early detection. The videos are posted on YouTube and IDF's Facebook, as well as their website.

    - Available on its website, the IDF's Patient and Family Handbook offers extensive information on SCID and its treatment. The organization is in the process of updating the online version. The handbook is readily available to anybody who requests it.

- There are several challenges to implementation. Funding has been identified by some states as the major barrier to implementation, with cost estimates ranging from $500,000 to $1 million. States also have prior commitments to other disease groups that they must implement before addressing SCID screening. Other challenges include the lack of an FDA-approved assay for the screening and the need for experts in immunodeficiency to handle the diagnosis and treatment.

- IDF recommends that states develop networks of specialists in immunodeficiency for diagnosis and treatment of patients. They should be encouraged to develop strategies that ensure patients have access to specialists. This may mean sending a patient out of state to medical centers with expertise in bone marrow transplantation for SCID.

- States need to develop mechanisms to educate and communicate with physicians and families the next steps following identification of a positive test result.

- IDF is working with a specialist in primary immunodeficiency to develop a brochure that will educate parents who receive a positive screen and emphasize the importance of confirmatory testing. It will explain what SCID and other T-cell lymphocyte deficiencies are and their appropriate treatments. It will relieve concerns by explaining what to do next, and it will give links to additional resources.

D. NBSTRN UPDATE

Michael Watson, Ph.D., F.A.C.M.G.
Executive Director
American College of Medical Genetics

One of the Newborn Screening Translational Research Network's (NBSTRN) fundamental interests is to build an infrastructure and put in place the support resources for investigators that support highly collaborative research for rare diseases such as SCID. The infrastructure must be protocol-driven to facilitate gathering compatible data from multiple investigator groups and states. NIH has participated in these efforts on the research, investigation, and science side. Dr. Michael Watson thanked Dr. Amy Brower for her leadership of this workgroup and for pulling all the players together for this research.

- In early summer of 2010, NICHD issued a subcontract to New York State. The four programs funded by this subcontract are New York, California, Louisiana (through the Wisconsin lab), and Puerto Rico (through the Massachusetts lab). The subcontract primarily funds the per baby screening. The NBSTRN coordinating center supplemented this effort by funding meetings of experts and resource development projects.

- Tools are being adapted to working prospectively in pilot projects that allow states to bring their data together and learn from each other. This approach generates larger datasets more rapidly and hopefully will identify the difficulties and lab complexities more quickly.

- NBSTRN activities in SCID include the following:

    - NBSTRN supports developing the infrastructure to support a collaborative approach to laboratory data sharing in pilot studies.

    - The resources and infrastructure to develop clinical datasets that describe the protocols for diagnosis, treatment, and monitoring have been established. This system allows us to get a longitudinal health record look at a patient. The NICHD has an interest in developing the clinical histories of these conditions. SCID screening is like hearing screening in that there are potentially several exceedingly rare conditions that can be diagnosed. By pooling resources and data together in an organized and protocol-driven manner that allows for compatibility of data, a better sense can be gained of what the no TRECs and low TRECS are about.

- Electronic language standardization is in the stage now of putting disease-specific parts of the protocol together for SCID. The focus is on bringing the diagnosis follow-up treatment languages into the national electronic health system language standardization process. This drives electronic medical record manufacturers to accept those as language standards, and they become integrated into the electronic health system of the United States, which creates compatible data that we can draw from many places over time.

- Developing IT and informatics to support point-of-care data collection will allow a provider to input data just once. Physicians will be able to capture data at the point of care and simultaneously share it with their institution's electronic medical record system, relevant surveillance registries, and any other necessary institutional databases.

- NBSTRN is in the process of developing ACT sheets to support the primary care provider's role in diagnosis and follow up of screen positive individuals.

- NBSTRN also wants to develop a directory of clinical specialists in pediatric immunodeficiencies and T-cell lymphopenias.

- The SCID expert group serves as the coordinating and support center for investigators who have expertise in these disorders. This group is developing measures for the collection of newborn screening data itself, as well as the diagnosis, treatment, and follow-up datasets that will be part of the long-term studies.

- One of first tools the NBSTRN adapted was the R4S, which was previously presented to this committee by Dr. Piero Rinaldo. Nearly all states and 40 countries are bringing their newborn screening data into this database. It has been a tremendous value as a quality improvement tool. The tool can be readily adapted to prospective use and pilot projects.

- The diagnosis and follow-up dataset, which is being built off a larger project involving all newborn screening, is still in the development stage. Thus far, it has gone through a long iterative process. The data points shared across all conditions in which NBSTRN has an interest in developing protocols include the following: demographics, SES, family history, prenatal history, neonatal history, birth measurements, newborn screening, diagnostic testing, past health history, emergency management, developmental screening, and imaging studies. This represents about 80% of the data points acquired at the point of care. To that we supplement the disease-specific data points in a highly protocol-driven way in hopes that the data is more compatible. Expert-developed, protocol-driven activities on the clinical side that allowed data to be pooled underpins the success of the national cancer cooperative study groups. Longevity and large datasets are critically important for rare conditions.

- To develop the disease-specific datasets, the NBSTRN is working with the Primary Immune Deficiency Treatment Consortium with funding from the Office of Rare Diseases, Rare Disease Clinical Research Consortia. This model identifies persons who are already funded to work in these areas and allows them to work within the tools NBSTRN is developing. They get both the expertise and the sharing of the tools that allow them to collaborate.

Mr. Ojodu thanked all the presenters for their updates. He also thanked IDF and the Jeffrey Modell Foundation for their active engagement in moving newborn screening forward in the states.

He provided a brief update about the "Newborn Screening for Severe Combined Immunodeficiency (SCID): Implementation, Challenges, and Successes" meeting held October 27–29, 2010. The well-attended meeting focused on laboratory testing models, follow-up, treatment, implementation, challenges,

and successes in newborn screening for SCID in state screening systems. Videos and slide presentations from the meeting can be seen online at http://www.aphl.org/aphlprograms/nsg/Pages/default.aspx.

Mr. Ojodu announced that, as of January 2011, Dr. Patrice Held holds the Ronald H. Laessig Memorial Newborn Screening Fellowship. It is a 2-year postdoctoral fellowship supported by the Jeffrey Modell Foundation, CDC, and APHL. Dr. Held works with the Wisconsin State Laboratory of Hygiene.

In closing, Mr. Ojodu requested the audience bear in mind the economic effects to states with each screening added to the screening panel.

Dr. Howell invited Dr. Michele Caggana, a subcontractor of the NIH who has conducted much of the work on this project, to comment.

- Dr. Caggana expressed her pleasure at being able to work with states at various stages of the screening implementation. The ability of funded states to put specimen data into a database will help us understand SCID and other conditions. Clinical input has been great, as has been the collaboration between states. She noted that new SCIDs are being picked up by screening. She expressed appreciation for help from NBSTRN, Dr. Amy Brower, Ms. Irina Smotrich, and Drs. Buckley, Puck, and Abraham of the Mayo Clinic.

Dr. Howell said it is exciting to see how rapidly this group has brought hundreds of thousands of newly screened babies to the table. He then invited Dr. Amy Brower and Dr. Tiina Urv to comment.

- Dr. Brower related that the SCID recommendation and implementation will lay the groundwork for LSDs and other nominated conditions. It will be used as a platform to showcase the NICHD-supported work, and continue work on long-term database follow-up.

- Dr. Urv added that even though funding for the blood spot program and others will come to an end, the system has been set up so new states coming on board with the screening can learn from states with experience.

Dr. Howell noted that this advisory committee has looked at the evidence and made the formal recommendation that SCID be added to the core screening panel. At the same time, the committee felt that it would be important to look at a lot of babies before all U.S. states came on board. He thanked the NIH for coming to the table with financial support. Once pilot data is available, the information will be available to enable states to adopt the recommendations.

Dr. Puryear asked that someone accept responsibility for preparing the required report for the Secretary by April 1 of this year. Dr. Tiina Urv and Dr. Carla Cuthbert agreed to work collaboratively to produce the report.

V. SUBCOMMITTEE MEETINGS

A. FOLLOW-UP AND TREATMENT

B. EDUCATION AND TRAINING

C. LABORATORY STANDARDS AND PROCEDURES

VI. SUBCOMMITTEE REPORTS

January 28, 2011

A. SUBCOMMITTEE ON LABORATORY STANDARDS AND PROCEDURES

Gerard Vockley, M.D., Ph.D.
Chief of Medical Genetics
Department of Pediatrics
University of Pittsburgh School of Medicine
Children's Hospital of Pittsburgh
Pittsburgh, Pennsylvania

During the subcommittee meeting, the group heard three presentations. The first, from Dr. Dieter Matern of the Mayo Clinic, was a comparison of newborn screening technology. That was followed by a discussion, led by Dr. Alberto Gutierrez and Dr. Bill Slimack, of the FDA proposed oversite of *in vitro* diagnostic devices and how they translate into lab-developed tests and impact NBS labs. The final presentation come from National Library of Medicine colleagues on messaging, ordering and receiving standards, and health information technology related to newborn screening labs.

- Part of the presentation from Dr. Matern included a discussion of new newborn screening initiatives, lysosomal storage diseases, Wilson's disease, x-linked adrenoleukodystrophy, and Friedrich's ataxia. In addition, the Mayo Clinic continues comparative metrics and testing.
    - The subcommittee urged consideration of the effect of adding tests to the screening panel. Even with tests that have exceptionally good predictive value and excellent laboratory performance, as tests are added to the panel, the level of follow up becomes an increasing drain on the system. This added stress to the system should be kept in mind for each test under consideration.

- Comparative studies are important because without them labs will be doing different procedures for different kinds of testing, which adds to the follow-up load.

- Even with a growing menu of tests, the numbers that Dr. Matern presented for the screening results in Minnesota were impressive. They are getting positive predictive values where one out of two or one out of three test results are something real.

  - The following platform options are being considered for comparative study of antigen-based technology:

    Luminex, a metabolite-based detection enzyme assay — it is a specific look at the product of an enzyme reaction rather than a non-direct look

    Digital microfluidic-based enzyme assays—"a lab bench on a chip" from Advanced Liquid Logic

    Comparing these with standard tradition enzyme assays from the field

  - The key issues related to evaluating a platform comparison are: can they be done in a multiplex fashion; how complex is it for the lab to run the test; are the performance metrics suitable to high throughput; and are they available at the facility.

  - This has been a challenge to get up and running and there are, as of yet, no results. All platforms are in place and in the coming year there should be some first-look data available.

  - Because of the additive effect of increasing the number of tests, the consideration for second tier testing to decrease the false positive rate becomes more important. There was some discussion of the need for consent not only for multiple tests but also for test development.

- Dr. Alberto Gutierrez pointed out that lab-developed tests fall into the FDA's device oversight infrastructure because, in context of newborn screening, the test is a device. The FDA looks at safety and efficacy issues. They have three levels of oversight that they bundle things into, and they make decision as to how rigorous to be with that oversight based on perceived risk. Newborn screening is viewed as a low-risk procedure in FDA terminology because of the elaborate follow-up mechanisms in place, which are there largely because of the work of this committee.

  - The next generation of testing involves the ability to understand and parse the key pieces of data from testing. The technology is there, but interpreting it is beyond current capacity. It will become more an issue of how to handle the data than the technology. There are significant gaps in what we know and what we can do in rare diseases, but rare disease is what is driving this now.

  - As a result of this very interesting discussion, Drs. Copeland and Vockley are going to put together a short statement to be sent to the FDA to encourage them to continue considering the ramifications of this kind of testing relative to rare diseases.

- The subcommittee was informed, by Dr. Clem McDonald's working group, that HL-7 messaging is in the final stages of testing in Kentucky and is scheduled to go live in the next month or two for their Health Information Exchange. They are making significant progress in other states. Based on the latest NLM review, HL7 messaging fully complies with HRSA

guidance. They continue to look at proposals for what information needs to be transferred relative to newborn screening and LOINC nomenclature.

- New LOINC codes are available for SCID and LSDs. They are looking into defining additional card variables for fields that need to be captured: data of last transfusion, soy/hydrolyzed formula answer, parental refusal answers, birth hospital, and post-discharge provider.

In closing, Dr. Copeland noted that Dr. Dieter Matern's project to develop newborn screening technology is funded by the NICHD through the Newborn Screening Saves Lives Act.

Dr. Howell confirmed that Drs. Vockley and Copeland will produce a document to be sent to the FDA about the level of risk in the newborn screening arena in response to guidance that will be sent out by the FDA as a request for comments.

B. SUBCOMMITTEE ON EDUCATION AND TRAINING

Tracy Trotter, M.D., F.A.A.P.
Senior Partner
Pediatric and Adolescent Medicine
San Ramon Valley Primary Care Medical Group

Dr. Tracy Trotter represented this subcommittee without Ms. Jana Monaco, who was unable to join the meeting.

- At the subcommittee meeting, Ms. Natasha Bonhomme reported that the beta website for the newborn screening clearinghouse is active at nbsclearinghouse.org. It offers a user guide, condition specific information, and blog posts from regional collaboratives. The name for the website under consideration is "BabysFirstTest." A request for proposal to design, develop, and implement the website drew 11 proposals resulting in three finalists; the final decision will be made February 1, 2011.

- Dr. Trotter announced RFPs for the first Newborn Screening Clearinghouse Challenge Awards are due in early March. About 4–8 groups will be awarded up to $25,000 (per project) for projects that will take about 6 months to complete.

- Dr. Trotter reviewed several significant programs that subcommittee members reported on at yesterday's meeting.

  - Ms. Emily Edelmen from NCHPEG updated the subcommittee on a tablet-based family history program for prenatal providers. This program is clearly beneficial for handling large amounts of data in clinical medicine arena. The project is moving along quickly, and information about the first testing, as well as a demonstration, will be presented at the subcommittee's May meeting.

- Mr. Brad Thompson, the father of a 21-year-old woman with special health care needs, introduced the subcommittee to the HALI project. Mr. Thompson trains parents to be ombudsmen for their children with special health care needs. He works in primary care offices, interacting with families of children with special health care needs and helping them with non-medical issues (organizing follow-up appointments with subspecialists, understanding how the system works, identifying community resources, dealing with the emotional needs and expectations of families, etc.). Dr. Trotter strongly recommended committee members become familiar with this work.

- Ms. Bonhomme provided the subcommittee a quick update on the HIT workgroup and the congenital conditions program.

- Dr. Trotter reviewed the purpose of the committee by citing S. 1111 of the Newborn Screening Saves Lives Act, 2008: "The Advisory Committee … shall include recommendations, advice, or information dealing with public and provider awareness and education." With this in mind, the subcommittee has developed a proposal for a national awareness campaign about newborn screening.

- Newborn screening is one of the more successful public health programs. It has been progressing under the radar, and the subcommittee believes it is now advantageous to increase public awareness of newborn screening. A better informed public makes better decisions. He cited campaigns around autism (CDC) and folic acid (March of Dimes) as examples of successful public campaigns.

  - The subcommittee asked Ms. Angela Colson of the CDC communications group to put together a proposal for a national awareness program. The proposal outlines a four phase nationally run national awareness program. The subcommittee's request to the committee is that it this campaign be something with which the committee should go forward.

  - Dr. Trotter reviewed the four phases of the proposed campaign, with special attention to phase 1, the planning and strategy development phase. Phase 1 has two segments: (1) a media and environmental scan, for which a stakeholder analysis is conducted, an understanding of current messaging is arrived at, information gaps are identified, and specific audiences are defined; and (2) a facilitated strategy summit is held to review the analysis, goals that come out of the environmental scan are solidified, and priorities and target audiences are defined.

  - The subcommittee recommends to the committee to move forward with such an awareness campaign and that the following four components be part of that: (1) identify very specific audiences to drive strategy, (2) clarify the message, which needs to be broad and simple, (3) have both qualitative and quantitative objective outcome measurements in place from the beginning, and (4) develop a realistic outline of phases 2–4 with a budget.

- The Genetics in Primary Care Institute (GPCI), will increase the number of primary health care providers who are competent and confident in providing basic information about newborn screening and common genetic disorders to their patients and their families. GPCI is a learning collaborative that pairs physicians from busy practices with experts in genetics and genomic medicine. The institute RFP is due January 31 and is a cooperative agreement. The proposals will be reviewed in March, and at the May meeting of the subcommittee there should be a start-up report from the awarded group.

Dr. Howell asked for further discussion on the public campaign with special attention to phase 1, with attention to the cost.

- Dr. Trotter reported that the estimated cost, derived by Ms. Angela Colson and Dr. Coleen Boyle from similar projects with the CDC, is $65,000 to complete phase 1. Figures are not yet available for phases 2–4.

- Dr. Howell clarified that phase 1 involves selecting a contractor to do the environmental and media scan as well as the stakeholder assessment and to conduct a partner strategy summit. The outcomes will be reported at the 24th meeting of this committee.

- Dr. Boyle commented that the rationale behind the first phase is to not reinvent the wheel and to bring stakeholders together. This way, information is consolidated and refined, giving an appropriate platform to move forward in terms of health communication, to really understand what the needs are and how they resonate with the community. As a baseline, this will tell us the likelihood of succeeding and inform us if it is the right way to go, setting the stage for phases 2–4.

- Ms. Sharon Terry, while supporting this measure, cautioned the committee in its choice of contractor. The landscape they will be scanning is complex with a lot of strong messages being sent from many angles. She also advised that, in the event the committee moves on to phases 2–4, government organizations and nonprofits tend to do a relatively poor job in campaigns compared to the private sector. She recommended the March of Dimes as an example of a successful campaigner.

- Dr. Christopher Kus asked if this would be a one-time campaign or an ongoing effort. Dr. Trotter responded that, while he feels sustaining it would be worthwhile, that is something that would have to be answered after phase 1 is complete. Dr. Boyle used the example of public education efforts around autism over the past decades to show that campaigns can change the culture and expectations of parents and providers.

- Dr. Alan Fleischman agreed with Sharon, and added that $65,000 is a small amount to create a strategy. He was pleased to see that the senior vice president for marketing at the March of Dimes, who was responsible for the folic acid campaign and prematurity campaign, had volunteered to be on this committee.

- **MOTION #1 PASSED: To move forward to a phase one evaluation of a national newborn screening public education/awareness campaign program, under the auspices of the Secretary's advisory committee. Dr. Tracy Trotter moved and Dr. Joseph Bocchini seconded the motion. The motion was approved with 11 YES votes. Four members were ABSENT (Dr. Alan Guttmacher, Ms. Jana Monaco, Dr. Michael Skeels, Dr. Peter van Dyck).**

C. SUBCOMMITTEE ON FOLLOW-UP AND TREATMENT

Coleen Boyle, Ph.D.
Committee Member

Jeffrey Botkin, M.D., M.P.H.
Committee Member

Dr. Coleen Boyle led the report to the committee from the Follow-up and Treatment Subcommittee with support from Dr. Jeffrey Botkin who was on the telephone. The subcommittee heard updates on medical foods activities and the linkage of newborn screening with vital records. The bulk of the meeting was a lengthy discussion on point-of-care screening.

- As a longstanding effort of the committee, letters on medical foods have been sent to the Secretary outlining the urgency of the subject with attention to insurance coverage. The Affordable Care Act provides an opportunity to reinforce the message. As part of her legislative update, Ms. Christine Brown reported that Senator Kerry will reintroduce the bill from the past congress. D. Susan Berry reported that a writing group is developing a draft manuscript of the medical foods survey (it is currently with the three participating Regional Collaborators for their input). The subcommittee discussed publishing the survey results under the auspices of the Regional Collaborative effort instead of a Committee work.

- The topic of linking newborn screening with vital records came out of a discussion a year ago about addressing short-term follow-up of newborn screening. Linking the screening results with vital records in real time would close the loop and provide assurance from a public health perspective that screening occurs. Dr. Brad Therrell developed a white paper that has recommendations to include a field for newborn screening on the birth certificate vital records form or electronic form of the birth certificate. Before distributing the white paper, the subcommittee wants to make sure all the principle players, NAPHSIS and NCHS, are on board with this recommendation. The subcommittee has received feedback that it is in the State's purview to make this happen. Dr. Therrell mentioned that Wisconsin has already included the field in their vital records electronic information in anticipation of guidance from the Committee. The subcommittee expects to provide a full report to the Committee at the May meeting.

- After the Committee's consideration at the previous SACHDNC meeting to include CCCHD in the panel, there was considerable discussion about how this screening represents a different paradigm than screenings such as dry blood spot. The difference affects the current system of public health assurance as well as short- and long-term follow-up issues. Dr. Jane Getchell posed a question about whether CCCHD screening ought to be in the recommended screening panel or is better suited as a professional recommendation. Since that meeting, Drs. Botkin, Kemper, Puryear, and Boyle developed a list of questions to help understand the differences between some of the new conditions coming before the committee and blood spot and hearing screening.

- By way of introduction to point-of-care screening, Dr. Puryear gave the subcommittee an overview the CCCHD workgroup meeting held two weeks ago.

- Ms. Sylvia Au, genetics coordinator for Hawaii health department, represented concerns from a state health perspective. She discussed the challenges in terms of effects on administration, policy, and financing. She emphasized that states are strapped in terms of their ability to manage what is already in their purview (ex. SCID, CF and EHDI challenges, and to make these programs successful, additional resources are required.

- Point-of-service screening creates a new paradigm that creates an interface between professional standards and public health programs. The crux of the question that requires further discussion is whether that interface changes depending on the condition and its attributes. There are many professional guidelines for systematic care of children within the context of well-child care. How do the conditions that are coming before the Committee (e.g., hyperbilirubinemia, CCCHD) differ from other recommended universal practices for good child well care (e.g., hearing, developmental, and vision screening) that are professional mandates?

    - With these new conditions, we need to consider the roles, responsibilities, resources, and liabilities involved and how these aspects may vary from condition to condition.

    - Diverse opinions have been expressed about the roles and responsibilities of public health. There might be a very limited role in the way of liaison and education, and perhaps surveillance and evaluation. Or public health might play a bigger role in terms of tracking and assuring the short- and long-term follow-up. This will vary from state to state in the roll-out.

    - Our Committee needs to be sensitive to the fact that incorporating a new screen into the recommended screening panel often translates into a mandate of services at the State level. An example by Dr. Bob Bowman was given of Indiana's legislation that requires the State to provide service for conditions included in the newborn screening panel.

    - The subcommittee recommended clarifying the definition of "point-of-service screening," as that term might not precisely capture what is intended.

- To help the full Committee wrestle with these issues, Dr. Marie Mann suggested revisiting the 2005/6 ACMG report that includes revised criteria for newborn screening to see how they resonate with the conditions the Committee is currently considering and how they might be revised.
- Dr. Botkin suggested the committee consider a two or multi-tiered recommendation for the panel. The issue of urgency and equity, and other criteria, would fit into that framework. Public health roles and responsibilities would be described in such recommendations.
    - Drs. Nancy Green and Marie Mann agreed to develop a matrix to illustrate and develop these ideas. They drafted a list of unique attributes of point-of-care newborn screening to help the committee determine where a condition falls. The list follows:
    - Point-of-care testing within the context of NBS is defined as universally performed (or available) tests that are performed for a newborn at the birth hospital prior to discharge home.
    - Justification of testing and lack of requirement for parental permission would parallel the features of the traditional metabolic testing, but be done at bedside for reasons of urgency, equity, and efficiency.
    - Some of the attributes listed below also may be applicable to testing performed later in childhood.
    - Critical issues of roles, responsibilities, resources, and liability would need to be addressed, generically, as well as specifically for any specific testing under consideration.
    - Public health roles would likely include, at a minimum, data reporting and program evaluation.
- Their key attributes include the following:
    - Condition: Urgency for diagnosis to institute treatment, condition is serious if untreated, newborn is the primary beneficiary
    - Screening Test: Easy/reasonable—not taxing for the infant, simple and quick procedure to perform, available manpower and instrumentation, screening result are quickly obtained on site and are interpretable, safe, available, acceptable, standardized, quality assurance is available locally, cost per child is modest
    - Diagnostic Test or Process: Available, feasible, definitive, safe, favorable ratio of potential benefit to cost

Dr. Boyle invited discussion and comments.

- Dr. Brad Therrell clarified that Wisconsin is not the only state that includes screening results on the birth certificate. The comment made to the subcommittee was that Wisconsin started doing it this year. Approximately eight to ten states currently practice this, and three or four of them have it as a mandate.

- Dr. Green suggested the Committee consider having formal representation from the American Hospital Association and/or other additional relevant hospital- associated agencies.

- In response to a question from Dr. Howell about whether the subcommittee discussed the differences in universal practices and mandated newborn screening procedures, Dr. Boyle said that there are professional guidelines (Bright Futures is the best example) that describe well-child care and appropriate screens that should occur for every child. She is most familiar with recommendations on autism, which has firm recommendations about developmental screening and autism specific screening. How does this differ from the urgency to screen; if missed, children will have poorer outcomes. Similarly, CCCHD has a brief time window for detection with perhaps death if missed. The subcommittee is considering how the attributes of some of the conditions that might come before this Committee differ in terms of deciding which ones fall under clinical responsibility versus the role of public health when a heavier hand is needed. Dr. Howell said that whether the condition is really a clinical practice issue that should be handled at a professional or hospital level or a screening issue might become increasingly critical.

- Dr. Christopher Kus suggested asking who *would* come up with a screening recommendation, if not this Committee, for a given condition. Take the life-threatening and rare condition of CCCHD versus hyperbilirubinemia—the Academy of Pediatrics would not make such a recommendation. This discussion probably will come up in the review of hyperbilirubinemia and this group will be able to help clarify the definition and the roles of public health and clinical practice.

- Dr. Anne Comeau added that the subcommittee discussed not only considering the condition, but also what the State does with the recommendation for the condition. Once a State decides to mandate a screen, state responsibility for follow up and quality assurance plays a role. If a state does not mandate the recommendation, but follows professional clinical care guidelines, there might be an advantage to use of a State database system for maintaining quality assurance. That boundary is a moving target when it is voluntary.

    - In response, Dr. Nancy Green explained that with a recommended panel, there is pressure and guidance from groups (e.g., March of Dimes) to have States and their health departments embrace the recommended panel. A tiered system might help states manage these conditions.

    - Dr Marie Mann commented that at the May meeting, it's the interface between public heath and clinical practice, helping to define gross responsibility and the resources.

- Dr. Puryear explained that there is a context for all Committee recommendations framed by the department's regulations for the prevention guidelines for the Affordable Care Act. The Committee needs to be cognizant of the implications of anything it puts on the recommended uniform screening panel. She read from the regulations: "The comprehensive guidelines that are illustrated in the uniform panel of the SACHDNC went into affect May 21, 2010. Plans and issuers are required to provide coverage without cost sharing for these services in the first plan year. In the individual market policy year that begins on or after May 21, 2011." Anything that goes into what is called the recommended uniform screening panel has implications not only for States but also for payers.

Dr. Boyle noted that Drs. Robert Bowman and Alan Zuckerman wanted to make a short recommendation as part of the subcommittee.

- Dr. Zuckerman explained that most of the work of the HIT Workgroup is embedded in the other subcommittees, as heard already with regards to lab messaging, vital records linkage, and tablets for family history. There are areas of comments on emerging regulations and activities outside of this Committee. In the past, this Committee commented on stage one meaningful use recommendations. The HIT Policy Committee has come out with a request for comments on stage 2 meaningful use. The Workgroup is drafting comments and they would like to circulate them by email next week to the Committee. The Committee can also anticipate, at stage 3, new types of evidence bases required to add objectives to meaningful use; so, the Committee can attempt to pursue these in the area of newborn screening, and rather than just influence regulations, take a bottom up approach to get stakeholders to apply meaningful use concepts (such as engaging patients and families, improving care coordination) even if newborn screening is not mentioned in the regulations. He asked if the Committee would be interested in reviewing draft comments which will be due February 25. Dr. Howell assured him that they would.

D. WORKGROUP ON EVIDENCE EVALUATION METHODS

Bruce Nedrow Calonge, M.D., M.P.H.
President and Chief Executive Officer
The Colorado Trust
Denver, Colorado

With a reminder that the committee's congressional mandate is to make evidence-based recommendations to the Secretary for conditions to add to the uniform screening panel, Dr. Howell explained that a workgroup has been established on evidence evaluation methods. Made up of a large and distinguished membership, it will look at the evidence methods used by this committee to make its recommendations. Dr. Howell introduced Dr. Ned Calonge to report on this workgroup's progress.

- Dr. Calonge reported that the workgroup has recruited methodological and evidence-based medicine experts from many national and international sectors to form its membership. Members include representatives of the U.S. Services Preventive Task Force, AHRQ, evidence-based practice centers, the Guide to Community Preventive Services, and the

Advisory Committee on Immunization Practices (which recently adopted evidence-based methodology based on a modification of the grade approach). The workgroup membership has good representation from the grade workgroup, which will bring to table additional methods that will help us deal with difficult contextual issues. It also has representatives from EGAPP and economic and modeling experts. The workgroup is poised to begin its work.

  - The workgroup's first meeting will be on April 13, at which members will share the methodological approaches from the other review groups, setting the stage for what is out there. The group will start thinking about how modeling will inform the work of the taskforce, and then how to move forward in refining methods to better address the issues that have been faced in recent recommendations.

- There are four main areas the workgroup will work in.

  1. **Quality of Evidence Assessment:** The workgroup will start from the framework from the clinical trials world and the McMasters evidence grading system (grade 1 evidence is randomized trials). For the rare disease that this committee will consider, grade 1 evidence is unlikely to exist. So the workgroup plans to consider how to assess the quality of evidence in very rare diseases of low prevalence with low incidence. What should we do when state-of-the-art evidence is simply a case series?

  2. **How to Approach Weak Links in the Chain of Evidence:** Using the example of a phrase used when discussing screening for major hypoxic heart disease, "we have a critical evidence gap," Dr. Calonge explained that these weak links in the chain of evidence will inevitably exist for the disease under consideration. For some committee members that will prove to be a hurdle in voting positively. Similarly, in the hyperbilirubinemia presentation, the phrase "we don't have evidence that treating hyperbilirubinemia prevents kernicterus" was used. The ensuing discussion employed persuasive, but not evidence-based, arguments that children have obviously been helped by the screening. This workgroup will wrestle with how to deal with these weaker links in the evidence in reaching a decision.

  3. **Role of Modeling:** Modeling will help address and inform these critical evidence gaps by giving a better sense of what the benefits might be. Modeling can be used to help us better understand the potential upper bounds of the benefits and harms.

  4. **Rethink Where the Certainty Bar Is Set:** By way of example, Dr. Calonge explained that the U.S. Preventive Services Task Force (USPSTF) uses a high bar of certainty. In other words, before giving an A or B recommendation, the level of certainty bar is set quite high in order to make sure the recommendations have a very good chance of doing more good than harm. In setting the methodology for the advisory committee, this committee has borrowed that high certainty bar level, causing some members to wrestle with making a positive recommendation. The working group will develop recommendations for an appropriate certainty point that will benefit the children in the United States and that can be consistently applied.

- The workgroup will also consider the committee's approach to decisions when the evidence leads to a higher risk of being wrong or a lower level of certainty. In conditions looked at so far, there has been some discomfort with those four categories. The SCID presentation at this meeting reaffirmed the decision we made in approving SCID and it lent a sense of legitimacy to the process we used in getting to the SCID recommendation. This category of a conditional approval where outcomes are reviewed ensures that we are doing more good than harm, that

we are not subjecting children to treatments that could be harmful in order to achieve a less than certain outcome. These reviews of the information are critical steps. We could create a conditional recommendation category, then have the discipline to re-examine the evidence after we have some experience, and even have the discipline to take a condition off the list if it looks like it is not meeting our objectives. There may be another category of recommendation to not put a condition on the uniform panel, but instead pursue it as a QI or QA standard of care, best practice, or other way to meet the needs of our country's children without mandating it in the uniform screening panel.

Dr. Howell invited questions and comments from those in attendance.

- Dr. Vockley commented that a strength of this committee is that each member has a different bar and different ideas on each condition. The heterogeneous nature of the group is important. He also reinforced Dr. Calonge's point that the SCID presentation validated the process we have been using. The same process was implemented to look at CCCHD. A certain amount of negotiation is inevitable in this process.

- Dr. Botkin addressed the need to focus on the evidence gaps. The group may want to consider getting away from a binary outcome (yes or no). There are going to be gray areas. The committee could use its authority and ability to leverage the system to create a process that helps fill those gaps in a timely way.

- In response to a comment from Dr. Boyle, Dr. Calonge assured the committee that the modeling will include economic assessments. This is essential because actual cost information on many of these rare diseases is not readily available.

- Dr. Dougherty expressed the point of view that the process the committee has been using does not have a place in it for the kind of evidence being used for SCID and CCCHD.

- **MOTION #2 TABLED: The committee's formal process include making a recommendation to proceed with further research as one of the possible recommendations. Dr. Dougherty moved and nobody seconded the motion. It was tabled for further discussion by the workgroup.**

VII. EFFICACY OF NEWBORN SCREENING FROM A FAMILY PERSPECTIVE: A NATIONAL SURVEY OF RECENT AND PROSPECTIVE MOTHERS ABOUT NEWBORN SCREENING

David Kaufman, Ph.D.
Director of Research and Statistics
Genetics and Public Policy Center
Johns Hopkins University
Washington, District of Columbia

Dr. Howell introduced the next presenter, Dr. David Kaufman, who is responsible for the design and analysis of the center's public and professional opinion surveys on a range of topics including newborn screening. In 2007, HRSA funded several studies to examine the efficacy of newborn screening from a

family perspective. Dr. Kaufman's presentation will present the results of one of those studies. The presentation was to be made at our last meeting, but we ran out of time and Dr. Kaufman agreed to return today to give this presentation.

- Dr. Kaufman explained that, while many surveys on newborn screening are done with parents of affected children or parents of children at high risk, HRSA thought it would be important to find out what the general public knows and thinks about screening. The goals of this survey were to (1) to measure the general public's knowledge and understanding of newborn screening; (2) assess public support for newborn screening; (3) assess the types of information people receive and would like to receive, as well as examine the kinds of diseases the public would like to have screened; and (4) test whether severity of the disease, age of disease onset, and positive predictive value influence support for newborn screening.

- Dr. Kaufman described the survey methods. Surveys were conducted online and took an average of 11 minutes. They used a national random sample of two groups of women (2,266) ages 18–45 that they accessed through Knowledge Networks. The women fell into one of two broad categories: women who had given birth in the past 3 years (1,258) and women who planned to have a baby in the next 3 years (1,008). All the mothers received 36 questions, and recent mothers had an additional 10 questions about their recent experience. The women were then randomized to one of four tests.

- Dr. Kaufman reported on results that show what the women knew about newborn screening.

    - The women were first asked if they had heard of newborn screening. Only two-thirds of recent mothers and 38% of prospective mothers had heard of it. Demographic factors showed that awareness increased significantly in both groups with education. Hispanic women were less likely to have heard of it. There was not much variation with respect to age or income.

    - Asking recent mothers about access to information about newborn screening, 39% said they had too little information, two-thirds knew babies were screened, 44% remembered receiving the results, and about 25% said they had a good understanding of the process.

    - Of recent mothers, 4 in 10 said they were not given enough or any information on screening during their pregnancy. About 37% said they received the right amount of information. Regarding information they did receive, 80% said they had a good or basic understanding of it.

    - One of the more significant findings was that information is not getting to the mothers soon enough. Asked when the mothers would first want to receive information about newborn screening, 85% of recent mothers and 90% prospective mothers want it before getting to the hospital. Yet, a mere 55% received information in the hospital, and some of them only if there is a problem.

    - In answer to what type of information is most important to receive, both groups of mothers had similar answers. They want practical information—what happens if the screen is abnormal, what to expect, the conditions that are being screened for, how will she receive the results, and the risks associated with having a sample taken.

- After giving the women a definition of newborn screening, they were asked what they thought of the idea. They extended broad support for screening for conditions where early diagnosis could improve the baby's health (98% of mothers). Significantly fewer, but still a majority, supported screening for conditions where early diagnosis might not improve the baby's health. Only 5% felt newborn screening should never be done.

- Over 95% in both groups of women said screening is important so parents can prepare to care for a child with a condition. A similarly high level felt screening is important to improve the baby's health, and 88% felt it is important so the parents can consider the risk associated with having another child with a similar condition.

- The greatest concern expressed about newborn screening is that it might not provide accurate information (nearly half of women). Fewer were concerned about it causing too much anxiety and taking money away from other health care needs.

- When asked if such screening were available, would they be interested in screening their babies for late onset diseases or special traits, the majority were interested in screening for diabetes and heart disease, colon cancer, Alzheimer's disease. A smattering indicated an interest in testing for traits (e.g., IQ, height, special abilities) as well.

- To determine how age of onset, severity of disease, and positive predictive values influence opinions on whether a disease should be screened for or not, each woman was read one of four fictional scenarios involving an unnamed incurable rare genetic disease. Two scenarios involved a disease with symptoms that appear late, at 12–15 years of age, and the other two scenarios involved a disease with symptoms that appear between 3–5 years of age. Two scenarios had a disease with no cure and eventual death, and the other two a disease that is chronic and gets worse but does not cause death. There were a total of four scenarios.

  - The concept of a positive predictive value was explained in simple terms and the women were asked if, with a 90% PPV, they would support having all babies screened for that disease. Then they were asked what they would think if PPV was 60%. Support for screening for disease varied most when the PPV changed, regardless of the scenario. There was a 10–13% variance in support between 60% and 90% PPVs.

  - The other factors, age of onset and severity of disease, did not make much difference.

- In conclusion, the survey indicated that the public needs and wants information on newborn screening. Awareness is low, and there is too little education occurring too late.

  - Although some providers explain that they do not provide the information because the women do not request it, this survey shows that, because of their unfamiliarity with newborn screening, patients do not know to ask about it. Doctors need to be proactive.

  - Women want concise, practical information offered at multiple junctures before they get to the hospital.

  - Hispanic women under the age of 25, especially those who have not completed college, are in greatest need of this information.

  - The goals of newborn screening are viewed very positively even by women who have gone through it recently.

- Accurate information is highly valued. The women worry about inaccuracy. Support for screening increased as the PPV increased.

- The majority of women were interested in testing for adult onset diseases, but there was a low level of interest in testing for traits.

- Dr. Kaufman noted some of the study limitations. What people say in a survey does not always correspond to what they will do. The survey, conducted in English, required English literacy so the Hispanic results may be higher than in reality. Much of what we observed varies by income and education, so a more stratified analysis may be in order (a lot of adjustment was done for the regressions).

- Dr. Kaufman thanked their partners: Genetics and Public Policy Center, Genetic Alliance, University of Maryland, and HRSA (funder), and Consumer Task Force.

- Dr. Howell asked if it would be possible to pull out the Maryland mothers from this survey. He is interested because Maryland requires informed consent and he would be interested in knowing if these mothers who gave consent actually knew they had had newborn screening. Dr. Kaufman replied that there were not many Maryland participants but they could pull them. He noted that they did ask some questions about consent.

    - Carrie Blout of the Maryland Health Department informed the committee that since 2008 Maryland no longer requires informed consent (just informed dissent), but many hospitals have continued to get informed consent. Dr. Kaufman said their data is old enough that informed consent in Maryland was still in place when it was gathered.

- Dr. Trotter asked for the rationale for not including a scenario of an infant onset disease with the ability to have appropriate intervention with either diet or therapy, as this represents most of what we screen for? Dr. Kaufman responded that the project board sought to differentiate areas where they anticipated the biggest differences of opinion. Ms. Carol Green of the University of Maryland, who participated in the survey development, explained that the survey was based on the basic definition of screening (explained as conditions that we treat) given to the women. The purpose of the survey was to look at things beyond that.

- Dr. Vockley asked if it were possible to know if any of the participants had literature given to them sooner than they report. Were they handed something in a prenatal visit that just did not register until perhaps later? Dr. Kaufman said there is no way to know that but it is likely. He added that nearly all the women said they want to receive information first from a nurse or doctor, secondarily from a pamphlet. Only 20% wanted to receive it from the Internet.

- Dr. Kus asked if any of the mothers' infants had false positive tests and, if so, were they positive about the screening. Dr. Kaufman responded that approximately 20 mothers had responded thus and that there were follow-up questions on that subject. He said the mothers were indeed positive about screening.

Dr. Howell invited comments from the public.

- Ms. Ann Comeau asked, given that many studies use Knowledge Networks for participants, if in developing the randomized group it is known whether or not any of these women had participated in other newborn screening surveys or if this was their first participation. Dr. Kaufman does not know, but he agreed that this is an important point and it should be acknowledged.

VIII. OVERARCHING QUESTIONS FOR NEWBORN SCREENING LONG-TERM FOLLOW-UP

Cynthia Hinton, Ph.D., M.P.H.
Subcommittee on Treatment and Follow-up
Health Scientist, Pediatric Genetics Team
Division of Birth Defects and Developmental Disabilities
National Center on Birth Defects and Developmental Disabilities

Dr. Howell introduced Dr. Cynthia Hinton, who discussed the committee's project to present the major overarching questions to be answered to ensure that newborn screening is meeting its goal of achieving the best quality outcome for affected children and their families.

Dr. Cynthia Hinton presented a paper that the Treatment and Follow-up Subcommittee has been working on as a proposed statement from the Committee. Its purpose is to present broad questions and important issues for consideration for assessing whether long-term follow-up is meeting its goals. (The paper is built on a previous paper that resulted in an article by Dr. Kemper and colleagues published in *Genetics in Medicine* in 2008.) The full paper is available in the briefing book for this meeting.

- Two years ago, the subcommittee met to focus on issues of variables. At that meeting, it was suggested that the role of the subcommittee is not to tell people what variables to collect, but to describe which questions need to be answered. Moreover, there has been collaboration in national and regional efforts working on standardizing the variables that are being collected.

- Per a statement from the Secretary's Advisory Committee, long-term follow-up (LTFU) care has four components: care coordination, evidence-based practice, continuous quality improvement, and new knowledge discovery. This paper builds on those goals and looked at materials presented by other LTFU working groups, such as the Regional Collaboratives, ACMG, NBSTRN, and CDC projects. .A 1-day workshop was developed to brainstorm about the questions underneath the goals that need to be answered. The questions were then shared with the other LTFU working groups, and APHL. Dr. Hinton reviewed in detail the matrix that the group developed. The matrix defines three perspectives: families, the medical home, and the state and nation. For each of these levels a list of questions was developed to address the four components of long-term follow-up care. Following the initial brainstorming session, the questions went through several iterations of refinement until the list was finalized. The final list is included in the briefing book.

- Part of the ongoing data collection process will help improve the development of best practices and care plans by physicians.

- The next steps are to:

    - Guide current and future data projects in regions and States to develop systems that incorporate measures to address issues within the four components.

    - Develop specific and measurable indicators for long-term follow-up care after newborn screening—there has been initial discussion with NCQA about using the matrix and questions to develop a framework for the overarching questions

- Assure adequate resources to accomplish the goals of long-term follow-up care after newborn screening, as well as ensure continuing resources for long-term follow-up care in the future—as we talk about data collection, we have to talk about ensuring quality and access and available resources.

Dr. Howell invited comments from the audience.

- Ms. Kay Johnson mentioned that opportunities created by expansion in children's health insurance are a tremendous support to this, especially in thinking of the role of Medicaid and CHIP, and children with special health needs programs, to help build a system of support for children and families.

- Dr. Puryear asked Dr. Boyle where she envisions this subcommittee going with this and what the future role of this Committee is. Is there more of a role for a federal agency funding some of this?

  - Dr. Boyle responded that the subcommittee has not yet had that discussion. The group started down the path of NCQA helping with guidance around measures as a next step, but whether that is in or out of the committee has not yet been discussed. She also thinks there are possibilities for next steps in Ms. Johnson's suggestion.

  - Dr. Kus noted that the system of long-term follow-up care does not have ongoing funding to collect information. This will stimulate the discussion about what can be collected. Then they will have to ask how it can be done.

- In response to a query from Dr. Boyle about the next steps for this paper, Dr. Puryear noted that since it has already been circulated for comments, it can be submitted to the committee for formal endorsement.

- **MOTION #3 PASSED: To submit this paper, "What Questions Should Newborn Screening Long-Term Follow-Up Be Able to Answer?..," to the Secretary's Advisory Committee for formal endorsement for publication. Dr. Coleen Boyle moved and Dr. Tracy Trotter seconded the motion. The motion was approved with 12 YES votes. Three members were ABSENT (Dr. Alan Guttmacher, Ms. Jana Monaco, Dr. Michael Skeels).**

IX. HEALTH CARE REFORM AND IMPLICATIONS FOR GENETICS

Dr. Howell introduced both Ms. Kay Johnson and Mr. Brent Ewig as the next two presenters. Ms. Johnson is recognized for her work in policy and finance in maternal and child health as well as Medicaid policy development. In his role as director of public policy and government affairs, Mr. Ewig works to advance maternal and child health programs by assisting in the development and implementation of the Association of Maternal and Child Health Programs' public policy and government strategies.

A. FINANCING AND STATUS OF REIMBURSEMENT FOR GENETIC SERVICES

Kay Johnson
Johnson Group Consulting, Inc.
Washington, District of Columbia

Ms. Kay Johnson introduced her topic by saying that, in terms of the Affordable Care Act (ACA), there are a lot of unanswered questions about health care reform. Many of the answers will only surface as the politics of the act roll out, but we do know some things about the law and there are opportunities now to think creatively and optimistically.

- The ACA builds on our existing system and policies. It is important think about children with heritable disorders as an important group within the context of a larger child health system. The ACA, builds on the Genetic Information Nondiscrimination Act (GINA), EPSDT, CHIP, and Medicaid. Coverage for children varies greatly state by state. For example, Vermont and Illinois make commitments to cover all children, while in Texas one out of five children is uninsured. Many states are moving rapidly to reauthorize or expand CHIP. We're building on the 1996 federal law that prohibits Medicaid and CHIP from denying children health care coverage based on their health status and building on the newborn screening and genetics programs.

- One in 33 babies suffers from a birth defect and 14% of children have special health care needs. We need to remind ourselves always that there are many groups of children who have conditions that we call by a lot of names and that we divide and categorize in different ways. The divisions are often driven by advocacy, federal funding, or professional units of service. As we think about context, it is important to frame children's health care needs in this larger group of children.

- To advocate with better leverage, we can think of the word advocate as a synonym for promote. We will have more leverage and more opportunities if children and their conditions are not broken into smaller special interest groups.

- In considering issues of accessibility and affordability, the ACA aims to make coverage more affordable for more persons. That includes children, but perhaps not so many children with heritable disorders because they are already receiving care under Medicaid and CHIP programs.

    - It will, however, benefit these children as they transition into adulthood and are able to remain covered on their parents' policies until the age of 26.

    - Lifetime limits are very important to these children as is regulating the payer's ability to drop children who become ill. Some providers have considered heritable disorders pre-existing conditions. The September 23, 2010, patient bill of rights prohibits denial of coverage for children because of pre-existing conditions and bans lifetime dollar limits on coverage.

- The main function of the health insurance exchanges is to give easy to understand standardized information on the available plans.

- The protections around preventive services will bring a lot of discussion. For new plans preventive services rated A or B will have no cost sharing. This will include PKU and newborn screening. A role of this committee is to be sure that PKU screening is considered a preventive service. Attention to the interpretation as the benefits and coverage packages roll out is critical. The DHHS has until the beginning of 2014 to establish an essential standard benefits package.

- As a consumer protection, GINA and the ACA govern certain elements of health insurance, but they do not amend one another. The laws interact and are complementary, not contradictory.

    - In a briefing packet of the congressional research office about how the two laws interact, they found that GINA privacy protections are stronger because GINA is civil rights legislation, that the Affordable Care Act take us farther into protection around health insurance, and that GINA plans cannot adjust premiums or cost sharing based on genetic information and ACA applies only to premium rates. GINA prohibits discrimination by all plans. This analysis is helpful in clarifying those points and Ms. Johnson urges committee members to look carefully at it.

- Benefits in this package, as defined in the law, cover a broad set of categories. The benefits list looks a lot like Medicaid coverage in that coverage includes many things not on the list. The list was not written in detail, but as broad categories that allow specific benefits to evolve. The intention is to provide comprehensive insurance to every American.

    - The genetic services bundle includes screening tests, diagnostics and predictive tests in high-risk populations, genetic counseling, and treatment. Committee members should bear in mind two questions: (1) Where do these fit into the broad categories? (2) What does the U.S. Preventive Services Task Force say about genetic testing and counseling? There is a lot of room for conversation and advocacy for development of a refined set of benefits under the categories as they exist. Of particular concern is what of long-term follow-up care should be financed through public health and what should insurance cover.

    - Lessons about benefits have been learned from the Massachusetts experience. Not every service or treatment will be defined as essential, neither in the benefit package nor by the medical director of the specific plan. The devilish details are described in the medical or clinical policies of the plan. A treatment essential for some may not be essential for all. So, we need to make sure that there is coverage, making sure that the detail is there, but cannot assume that genetics will be listed as a headline of the essential benefit package.

- This legislation provides an opportunity to consider the context of understanding disparities as they relate to race, gender, ethnicity, and heritable disease status. There are concerns about that in today's system.

- The integration of the legislation with public health is an area of fundamental concern. The public health fund builds from $500 in FY 2010 to $2 billion in FY 2015. Obvious questions include: Will funds be committed to genetic and newborn screening? Will child health, and not just adult chronic conditions, be a priority for the spending?

    - This committee will want to make sure that genetics and newborn screening remain on the radar screen of the national prevention strategy.

- Community transformation grants provide an opportunity for evidence-based activities and thinking about projects related to long-term follow-up and building the evidence.

- There are a lot of opportunities for the child health systems under this act. There will be more opportunities as long as we continue to remind people that these strategies need to include pediatric approaches. The ACA may fall short of expectations on any one item, but in many ways it exceeds what most thought might get done through it. The public messages do not begin to scratch surface about the actual potential to improve things like justice and fairness and medical progress.

B. CURRENT EFFORTS RELATED TO IMPROVED FINANCING AND HEALTH CARE REFORM

Brent Ewig
Association of Maternal and Child Health Programs
Washington, District of Columbia

Mr. Brent Ewig declared newborn screening a public health success story. He thanked those in the room for their leadership and work to this arena. In his presentation he provided reactions and perspective, with a focus on implementation, based on the presentation by Ms. Johnson. He explained that, while we are well aware of the politics around health care reform and how it intersects with policy and affects the varying levels of enthusiasm, it is the job of executive branch employees to implement and execute the law and maximize the opportunities.

While there was a lot of initial enthusiasm around the health care act, by the fall it was clear that a number of challenges were being erected at both the federal and state levels. Lawsuits, interpretations, and elections changed the tone. We face unprecedented budget challenges. The level of cuts being discussed on Capitol Hill will cripple several state maternal and child health efforts. The efforts to repeal the law created confusion about how to move forward. In January, the House of Representatives voted to repeal the bill, but the Senate made it clear they will not take it up. It is safe to say that for the next 2 years the statutory framework is safe.

- Funding - where the prevention fund and the link to technical support for newborn screening comes into play. There has already been one attempt to use the prevention fund to offsets other policies (Senate vote, failed); in fiscally tight times, any money not yet obligated is vulnerable. So, we need to track that carefully to ensure those funds remain strong.

- Litigation around the act - a number of states have joined in lawsuits that have challenged the individual mandate. Of the rulings so far, two judges ruled it constitutional, one that it is not. It will go to U.S. Supreme Court for the final say. A Florida lawsuit challenges Medicaid as well as the individual mandate. For children's coverage and the role that Medicaid plays as a primary payer for so many children with birth defects, the future of this suit is of great interest.

- The ACA bill is large and complex with a lot of moving pieces. Those working to implement it cannot succeed by viewing everything as a priority—nothing would get done. With the membership of state MCH leaders, Mr. Ewig breaks the legislation into slices: (1) coverage provisions, benefits provisions, and public health and public health system prevention

investments; (2) immediate opportunities where money is available (mandatory appropriations that were made in FY 2010); (3) intermediate activities, such as policy setting that happens now and developing a long-term focus looking at the 2014 deadlines.

- A big step forward with this legislation's affordability and individual mandate is the elimination of people cycling on and off coverage. Until this point, many states made it hard to get and maintain eligibility for special coverage program. The individual mandate changes that perspective; rather than keeping people off the rolls, the real challenge for states becomes how they design integrated systems between their exchange and Medicaid that assure that not only will people get on but they also will have stable and affordable coverage.

- There are many opportunities in the benefits area. AMCHIP wants to see as many people covered as possible with packages that are as comprehensive as possible that meet the unique needs of women and children, particularly in dealing with special health care needs. If we can design a system that works for special needs, then we will have system that works well for all children (Mr. Ewig credited Dr. Kus with this line). AMCHP is pleased to see the prevention regulations that put the statutory framework for Bright Futures into place as the preventive standard with no cost sharing. Bright Futures states that anything that gets an A or B from the Preventive Services Task Force will be covered for new plans. For children, anything recommended by Bright Futures becomes the standard care, and the standard panel recommended by this committee for newborn screening will be covered with no cost sharing.

    - Now AMCHP wants to make sure the long-term follow-up benefits package is adequate. The department has recently contracted with the IOM to begin that process. They have put together a panel that met a few weeks ago to begin dialog on the scientific basis and process of developing that essential benefits package, knowing that at the end of the day it will be HHS that defines that. There will be opportunities for open comment, and that is where groups such as this committee and AMCHIP will be watching carefully and using the opportunity to comment on a package's adequacy for children with special health care needs.

- Mr. Ewig called everyone's attention to the CMS intervention center created by the law. It has a mandatory $10 billion appropriation over 10 years and will be the centerpiece of the department's efforts to promote medical homes and bundling of payment services to drive more integrated care. In their initial letter, they put out guidance to state Medicaid programs on how to access the money available for the medical home pilots. That will be a driver of innovation in medical home and integrated care.

- The prevention fund is recognition in federal law that public health has been chronically underfunded and needs stability. The early focus will be on chronic disease. To the extent that that promotes good health in women of reproductive age, it will improve birth outcomes. As the fund grows and resources become available, AMCHP wants to make sure an adequate portion goes to maternal and child health.

X. THE COMMITTEE'S ANNUAL REPORT TO CONGRESS

Alaina Harris, M.S.W., M.P.H.
Maternal and Child Health Bureau
Health Resources and Services Administration
Department of Health and Human Services
Rockville, Maryland

Dr. Howell introduced Ms. Alaina Harris who presented a suggested outline for the Committee's report to Congress, which is due April 28, 2011. Ms. Harris explained that this report is required by section 1111 of the Newborn Screening Saves Lives legislation that reauthorized and expanded the activities of the SACHDNC. It requires that, after three years, the Committee publish a report on peer-reviewed newborn screening guidelines, including follow-up and treatment. The legislative intent is to provide a summary of the accomplishments to date and future plans. The goal of the annual report is to outline the next steps for Congress to support state newborn screening programs. This is an important opportunity for the Committee to have Congress's attention.

- Ms. Harris went through the proposed outline for the report, after which she requested comments from the members.

  I. Background on screening newborns and children for heritable disorders

  II. Section 1111

    A. Legislation summary

    B. Overview of the committee, subcommittees, workgroups, etc.

  III. Committee activities [of the previous three years]

    A. The committee's recommended uniform screening panel (RUSP): Summarize the conditions examined and the committee's decision processes

    B. The committee's model decision-matrix and evidence review process

    C. Other committee recommendations

    D. Committee reports and briefing papers

  IV. State of the states' capacity to screen for the RUSP

    A. Information on the heritable conditions that states require and offer in their newborn screening programs

    B. The incidence and prevalence of conditions on the recommended screening panel

    C. Other items related to section 1111(b) 6 of the legislation [The legislation is included in the briefing book for this meeting.]

  V. Implementation of the heritable disorders program (sections 1109–1116 (minus 1111))

    A. Section 1109: Grant program for system infrastructure—HRSA

B. Section 1110: Grant program to evaluate the effectiveness of screening, counseling, or health care services—HRSA

C. Section 1112: Clearinghouse of newborn screening information—HRSA

D. Section 1113: Laboratory quality assurance—CDC

E. Section 1114: Interagency coordinating committee—HRSA

F. Section 1115: Contingency planning—CDC and HRSA

G. Section 1116: Hunter Kelly research program—NIH

VI. Current issues

VII. Future issues

Appendix A: Articles published by the committee

Appendix B: Briefing papers from the committee

- Dr. Kus noted that rather than limit our terminology to a "states' capacity to screen" we need to say "the states' capacity to ensure screening, diagnosis, and treatment." This is a point we need to drive home; it is not just the test, screening requires a lot of work and resources afterwards.

- Dr. Vockley noted that this Committee's task is to recommend the optimal guidelines, but states are dealing with the bricks and mortar of implementation, and clinicians are in the field with no protection. The practitioners are working to take care of all the children the states manage to find. There is a continuum of obligation that begins with this Committee. Only part of the obligation is funding, the rest is the process of making sure the loops are closed. It is difficult for those in the field to see how they are going to implement everything that comes out of this Committee.

- Dr. Fleischman commented that this is a very productive and successful advisory committee with a tremendous future agenda. In the section on future issues, he suggested noting the strong work on implementing the recommendation on SCID and CCCHD and the report on educational planning given by Dr. Trotter.

- Dr. Howell agreed that it has been remarkable to see the states move rapidly ahead in the area of newborn screening. He noted that most of the patients identified with newborn screening have always been there and they were being treated in some way. The screening is not actually finding new patients; it is just identifying them earlier and to the benefit of them, their families, and society.

- Ms. Harris shared a well-received idea to liven up the report. She would like to add text box sections throughout the report of persons who have been positively affected by newborn screening in order to showcase the benefits of the committee's work.

- Ms. Harris reported that the next step is to contract with Ms. Alissa Johnson to pull the report together. A draft will be circulated to committee members in the beginning of March.

- Ms. Harris provided a list of possible current issues for inclusion in the report. They include privacy and confidentiality issues and their public perception, the vast amount of work coming out of the health information exchange, highlights of SCID and CCCHD screening implementation, and the newborn screening awareness campaign.

- Future issues for inclusion in the report include point-of-care testing, timing of screening after the newborn period, infrastructure needs, and integration of screening for heritable disorders through childhood. Dr. Howell asked that they also comment on genetic carrier screening, of which there has been quite a bit of recent activity.

- Ms. Harris concluded by requesting that Committee members please share further comments on this report with her via email or telephone.

XI. REPORT FROM THE CCCHD MEETING

R. Rodney Howell, M.D.
Professor, Department of Pediatrics
Leonard M. Miller School of Medicine
University of Miami
Miami, Florida

Because Dr. Tracy Trotter was unable to join us at the meeting of the CCCHD workgroup, Dr. Howell reported on the meeting.

- In September, the committee reviewed the final draft report of the evidence review for critical congenital cyanotic heart disease and voted to add this disorder to the panel with the understanding that the following activities would take place in a timely manner:

    - The NIH shall fund research activities to determine the relationships among the screening technology, diagnostic processes, care provided, and the health outcomes of affected newborns with CCCHD as a result of prospective newborn screening.

    - The CDC shall fund surveillance activities to monitor the CCHD linked to infant mortality rates and other health outcomes.

    - HRSA shall guide the development of screening standards and infrastructure needed for the implementation of a public health approach to point-of-service screening for CCCHD.

    - HRAS shall fund the development of, in collaboration with public health and health care professional organizations and families, appropriate education and training materials for families and public health and health care professionals relevant to the screening and treatment of CCCHD.

- Committee members were provided with a confidential prepublication document on research done in the United Kingdom on CCCHD screening. The research has extensive data that the workgroup considered along with extensive data from Sweden. (The United Kingdom research results needed to be returned to HRSA before leaving this meeting.)

- The workgroup convened on January 13–14, 2011, hosted by the Heart House, home of the American College of Cardiology. Dr. William Mahle led the meeting. Approximately 35 experts representing 33 participating organizations were in attendance. Invited speakers included Andrew Ewer (United Kingdom), Anne Granelli (Sweden), Marcia Feldkamp, Alex Kemper, Lazaros Kochilas, William Mahle, Gerard martin, Matthew Park, Annamarie Saarinen, and Rodney Howell.

- There was wide support amongst the participants to begin screening. The assembled group reviewed a great deal of evidence, some unpublished, that suggests the number of additional echocardiograms will be small if cut-off thresholds are set appropriately. Messaging is critical. We need to be clear that not every kind of heart disease will be picked up by screening and that some non-cardiac diseases will be identified.

- The group reviewed screening specifications in detail.

    - Using a new generation pulse oximeter is important for reducing the effects of motion sensitivity, thus improving accuracy. Probes placed on both hand and foot measures most effectively.

    - Reusable probes help decrease the cost of screening.

    - Full-term infants should be measured after 24 hours of life for accurate results.

    - Current data suggests that the optimal cut-off value is 95% or a 3% difference between the extremities. More data is needed about the impact of high altitudes on cut-off values.

- Diagnosis and short-term follow-up include an examination to rule out non-cardiac causes and, if called for, an echocardiogram (not all facilities have echocardiography, so consideration for transfer or telemedicine must be considered). Nursery protocols need to be developed before screening begins so there is a consistent pattern for handling diagnosed infants. Dr. Howell commented that one of the few well-organized systems in U.S. medicine is the handling of sick babies. Virtually every small place has a system whereby if the baby has a problem, there is a plan for what to do. This is obviously going to be invaluable.

- Training and education includes protocols for parents to opt in or opt out of screening; training for screeners, newborn care providers, and sonographers; and public and parent education. Some material has already been developed, such as a toolkit developed at Children's National Medical Center. There is a need for a clearinghouse of information.

- Nursery costs include set up (oximeters, probes, systems for diagnostic evaluation), equipment maintenance, screening (time and probes), diagnostic, and insurance coverage (currently there is a code for pulse oximetry as a clinical indication, but not as prevention).

- In the realm of surveillance and quality improvement, the group discussed (1) handling the results of screening and diagnosis, embedding it into electronic records and using existing codes where possible, (2) promoting health information exchanges to facilitate surveillance, (3) having public health programs participate in quality assurance and quality improvement measures, and (4) tracking the impact of screening through birth defect registries.

- The next step is to develop a white paper to describe implementation plans, with specific suggestions on how to do that, and present the paper to this committee. The white paper will, through consensus, develop a screening algorithm; identify the research gaps; structure a central clearinghouse of information for policymakers, health care providers, parents, and the public; and describe the roll out to nurseries once implementation and surveillance plans are in place.

- Dr. Howell summarized the meeting by saying the attendees shared considerable enthusiasm and awareness of what needs to be done to roll out the CCCHD screening and a feeling that there should be substantial effort put into pilot programs. There was general agreement that many systems are already in place to help with handling data that comes out of these programs. He invited comments from the audience.

- Dr. Frederick Chen asked if this effort was already underway before the committee took its action. Dr. Howell explained that the members of the workgroup have been thinking about and doing research on hypoxia for a long time prior to the formation of the committee. They were enthusiastic that the committee had taken it up.

- Dr. Kellie Kelm pointed out that Dr. Mahle was a lead author on the 2009 policy statement that recommended this screening as tertiary care. He felt that the evidence had changed significantly enough in the past 2 years to make it a screening recommendation. She also noted that while most at the meeting were not traditional screening people, one of their key concerns was reducing the false positive rate.

- Dr. Boyle commented that it was interesting to observe the evolution of the cardiologists' thinking through the complexity of false positive results, being very conservative about setting the screening threshold with the idea of trying to do more good than harm. They gave a lot of thought to the complexity of the process for short-term and long-term follow-up. Minimizing the potential impact on the system was the reason a cut-off value for the initial screen was reconsidered overnight.

- Dr. Watson remembered that when the committee reviewed this in September, the recommendation was for a single ductal pulse oximeter reading and asked if that has changed. Dr. Howell confirmed that the workgroup is now recommending measurements be taken from both an upper and a lower extremity. Dr. Puryear added that they are recommending up to three screens be done if the previous one is negative.

- Dr. Howell noted that, since the workgroup meeting, there has been a considerable amount of ongoing communication regarding the cut off.

- Dr. Watson said that it will be important to integrate information going to registries at NHLBI across newborn screening; otherwise it will be confusing, because SCID screening is going to be picking up DiGeorge and other conditions that can be picked up with CCCHD. We need to caution against getting a phenotype without etiology.

    - Dr. Howell does not think anybody had a clear idea that CCCHD would be placed in the NHLBI registry, but they did discuss how those registries would relate to that. The group is very sensitive about how the data will be handled and there will be more discussion on this subject.

    - Dr. Puryear noted that the registry used by cardiac surgeons for every infant who receives genetic testing is better.

- Dr. Kus requested clarification on how the birth defects registries will be able to monitor these outcomes, as that is not something they regularly do, at least not in New York. His concern is capacity across the country. Dr. Puryear noted that, at the workgroup meeting, Dr. Phyllis Sloyer of Florida raised similar concerns. Birth defect registry representatives from Utah and New York were at the workgroup meeting to discuss this. No agreement was reached at that time. Utah has an excellent system that encompasses more than surveillance.

- Dr. Puryear reported the federal agencies (NIH, FDA, CDC, HRSA) will prepare a review of the recommendation for the Secretary.

- Dr. Botkin asked whether and how we acquire baseline data on current practices. It would be helpful to understand the current state of universal screening within birthing centers, perhaps with some sentinel states. He asked if there was discussion on baseline data acquisition to help determine efficacy of implementation of the screen.

  - Dr. Puryear responded that, with Dr. Kemper's assistance, HRS is doing a survey of nurseries, and that there is no specific nationwide baseline data.

  - Dr. Botkin suggested the group consider a way to get that baseline data before the process gets too far along. Information such as what percentage of nurseries are doing what types of screening and what types of pulse oximetry technology they might have would be useful information.

  - As a member of the workgroup, Dr. Zuckerman commented that one of the complexities, and one of the probable needs for better baseline data, that came out during the meeting was that a significant number of children are diagnosed prenatally through other technologies. This will be an unusual newborn screening because ultrasounds will often have identified the problem before birth. We may want to include this issue in evaluating the effectiveness of the screening. The Society of Thoracic Surgeons tries to capture this data in their database. Dr. Howell amended that nowhere near all infants are detected prenatally.

  - Dr. Boyle added that this is where the birth defects surveillance programs come into play. They do capture infants diagnosed prenatally, although not all states do so equally. They would also capture false negatives (children who were missed by screening for various reasons).

- Dr. Boyle returned to an earlier comment suggesting the committee have a representative from the AHA. Such a person would bring expertise to help answer these types of questions.

  - Dr. Puryear pointed out that to do that the committee would have to evaluate its current list of organizational representatives to determine if it provides the expertise needed as it goes forward. They can decide to remove organizations from the committee to bring on others, as appropriate.

  - Dr. Watson cautioned the committee to also consider the Joint Commission if reconstituting the make-up of the committee. The AHA is loath to have any more standards imposed on them; there are huge costs to hospitals. We will want to make sure we have both pieces in play at the same time so we do not bring on a group that is very resistant to the standards before we get the standards in place.

Dr. Howell concluded the presentation by saying that the committee can expect a white paper from the workgroup.

XII. PUBLIC COMMENTS

Dr. Howell opened the floor to public comments.

A. KELLY LEIGHT, Preserving the Future of Newborn Screening Coalition

Kelly R. Leight, J.D.
Preserving the Future of Newborn Screening Coalition

- Thank you Dr. Howell and committee members for allowing me to address you today.

  As a parent of child with a genetic disorder and the coordinator of Preserving the Future of Newborn Screening, a coalition of parents, health care and public health professionals, corporations and other interested individuals passionate about newborn screening education, I urge the committee and the Secretary of Health and Human Services to promptly approve and implement a national program to educate the public about newborn screening. I also urge that sufficient funding be appropriated to ensure the sustainability of educational efforts and so that a broad-based communications strategy can be implemented. In particular, we must make sure that any strategy can reach our non-English speaking populations and those without access to the Internet or cell phones.

  Based on testimony we have heard today and discussion in the education committee, there is an urgent need for prenatal education about newborn screening. Providing information in the hospital after birth is wholly inadequate. Mothers are not able to absorb information about newborn screening when recovering from childbirth. Right now, this is when information about newborn screening is provided, if it is provided at all.

  Moreover, groups with political agendas have been spreading disinformation about newborn screening and about the safety and security of newborn blood spots and infants' screening information. Unfortunately, news headlines like "The Government has Your Baby's DNA" are becoming more and more common. Some parents are developing a distrust of the newborn screening programs and the entire newborn screening process as a result of bad information.

  The solution is providing accurate information during the prenatal period about the newborn screening process and its benefits to our children, along with information about each state's storage and use policies. I strongly urge the committee to integrally involve prenatal caregivers such as the American College of Obstetrics and Gynecology, the Association of Women's Health, Obstetric, and Neonatal Nurses, and the American College of Nurse Midwives in the process to ensure buy-in from them and obtain their cooperation in providing educational efforts.

  As a final point, I would like to ask that our coalition and its members be included in or consulted during phase one of the educational efforts. We have a strong interest in and have given a lot of thought to the issue of prenatal education about newborn screening, and we may be able to provide a specialized viewpoint in the planning of an educational campaign.

Thank you very much.

Dr. Howell thanked Esq. Leight for her comments. He commented that she mentioned a group we have not heard a lot from, the nurses. Nurses are the primary informers about health care and Dr. Howell believes that we need to hear more from them.

B. JIM BIALICK, Newborn Coalition

Jim Bialick
Executive Director
Newborn Coalition
Washington, District of Columbia

- Thank you very much for this opportunity to comment. The Newborn Coalition was lucky enough to be involved in the congenital heart defect workgroup before this and saw the great consensus that was reached by many professionals in the community as well as some of the amazing projects that are underway nationwide and in some major centers that can be great examples of what we are working for.

  I'm going to speak directly to my expertise, which is more on the technology and policy side. I want to talk about the recommendation and some of the nuance policy measures that are taking place, and how we can work within the recommendation to make sure that the needs of many of the states that are sometimes held up by legislative nuance can be moved forward.

  Adding to the core panel, the states, through their own language, can mandate the level of follow up that takes place on the state level. Dr. Howell showed in his presentation that the follow up in the short term actually takes place at the point of care. That is on the provider and has always been on the provider. This is not shifting it through legislative change. This is expected as a normal part of the process. We are not saying remove public health from the process, at all. We are just saying, revise its role when it is not a blood spot. We are talking about something different here.

  The addition of the newborn screening panel can be called an examination at a point in care, an evaluation for the purpose of the recommendation. So, we are talking again about the nuanced difference between a screen and an evaluation at the point of care. I think that is a very interesting issue and a very important issue to discuss when it comes down to the nuance language of state law. Augmenting existing terminology does alleviate some of the issues, but it is not a catchall. Indiana was brought up yesterday as an example where some of the things that are added as the screen are then required to be looked at under a different lens, and if it was a point-in-care evaluation, there are many states like that. I think that bringing this up that is slightly different, again, it is part of the nuanced screening program, but it is not a blood spot screening, so treating it differently.

  Organizationally, we are working in short order to develop briefing and education materials to show the difference between metabolic screening and a point-in-care exam. We think this is something that, with the permission of the advisory committee, can be circulated that will show there are some differences that would easily alleviate some of the issues we are dealing with on a state-by-state basis, but as well, draw the clear distinction that we are discussing here.

We look forward to working with the committee further and working with the subcommittee on congenital heart defects. Thank you.

C. ANNAMARIE SAARINEN, Newborn Coalition 1in100

Annamarie Saarinen
Founder
Newborn Coalition, 1in100
Shoreview, Minnesota

- Thank you Dr. Howell and committee for your diligence, process, and hard work to look at critical congenital heart disease. It is not an easy one, it is different, and it changes the paradigm a little bit. I am very grateful for that work. I am also grateful for the implementation workgroup and allowing my participation and that of Jim and the health IT geeks who are trying to fight our way through this process and make it actually easier on everyone, including the state department of health folks, who by the way I have the utmost respect for. I have worked on a dozen projects over the years with these fine people. I think their role is going to be critically important. The first call I made when I wanted to see if this was a possibility to do a statewide screening program for critical congenital heart disease was to our state department of health and their newborn screening folks.

  The title of your committee does not include the words metabolic or genetic. I know that is much of the work you do, but let's recognize that there are other things that affect newborns and children that are critically important and, I believe, are the charge of this workgroup that fall outside of blood spots. So, if we can remember that as we move forward and know that not everything is going to fit into the same box, but there is still good collaboration and great work being done. So, thank you again.

Dr. Howell thanked the speakers for their comments. He asked if there were any other items of business that should come before the committee. There were none.

XIII. ADJOURNMENT

In closing, Dr. Howell announced that the dates of upcoming meetings are May 5–6, 2011, and September 22–23, 2011. Please forward your agenda items to Dr. Michele Puryear.

- **MOTION #4 PASSED: To adjourn the meeting. Dr. Tracy Trotter moved and Dr. Jeffrey Botkin seconded the motion. The motion passed unanimously with 10 YES and no abstentions. There were five absences (Dr. Dougherty, Dr. Guttmacher, Ms. Monaco, Dr. Ohene-Frempong, and Dr. Skeels).**

- The meeting was adjourned at 2:30 p.m.

We certify, that, to the best of our knowledge, the foregoing meeting minutes of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children are accurate and correct.

/S/_____/S/_____

R. Rodney Howell, M.D. — Michele A. Lloyd-Puryear, M.D.,Ph.D.

SACHDNC Chair — SACHDNC, Executive Secretary

The committee at its next meeting will formally consider these minutes, and any corrections or notations will be incorporated in the minutes of that meeting.