Secretary's Advisory Committee on

Heritable Disorders in Newborns and Children

Summary of 22nd Meeting

September 16-17, 2010

Washington, DC

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children was convened for its 22th meeting at 8:30 a.m. on Thursday, September 16, 2010, at the Washington Marriott Hotel in Washington, DC. The meeting was adjourned at 2:50 p.m. on Friday, September 17, 2010. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments.

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Contents

I. Welcome and Committee Business

Thursday, September 16, 2010

R. Rodney Howell, M.D.
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Leonard M. Miller School of Medicine
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Dr. Rodney Howell welcomed Dr. Jeff Botkin and Dr. Joseph Bocchini as newly appointed members of the committee. He also welcomed Dr. William Hogge as the new organizational representative for the American College of Obstetricians and Gynecologists. Dr. Hogge is currently the chair of the ACOG Committee on Genetics.

Dr. Tracy Trotter moved to approve the May 2010 Committee Meeting minutes and Dr. Gerald Vockley seconded the motion. The minutes were approved unanimously, with one member absent (Dr. Alan Guttmacher).

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

- The Secretary of Health and Human Services, Kathleen Sebeilus, wrote to the committee to announce that the department will adopt the committee's recommendations for a Uniform Screening Panel of 30 core conditions and 26 secondary conditions. She notes that this will now be a national standard. She also requested report on the status of states' implementation of SCID screening by May 2011.
- Yesterday, the Newborn Screening Translational Research Network held a workgroup meeting regarding the SCID trial.
- In October, the Newborn Screening for Severe Combined Immunodeficiency Implementation Challenge will be hosted by CDC, APHL, and HRSA.
- The California Department of Health sent information concerning a pilot study of SCID that began last month. After the mandated screen is complete, they will use TRECS followed up with flow cytometry. The positive screens will be reported to the primary care physician and referred to one of two specialists. It is expected to last for 18 months and will include approximately 800,000 specimens.
- Dr. Michael Watson commented on American College of Medical Genetics' meeting for the Newborn Screening Translational Research Network. Attendees included all of the states involved in the NICHD funded pilots and/or the CDC funded pilots. During the meeting, the group focused on standardization, sorted through the protocols for screening, and looked at the follow-up issues such as ensuring that there are networks of providers available in the pilot areas and nationally. Wisconsin and Massachusetts have been funded for three year projects by the CDC and are approaching the end of the second year. NICHD funded a subcontract to New York State to screen additional patients from Puerto Rico in a Massachusetts lab. The Wisconsin lab will be screening some patients from Louisiana. Finally the California screening pilot is ongoing.
- The Patient Protection and Affordable Care Act signed into law on March 30, 2010 and on July 14, the Departments of Health and Human Services, Labor and Treasury issued an interim final regulation. The Committee's recommended screening panel is covered under the interim final regulations as a preventive service.

- The committee sent a letter to the Secretary that included the White Paper on health care reform. The Secretary will either need to approve or disapprove by September 19. The committee also sent letters to the Secretary about insurance coverage of medical foods.
- The committee also sent a letter to the Secretary about Sickle Cell Trait and the NCAA recommendation that all athletes be screened for SCT. The letter went out before the final report because the issue is timely.
- The committee received the latest version of the NCC Collaborator, which includes a draft of the Institute of Medicine's workshop on handling dried blood spots.
- The committee recognized and thanked committee members, Ms. Jana Monaco, Dr. Kwaku Ohene-Frempong, and Dr. Michael Skeels, whose terms expire at the end of September.

II. Report on Briefing Paper from the Sickle Cell Disease Carrier Screening Workgroup--Draft

Kwaku Ohene-Frempong, M.D.
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Director-Emeritus, Sickle Cell Center
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Dr. Rodney Howell introduced Dr. Kwaku Ohene-Frempong and explained that this is the second presentation that the committee has heard on Sickle Cell Trait (SCT) screening for college athletes and the implications of this requirement on policies and practices on the public health system. At this meeting, Dr. Ohene-Frempong is providing an update on the workgroup's findings as they prepared an extensive briefing paper and recommendations for the committee to vote on before they go to the Secretary of Health and Human Services.

- SCT is a common genetic condition that arises due to the inheritance of a normal Beta A hemoglobin gene from parent and a Beta S or sickle hemoglobin gene from the other parent and forms part of a group of disorders called hemoglobinopathies, the most common genetic diseases in humans. Each red cell contains both hemoglobins A and S, but in SCT there is always more A than S, which is what makes the condition a benign condition. However, when people with SCT are subjected to strenuous exercise under ambient conditions of high temperature and water depravation, it is possible for some of their red blood cells to sickle because some of the assembled hemoglobins are induced to polymerize.
- It is estimated that over 300 million people in the world have SCT. The highest prevalence rates are in Sub-Saharan Africa where about 15% of 800 million people have SCT. There are also regions of India with very high prevalence of SCT and it is present in the Middle East, Caribbean and South America. Approximately 1.31% of newborns in the United States have SCT which means more than 4 million people in the United States are living with it. By contrast, it is estimated that Nigeria has more than 30 million people with SCT.
- Unlike Sickle Cell Disease, SCT has no pattern of key risks or inclusive events. People with SCT do not get pain crises. However, starting three or four years of age, they may have the inability to concentrate urine (hyposthenuria) due to the loss of renal medulla cell because of sickling.

- In 1979, Heller and colleagues reported on the health consequences of SCT in the New England Journal of Medicine. They looked at 65,000 consecutively admitted black male patients in 13 VA hospitals. The study concluded that Sickle Cell Trait had no effect on average age at hospitalization or death, overall mortality, length of hospitalization on medical or surgical wards or frequency of any of the common major diagnoses. However, they found a positive association between SCT and essential hematuria, hematuria of otherwise unknown cause and pulmonary embolism. Venousthromboembolism was substantiated in a more recent study. There are several instances of people with SCT experiencing splenic infarction at high altitudes and many reports of exercise or heat related sudden death in people with SCT.
- John Clark and colleagues first reported sudden heat or exercise-related deaths of people with SCT in 1987 after they conducted a retrospective review of five years of medical records data on 2.1 million enlisted recruits. The deaths in this group that occurred during basic training were classified as either non-sudden, sudden explained or deaths unexplained by pre-existing disease from autopsy and clinical records. Out of these 2.1 million people, there were 37,300 recruits with Sickle Cell Trait who were classified as black and another 1,300 with Sickle Cell Trait classified as non-black.
- From 1982 to 1991, Kark conducted an intervention study in certain military training centers to restrict strenuous exercise for all center recruits in high heat conditions and to ensure the recruits were drinking the prescribed amount of water. Over the 10 year period, 2.3 million recruits trained in the centers participating in the intervention. Out of the total group, 40,000 had SCT. Statistically, there should have been 15 deaths amongst the SCT group; however, there were none. In the non-Sickle Cell Trait group the statistical prediction was that there would be 19 deaths; however, there were 11. For the training centers that did not participate in the intervention program, the death rates were the same as had been reported previously. The conclusion was that this simple intervention of increased hydration and careful monitoring of ambient temperature and humidity were effective in preventing deaths.
- There have been many single cases of sudden death in people with SCT reported in the mass media. In many cases, the hemoglobin diagnosis was not entirely clear since it was made post-mortem and we do not know if a test was conducted on the actual hemoglobin during the autopsy.
- Sudden exercise-related death most commonly occurred in college football players but it has been seen in other sports as well and the majority of people affected are male. There have not been any large epidemiologic studies of these deaths or any trials of simple interventions to reduce the risk of heat related illness.
- The Journal of Applied Physiology published an article called “Point, Counterpoint Sickle Cell Trait Should or Should Not Be Considered Asymptomatic and as a Benign Condition during Physical Activity”. It included reporting on several teams in the United States, Caribbean and Africa, where the representation of SCT people at national level or college level athletics was the same as in the general population. The counterpoint presented anecdotal cases of injury or deaths in people with SCT.
- The NCAA enacted some major policy changes due to the case of Dale Lloyd II, who was a football student-athlete at Rice University and who collapsed after 16-100 yard sprints in September 2006 and died one day later in the hospital. The official autopsy listed the cause of death as acute exertional rhabdomyolysis, secondary to SCT. Lloyd had been screened as a newborn and diagnosed with SCT, but was not aware of this at age 19. The family sued Rice University, the football coach, and the NCAA and two nutritional supplement companies for wrongful death. The case was settled out of court, the NCAA agreed to amend its Sports Medicine Handbook Guidelines, section 3C, to state that while SCT screening is normally performed on all U.S. babies at birth, some student athletes may not know if they have the trait.

The NCAA donated $50,000 to the Sickle Cell Disease Association of America, contributed $10,000 to a scholarship fund in the name of their son, and prepared an educational video about SCT for their website.

- The NCAA also introduced new regulations regarding SCT screening for their athletes in April 2010 for Division I athletes only, requiring that they either be tested for SCT, show proof of a prior test, or sign a waiver releasing an institution from liability if they decline to be tested. The rule is taking effect in the 2010-2011 academic year. NATA, the National Athletic Trainers Association, also made a set of recommendations that athletes with SCT should:
    - Build up the intensity of their training more slowly with pace, progression, and longer periods of rest and recovery between repetitions.
    - Undergo strength and conditioning year round so that they do not de-condition prior to returning in the preseason.
    - Be excluded from mile runs or sprints.
    - Cease activity on the onset of symptoms and set their own pace. The NATA handbook goes on to describe the symptoms that these athletes and trainers should look out for. It also describes adjusting work cycles and educating the athletes to report any symptoms.
- Perhaps these recommendations will have an impact on the newborn screening programs as student-athletes go back to seek the results of their newborn screening. Not all states' screening programs will be able to provide information on a screening that was conducted many years ago in addition to the appropriate counseling.
- The NCAA recommends the simplest, cheapest form of screening, which is a solubility test or a sickling test. However, a positive result only suggests that the patient has an appreciable amount of Hemoglobin S is the red cells but is not an actual diagnosis of SCT. In addition, it misses other abnormal hemoglobin conditions. The NCAA suggests that a positive solubility test should be followed by a more definitive test.
- The SCT Workgroup believes that there is a need for proper counseling for the athletes both before testing and also after testing based on their results, which the athletic departments are not likely to provide. In addition, there are significant concerns about the privacy of the athletes' health information. Finally, there is concern about discrimination based on genetic information.
- The SCT Workgroup made the following recommendations:
    - All individuals should have the opportunity to find out their risk for various medical disorders including their SCY status.
    - Genetic testing should not be a prerequisite for participation in sports.
    - Evaluation and testing for Sickle Cell Disease and other genetic conditions should take place within the individual's medical home.
    - Evaluation should include counseling regarding the implications of the information for the individual and assurance of the privacy of genetic information.
    - All potential athletes should be educated on safe practices for prevention of exercise and heat related illnesses as part of their medical evaluation for participation in organized sports.
    - Athletic programs should apply universally simple measures successfully used to prevent exercise and heat related deaths in student-athletes, similar to military recruits.

- The Secretary of Health and Human Services should instruct this Committee to work with the Sickle Cell Disease Association of America, relevant Federal agencies including NIH, HRSA, CDC, the athletic associations, community based and health care professional organizations to develop guidelines and educational resources about screening for Sickle Cell Trait in all persons including athletes.
- The National Institutes of Health and the Center of Disease Control and Prevention conduct and support research to ascertain if some athletes with Sickle Cell Trait are at increased risk of exercise related sudden death.

- The NIH convened a special meeting in June to develop a research agenda on SCT and sudden death. The current issue of the New England Journal of Medicine has an interesting article by Bonham, Dover and Brody on screening student athletes for SCT that discusses some of the ethical and social issues. The Sickle Cell Disease Association of America will devote a special session to SCT at their annual convention in Washington next week.
- Dr. Michele Lloyd-Puryear remarked that NIH, the Genome Institute and HRSA have begun an evidence review of the literature around health outcomes for individuals with Sickle Cell Trait and should have the preliminary results in time for the next Committee meeting. HRSA plans to publish the results.
- Dr. Rodney Howell asked if the SCT Workgroup planned to publish the report. Dr. Ohene-Frempong responded that they would publish the report if the committee desired.
- Dr. Jeff Botkin asked for clarification on the discrepancy between the first bullet in the letter to the Secretary and the wording on the slide. He preferred the phrasing "all individuals should have the opportunity to find out their risk" rather than "all individuals should know their risk" because the latter is too broad.
- Dr. Frederick Chen asked when the recommendations were refined and Dr. Lloyd-Puryear replied that it occurred after the last meeting.
- Dr. Coleen Boyle questioned whether or not the committee should address the liability issues that are behind the new NCAA policies. Dr. Christopher Kus commented that the report suggests that all athletes (SCT or non-SCT) should adhere to healthy practices Dr. Rodney Howell stated his belief that the committee's recommendations should be based on the best scientific information and not merely a reaction to a legal settlement. Dr. Tracy Trotter concurred and observed that the committee's recommendation could affect legal liability.
- Dr. Michael Skeels observed that in the process of conducting a thorough medical exam on a potential athlete (as suggested in the proposed recommendations), the examining physician may decide to order genetic test. He was concerned that the wording implied a prohibition on genetic testing during the regular medical evaluation even if the physician felt it was necessary. Dr. Michele Lloyd-Puryear reminded the committee of historical precedents of requiring Sickle Cell Disease testing as a pre-requisite for jobs, insurance and marriage licenses. She suggested adding a clarifying sentence to the bullet to assure physicians that it is their decision to conduct genetic screening if they feel it is necessary.
- Dr. Nancy Green remarked that, unlike the military recruits intervention example, the NCAA is not setting up any mechanism to measure outcomes. She asked the committee to consider making a recommendation about evaluation of outcomes.

MOTION #1 PASSED: To publish the paper on Sickle Cell Trait Screening in College Athletes. Dr. Tracy Trotter moved and Dr. Rebecca Buckley seconded the motion. The motion was approved, with 14 YES votes. One member was ABSENT (Dr. Alan Guttmacher).

MOTION #2 PASSED: To send the paper and recommendation on SCT screening for College Athletes to the Secretary of Health and Human Services Dr. Tracy Trotter moved and Dr. Rebecca Buckley seconded the motion. The motion was approved unanimously, with 14 YES votes. One member was ABSENT (Dr. Alan Guttmacher).

- Dr. Ohene-Frempong remarked that following the successful intervention with military recruits, the military no longer requires SCT screening.

III. SACHDNC's Role in Meaningful Use

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Sharon F. Terry, M.A.
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Dr. Rodney Howell introduced the co-chairs of the Health Information Technology Workgroup, Dr. Alan Zuckerman and Ms. Sharon Terry and explained that they would be reviewing potential quality measures for newborn screening and the committee would be asked to approve a letter to the National Quality Forum (NQF) regarding measures proposed by CDC, HRSA and NCQA.

- Ms. Sharon Terry explained that HITECH, the Health Information Technology for Economic and Clinical Health Act, authorizes the Department of Health and Human Services to establish programs to improve health care quality, safety, and efficacy through the promotion of HIT, Health Information Technology. Under HITECH, eligible health care professionals and hospitals will qualify for Medicare and Medicaid incentive payments when they adopt certified EHR technology and use it for specified objectives. The Health IT Workgroup would like to ensure that newborn screening is part of those objectives. The incentives are as follows:
    - Meaningful Use Objectives are issued by CMS to define minimum requirements that providers must meet to qualify for bonus payments. The program is organized in three phases—2011, 2013 and 2015. Providers are required to report data, measure quality, and improve quality. The measurements are patient focused and directed towards care coordination.
    - The Office of the National Coordinator for Health Information Technology (ONC), issues standards and certification criteria for the technical capabilities required for EHR technologies.
- During the first phase of the Meaningful Use Objectives, there are three population health activities— sending immunization data to an immunization registry, reporting disease surveillance and sending lab data from hospitals to public health to monitor disease patterns such as influenza. Objectives for newborn screening could be added to the second phase as long as the specific quality measures are available and tested. The committee already submitted comments to CMS in May and they were well-received.

- The Meaningful User Objectives program would need assistance from this committee in maintaining an up to date problem list of current and active diagnoses, incorporating clinical laboratory test results into the EHR as structured data, and reporting clinical quality measures to CMS and the states. The items most relevant to Newborn Screening are:
    - Generate lists of patients by specific conditions for quality improvement;
    - Send reminders to patients for preventative and follow-up care; and
    - Provide patients with timely electronic access to their health information.
- There are many entities with a role in developing and implementing measures:
    - Expert panels: define what the standard of care might be
    - National Committee on Quality Assurance (NCQA): translate standards of care into actual data measures
    - National Quality Forum (NQF): review measures and develop candidate lists of approved measures
    - ONC and CMS: select measures from candidate lists for incentive programs and other types of regulations. Following implementation, they will review the reports and apply the appropriate incentives.
    - State Newborn Screening Programs: implement the measures
    - Providers of care in hospitals, ambulatory practices and specialty clinics: implement the measures
    - JCAHO: require active participation in quality improvement efforts for hospital certification and maintenance of certification under many specialty societies.
- The NQF is currently conducting a special initiative on child health quality measures and this committee submitted 11 measures dealing with newborn screening. They require that the proposed measures be in the public domain, a particular entity has ownership or stewardship to maintain and update the measures and the measures play a role in quality improvement. They would also like the measures to be tested prior to submission, but there is a exemption currently to give providers an opportunity to use and apply the measures. Finally, NQF would like to see evidence that there are quality problems in newborn screening and that the measures represent an opportunity for improvement.
- The majority of EHR Meaningful Use Objectives address the process of care, but there are additional opportunities to look at outcomes and at the patient experience. NQF has detailed criteria on scientific acceptability including validity, reproducibility, usability and feasibility. The proposed measures should describe quality and be understandable to laypeople. NQF is particularly interested in electronic quality measures that do not add to the cost of care because they are generated as a bi-product of care and are already available in existing sources.
- HRSA is attempting to add a measurement of the percentage of children that fully comply with all of the state mandates. For this effort, it is critical to be able to define the denominator and to define any exclusions in the numerator.
- NCQA is introducing a very new set of measures based on the medical home. They are reviewing the charts of six month old infants, to look for documentation both the metabolic and hearing screening in the chart along with documentation of additional testing and referral. Unfortunately, by reviewing at six months, they might be catching problems that should have been corrected much earlier.

- What is the appropriate role for this Committee in this process of introducing quality measures? Ms. Terry and Dr. Zuckerman proposed the following possible roles for the committee:
    - Recommend use of specific measures for newborn screening.
    - Urge the Meaningful Use incentive programs to include specific newborn screening measures as a part of the Population Health Meaningful Use Measures for 2013.
    - Encourage the development of the follow-up and treatment quality measures. Other organizations could be encouraged to make newborn screening as part of their quality improvement agenda. For example, JCAHO has great potential to influence the role of hospitals in short term follow-up.
    - Encourage organizations to fill in the data gaps about newborn screening quality. There is some evidence that the quality of newborn screening varies. Is there evidence that there are health disparities in newborn screening? Is there evidence that risk adjustments in clinical exclusions are needed to measure the quality of newborn screening?
    - Add outcome measures to the current process and structure measures.
    - Address barriers to the implementation of quality measures. For example, pooling funds from different federal agencies and different categorical disease programs may speed the adoption of HIT.
    - Provide input into addressing privacy for EHDI data collection and sharing. Integration of child health programs such as immunization registries, lead screening and newborn screening may facilitate quality improvement.
- Ms. Terry and Dr. Zuckerman asked the committee to decide whether or not it should take on new roles of recommending specific quality measures; if it should make specific recommendations to NQF at this time; and if it should encourage the Follow-up and Treatment Subcommittee to continue developing quality measures and filling data gaps. Dr. Rodney Howell suggested that the HIT Workgroup return the following day with a specific list of concrete items where Ms. Terry and Dr. Zuckerman believe the committee can provide assistance.
- Dr. Ned Calogne remarked that the committee cannot decide whether or not it should be involved in the effort until it has a chance to see some measures but he believes that there is a role for this committee in recommending some quality metrics around newborn screening.

IV. Development of Coding Standards for Newborn Screening Tests

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Newborn Screening and Molecular Biology Branch
Centers for Disease Control and Prevention

Clement McDonald M.D.
Lister Hill National Center for Biomedical Communications
National Library of Medicine
National Institutes of Health, HHS

Dr. Rodney Howell introduced Dr. Carla Cuthbert, the Chief of the Newborn Screening and Molecular Biology branch at the National Center for Environmental Health at the CDC and Dr. Clement McDonald, the Director of the Lister Hill National Center for Biomedical Communications at the National Library of Medicine. They are representing the Vocabulary and Coding Team.

- Dr. Cuthbert explained that a key goal of the group was to expand the newborn screening coding and terminology guide to include new requirements for data coding and language standardization. The initial project is to request new LOINC variable codes for the screening methods currently in place for SCID and Lysosomal Storage Disorders. Also, they would like to request new LOINC newborn screening answer codes for the hemoglobinopathies.
- The LOINC code request process involves submitting a name, what the submitter believes the name should be of the particular condition or test, and a brief description of the condition or of the test and its use, the clinical significant of the disease or the test, the usual units of measurement for the test, and the typical normal range for the test. The formal LOINC code will also include the component, property, timing, sample, scale and method. The LOINC users' guide, which is posted on their website is a guide to the codes.
- LOINC has designated the first part of the formal name to be the name of the analyte that is measured rather than component used to measure. Sometimes there are other components to the test that are not relevant to newborn screening. The second part of the formal name is the property or the quantity that is being observed. For the most part, newborn screening measurements will be PT, or one particular point in time. The next part of the formal name is the scale of measurement, which will sometimes be quantitative or ordinal and sometimes narrative (for example, color). The last part of the formal name is the method, which is only used when there is a distinction between two or more tests that measure the same component.
- For example, a SCID submission would look like the following: SCID is characterized by the absence of both humoral and cellular immunity at least 15 different genes are known to cause SCID when they are mutated. Patients with SCID have very profound defects in T lymphocyte differentiation and function. As maternal antibodies decrease during the first few months of life, the affected infants will develop infections due to common and opportunistic pathogens. Treatment and prevention of infections can prolong life. The best hope for these patients is hematopoietic stem cell transplantation before the onset of infections.
    - TREC stands for T-cell Receptor Excision Circles, which are bi-products of the rearrangement of t-cell receptor genes during thymocyte maturation in the thymus. They are episomal and don't replicate during mitosis. Peripheral blood TREC levels reflect t-lymphocyte production in the thymus.
    - The assay used to detect SCID is real time PCR. There are variations in the TREC assay procedures based on primer selection and probes and on DNA extraction procedures.
    - The proposed coding name is is TREC, which stands for the t-cell receptor excision circle. The property is a number concentration because the TRECS are always reported as the number of TREC copies per microlitre. Timing is defined as a sample taken at a specific moment in time. Blood filter paper is the sample type; the scale of measurement is a quantitative assay; and the method is PCR.
- There are two main approaches for evaluation of newborn screening for lysosomal storage disorders, which both include mass spectrometry and fluorometry. For mass spectometry evaluation, substrates have been provided for Fabry, Gaucher, Krabbe, Neimann-Pick A/B, and Pompe. Fluorometric evaluation involves four substrates. For mass spectrometry assay, there are separate incubations of for each of the reactions for the different diseases. They are incubated in terms of the assay for 20 hours and then combined; they undergo liquid extraction, solid phase extraction, elution, drying and are placed on the mass spectrometer.

    - In the mass spectrometry example, the component would be an acronym for the different diseases. The property is that of catalytic concentration because they are reported as milimoles per liter per hour; timing is defined as a sample taken at a specific moment in time; the sample type is blood filter paper; the scale of measurement is quantitative assay; the method is mass spectrometry, but at this time there is not a LOINC-recognized name for this.
    - In the fluorometry example, there is an assay in which the blood spots are incubated with a stop buffer, which increases the PH. This is evaluated by fluorometry. The property is a catalytic concentration reported in milimoles per litre per hour; timing is defined as a sample taken at a specific moment in time; sample type is blood filter paper; scale of measurement is quantitative assay; the method is fluorometry, but at this time there is not a LOINC-recognized name for this.

- There are method codes in place for hemoglobinopathies; however, new answer codes are needed. There was a harmonization meeting held in Oakland in May. Fifteen states intend to request new answer codes for differences in reporting newborn screening results in the hemoglobinopathies. Dr. Cuthbert and Dr.McDonald believe that this committee should appoint a task force that will report to the HIT Workgroup, to develop a draft White Paper on hemoglobinopathy answer codes.
- Dr. McDonald presented on the progress and success with the HRSA/NLM guidance for messages about newborn screening. A paper will be published in November to describing the process and show some real examples. The objective is to increase the use of quantitative reporting and improve reporting from largely non-structured, narrative for newborn screening to structured reports that are standardized and universally interpretable.
- The task force has worked with PHII to integrate order, specifications and their previous work in this area. The standards for structures are HL7v2.5.1. New LOINC codes are being proposed for the questions or the variable and SNOMED CT codes are being proposed for the answers.
- The three major vendors, Perkin Elmer, Natus/Neometrics and Oz Systems, that cover approximately 65% of laboratories in the United States have quickly have adopted the standards and can show examples of the real messages coming or going. Pennsylvania is currently sending standard LOINC codes and Kentucky will add them on November 1. New York State is trying to connect individual hospitals to HIE. Iowa and Texas have legacy electronic interfaces for newborn screening, which will be updated in the near term. Indiana has an interaction set up between the laboratory and the public health system. Colorado, Ohio and Utah also are working towards these goals.
- The least difficult communication pathway is between the newborn screening laboratories and health information exchanges or other equivalent web services and regional centers. The greater challenge is communications between newborn screening laboratories and hospitals and individual practitioners. One challenge is that the baby's name is not always known at the time the sample is taken. Also, hospitals are facing many new standards and requirements such as ICD10. Finally, hospitals are accustomed to standing orders, rather than orders and results.
- Dr. McDonald believes that if newborn screening and reporting back was part of Meaningful Use, it would get much more attention and be implemented faster. There is also a lot of activity in the field to develop follow-up variables.
- Dr. Rodney Howell asked if there were specific actions the committee could take to assist with the work. Dr. McDonald responded that the main item would be to raise the visibility of newborn screening particularly for organizations such as ONC, so it remains on their agenda. It would also be very helpful to have newborn screening as one of the Meaningful Use reporting standards.

- Dr. Lloyd-Puryear asked what activities were ongoing for point of care or point of screening activities such as hearing screening. Dr. McDonald replied that hearing screening was part of the package and that the task force was collaborating with CDC. Hearing screening is simpler because there are only 2-3 variables and no specimens that need to be sent away to a laboratory.

V. Committee Report on the Retention and Use of Residual Dried Blood Spot Specimens After Newborn Screening

Alissa Johnson, M.A.
Principal Consultant
Johnson Policy Consulting

Dr. Rodney Howell reminded the committee that there has been concern about the use of residual dried blood spots for some time. For example, a report on residual dried blood spots that was completed in May was posted for public comment and received a large number of comments. Ms. Alisa Johnson analyzed the public comments and worked to incorporate them, as appropriate, into the final report.

- Ms. Johnson thanked Ms. Lisa Vasquez and Dr. Michele Lloyd-Puryear for assisting her with sorting through and analyzing the public comments. Approximately 550 individuals and 13 organizations submitted comments. Groups of commenters felt that the report:
    - Recommends the Committee "simply" develop national guidance for consent or dissent for the secondary use of specimens
    - Asserts a public claim on the DNA of newborn citizens
    - Claims that "newborn blood" is necessary for "population surveillance"
    - Claims that newborn screening test development is not research
    - Claims that state screening programs are charge with "stewardship" of newborn DNA samples—ensuring "appropriate use"—rather than charged with "simply" testing each newborn
    - Fails to recommend informed written consent requirements for the storage and use of "newborn DNA" for research and other purposes.
    - Does not support the 22 state genetic privacy laws and the 5 state genetic ownership laws that may or do require consent
    - Does not include public opinion data from the University of Michigan study regarding "unconsented" storage and research
    - Recommends parent education instead of informed parental consent, which would enforce the education
    - Interpretation that the recommendations for the storage and use of "newborn DNA" do not acknowledge the consent, privacy, parent and DNA property rights of the individual
    - Belief that the committee is advocating for the expansion of government power over the individual's "most intimate property"

    - Opinion that the recommendations advocate for the reduction of constitutional rights of individual citizens, and as proposed, do not comply with the legal individual rights and informed written consent requirements as secured by the Fourth Amendment privacy and property protections.
    - Perception that the committee seeks to establish and support government banking and ownership of "citizen DNA" at birth through the creation of 50 state government DNA warehouses for nationwide genetic research on the American public without the informed, written consent of citizens.

- The writing team added language to the final version of the paper to address the commenters' concerns. Namely, they tried to explain what the standard uses for residual blood specimens versus other uses. They believe all uses of residual blood specimens should uphold the core principles of benefitting infants, families and society. The other uses should not weaken or interfere with the regular program activities of newborn screening programs.
- Some sections were renamed and the paper was reorganized with separate sections on international policy, federal policy and state policy under ethical, legal and social issues. The writing team also highlighted and added to sections on engaging the providers and the public. At the moment, the writing team has listed parental request for other testing under "other uses".
- The writing team also clarified the purpose of the paper. The primary purpose is to review the issues facing state newborn programs regarding the retention and use of residual dried blood spot specimens. The second purpose is to lay the foundation for the development of national guidance for states.
- On page 7, the authors clarified that newborn blood specimens represent a unique time frame where most influences of the contents of the blood are in utero exposures.
- On page 9, the authors added a sentence to clarify that great public understanding of protections mandated by GINA could mitigate parents' concerns about the possible risk of genetic discrimination if their children's blood spots are retained.
- On page 11, the authors expanded the section on the method by which a voluntary national repository could be established. They also discussed the challenges due to variations in state law, regulation and policy. They removed a sentence that referenced the National Children's Study. In addition, they added a section on national IRB.
- On page 13, the authors removed examples of state forms from the text and appendix and referred the reader to the new table on state statutes and regulations on the storage and use of residual dried blood specimens.
- The working group wants to set up an ad hoc group to evaluate example opt in and opt out forms along with educational material. Dr. Lloyd-Puryear observed that the NIH comment emphasized this point. Dr. Alan Fleishman observed that, even though NIH was requesting opt in and opt out forms, not enough work had been done yet to give states specific recommendations on how to address this.

- Dr. Michael Skeels asked about the ownership, not just of the original dried blood specimen, but the ownership of the amplicons from the samples. Ms. Johnson explained that the working group had discussed the issue and there was a suggestion to remove the term "ownership" and to substitute it with "authority over decision-making". Dr. Christopher Kus noted that the section header mentions "ownership" yet it is not discussed in the rest of the section. Dr. Lloyd-Puryear disagreed, noting that the paragraph mentions ownership several times, and her belief that all newborn screening programs have a stewardship responsibility. Dr. Gerald Vockley opined that it would be a mistake to remove the term "ownership" from the paper, since that is the term that is in common use; however, he believes it is a good idea to reframe it as "authority to make decisions". Dr. Jeff Botkin agreed with Dr. Vockley, adding that the main problem with the ownership concept is that it appears that there are no limits on what might be done with the specimens. Ms. Sharon Terry remarked that the authors should include the fact that the concept of ownership varies from state to state.
- On pages 14-15, the Michigan Department of Health provided some clarifications on the Michigan Biotrust for Health and the appropriate changes were made. The information on the Denmark Biobank was placed in a separate text box. The authors also expanded the section on consent and dissent.
- On page 18, the authors added a new paragraph on several methods newborn screening programs might use to provide parents and guardians with alternatives to specimen storage and use. Some of those potential methods opt in or opt out processes.
- In the conclusion, some sentences were reworded due to public concern about the storage of residual newborn screening specimens even for standard uses. The sentences now refer the reader back to the standard uses laid out earlier in the paper. The authors also emphasized that the research uses should not harm longstanding and highly effective state newborn screening programs.
- On page 24, the authors changed the recommendations so that there is just one brief sentence in the executive summary and the more extensive explanations fall in this section. They added a sentence to say that the committee recommends the Secretary provide administrative funding and support for education and facilitating a national dialogue. Recommendation 8 is new—that the Secretary should explore the utility and feasibility of establishing a voluntary national repository. Issues to be addressed include stewardship of the collection, establishment of oversight systems, national human subjects review structure, access and retention policies, and how legal and ethical issues would be addressed including variations in state laws. Dr. Jeff Botkin asked for clarification on the term "voluntary"—is it voluntary on the part of the state or voluntary on the part of the parents? Ms. Johnson confirmed that the meaning is voluntary on the part of the parents.
- Dr. Jane Getchell inquired if APHL provided any comments on the paper. Mr. Jelili Ojodu confirmed that comments were provided in January, which fell before the official public comment time. Ms. Johnson confirmed that all of the comments from APHL had been incorporated.
- Dr. Michael Skeels noted that on page 11, CLIA actually stands for Clinical Laboratory Improvement Advisory Committee. He also noted that Oregon has a genetic privacy law and Idaho and Oklahoma recently passed ones. Texas has information on studies dating back to 2001. Ms. Johnson responded that she would follow up on these laws.
- Dr. Christopher Kus objected to the term "primary target" and preferred the term "primary focus" instead. Dr. Lloyd-Puryear clarified that it should say "educational programs primarily should focus on prenatal care providers".

- Ms. Kelly Leight inquired why education would be focused on providers rather than expectant parents. Ms. Johnson explained that there was a separate recommendation for consumer education and would provide some clarification in the provider section.
- Dr. Rodney Howell asked if there were any substantive comments from the major organizational commenters that were not incorporated into the document. Ms. Johnson replied that the major issue was developing a model consent and dissent form, which they believe requires further study. Dr. Coleen Boyle noted that the IOM held a workshop on the storage of residual blood spots for translational research, with the intention of receiving wide public comments. She believes some of the outcomes of the IOM workshop should be included in the paper. Dr. Boyle also noted that CDC would be willing to assist with public communication campaigns to inform the public. Finally, Dr. Boyle believes that page 7 should clarify anonymized uses of dried blood spots.
- Dr. Roger Eaton remarked that the use of anonymized residual dried blood spots is a standard use.
- Dr. Coleen Boyle questioned why the document states once the use of residual newborn screening specimens moves beyond the state mandated and related standard program uses, each state should consider whether separate or blanket consent/dissent processes for approved studies is required from parents, legal guardians, or individual screened for the use of residual newborn screening specimens. Dr. Lloyd-Puryear responded that federal research requirements do not always require consent if they are anonymized. Dr. Alan Fleishman remarked that the section should be reworded so it is less confusing and consistent with federal research requirements. Dr. Jeff Botkin observed that the recommendation is setting a higher standard than what the federal regulations require.
- Dr. Jeff Botkin and Dr. Lloyd-Puryear both believed that the findings from the IOM workshop should be incorporated into the document. Dr. Denise Doughtery suggested that the Secretary facilitate a dialogue with the stakeholders within a specific timeframe (two years).
- Dr. Howell asked if the committee was comfortable voting on the document without seeing the final version with all of the suggested edits. Dr. Gerald Vockley responded affirmatively. Dr. Coleen Boyle asked if the committee could see the final report before it went to the Secretary and Dr. Howell said that the committee would have a week to review it.

MOTION # 3 PASSED: To publish the report on the Retention and Use of Residual Dried Blood Spot Specimens After Newborn Screening and send it to the Secretary. Dr. Gerald Vockley moved and Dr. Tracy Trotter seconded the motion. The motion was passed unanimously 14-0, with 14 YES votes and one absence (Dr. Alan Guttmacher).

VI. CLIAC Recommendations for Development of Good Laboratory Practice Guidelines for Biochemical Genetic Testing and Newborn Screening

Carol Greene, M.D.
University of Maryland Medical System
Pediatric Genetics

Bin Chen, Ph.D., FACMG
Division of Laboratory Science and Standards
Office of Surveillance, Epidemiology, and Laboratory Services
Centers for Disease Control and Prevention

Dr. Rodney Howell introduced Dr. Carol Greene and Dr. Bin Chen and invited them to present the Clinical Laboratory Improvement Advisory Committee recommendations for good laboratory practices for biochemical testing and newborn screening for inherited diseases. He explained that the CDC is in the process of developing guidelines based on these CLIAC recommendations and is seeking input for this Committee for the purpose of developing a new MMWR guideline. They would like to know if there are specific issues that CDC should address that are not already addressed in the CLIAC recommendations and how CDC could encourage the implementation of the recommended practices through partners and collaborators. CDC is proposing to fund a teleconference for this committee at the end of October so the members can provide input after a thorough review of the background materials.

- Dr. Bin Chen explained that CLIAC is a federal advisory committee established in 1992 to provide scientific and technical advice regarding laboratory standards, including CLIA regulations, and their impact on medical and laboratory practices. In addition, CLIAC suggests modifications to the regulations in order to accommodate technological advances.
- CLIA regulations apply to all testing performed on all U.S. patient specimens. There is a specialty in clinical cytogenetics with specific quality control requirements and certifications for the technical supervisors. There are no special requirement for molecular or biochemical genetic testing. CLIA regulations emphasize the analytical validity of a laboratory test rather than the clinical validity and are not intended to address clinical utility.
- In 2007, CMS developed an action plan to enhance the oversight of genetic testing by providing guidance rather than prescriptive regulations. CLIA provided recommendations for good laboratory practices in molecular genetic testing, which were included in the CDC and MMWR document. Following a CLIAC recommendation to develop a separate guideline for biochemical genetic testing, CDC performed a gap analysis and needs assessment and formed a CLIAC workgroup. The workgroup provided feedback and input to CLIAC, which developed the recommendations for good laboratory practices. Currently CDC is preparing a MMWR document on biochemical genetic testing. The CDC/MMWR molecular genetic testing document is the model for this forthcoming document. CDC would like to solicit additional input to complement the feedback already received from the CLIAC workgroup.
- During the needs assessment phase of the document development, CDC identified a need for clarification of the scope of future MMWR guidelines because the existing definitions for biochemical genetic testing are quite variable. Therefore, CDC set up a workgroup, chaired by Dr. Greene, charged with suggesting which laboratories and tests need addition laboratory practice guidelines based on the comprehensive evaluation of all the relevant laboratory standards and professional guidelines.

- Dr. Carol Green reviewed the elements of the CLIAC recommendation most relevant to newborn screening. For example, there is a recommendation that blood spot samples should not be batched, which is relevant to newborn screening, more than other types of biochemical screening. There are also specific state laws for consent for newborn screening.
    - Recommendations address the types of information that should be available from a laboratory to the end-users of the laboratory. Some information needs to be made available to end-users before testing. The purpose might be to avoid contamination and to ensure proper sample collection or so the tests are ordered for the appropriate patient population.
    - CLIAC recognizes that informed consent is between health care providers and patients and their families, rather than the responsibility of the laboratory. However, the laboratory may have responsibility for documenting the informed consent in some states. CLIAC agreed in principle that explicit written consent is not necessary for mandated public health newborn screening but is appropriate for research uses.
    - Under specimen handling, there was a specific prohibition on batching blood spots, which applies directly to newborn screening. There was also an issue with "unsatisfactory specimens", a problem which arises when a child is critically ill and the sample is technically too small but there is an emergency need for a result. Taking these situations into consideration, there should be a distinction made between a sample that is unsatisfactory for all purposes or just for some purposes.
    - In the analytic phase, CLIAC recognizes that some elements of performance and verification are different when comparing diagnostic and confirmatory testing with screening. For example, the term "cut-off" is not used outside of newborn screening. Also, control procedures are stronger in newborn screening.
    - In the post-analytic phase (test results phase), CLIA has detailed recommendations on what should appear in a test report. This would vary depending on the type of test performed. CLIAC also made a strong statement regarding the retention of newborn screening samples and clearly states that Quality Assurance/ Quality Control is not a research use; rather, it is essential in maintaining the quality of newborn screening practices. Personnel qualifications and responsibilities for newborn screening will look similar to the cytogenetics recommendations. The technical supervisor has the specific knowledge and expertise. The concept of quality management systems is included in many parts of the recommendations.
- Dr. Bin Chen explained that CDC had already obtained input from the Secretary's Advisory Committee for Genetic Health and Society, the Association of Public Health Laboratories as well as this committee.
- Dr. Rodney Howell asked about CMS-approved board certification and laboratory involvement in informed consent. Dr. Carol Greene clarified that CMS recognizes certain boards, which enables them to offer board certification. Also, the document states that informed, written consent is not within the purview of laboratories. However, the laboratory has a responsibility to provide information about the test and its limitations to the health care professionals that may be ordering the test on behalf of their patients and to assist in determining the appropriate level of informed consent. Dr. Michele Lloyd-Puryear noted that newborn testing is generally ordered by a hospital rather than a health care provider.

- Dr. Michael Skeels, who operates a CLIA-certified laboratory and administers the CLIA program in Oregon, noted that his laboratory sometimes struggles to determine whether or not a particular procedure falls under CLIA depending on whether it is assessing future health risk or assessing current health status. Dr. Chen responded that CLIA definitions prescribe which laboratory tests are subject to CLIA regulations, which do not differentiate predictive testing from diagnostic testing or screening. Dr. Skeels followed up, asking if there was a potential for there to be CLIA-certified laboratories operating independently of the medical care system, since not all states require that samples be submitted by licensed medical practitioners. Dr. Chen replied that 37 states allow direct-to-consumer testing.
- Dr. Alan Fleischman remarked that even though laboratories are not directly responsible for informed consent, it is important that they understand the complexity surrounding the issue because they are often asked to give their opinion on these issues to key decision-makers within their states.
- Dr. Rodney Howell suggested that the CLIA group continue its discussion at the meeting of the subcommittee on Laboratory Standards and Procedures.

VII. Report on the HRSA-NNSGRC-APHL Hemoglobinopathy Issues and Answers Conference

Bradford Therrell, Jr., Ph.D.
Director
National Newborn Screening and Genetic Resource Center

Dr. Rodney Howell invited Dr. Brad Therrell, the Director of the National Newborn Screening and Genetics Resource Center, to report on the HRSA-NNSCRC-APHL Hemoglobinopathy Workgroup meeting.

- Dr. Brad Therrell explained that the purpose of the HRSA-NNSCRC-APHL Hemoglobinopathy Workgroup meeting was to reenergize the community, conduct a question and answer session and look at future issues. There were 60 participants and it was held at the Children's Hospital of Oakland.
- Dr. Therrell presented a series of maps representing approximately 10 different laboratory models for newborn screening throughout the United States. Most states still use their own public health laboratory although others are using other states' laboratories or contracting out the screening to other laboratories.
- Most states use isoelectric focusing (IEF) as the primary screening for hemoglobinopathies and a few states are using high performance liquid chromatography. Minnesota is the only state that performs both screening methods on all specimens.
- The majority of states are now able to screen for Hemoglobin H disease using Bart's with HPLC and it would not take much to get the remaining states to comply. A few states have DNA available in the second tier for hemoglobinopathy screening.
- The first hemoglobinopathy screening program was established in New York in 1975. By 1995, almost the entire country had this type of screening program, due in part to a NIH consensus conference and HRSA funding. By 2006, hemoglobinopathy was mandated and now every state has a screening program.

- HRSA-NNSCRC-APHL Hemoglobinopathy Workgroup meeting also included a definition section to refresh the memories of participants. For example, Sickle Cell Disease actually covers multiple disorders such as Sickle Cell Anemia. There was also a educational discussion about Hemoglobin Bart's because some participants came from states that are not yet screening for this disorder.
- There was a presentation by Dr. Carla Cuthbert on some of the proficiency testing issues CDC is investigating as well as new disorders it might begin screening for in the future. Year over year clinical assessment errors became smaller and smaller until last year when there was an increase. The reason is that CDC no longer has a pool of specimens from which to draw proficiency testing samples. There was also a discussion of different state program models and how they are organized. There was a presentation by Ms. Cathy Hassel on non-targeted hemoglobinopathies and the concept of scope creep. For example, programs started off screening for Sickle Cell Anemia, but they have expanded into screening for Sickle Cell Disease. Finally, there were presentations by Dr. Roger Eaton on harmonizing coding standards; Dr. Elliott Vinchinsky on Hemoglobin H, its epidemiology and natural history; Dr. Fred Lorey on Thalassemias screening program; Dr. Carolyn Hoppe on confirmatory testing and follow-up in California; and Dr. Kwaku Ohene-Frempong on evidence review of Hemoglobin H.

VIII. Subcommittee and Workgroup Reports

September 17, 2010

Dr. Rodney Howell resumed the meeting and explained that the committee would first hear the reports from the subcommittee meetings that took place the previous afternoon.

A. Subcommittee on Lab 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

Dr. Gerald Vockley reported back to the committee on the proceeding of the Laboratory Standards and Procedures Committee.

- Dr. John Vogt provided the subcommittee with an update on SCID testing quality control. Six newborn screening programs are using TREC while others are using quantitative PCR. The group discussed the technical details necessary to expanding the TREC screening program nationwide.
- The group held a follow-up discussion on the need for additional treatment centers for long-term follow-up. The larger committee and the Treatment and Follow-up Subcommittee should address this.
- Dr. Clem McDonald asked for input on data entry fields for newborn screening information that will be integrated into HL7. The subcommittee discussed some issues that may appear trivial but require attention in order for the data sets to be consistent.
- The subcommittee spent the majority of the session discussing the CLIA report. Overall, it is a very comprehensive document with a lot of information; however, the group disagreed on what exactly should be in the MMWR document. The CDC representative noted that the MMWR document contains suggestions and not regulations. Specific concerns included:

    - The committee's expertise on newborn screening was not brought into the process. Therefore, any guidelines, including the MMWR must differentiate between recommendations that apply to diagnostic tests and those that apply to the newborn screening program.
    - The document exceeds the scope of laboratory practice particularly in the area of informed consent.
- The subcommittee reached the following conclusions on the CLIA report:
    - Someone from the subcommittee will assist with putting together the MMWR document, with a focus on laboratory best practices. There will also be some language explaining the differences between the diagnostic testing and newborn screening.
    - In future, the committee should be involved in any attempts to change or develop new regulations. They believe that there should be some formal communication from the committee to the CLIA agencies requesting the opportunity to formally weigh in on this and future documents.
- Dr. Rodney Howell asked if there was support for formal correspondence to the CLIA agencies and the committee members agreed. A formal letter that includes all of the points discussed will go to CDC, the agency that manages the CLIA activities. Dr. Michael Skeels opined that in addition to points of concern, the letter should also commend the people who worked on the document and its thoroughness.
- Dr. Coleen Boyle moved to send a letter about CLIA report to CDC. Dr. Michael Skeels seconded the motion and it was approved unanimously 14-0, with no abstentions or absences.

B. Subcommittee on Education and Training

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

Dr. Rodney Howell announced that one of the new members of the committee, Dr. Joseph Bocchini will be serving as a member of the Education and Training Subcommittee. Ms. Jana Monaco and Dr. Tracy Trotter provided a report on the proceedings of the Education and Training Subcommitee.

- Ms. Natasha Bonhomme provided an update on the Newborn Screening Clearinghouse, which is a growing resource. Currently, they are thinking of renaming themselves with a catchier name such as Baby's First Test.
- Ms. Emily Edelman from NCHPEG gave an update on a beta version of a tablet-based family history form for prenatal providers. The product may be available by January 2011, with a full review of program by May 2011.
- Dr. Frederick Chen discussed the Genetics in Primary Care White paper. It may be available in draft form in time for the next committee meeting.
- Ms. Sharon Terry reported on the Health InformationTechnology workgroup.

- Ms. Summa Finn spoke about the congenital conditions program and the SACGHS Education Workgroup. The final report will be out by the first quarter of 2011.
- Ms. Liza Creel and Ms. Kathy Harris reviewed a NYMAC presentation on Emergency Preparedness.
- Dr. Tim Geleske from the American Academy of Pediatrics reviewed a quality improvement program within the academy on newborn screening for primary care. The standard is that the newborn screening result should be in the child's chart and reviewed with patient's parents within 2-4 weeks of the child's birth.
- Genetics and Primary Care Training Institute issued an RFP for a learning collaborative to pair physicians with busy primary care practices together with genetic experts for one year with mentoring on a monthly basis. Unfortunately, none of the applications were fundable, so the institute will be coming out with a revised RFP in the near future.
- Thus far, the Education and Training Subcommittee has emphasizing the primary care approach with the understanding that if the obstetricians, family physicians, and pediatricians are more well-informed and more on the team regarding newborn screening, all of their patients benefit. The subcommittee would like to adopt a new emphasis on a National Newborn Awareness Screening Campaign to raise awareness among pregnant women and their partners. Although Newborn Screening is the most successful public health program ever, there is some erosion in support. Surveys have revealed low awareness of newborn screening amongst women who have delivered children within the past month. The campaign needs to be targeted at providers as well because patients are going to come back to their providers with questions. The subcommittee believes that a good model might be the CDC's Autism Awareness Campaign "Learn the Signs. Act early". A national campaign will likely require securing some federal funds.
- Dr. Rodney Howell expressed concern that although newborn screening is a highly successful program, media attention focuses on the rare negative effects. He believes that a national awareness campaign would be extremely worthwhile. Dr. Tracy Trotter agreed with Dr. Howell, noting that the laws were passed due to the testimony of families whose children had died or were severely impaired due to undetected genetic disease yet these families get very little media attention these days.
- Dr. Alan Fleishman remarked that the CDC has much experience and expertise with national awareness campaigns. However, unlike other campaigns, the public is not being asked to take action such as get an immunization. Rather, the campaign focuses on setting the mother's expectation and giving her some knowledge of what information she might receive from her child's pediatrician. The clinical community would require partners such as the March of Dimes.
- Dr. Coleen Boyle suggested that, if the committee approved, she would develop a 2-5 page concept paper and present it at the next committee meeting. Dr. Peter van Dyck stated that HRSA would also with developing the concept paper.
- Dr. Jeff Botkin noted that research reveals that people who have more information about newborn screening programs tend to be more supportive of them. He also believes that states might be interested in branding these programs within their own communities, which could be accomplished in coordination with a national campaign. Dr. Ned Calogne endorsed the concept of allowing states to brand their own programs. Dr. Botkin believes that the proposed campaign is a social marketing campaign without a call to action, which is different than many prior campaigns. Therefore, special attention must be paid to the expected deliverables. He also pointed out the need for infrastructure to look at the issue longitudinally.

- Dr. Christopher Kus asked about the length of the proposed campaign and whether or not it would need to repeated every five or ten years.
- Ms. Sharon Terry from the Genetic Alliance, noted that her organization has been involved in state lawsuits and generally there are not many families with success stories to counterbalance the vocal minority who oppose newborn screening.
- Dr. Michael Skeels believes that the campaign must raise awareness among elected officials in state legislatures in addition to parents and providers.
- Dr. Joseph Bocchini remarked that the issue the proposed campaign will target parallels the issue of vaccine hesitancy and anti-vaccination movements. Five years ago, the AAP worked with a consortium of public agencies and other organizations to do public education and social marketing. Dr. Howell echoed Dr. Bocchini's analogy with immunization campaigns.
- Dr. Rodney Howell stated that he would appoint a working group, led by Dr. Coleen Boyle charged with developing a 2-5 page concept paper, which they will bring to an upcoming committee meeting for review and discussion.

C. Subcommittee on Follow-up and Treatment

Jeffrey Botkin, M.D., M.P.H.
Professor of Pediatrics and Medical Ethics
Associate Vice President for Research
University of Utah

Dr. Jeff Botkin reported back to the committee on the proceedings of the Follow-up and Treatment Subcommittee.

- Dr. Brad Therrell presented a draft white paper on improving data quality assurance in newborn screening , which had four recommendations:
    - State programs should use standardized formats for serial numbers
    - Inform NAPHSIS of the importance of including serial numbers on birth certificates
    - Include a field for serial numbers in the next revision of the US standard birth certificate
    - Cross-validate demographic information between the dried blood spot and the birth certificate.

  There was much discussion about avoiding a single national identifier , which is opposed by many civil liberties groups. The white paper will be completed and submitted to SACHDNC in time for the January meeting.

- Dr. Christine Brown presented the impact of health care reform on heritable disorders. She revealed that there is a lack of coverage under the Affordable Care Act for medical foods, which are excluded from list of essential health benefits. In addition, some of the mandates to protect children from being dropped due to preexisting conditions do not apply to heritable conditions, because they are not part of the essential health benefits. Finally, the legislation does not apply to TRICARE. Federal and state high risk pools will be helpful to families with heritable disorders and some states have mandated coverage of medical foods. Dr. Lloyd-Puryear clarified that the Secretary is going through the current health care plans, Medicare and Medicaid over the course of the next two years to determine a basic package of essential benefits. Dr. Brown explained that the committee also discussed other services that might be essential for families with heritable disorders such as nurse psychological evaluations and the genetic evaluation of siblings and parents. Dr. Susan Berry volunteered to lead a workgroup to look at these issues in depth.
- Dr. Carl Cooley provided an overview of the medical home concept, where care is integrated through communication between primary care and subspecialty providers. The medical home is a place and process, leading to the development of integrated systems of care. Various subcommittee members offered variant models of medical homes led by specialist providers, rather than primary care providers. There were also concerns about how to integrate midlevel providers such as psychologists into the medical home, since they may not have access to medical record systems. Dr. Cooley invited members of the subcommittee to assist the National Medical Home workgroup with developing medical home models for families dealing with heritable disorders.
- Ms. Cindy Hinton discussed the overarching questions in long-term follow-up, which have been developed into a white paper. Ms. Hinton would like to receive any final comments within the next two weeks and then the paper will be submitted to the full committee for evaluation at the next meeting.
- Dr. Susan Berry presented the results of the Medical Foods Survey, which she will present to the full committee today. The key question concerns whether or not additional data is necessary before we can publish the results.
- Ms. Amy Brower reviewed the NCC long-term follow-up supplement, including an update and recommendation for next steps. The key is to get uniformity across systems so that systems have the same data elements and data can be shared appropriately. Important steps in achieving this objective include coordinating and accelerating the adoption health information technology for the long-term follow-up; actively developing uniform data sets, disease-specific data sets and engaging in some pilot projects.
- Dr. Robert Bowman provided an update on the HIT workgroup. Discussion centered on the role of the subcommittee and larger committee in developing quality measures. Subcommittee members believed that its role is to provide input on measures that have already been developed and proposed, rather than developing measures itself. There is a October 15 deadline for comments on national quality priorities.

D. Workgroup on Health Information Technology

Alan E Zuckerman MD
Lister Hill National Center for Biomedical Communications
National Library of Medicine, National Institutes of Health, HHS
Sharon F. Terry, M.A.
President and CEO
Genetic Alliance

Dr. Rodney Howell introduced Ms. Sharon Terry and Dr. Alan Zuckerman and invited them to give an update on the proceedings of the Health Information Technology Workgroup meeting.

- The workgroup will continue its work on HL7 and Coding activities.
- The workgroup reviewed quality measures related to the Recovery Act, which are time-sensitive. In order for newborn screening to be included in the ARRA Meaningful Use Incentives during phase II/phase III, there have to be measures available that have been endorsed and tested. The National Quality Forum reviews and endorses measures that have been developed and are in use by other organizations. Eleven newborn screening measures were submitted, and they will be reviewed through a consensus process that will be complete before the next committee meeting. The workgroup believes that the committee should endorse these measures and has included a simplified recommendation to the committee in a handout. The measures include:
    - A measurement of the portion of infants covered by newborn blood spot screening. So the number of infants are going to come from the birth certificates and hospital discharge records, but the details of what counts as having complied will depend on state mandates that may exclude infants for various reasons.
    - There are eight measures on early hearing detection and intervention. Three of them focus on completing the initial screening. The first one is the percentage of newborns that are screened before hospital discharge. The second measure is the referral rate at hospital discharge. The third measure is how often is outpatient hearing screening isperformed on children who did not complete their screening prior to hospital discharge. The measure calls for 31 days of age as the time to assess.
    - Another group of measures relate to risk factors in the medical home. The first measure addresses deals whether or not the medical home done a risk assessment on identified children who, because of their newborn history, should looked at a second time after the initial hospitalization. The second measure begins to look at whether the identified children have had audiological diagnosis.
    - The next group addresses diagnostic evaluations and referrals for interventions. The first measure is whether or not audiological evaluation occurred before 3 months of age for children who did not pass their initial screenings. The second measure addresses whether or not the children began language by 6 months of age. The third measure addresses whether or not a referral for educational intervention took place within 48 hours the confirmation of a permanent hearing loss
    - In order for newborn screening to be included in ARRA endorsed and tested measures Recommend that this committee HRSA, EHDI NQF endorse 11 newborn screening measures submitted and will go into consensus process

- The NQF is shifting from evaluating overall state programs and hospitals to evaluating newborn screening in electronic medical records and within the medical home. They currently have two measures: one for hearing, one for metabolic screening. These measures are tagged at 6 months of age because they represent one piece of a comprehensive well child profile that ia being audited simultaneously.
- Today the committee needs to vote up or down on these particular measures. The committee can also submit comments on potential changes the measures and work to improve these measures as they go into their test phase.
- Dr. Ned Calonge moved to endorse the proposed newborn screening quality metrics and Dr. Kwaku Ohene-Frompong seconded the motion. Dr. Lloyd-Puryear suggested adding a recommendation to the endorsement for NQF to measure care coordination before the completion of screening activities and referrals. Dr. Denise Doughtery expressed concern that NQF does not perform independent quality reviews on measures and questioned whether or not the committee should endorse the measures. Dr. Rodney Howell clarified that the committee was not endorsing implementing the measures; the committee was endorsing further assessment of the measures. Dr. Lloyd-Puryear suggested that a small group meet during lunchtime to re-word the recommendation and the committee agreed. Dr. Frederick Chen asked about the implications of submitting eight hearing measures but only three measures that are broadly focused on newborn screening. Dr. Sarah Copeland clarified that no newborn screening blood spot measures have been validated and tested; however, EHDI has tested and validated the hearing screening measures.

IX. Evidence Review Workgroup Report: Report on the Candidate Nomination Critical Congenital Cyanotic Heart Disease

Alex Kemper, M.D., M.P.H., M.S.
Associate Professor
Department of Pediatrics
Duke University

Dr. Alex Kemper presented his Report from Evidence Review on Critical Congenital Cyanotic Heart Disease (CCCHD) and followed up on the reports on Hemoglobin H and Neonatal Hyperbilirubinemia.

- The Hemoglobin H report has been completed and a manuscript was submitted to the Journal of Pediatrics
- The Neonatal Hyperbilirubinemia evidence review is in progress.
- In the CCCHD report, the evidence review team included a detailed description of literature review of methods, a summary of the evidence in the literature, expert unpublished data, tables highlighting key data from abstracted articles along with a complete bibliography. The preliminary literature review on pulse oximetry screening was presented to the committee in May 2010. Natural history, diagnosis, treatment, economics and updated screening literature review included in the latest report.
- The evidence review team focused on critical congenital cyanotic heart disease lesion that present with hypoxemia in most of all cases.

- The evidence review team conducted a systematic literature review that summarized evidence from published studies and consulted with multiple CCCHD experts to identify relevant unpublished data.
- The rationale for conducting this evidence review is that there is significant morbidity and mortality associated with CCCHD, the identification of CCCHD in neonates might improve health outcomes and several large studies have examined newborn screening for CCCHD with pulse oximetry.
- The evidence review team used a technical expert panel to develop a case definition and discuss key questions. The case definition was agreed upon by the ERG and the AC Nomination and Priorization committee. Definition: CCCHD is a heart defect that usually requires surgery or catheter intervention in the first year of life and presents with hypoxemia in most or all cases. The specific conditions included in the review are hypoplastic left heart syndrome (HLHS), pulmonary atresia, intact septum, tetralogy of fallot (TOF), total anaomalous pulmonary venous return (TAPVR), transposition of the great arteries (TGA), tricuspid atresia, and truncus arteriosus.
- The evidence review included articles published January 1990-June 2010 in Medline, OVID In-Process and other non-indexed citations, in English, and involving human case studies only. If there were duplicate publications, the team selected the most recent or complete version. In the end, 367 articles were selected for preliminary review, 67 articles were selected for in-depth review, and 26 articles that met inclusion criteria for abstraction.

Papers Meeting Review Criteria

Study Design	Number of Papers
Experimental intervention	0
Cohort study	0
Case-control study	0
Case series	7
Sample size ≤ 10	0
Sample size 11 to 50	0
Sample size 51 to 100	0
Sample size ≥ 101	7
Economic Evaluation	1
Cross-sectional study	11
Systematic Review	7
Total studies	26

- In addition to the published literature, the review committee interviewed outside experts and screening advocates with either a written survey or interview.
- The evidence review team came up with the following key questions related to natural history:
    - What is the prevalence of CCCHD among those neonates eligible for screening?
    - What is the natural history, including the spectrum of severity of CCCHD among neonates eligible for screening?
- The evidence review team uncovered eleven articles pertaining to natural history. For each individual condition they obtained the estimates of the prevalence, age of onset and rate of survival. All conditions are important to identify because untreated survival rates are poor for HLHS, Pulmonary atresia, inact septum, TOF and TAPVR while TGA, tricuspid atresia, and truncus artreriosus are very serious.

Abstracted Literature Pertaining to Natural History

Type of evidence	**Number of articles**
Total	**11**
Review article	7
Multi-institutional case series (tricuspid atresia; pulmonary atresia; intact septum)	2
Single institution, largest case series available (TAPVR; truncus arteriosus)	2

Natural History Summary

Heart Defect	**Hypoxemia**	**Ductal-dependent**	**Prevalence** (per 10,000 live births)	**Age at symptom onset**	**Untreated survival**
HLHS	All	All	1 – 7	Immediately or within the first two months of life	Universally fatal if untreated
Pulmonary atresia, intact septum	All	All	0.7 - 0.9	Immediately	Neonate becomes severely ill when the ductus closes, leading to death
TOF	Most	Uncommon	3	Neonatal period	Amount of pulmonary blood flow obstruction determines onset and severity of symptoms
TAPVR	All	None	0.7 – 2.7	Immediately or within the first two months of life	Survival unlikely if untreated

- The evidence review team came up with the following key questions related to screening:
    - What is the accuracy of pulse oximetry in the newborn period for CCCHD? How does this vary by age of the neonate, placement of probes, and threshold value for action?
    - How many additional cases of CCCHD would routine neonatal screening with pulse oximetry detect prior to hospital discharge, compred to current care, including screening prenatal ultrasounds and routine newborn clinical history and examination?
    - What is the flase positive and false negative rate of routine neonatal screening with pulse oximetry for CCCHD?
    - What are the potential harms or risks associated with screening?

Quality Assessment: Screening Test

Type of evidence	**Number of articles**
Total	**11**
Overall sensitivity and specificity of screening	**11**
Data obtained from screening programs in U.S. population or similar.	2
Data from systematic studies other than from whole population screening.	9
Estimated from the known biochemistry of the condition.	0
False positive rate	**8**
Data obtained from screening programs in U.S. population or similar.	0
Data from systematic studies other than from whole population screening.	8
Estimated from the known biochemistry of the condition.	0
Repeat specimen rate	**1**
Data obtained from screening programs in U.S. population or similar.	0
Data from systematic studies other than whole population screening.	1
Estimated from the known biochemistry of the condition.	0

Quality Assessment: Screening Test (Continued)

Second-tier testing	**5**
Type of Evidence (Continued)	**Number of Articles (Continued)**
Data obtained from screening programs in U.S. population or similar.	0
Data from systematic studies other than whole population screening.	5
Estimated from the known biochemistry of the condition.	0
Other screening test characteristics	**0**

- First tier of screening for CCCHD is pulse oximetry to estimate the percentage of oxygen-saturated hemoglobin in the blood. The second tier is echocardiography.
- Contrasting the clinical exam with pulse oximetry, there was no significant increase in the number of CCCHD cases caught through echocardiograms . By contrast, a 2005 study that compared pulse oximetry with clinical exams and both methods found a significant benefit from using both methods. Some experts reported that in the regions of their practices, more than half of CCCHD cases are diagnosed prenatally. However, prenatal ultrasounds typically look at the four chamber view of the heart and this technique may miss some CCCHD conditions such as TAPIR or TGA. Telemedicine can used to follow-up on babies with cardiac legions either through a store and forward process where the result is reviewed later or through live telemedicine e.g. reviewing as image is being taken in real time.

Screening Literature: True and False Positives and Negatives

Study's First Author	Hoke 2002	Richmond 2002	Koppel 2003	Reich 2003	Bakr 2005	Rosati 2005	Arlettaz 2006	Meberg** 2009	Sendelbach 2008	de Wahl Grannelli 2009	Riede 2010
Number Screened	2,876	5,622	11,281	2,114	5,211	5,292	3,262	50,008	15,233	38,429	41,445
Age at Screening	<6 hours, 24 hours and/or at discharge	Between >2 hours and discharge; average 11.7 hours of age	>24 hours of age or at discharge; average 72 hours of age	>24 hours of age; as close to discharge as possible	Prior to discharge; average 31.7 hours of age	>24 hours of age or at discharge; median 72 hours of age	6-12 hours of age; average 8 hours of age	6-16 hours of age	4 hours of age and pre discharge	90% at <72 hours of age; median 38 hours of age	24-72 hours of age
Cutoff for normal	≥92%	≥95%	≥96%	≥95%	≥94%	≥96%	≥95%	≥95%	≥96%	≥95%	≥96%
Location	Maryland, USA	UK	New York, USA	Florida, USA	Saudi Arabia	Italy	Switzerland	Norway	Texas, USA	Sweden	Germany
Prevalence*	7/10000	12/10000	4/10000	9/10000	8/10000	2/10000	25/10000	10/10000	1/10000	3/10000	3/10000
Probe Location	H & F	F	F	H & F	H & F	F	F	F	F	H & F	F

*Prevalence is calculated from screened asymptomatic newborns

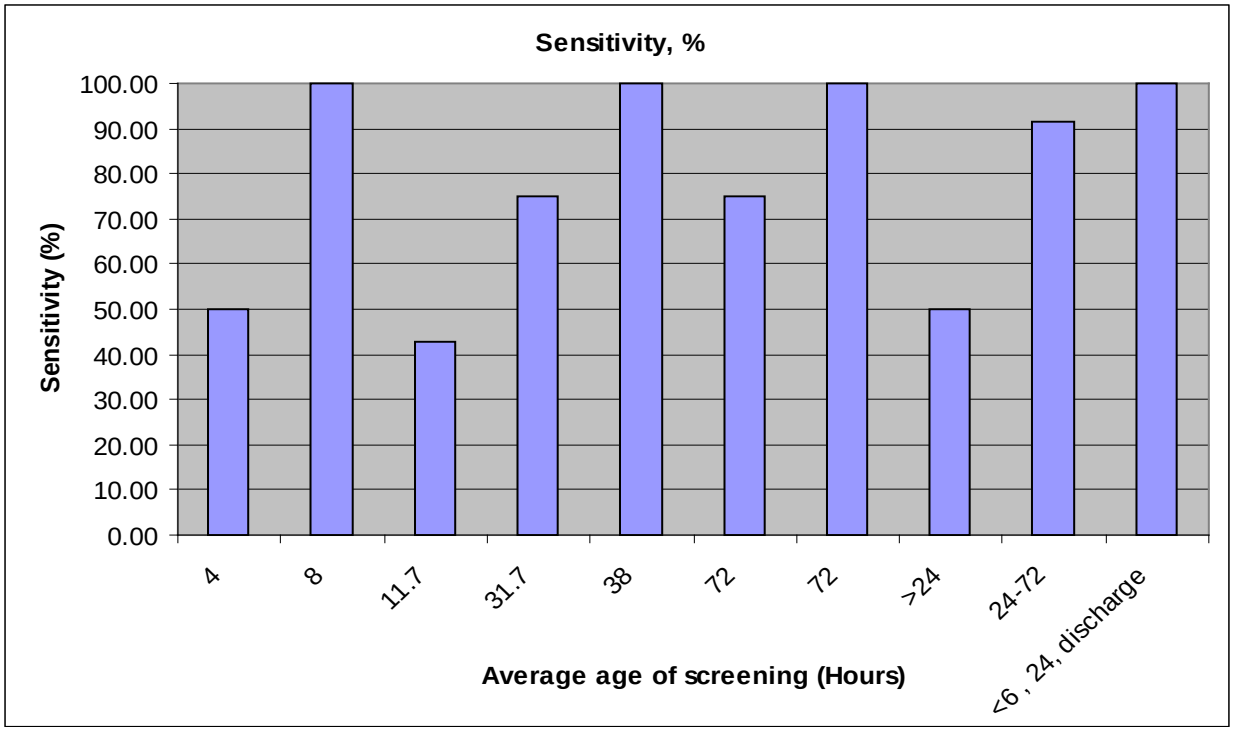
**Unable to determine specific values for CCCHD only

H & F denotes right hand and foot; F, foot;

FP; False Positive; POx, Pulse Oximetry; NA, Not available

- The table above summarizes study characteristics such as the number of children that were enrolled in screening studies, the threshold for a normal pulse ox result, where the screening was done, and where the probes were placed.
- There is some variation in the prevalence of critical congenital heart disease based on the cases that were found in the study. The large variation probably reflects differences in prenatal care, as well as how clinical exams were conducted.

Screening Sensitivity



- There was a variation is the age of the infants screened with a range from 4 hours of life to 24 hours of life or later.
- The data in the last column is derived from a study that looked at screening at three different time points in neonates who were younger than 6 hours of age, who were 24 hours of age and at discharge. One study that did not have the necessary data to calculate sensitivity. There is variation ranging from 50 to 100% percent sensitivity for critical congenital cyanotic heart lesions, and the average is around 60-70%.

A. Committee Discussion

- Dr. Ned Calogne observed that there were not any patterns in sensitivity. Dr. Alex Kemper confirmed that this was the case and the reasons behind the variation is unknown.
- Dr. Coleen Boyle asked if different cut-off values might be the cause of the variations. Dr. Alex Kemper replied that this is one potential explanation, as well as the age of the infant at screening and the placement of the probe as well as the actual probe technology used.
- Dr. Alan Fleishman asked if the variation might be due to the closing of the ductus after birth as the infant transitions to life outside of the womb. Dr. Gerald Martin, a pediatric cardiologist from the Children's National Medical Center responded that timing is critical to when the pulse oximetry screening is done both from a sensitivity and specificity standpoint. Because of the presence of the ductus, a child may present with normal saturation during the first 24 hours, and is a critical reason why some cases of CCCHD are missed. There can be some false negatives during that time period based upon either the disease severity or the presence of the ductus. Most experts prefer to screen 24 hours after birth.

- Depending upon the lesion, it seems that mortality is significantly altered by timely surgery. There is no data available on whether or not detection with pulse oximetry prior to when the legions become clinically apparent makes a difference. Mortality for hypoplastic left heart syndrome is around 65% at 5 years of age. Mortality for pulmonary atresia is 81%. By contrast, tetralogy of fallot has a typically 25-year survival rate. All legions have interventions that happen early in life and intervention mortality is improved.
- Dr. Kemper and the evidence team also reviewed studies on the economic costs of screening tests and the economic costs of failing to diagnosis CCCHD. The evidence review team found one study on cost-effectiveness in UK setting that compared three different strategies: clinical examination alone, clinical examination with pulse oximetry performed within the first 24 hours of life, and then clinical examination with screening echocardiography . The study concluded that echocardiography as the first course of action produced only a slight increase in identification screening with a massive increase in cost.
- Each of the seven CCCHD conditions considered by the evidence review team have onset of symptoms that occur within the neonatal period. The symptom onset ranges from birth to a few months of age when symptoms can develop, again depending upon the lesion, and there is some variability in the onset and severity. The two lesions that are most missed by physical exam alone are transposition of the great arteries and total anomalous pulmonary venous return. Pulse oximetry appears to identify CCCHD in neonates that prenatal and clinical exam alone may miss.

B. Public Comments

- Dr. Gerald Martin, who is the Senior Vice President for the Center for Heart, Lung, and Kidney Disease at Children's National Medical Center in Washington DC and a practicing pediatric cardiologist, offered comments about his experience with pulse oximetry to detect CCCHD. Early in his career, he did not believe that pulse oximetry screening for newborns to detect CCCHD was an important issue. However, when he approached the Children's Heart Information Network, they said that it was most important issue based on the feedback they heard from parents across United States. For clinicians working in the ER, it is common to see a child in the ER in shock who has heart disease that was not diagnosed at birth. He believes that if teaching hospitals are not training clinicians to perform pulse oximetry screening on newborns, they are teaching for failure.
    - Dr. Martin and his colleagues from the Children's National Medical Center went to a community hospital to set up an intervention for routine CCCHD screening on newborns through pulse oximetry. They analyzed the results for feasibility, barriers, and any additional staffing needs.
    - The findings revealed that the hospital did not have to add any staff. Furthermore, there was a very low rate of false positives. There are now at least 13 hospitals in the Washington area that are in various stages of adding pulse oximetry to their normal vital sign sets to help the pediatricians at those hospitals identify babies with CCCHD and other life-threatening conditions.There are some concerns with sensitivity and specificity and availability of echocardiography; however, those issues should not prevent routine pulse oximetry
- Dr. Balaji Govidnaswami shared his experiences with pulse oximetry screening for newborns at Santa Clara Valley Medical Center in San Jose. By January 2011, all of the sites within this medical center are poised to begin screening 10,000 babies every year in San Jose.

- The cost for a pulse oximetry screen for a newborn averages about $5 per patient at his institution. Dr. Govidnaswami and his colleagues reviewed the same literature and decided to exclude some of the studies that started screening very early because there would be a high false positive rate. They also excluded a couple of the studies that sensitivities of 15% because they used technology that was not appropriate for babies. Dr. Govidnaswami believes the actual range of sensitivity is 75 to 100%.
- In reviewing all of the studies that start at or after 24 hours of life and use hand and foot probes, never show a sensitivity less than 82%. The specificity is 99.99%, and the negative predictive value is 99.98%. This is acceptable for a lesion that has tremendous implications for morbidity and mortality, particularly since the technology is relatively simple and is already present in almost all of the hospitals in the United States.

- Ms. Annamarie Saarinen is a parent representing the organization 1in100. Her daughter, Eve, is an example of a positive outcome because her heart defect was caught early. At 40 hours of age the defect was discovered and Eve was kept alive with a cocktail of medications until she was able to have two heart procedures. Approximately 28,000 babies lose their lives before age one in the United States and approximately 4,000 of those deaths are due to heart disease or heart defects. Ms. Saarinen drew attention to a recent German study that showed a false positive rate for screening with pulse oximetry and Dr. Julia Hoffman's study that showed a seven-fold increase in detecting heart defects through pulse oximetry screening. Given that most newborn nursery staff already know how to use pulse oximeters, it should be a priority. When hearing screening was first implemented, there were some hurdles in terms of costs and training; however, it was still done and has had a significant impact on children. If this committee made a recommendation, many more hospitals would overcome the perceived barriers and implement pulse oximetry screening.
- Dr. Olivia Easley is a parent representing the organization Bless Her Heart. She spoke at the previous committee meeting in May to share the story of her daughter Veronica and to remind the committee of the personal toll when babies are not screened and heart defects are not detected. Many CCCHDs are missed in the physical exam but could be detected through pulse oximetry. She urged the committee not to forget the babies while they are considering the data. They should also keep in mind that rural hospitals have access to tertiary care, so the need for referrals should not be a barrier in implementing pulse oximetry screening.
- Ms. Vi Kennedy is the mother of Taryn, who passed away at 29 days of age, while showing no signs of having a congenital heart defect prior to 27 days. Following this tragedy, Ms. Kennedy founded the organization Bless Her Heart to provide information to parents and to advocate for increased screening of newborns for CCCHD. She has been advocating within her home state, Texas, to increase the use pulse oximetry screening and has heard many excuses from various officials about why it is impossible to implement. For example, some administrators believe that it is too complicated to develop separate polices for pulse oximetry in the NICU and pulse oximetry in the newborn nursery. Another barrier cited is the difficulty in transporting babies from a rural hospital to tertiary care. Following the death of her daughter, Ms. Kennedy received a bill for $138 for hearing screening. Although her daughter's hearing was screened, she was not screened for CCCHD, which could have potentially saved her life. It is impossible to put a dollar value on the opportunity to minimize complications and prevent deaths. Newborn pulse oximetry screening can change outcomes for other families and prevent other deaths.

C. Committee Questions and Comments about Candidate Nominations for Critical Congenital Cyanotic Heart Disease

- Ms. Jana Monaco thanked the experts and the consumers for their input. She believes this is a relatively easy recommendation to approve because the consequence of not screening is that the babies do not survive. The committee can make a broad recommendation and allow the cardiologists and other experts to work out the details of how to perform the pulse oximetry, the best age for the screening and how to resolve rural disparities.
- Dr. Gerald Vockley commented that CCCHD is a disastrous disease that can easily be identified in the hospital setting with technology that is already readily available. Although there is some geographic mismatch between diagnosis and treatment, these issues have been resolved for other conditions. He noted that the evidence for pulse oximetry screening is stronger than for many other screening recommendations that the committee has already passed.
- Dr. Michael Watson speculated that the variation in sensitivity found in the studies presented was due to differences in study design which would lead him to conclude that there were differences in the quality of evidence. Dr. Alex Kemper replied that the differences were likely due to differences in technology used and in the cut-offs.
- Dr. Ned Calogne noted that the differences in outcomes of screened versus unscreened cases are all based on observational data. Dr. Alex Kemper confirmed that there are no randomized trials of screening versus usual care. However, given the nature of the legions it is relatively clear that leaving them untreated would almost certainly result in death or disability. Dr. Ned Calogne commented that there is a critical evidence gap because the screen-detected cases and non-screen-detected cases are not the same. He also urged the committee to consider the implications for training staff and implementing these recommendations within rural hospitals.
- Dr. Alan Fleishman reminded the committee that, particularly in the area of neonatology, rural hospitals are linked to tertiary care. He also noted that the symptoms are devastating and develop very rapidly. This is why there would be a great improvement in outcomes if clinicians had the ability to detect the conditions pre-symptomatically. He believes that experts should be consulted to determine the best method for conducting a pilot of a pulse oximetry screening program, particularly with regard to the timing of the test since most infants leave the hospital before they are 72 hours old. Finally, he would like to see a phase IV study to assess the impact over time. Dr. Fleishman thinks the committee should endorse the recommendation along with a pilot study and a longitudinal study of the impact.
- Dr. Gerald Vockley believes that any additional evidence would only affect the committee's recommendations concerning implementation, but not the actual recommendation to screen. In his view, the adverse effects of not identifying CCCHD in newborns and the subsequent mortality outweigh the specific considerations about the type of screening technology used and the timing.
- Dr. Frederick Chen questioned whether or not the committee has the authority to make recommendations for pulse oximetry screening because CCCHD is not a metabolic disorder and does not involve the state public health laboratories. He also noted that the committee did not act on the universal newborn hearing screening; the recommendation came from a NIH consensus panel instead. We do have primary care organizations here. We do set clinical guidelines and clinical policies. In terms of implementation, pulse oximetry screening is much more complicated than recommending another newborn screening heel stick test and requires careful thought about potential partners to guide the implementation. Dr. Rodney Howell replied that the committee did pass a recommendation for newborn hearing screening as well as for hypothyroidism and that pulse oximetry screening is within the purview of the committee.

- Dr. Jane Getchell questioned if pulse oximetry screening belongs on the state-operated newborn screening standard panel. She believes that it might be a hospital physician responsibility, rather than a state responsibility. Dr. Rodney Howell clarified that the committee has the responsibility for recommending screenings that can benefit children with heritable disorders broadly. Dr. Bonnie Strickland, who implemented the hearing screening recommendation, noted that the committee has the responsibility to ensure that each part of the system works together to do the right thing for every child. If the committee decides it is not the appropriate entity to pass the recommendation, it needs to ensure the issue is carried to the appropriate venue. Dr. Lloyd-Puryear urged the committee to take a systems approach or public health approach to implementation.
- Dr. Michael Watson asked Dr. Alan Fleishman to comment on oversight and accountability. Dr. Fleishman replied that if the committee wants every child in America to be screened, then they need to ensure that there is accountability at the public health level. The precise form of accountability may differ with each State, but the committee should make accountability an important goal. There are about 3,000 birthing hospitals in the United States and over a third of those hospitals have less than 500 deliveries. There needs to be accountability rather than leaving each rural hospital or other site to make its own decision on screening. It will be relatively easy to obtain outcomes data because that will come through cardiologists at academic medical centers. Ms. Annamarie Saariman noted State Department of Health in Minnesota has integrated the newborn hearing screening with the metabolic screenings into a full newborn screening package and would likely integrate pulse oximetry screening as well. Dr. Rodney Howell noted that states that have connected their hearing screening to their newborn screening programs have been more successful.
- Dr. Tracy Trotter explained that newborn pulse oximetry screens are mandated by the Departments of Pediatrics in the hospitals where he currently practices and he is surprised that it is not currently a recommendation. He noted that the false positives that are not due to CCCHD are likely due to some other type of disease that needs to be treated right away. It is rare to find a newborn with a pulse oximeter reading under 90 who has no disease at all. The implementation obstacles cited are fairly small and easily overcome. The recommendation is practical, feasible and saves lives.
- Dr. Rebecca Buckley reminded the committee that CCCHD is leading cause of death in first year of life and that 25% of cases are missed at birth. Pulse oximetery screening is similar to the hearing screening in that it occurs in the hospital but the technology training issues are easier to overcome because most nurses already know how to use a pulse oximeter. She believes that the implementation details can be worked out later.
- Dr. Lloyd-Puryear cited the committee's charter which states that it has responsibility not just for recommending screening, but also for providing advice about aspects of newborn and child screening and technical information for the development of policies and priorities that will enhance the ability of the State and local health agencies to provide for newborn and child screening, counseling, and health care services in newborns and children.
- Dr. Gerald Vockley remarked that the technical and implementation issues with pulse oximetry are much simpler than with tandem mass spec, the implementation of which led to significant reductions in morbidity and mortality.
- Dr. Christopher Kus noted that there is already a regional system for neonatology in place to build on. Dr. Kus also believes that the committee and the public health system should ensure that every child receives this screening and that this should be achieved through accountability.

- Dr. Jeff Botkin commented that although the recommendation sounds eminently reasonable, Dr. Kemper's evidence report suggests that there is a gap in the evidence to suggest that early intervention leads to improved clinical outcomes. While the committee does not want to hold up a potentially a life-saving intervention to wait for data, he has not seen enough data to feel fully confident that this is clearly the most appropriate recommendation. Dr. Botkin also would like to hear more about the phenomena of sudden death—what is the marginal improvement of early detection and preventing early death from pulse oximetry screening in this population? Are there autopsy reports? Are there data sets out there that could give the committee a stronger sense of how well early intervention might be effective in that catastrophic outcome? Dr. Botkin believes that any recommendation from the committee should include an imperative to actually collect the data necessary to determine hence that this was the right decision in three years' time. Otherwise, the data on pulse oximetry to detect CCCHD in newborns may never be collected. The committee should strongly encourage pilot implementation and data collection through the implementation processes to strengthen the basis of the recommendation and encourage states to work through the implementation issues.
- Dr. Alex Kemper remarked that there is no data on whether or not children who are identified before they are symptomatic have better outcomes than children who are detected clinically. He endorsed the idea that the committee should not simply make a recommendation but should also include recommendations for further data collection and monitoring of the outcomes as the recommendation is implemented.
- Dr. Tim Geleske commented that although the outcomes of pulse oximetry have not yet been evaluated, the use of pulse oximetry improves clinical acumen and gives the medical staff some additional data to assist them in giving appropriate care.
- Dr. Denise Doughtery asked how many unnecessary surgeries would be expected to take place as a result of false positives. Dr. Rodney Howell and Dr. Ned Calogne commented that there would not be any unnecessary surgeries because a positive pulse oximetry result would be followed by an echocardiogram to determine if surgery was necessary. In the process of conducting the evidence review, Dr. Alex Kemper had found one case where a baby was put on prostaglandins and then transferred inappropriately before it was realized that there was no underlying heart defect. Dr. Doughtery cited the AAP and American Heart Association recommendation for routine pulse oximetry for newborns who are 24 hours old in hospitals that have on-site pediatric cardiovascular services incurs very little cost and risk of harm. Future studies in larger populations and across a broad range of newborn delivery systems are needed to determine whether this practice should become standard of care and routine assessment.

- Dr. Rodney Howell observed that the committee appeared to have some enthusiasm for moving forward with a recommendation, but they wanted any potential recommendation to include infrastructure requirements to ensure a public health approach to implementation such as the collection of data and an analysis of the outcomes. Dr. Alan Guttmacher concurred, adding that the initial recommendation should be for a pilot with the committee taking responsibility for looking at the data when they become available and to develop some firmer, more longstanding conclusions. Dr. Gerard Vockley disagreed with recommending a pilot only and stated that the evidence gap does not concern whether or not early intervention helps or saves lives, so the recommendation should be more emphatic. He reminded the committee that every baby already receives a physical exam but this recommendation would add a much more sensitive screening test. Dr. Ned Calogne dissented because an increased rate of detection does not always translate to improvements in health outcomes. The evidence gap is important because any recommendations from the committee on this topic will have implications for any future conditions and other technologies that it might review. Ms. Jana Monaco agreed with some of Dr. Calogne's points because many conditions do not present clinically until later in the child's life and they can be addressed effectively then; however, there are currently 4,000 babies dying from CCCHD before their first birthday every year and that is clearly evidence that the committee needs to take some action. She went on to observe that if the committee made a recommendation, it would raise the standard of care so that small community hospitals would be equally accountable for conducting pulse oximetry screening as larger medical centers.
- Dr. Coleen Boyle commented that there are birth defects surveillance programs in most states, which means that there is a mechanism to track changes over time and link them to vital records information. She asked Dr. Alex Kemper if he had a chart that was similar to the sensitivity chart, which would highlight some other attributes, such as the date the study was conducted and the technology used. Dr. Kemper replied that there is a larger chart inside the actual report and that it confirms that the majority of variation in sensitivity is likely due to either older studies or different equipment. It seemed that anomalous pulmonary venous return, a particular legion that is missed on prenatal ultrasounds and is difficult to find clinically, is the condition is driving much of the benefit behind pulse oximetry screening.
- Dr. Kellie Kelm researched regulations on the FDA website and discovered that the FDA requires pulse oximeter manufacturers to submit clinical data for accuracy with a special separation of neonatal data from pediatric data. She suggested that the committee could limit its recommendation to pulse oximeters where there is some clinical data that demonstrate that those models are accurate and precise in neonates.
- Dr. Michael Skeels commented that although there was only one economic analysis identified through the evidence review, the cost per case identified is relatively low compared to other screens the committee has recommended.
- Dr. Jeffrey Botkin asked if, within the committee's set of graded categories, there was a category of recommendation that encourages further development and additional research. Dr. Rodney Howell replied that there was only one category for recommending that a screen be added to the core panel.
- Dr. Gerald Vockley moved that pulse oximetry should be added to the newborn screening panel and Ms. Jana Monaco seconded the motion. The committee decided that there needed to be some qualifications for further data collection and research before the motion could be voted on. The decision was made to review the recommendation to add SCID to the core panel, which included a specific descriptor of data that the committee wanted to review in the first year of implementation, with the view of producing a similar recommendation for pulse oximetry.

X. Committee Internal Evidence Review Process

Bruce Nedrow (Ned) Calonge, M.D., M.P.H.
Chief Medical Officer
Colorado Department of Public Health and Environment

Dr. Ned Calogne explained that at the last meeting, it became clear that rare conditions posed a special challenge for assessing evidence. Dr. Calogne and other committee members have outlined the specific challenges and have suggested some potential solutions.

- It is challenging to assess the readiness of public health programs to incorporate new technologies into their systems. When approving new newborn screenings, the committee must also think about the process and how the new screens can be incorporated into the existing programs. For example, one unanticipated issue that came out of approving the SCID screening is that Medicaid will not pay for babies to be transported across state lines for a transplantation procedure. This policy, in effect, forces infants to go to medical centers with less experienced staff. Dr. Calogne believes that the committee should send a letter to Secretary Sebelius highlighting how the federal component of Medicaid can ameliorate this issue.
- The committee should change the way it discusses science and the evidence because the rarer the disease is, the greater the gaps in the evidence. We can set up a standardized process to summarize the evidence prior to voting through a table of studies and the directness of their evidence. This tool quickly highlights evidence gaps and helps with decision-making
- Dr. Calogne also proposed holding executive sessions for discussion of the evidence, where the deliberation occurs within the committee itself, away from special interests, advocacy and politics. It is possible to maintain transparency and public input while reserving the executive sessions for deliberations and frank discussion of the evidence. Public comments can still occur prior to the vote.
- The committee should explore modeling approaches for very rare disorders and make it part of an explicit standardized process for reviewing evidence. The committee could use the estimated incidence to determine the potential bounds of an improved outcome as well as the potential harms. For example, if there are only 100 cases per year, it is only possible to help 100 children. This assumes that there is a screening test with known sensitivity so providers can detect the children and also that there is a therapy or management strategy that alters the health outcome. The committee should have some sense of the efficacy of the treatment and management, so it can estimate the upper bounds of potential benefit. For example, therapy could help 50 out of the 100 children identified per year. The committee could use the specificity of the screening test to determine the upper bounds of potential harms. For example, all of the additional testing, unnecessary treatment, anxiety and ELSI issues generated by false positives. It is also difficult to measure incomplete penetrance i.e. true positives that cannot benefit from therapies. Once a screening test for a rare disease has been implemented, a data safety and monitoring committee could look at the Phase IV data to determine when the committee has enough evidence to know if the screening test is actually making a benefit.
- Dr. Michael Watson stated that he agreed with the concept of monitoring Phase IV data with states that are committed to implementing a population-based pilot. Dr. Calogne responded that sensitivity analysis can assist with assumption building.

- Dr. Coleen Boyle remarked that Dr. Calogne seemed to be proposing two items: an executive committee session and a workgroup that would make proposals for rare conditions. She moved to pass both items and Gerald Vockley seconded the motion. The motion passed unanimously 13-1-0 with one abstention (Peter van Dyck).
- Dr. Lloyd-Puryear asked for clarification if the organizational representatives would participate in the executive sessions. Dr. Denise Doughtery believed the executive sessions should only contain committee members. Dr. Michele Lloyd-Puryear did not believe that there was an exact definition of an executive session and believed that the committee can define it the way it wants. Dr. Calogne stated that the liaisons provide valuable input and he believed that they should be included. Dr. Joseph Bocchini concurred with Dr. Calogne.
- Dr. Ned Calogne moved that the executive session should include liaisons as well as committee members and Rebecca Buckley seconded the motion. The motion passed unanimously 13-1-0 with one abstention (Peter van Dyck).
- Dr. James Perrin presented methods of improving the grading of the evidence, including improving the tables of evidence that the committee reviews prior to a vote. Originally, the committee had a list of list of 8-12 questions that were to be included in any evidence summary but the committee does not typically discuss all of the questions for each condition. Instead, they typically focus on 3-4 questions. Generally the questions concern test characteristics, evidence base, and the populations affected. Population-based testing data is typically one of the critical questions for the group. Other key questions concern the value of early identification, whether or not treatment helps the patients and the availability of follow-up diagnosis and treatment. Incidence and prevalence is normally seen as less critical, although it helps the committee establish the bounds of harms and benefits. Finally, the committee has looked at the natural history of the condition without treatment.
- The evidence the committee review frequently varies in quality and consistency. There is often quite limited evidence of the availability of follow-up care and the effectiveness of early intervention. Dr. Perrin believes that the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach would be a relevant one for the committee and noted that AHRQ-funded evidence centers were now using it as a strategy for categorizing data. High evidence means that further research is unlikely to change confidence in the estimate of the effect, while low evidence means that the effect of further research is very uncertain. The majority of GRADE efforts have applied to treatments rather than diagnostic screening and assessment. It is rare that a researcher would conduct a randomized control trial of screening versus no screening; however, randomized control trials are considered high quality evidence within the GRADE approach. Cross-sectional or cohort studies are also considered high quality evidence and sometimes these models are used by researchers investigating screening. Normally, the evidence presented for screening is historical control and the biases are relatively high. Almost all of the studies the committee is likely to review will be in the form of screening versus published comparisons, with no direct comparison. This would be rated low or very low under the GRADE method. Dr. Perrin proposed forming a workgroup to come up with a better method of labeling quality in studies when the GRADE label would be low or very low.
- Dr. Michael Skeels noted that it would be helpful to include economic analyses in the evidence presented to the committee. When committee members return to their home states they often face basic questions about costs and it helpful to have those studies identified. Dr. Calogne noted that it is fairly rare to see cost effectiveness studies of screening. Dr. Timothy Coate, the Director of Orphan Products at FDA, noted that the FDA process of assessing the value of a new drug has relevance to newborn screening.

MOTION # 4 PASSED: To set up a workgroup to improve the evidence grading system Dr. Ned Calogne moved the motion and it was seconded by Denise Doughtery. The motion passed unanimously, 15-0-0, with 15 YES and no abstentions or absences.

- Dr. Rodney Howell explained that the HRSA had done further research and discovered that there are some limits on closing advisory committee meetings. The regulation states that requests for closed meetings must be approved by GSA's Office of General Counsel at least 30 days in advance. It is not possible to hold a closed session today, but may be possible for future meetings.

XI. Access to Medical Foods and Formulas: Summary of Regional Surveys

Susan A. Berry, M.D.
Professor and Director
Division of Genetics and Metabolism
Department of Pediatrics
University of Minnesota

Dr. Rodney Howell introduced Dr. Susan Berry, a Professor of Pediatrics and Genetic Cell Biology and Development in Minnesota and asked her to present a summary of the regional surveys on medical foods the Follow-up and Treatment subcommittee conducted.

- Dr. Susan Berry acknowledged the members of Medical Foods Expert Panel, a subset of the Follow-up and Treatment subcommittee. She also acknowledged the expert participation of Dr. Mary Kay Kenny from HRSA in assisting with the data collection and analysis. The main purpose of the survey was to develop recommendations for overcoming barriers to short-term and long-term screening results. The subcommittee believed that there could not be improvement in newborn screening results if the patients were not able to access the treatment. Families often share their concerns about the costs of medical foods with the subcommittee.
- Dr. Berry read a comment from the mother of a child who needed medical foods. While the mother received assistance for her child's medical bills, she did not receive any assistance in paying for the MCT oil and the fat-free/ low-fat medical foods the child required to survive.
- Medical foods, also known as special formulas or protein substitutes, are not drugs they are substances of nutritional value required for the treatment of inborn errors of metabolism. The treatment is lifelong because traditional foods are harmful to people with inborn errors of metabolism. Because they are foods, they are typically excluded from coverage by many insurers and the affected persons are put in a position where they cannot survive without the foods but they cannot afford to buy them.
    - The formal definition of medical foods is "a food which is formulated to be consumed or administered internally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation". They provide a substantial portion of the nutrition and typically have a restricted amino acid component.
    - There are also supplements sometimes called neutraceuticals, which are pharmacologic doses of vitamins or cofactors.

    - Another item that falls under the definition are specially manufactured modified low-protein foods that enable the affected child to have a more normal lifestyle.

- Medical foods require physician supervision and are essential elements of therapies for the treatment of inborn errors of metabolism.
- In June 2008, representatives of the Follow-up and Treatment subcommittee met with representatives from insurance companies and discovered that each plan has a different set of rules and practices and laws vary from state-to-state.
- Therefore, to inform public policy, the subcommittee decided to conduct a medical foods parent survey of insurance coverage of medical foods for children with metabolic conditions. It took about two years to complete. The objective was to look at the families' coverage and the actual costs of the medical foods and the materials needed to administer them. The survey asked about the children's requirements for medical foods and formulas, modified low-protein foods, prescribed supplements and materials needed to administer them. The survey asked parents to estimate out of pocket expenses and covered costs. The subcommittee completed cognitive interviews and pre-tested the validity at three sites. An important caveat is that this is a survey of convenience—the children and their families were 305 volunteers who resided in the NYMAC region (region 2), the Southeast region (region3), and two centers in region 4. The regional centers collected data and provided it to HRSA for analysis. Findings:
    - Approximately 25% of the children more than one funding source. Only 3 children did not have any insurance.
    - About 30 of families with children under age 3 used WIC.
    - If families obtained the medical foods or other products from a pharmacy, it was typically covered by insurance. In many states, medical foods are supplied through a state or county health department. However, if the medical foods were obtained directly from the manufacturer or over the internet, the families generally paid out-of-pocket. Medical foods obtained from medical supply and home health companies vary on whether or not they are covered.
    - Dietary supplements are typically supplied by pharmacies through a prescription and are covered by insurance.
    - Feeding supplies are typically covered by insurance.
    - The major cost impact on families was for medical foods obtained directly from the manufacturer or over the internet. Many families were using multiple sources (Medicaid, State, private coverage and out-of-pocket) to paid for the medical foods, particularly the modified low-protein foods. An average family would pay approximately $3,800 per year out-of-pocket. Around 20% of the families using medical foods, 30% of the families using supplements, 35% of the families using feeding supplies, and for about 60% of the families using modified low-protein foods had to pay out-of-pocket.
- The subcommittee will continue to monitor the progress of the Medical Foods Equity Act and the benefits package. Medical Foods may possibly be made an essential benefit under the new health care reform regulations. They also intend to continue to work with the FDA's Office on Orphan Products in addressing regulations.

- Dr. Timothy Cote, the Director of the Office of Orphan Products, explained that the term "Medical Foods" is only defined in the law in one place, the Orphan Drug Act. Because that definition is so broad that it is difficult to form any regulations around it. Dr. Cote believes that the group should identify the products that actually treat disease and come up with a new term such as "metabolic product" as a subset of the medical foods that specifically treat the 29 metabolic diseases identified by the committee. Some options include citizen's petitions which force the agency to move forward with promulgating a proposed notice of rulemaking.
- Dr. Michael Watson asked if the letters drafted by Dr. Susan Berry mentioned only the disorders identified through newborn screening or all metabolic disorders. Dr. Howell replied that the letters mention the 29 disorders identified by the committee, but reference other relevant metabolic disorders.
- Dr. Gerald Vockley believed that it is important to publish and make the information more broadly visible. He did not believe that extending the survey to other regions or age groups would not do much to move it forward.
- Dr. Ned Calogne opined that the letter to the Secretary would be stronger if it included a prioritized list of products.
- Dr. Coleen Boyle reminded the committee that repeating the survey could be an important method of gauging the effectiveness of any policy changes.
- Dr. Susan Berry remarked that several regions believed that there would be additional impact if the survey was extended to other regions.
- Dr. Frederick Chen noted that if the FDA's medical foods proposal made it through the Federal Register process, the committee should comment on it.
- An unknown person remarked that the problem of coverage of medical foods is much more pronounced for patients over 18 years of age. Ms. Jana Monaco agreed with this comment. Dr. Rodney Howell noted that the purview of the committee is children and an adult survey may be better accomplished through the regional collaborative networks.

XII. Continuation of Committee Discussion on Candidate Nomination for Critical Congenital Cyanotic Heart Disease

During the lunch break, Dr. Gerald Vockley and Dr. Jeff Botkin developed a recommendation for CCCDH screening with pulse oximetry that included many of the considerations and qualifications for additional data collection and review that were brought up during the prior discussion session.

- Dr. Rodney Howell observed that the opinions of the committee members seemed to fall between categories 1 and 2 in the committee's category of recommendation grid. The committee seemed to require a little more evidence or qualifying language to make it comfortable with a category 1 recommendation.
- Dr. Gerald Vockley moved that the Committee make the following recommendation: "NIH shall fund research activities to determine the health outcomes of affected newborns with CCHD as a result of prospective newborn screening. CDC shall fund surveillance activities to monitor disease incidence. Pass it around. HRSA shall guide State health departments in the integration of screening into their programs, and then HRSA shall also fund the development of, in collaboration with public health, health care professional and family organizations, appropriate education and training materials for family and public health and health care professionals relative to screening and treatment of CCHD." Dr. Jeff Botkin seconded the motion.

- Dr. Ned Calogne remarked that the proposed recommendation lacks specific cutoffs, types of technology and timing; therefore, it is uncertain the exact nature of the screening that the committee would be recommending. Furthermore, there is a critical evidence gap of the benefit of adding a pulse oximetry screen compared to usual care. He does not believe that false positives are much of an issue if the screening is timed correctly. His greatest concern is that there is a risk that the committee will be shown to have made the wrong decision at a future point in time. At times it may be necessary to move beyond evidence in making a recommendation, but the committee needs to be honest with itself that this is what it is doing.
- Dr. Denise Dougherty remarked that there needs to be a way to measure the processes of care and the instruments that are being used to see if there is a connection between the screening, the processes of care afterwards, and the outcome. Dr. Coleen Boyle replied that the surveillance piece should give the committee the required outcomes if they are linked to infant mortality. The objective is not simply to monitor children who have congenital heart disease, but to use the surveillance system to determine whether or not mortality is impacted by the implementation of the screening. Dr. Rodney Howell reminded the committee that there were a similar set of recommendations made when they added SCID to the screening panel and that Secretary Sebillus is expecting a report those activities in May 2011 and has provided funding to do the data collection and analysis necessary.
- Dr. Michael Skeels asked if, by adding qualifications to the recommendation, the committee is moving beyond its agreed upon framework for making recommendations to the Secretary of Health and Human Services. Dr. Rodney Howell replied that the committee is functioning within the framework in the same way it did when making the SCID recommendations.
- Dr. Ned Calogne was part of the workgroup that drafted the original recommendation framework and commented that there was originally a provisional category where pulse oximetry would have fit better but the committee ultimately decided to discard this category. However, all evidence-based methods are meant to evolve and perhaps the committee should revisit adding some type of provisional category to its framework.
- Gerald Vockley observed that he doubts that many of the diseases the committee will likely deliberate could unequivocally meet the category one criteria because the rigorous evidence does not exist in most cases. He would recommend adding a provisional category back into the framework.
- Dr. Michelle Lloyd-Puryear reread the recommendation with the additions to the wording: "Although there are recognizable evidence gaps, there are compelling reasons for recommending for using pulse oximetry to screen newborns for critical congenital cyanotic heart disease (CCCHD). SACHDNC recommends the addition of screening for CCCHD to the recommended uniform screening panel with the understanding that the following activities will also take place in a timely manner:
    - The National Institutes of Health 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 Centers for Disease Control and Prevention shall fund surveillance activities to monitor disease link to infant mortality and other health outcomes;
    - The Health Resources and Services Administration "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."

- Dr. Ned Calogne remarked that he was reluctant to tell states and clinicians to do pulse oximetry screening without specifically recommending how to do it. Dr. Christopher Kus concurred with Dr. Calogne. Dr. Tracy Trotter asked if the committee has ever specifically weighed in about cutoffs and specific technologies. Dr. Rodney Howell replied that it had not. Dr. Jeff Botkin suggested adding some language to say that HRSA shall guide the development of screening standards. Dr. Lloyd-Puryear added the line "The Health Resources and Services Administration 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."
- Dr. Kwaku Ohene-Frempong suggested that the committee should recommend the measurement of oxygen saturation itself rather than the specific tool currently used to do this (pulse oximetry), because future technological advances may render pulse oximetry obsolete. Dr. Balaji Govidnaswami commented that the current evidence-based screening method is transcutaneous pulse oximetry. Oxygen saturation can also be measured directly through the blood stream, but this method is not as accurate.
- Dr. Michele Lloyd-Puryear projected the following recommendation on the screen: ""Although there are recognizable evidence gaps, there are compelling reasons for recommending screening newborns for critical congenital cyanotic heart disease (CCCHD). SACHDNC recommends the addition of screening for CCCHD to the recommended uniform screening panel with the understanding that the following activities will also take place in a timely manner:
    - The National Institutes of Health 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 Centers for Disease Control and Prevention shall fund surveillance activities to monitor disease link to infant mortality and other health outcomes;
    - The Health Resources and Services Administration "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."
- Dr. Jane Getchell asked if the committee made the recommendation would the responsibility for screening automatically become the responsibility of state programs. Dr. Rodney Howell confirmed this and Dr. Coleen Boyle commented that many states have birth defects monitoring programs that are linked with infant mortality, and these programs can do linkages to hospital discharge. Dr. Watson commented that according to the Newborn Screening Saves Lives Act, if a state does not meet the standards established by this committee, there could be an impact on their federal funding.

MOTION #5 PASSED: Although there are recognizable evidence gaps, there are compelling reasons for recommending screening newborns for critical congenital cyanotic heart disease (CCCHD). SACHDNC recommends the addition of screening for CCCHD to the recommended uniform screening panel with the understanding that the following activities will also take place in a timely manner: 1. The National Institutes of Health 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; 2. The Centers for Disease Control and Prevention shall fund surveillance activities to monitor disease link to infant mortality and other health outcomes; 3. The Health Resources and Services Administration 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; 4. The Health Resources and Services Administration 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. Dr. Gerald Vockley moved the motion and it was seconded by Dr. Jeff Botkin. The motion was approved 13-1-1 with 13 YES votes, 1 NO vote (Dr. Ned Calogne) and no absentions. One member was ABSENT(Dr. Alan Guttmacher).

- Dr. Rodney Howell requested that committee members send agenda items for the January meeting to Dr. Michele Lloyd-Puryear. He noted that the other committee meeting dates for 2011 are January 28-29, May 5-6 and September 22-23.

MOTION #6 PASSED: To endorse the newborn screening quality measures proposed by the National Quality Forum. The recommendation includes the caveat that the National Quality Forum should assess the validity, feasibility and scientific acceptability of the quality measures Dr. Ned Calonge moved the motion and it was seconded by Dr. Kwaku Ohene-Frompong. The motion was approved 13-1-1 with 13 YES, 1 NO (Dr. Denise Doughtery) and no abstentions. One member was absent (Dr. Alan Guttmacher).

MOTION #7 PASSED: To adjourn the meeting. Dr. Gerald Vockley moved the motion and it was seconded by Dr. Rodney Howell. The motion passed unanimously14-0-1 with 14 YES and no abstentions. There was one absence (Dr Guttmacher).

- The meeting was adjourned at 2:50 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.

Appendix A. Written Public Comments

Comments On Congenital Heart Disease (CCCHD)

1. Balaji Govindaswami, M.D., M.P.H., Chief and Director, The Valley Medical Center NICU
2. Annamarie Saarinen, Parent Advocate, 1in100 and Newborn Coalition

1. Balaji Govindaswami, M.D., M.P.H.

Chief and Director, The Valley Medical Center NICU

HHS Advisory Committee on Heritable Disorders in Newborns and Children

September 17, 2010

2. Annamarie Saarinen

Parent Advocate, 1in100 and Newborn Coalition

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