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

Summary of 25th Meeting

September 22–23, 2011

Washington, DC

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children was convened for its 25th meeting at 8:40 a.m. on Thursday, September 22, 2011, at the Renaissance Washington Dupont Circle Hotel in Washington, DC. The meeting was adjourned at 12:40 p.m. on Friday, September 23, 2011. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments.

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Thursday, September 22, 2011

I. COMMITTEE BUSINESS

R. Rodney Howell, M.D.
(Committee Chairperson)
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In welcoming the Advisory Committee members and audience to the 25th meeting of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, Chairman Rodney Howell noted that this meeting would take advantage of the transition of several committee members to review the past, present, and future work of the Advisory Committee.

- Dr. Howell introduced the following new members of the Advisory Committee:
    - Dr. Charles Homer, cofounder of the National Initiative for Children's Healthcare Quality, of which he is the president and chief executive officer; associate professor in the Department of Society, Human Development, and Health at Harvard University School of Public Health; and associate clinical professor of pediatrics at Harvard Medical School.
    - Dr. Stephen McDonough, board certified pediatrician in North Dakota; active with North Dakota Department of Health; served as medical director of the newborn metabolic screening program.
    - Dr. Dietrich Matern, associate professor of laboratory medicine at the Mayo Clinic College of Medicine; co-director of biochemical genetics laboratory at the Department of Laboratory Medicine at Mayo Clinic.
    - Ms. Cathy Wicklund, head of genetic counseling program at Northwestern; active in field of newborn screening; served on the Secretary's Advisory Committee for Genetics, Health, and Society; active in Institute of Medicine roundtable on translating genome-based research into health.
    - Ms. Andrea Williams, founding executive director of the Children's Sickle Cell Foundation; has been serving on SACHDNC Education and Training Subcommittee
- Noting that this would be his last meeting as chair of the Advisory Committee, Dr. Howell thanked departing committee members Rebecca Buckley, Ned Calonge, Tracy Trotter, and Gerry Vockley.
- Dr. Joseph Bocchini moved to approve the May 2011 meeting minutes and Dr. Tracy Trotter seconded the motion. The minutes were approved unanimously with one member absent (Dr. Alan Guttmacher).
- Recent Advisory Committee correspondence includes: (1) a response from the Secretary on screening for sickle cell carriers, (2) the Secretary's expression of appreciation for the report this Advisory Committee prepared regarding SCID, (3) a response from the Secretary to our recommendation on a newborn screening emergency preparedness for the HHS contingency plan, and (4) a response from the Secretary to this Advisory Committee's recommendation concerning critical congenital heart disease screening.

- The Secretary has decided to adopt the Advisory Committee's recommendation to add critical congenital heart disease (CCHD) to the recommended uniform screening panel for newborns (RUSP). This will be the second addition to the RUSP.
    - The Advisory Committee's CCHD recommendation included four additional recommendations, which the Secretary has accepted, for federal action to address evidence as implementation moves forward. To the response letter, the Secretary appended the Interagency Coordinating Committee (ICC) Federal Plan of Action that commented on each of these areas. The Plan identifies specific federal government agencies responsible for carrying out these activities.

- Dr. Jeffrey Botkin expressed hope that this Advisory Committee will have an ongoing role with evaluating and coordinating the data as it is generated.
    - The Secretary supported the Advisory Committee's first three recommendations regarding sickle cell disease carriers: (1) individuals should know their medical risk for various disorders, including their carrier state for sickle cell disease, (2) evaluation and screening for sickle cell disease and other genetic conditions should take place within the individual's medical home, with counseling about the implications of the information, and (3) during routine annual medical evaluations, all potential athletes should receive education on safe practices for the prevention of exercise and heat-induced illnesses. The Secretary recommended the Advisory Committee work with other agencies to further develop guidelines and education resources for the other two recommendations.

- Dr. Howell noted that several articles are included in the briefing materials, including Dr. Andrew Ewer's article on pulse oximetry screening for newborns that was presented to our CCHD evidence review workgroup in January and Dr. Alex Kemper's article on strategies for implementing CCHD screening for infants published by the American Academy of Pediatrics.

II. A CELEBRATION OF THE COMMITTEE'S PAST

A. CDC Lists Advances in Maternal and Infant Health as One of the Past Decade's 10 Great Public Health Achievements.

Coleen Boyle, Ph.D.
Committee Member

Dr. Coleen Boyle reported, via telephone, that the CDC has identified the expansion of screening newborns for metabolic and other heritable disorders as one of the 10 great achievements in public health for the past decade. This recognition reflects the achievements of the hard work of the Advisory Committee. Improvements in technology and endorsement of a uniform newborn screening panel have led to earlier intervention and lifesaving treatment.

B. History of the Evidence Review Process

Jim Perrin, M.D.
External Evidence Review Workgroup

Dr. James Perrin reviewed the work of the External Evidence Review Workgroup over the past 4–5 years. The workgroup attempts to provide clear and transparent evidence to help the Advisory Committee make difficult decisions with respect to new conditions.

- In 2007, with the help of Mass General Hospital and Duke Clinical Research Institute, a process for systematic review of evidence was outlined and tested.
- Guiding principles of the review are (1) adaptation of established review processes to the challenges of rare disease evidence review; (2) transparency in our operations in data abstraction and approach to the review; (3) recognition of the challenges regarding evidence about rare disease; and (4) inviting stakeholder access and input to the process.
- Objectives of the review are to provide timely information to the Advisory Committee for its consideration of new conditions for newborn screening.
- They developed a clear conflict of interest policy modeled after the Institute of Medicine's requirements for committee membership. It applies to all staff members, anyone who serves as a consultant, and anyone else the group talks with about the condition to assure that no person external to the group has been able to unduly influence the decisions ultimately made by the Advisory Committee as a result of the ERWG's work.
- The evidence review workgroup provides data as transparently and objectively as possible to the Advisory Committee; it does not make decisions.

- As each evidence review process starts, the workgroup attempts to define the key questions and develop a case definition. To assist with developing the case definition, experts are brought into the group early in the process. Ultimately, the nominator in conjunction with the Evidence Review Group establishes a case definition.

- The next step is a systematic review of the existing literature in order to develop a clear understanding of the known information in published literature and to determine whether there are any questions that need further expert information. The literature review is limited to English language studies that are peer-reviewed and that are human studies. Materials used must meet the case definition and must answer some of the key questions asked. Three investigators review the abstracts from which each develops a subset of articles.

- To gather additional information, the ERWG contacts key investigators who have worked extensively in the area. These experts are not limited to the United States. The ERWG asks these experts to provide unpublished raw data (if possible). This has been the highest focus because it helps the ERWG understand the full scope of the situation. It can be difficult to get raw data because if unpublished data is used, it becomes part of the public record.

- When evidence review results are presented, they follow the order and content of the main questions, and include decision analysis and decision model findings. Key findings are presented in summary and table form, and they indicate where evidence is absent.

- The key questions about the evidence ask whether there is direct evidence that the screening will improve outcomes; whether a case definition exists and what is known about the natural history, spectrum, incidence, and severity of the disease; whether the screening test has analytic and clinical validity and has utility (also ask about the specifics of timing of the screening and its follow-up); and whether the treatment improves health outcomes and is standardized and widely available.

- The evidence review attempts to understand the benefits of treatment, and the costs and harms of screening, diagnosis, and treatment. There is usually little information available about harms and risks, and even less available on costs.

- The challenges faced by the ERWG have included (1) the lack of a clear case definition (e.g., Krabbe's disease has a wide variation across the spectrum of disease severity for people who are screened positive); (2) the conditions, although very severe with often fatal outcomes, are extremely rare and thus there is a lack of randomized trial data; (3) a lack of good population studies of screening (to document them well for sensitivity and specificity several years of studies are required); (4) costs and benefits are rarely well documented; (5) in some cases, critical sources of information are unpublished and difficult to ferret out.

- The evidence review workgroup has produced six reports for the Advisory Committee: Pompe disease (2008), severe combined immunodeficiency (2009), Krabbe disease (2009), hemoglobin H disease (2010), critical congenital cyanotic heart disease (2010), and a preliminary report on neonatal hyperbilirubinemia (2011). Other activities of the workgroup include four journal articles published in 2010 and 2011.

The Committee was invited to comment or ask questions.

- Dr. Howell asked which challenge was the most perplexing. Dr. Perrin replied that one of hardest areas is the weighing of the evidence. In traditional terms, the evidence available varies from weak to awful in most cases. From the viewpoint of public policy that is not satisfactory. The task is to find a satisfactory way to present evidence to the Advisory Committee such that it clarifies where the evidence is truly helpful and where it is suspect.

- Dr. Howell followed up by asking how the workgroup's efforts are viewed by the hard-nosed evidence review world. Dr. Perrin answered that the group has developed credibility within the community, garnering recognition that their work is responsible and transparent and that it tries to make the best use of available evidence.

    - Dr. Ned Calonge added that the evidence synthesis and translation community understands this is a difficult problem. The most important thing was putting that group in a room to understand the problem and understand that the group was moving forward to address the issues of translating and synthesizing evidence in the face of no evidence. This provided a launching point for decision making and modeling. The group's ongoing commitment to refine evaluation methods in this area is a much-needed long-term commitment.

    - Dr. Alan Fleischman commented that one of the great contributions of the Advisory Committee chair and the workgroup chair has been to give credibility to the process. Prior to that very structured, competent, thoughtful review, there were critics in the evidence-based world and the bioethics community who questioned the process. This team has brought credibility to a public health problem that needed to be addressed.

- Dr. Jerry Vockley commented that the big remaining challenge in the evidence-based process rests with individuals in the field dealing with patients and their families.

- Dr. Botkin feels that our greatest challenge is continued data collection after the initial implementation and periodic reviews of the data for reconsideration.

    - Dr. Howell added that a great example of doing this was the group's work on SCID, where it was clear that screening was a very good idea but a large population study was needed to demonstrate the effectiveness of the screening test. The same must be done for CCHD as new data become available.

    - Dr. Perrin concurred that the Advisory Committee will probably never have enough evidence at the time it must make a decision, and revisiting later evidence as it develops would be fruitful.

    - Dr. Howell noted that the newborn screening translational research network was established so there would be a systematic evaluation of new technologies and treatments that can inform the Advisory Committee.

- Dr. Rebecca Buckley has spent the past few months working with newborn screeners in establishing the SCID screen. She frequently hears from them that, for all the things they screen for, not many cases are found. She expressed interest in whether the Advisory Committee will be reviewing those.

- Dr. Perrin explained that the evidence review group only reviews at the bequest of the Advisory Committee, but that anyone can submit a nomination for a condition review.

- Given the current financial climate, Dr. Christopher Kus would like to find a way to improve our handle on the cost benefit aspects of the conditions and their screening.
  - Dr. Perrin suggested that the Advisory Committee devise other strategies for developing estimates in that area, because there is no published or easily available evidence on which to base such an analysis.

- Dr. Don Bailey suggested that the workgroup consider producing recommendations for advocacy groups, clinicians, and researchers who seek to promote a specific condition for nomination. The recommendations could include examples of creative approaches to studying rare diseases and bringing the evidence forward that is useful to the evidence review workgroup.
  - Dr. Perrin noted that the workgroup is preparing a manual of procedures, and suggested that some public modules for families and clinicians could be derived from that manual.
  - Dr. Denise Dougherty would like to see the Advisory Committee become proactive in recommending research infrastructure and general protocol to be used so it can get better evidence and is not always playing catch-up.

- Dr. Calonge noted that this group has an opportunity to lead the way in the using modeling for decision making. The Advisory Committee can make recommendations for research that would fill in the evidence gaps and more broadly indicate what type of research would benefit us in terms of the assumptions. He noted that the Advisory Committee essentially attempts to decrease the risk of being wrong; a condition is added to the list when Advisory Committee members are relatively certain they are not wrong. A landmark of the CCHD review was that it was modeled with the assumption that the gaps would get filled in as it rolled out. He hopes that in 10 years the Advisory Committee will have the discipline to review new evidence and reverse prior decisions as appropriate.

C. History of the Other Work of the Committee

Alex Kemper, M.D., M.P.H.
External Evidence Review Workgroup

Dr. Alex Kemper opened his presentation stating that the work of SACHDNC has led to improvements in the lives of children and their families. The Advisory Committee addresses broad issues related to improving health outcomes through newborn screening. Much of that work is done through its subcommittees, which generate surveys, white papers, and recommendations to SACHDNC. In this history, Dr. Kemper focused on the recommendations that the Advisory Committee forwarded to the Secretary.

- SACHDNC was chartered in 2003 with a broad scope to provide advice and recommendations to the Secretary of Health and Human Services, to provide technical information to the Secretary for the development of policies and procedures, and to provide advice and information that would enhance the ability of the Secretary to reduce the mortality or morbidity from heritable disorders.

- Some of these activities were further defined and expanded through the Newborn Screening Saves Lives Act of 2007. Under this act, the Advisory Committee was charged with making systematic evidence-based and peer-reviewed recommendations, developing a decision-matrix model, standardizing language used for newborn screening programs, addressing issues of state capacity for screening and follow-up, developing educational programs for providers and parents, assessing costs and effectiveness of newborn screening activities, considering quality assurance, and coordinating surveillance activities.

- Dr. Kemper identified five primary areas of activity: health reform (including coverage for medical foods), education, long-term follow-up, a national contingency plan, and sickle cell disease.

    - Health reform and coverage for medical foods

        - A letter was sent to the Secretary on May 19, 2009, stating the Advisory Committee's concern for improved coverage by health care payers of medical foods and requesting amendments to Medicaid legislation regarding uniform coverage.

        - In response, on October 2, 2009, the Secretary wrote that she was neither adopting nor rejecting the Advisory Committee's recommendations because enacting legislation is not within her purview.

        - The Advisory Committee sent a follow-up letter to the Secretary on March 23, 2010, in which they encouraged (1) the CMS to streamline the billing process for newborn screening, (2) the CMS to pilot payment method for integrated care through the medical home for children screened positive for a heritable disorder, and (3) adoption within HHS of the newborn screening use case for the electronic exchange of data. The letter also requested support for the closure of gaps in insurance coverage for medical foods.

        - On June 14, 2010, the Advisory Committee sent another letter to the Secretary emphasizing the importance of the medical foods coverage issue.

        - The Secretary responded on September 23, 2010, to the March 23 letter with acceptance of the first three recommendations. The medical foods recommendation was again not accepted.

        - In response to the June 14 letter, the Secretary wrote on December 14, 2010, that she appreciated the information sent on medical foods and affirmed that she would use it in the decision process, but that she needed to wait on the recommendations of other government agencies, at which point serious consideration would be given to the issue.

        - The Advisory Committee has a good relationship with the HRSA-funded regional collaboratives (RC) that work on improving the process of newborn screening. The RCs have conducted surveys to understand what is challenging families around the receipt of medical foods and have developed projects to help families. Through the national coordinating center, the RCs are able to disseminate best practices to other RCs. SACHDNC, through its recommendations, is having an important effect on the RCs.

        - An illustration of the importance of the Advisory Committee's work is exemplified in one of its subcommittees' definition of long-term follow-up care—newborn screening is not just a matter of case identification but includes a lifespan component.

    - Education

        - The early work of the Advisory Committee anticipated the Newborn Screening Saves Lives Act. In a letter dated December 19, 2006, the Advisory Committee recommended that the Secretary develop a mechanism to review the methods use to educate parents about newborn screening, and this has remained an important theme of the Advisory Committee's work.

        - The education subcommittee developed a report describing the need for primary care education that was endorsed by the SACHDNC. This led to funding, through HRSA, of a training institute about genetics in primary care.

    - National Contingency Plan

        - The plan, presented to the Secretary on August 6, 2010, recommended that each state have a newborn screening contingency plan. With support from HRSA, the CDC will lead efforts to coordinate implementation with the assistant secretary for preparedness and response. The RCs have taken an active role in disaster planning.

        - A letter arrived this month wherein the Secretary has further endorsed the contingency plan.

    - Sickle Cell Disease

        - The Advisory Committee's recommendations regarding testing of athletes for sickle cell trait gained support from the Secretary in a letter dated June 27, 2011. This is another example whereby the Advisory Committee took on a complex issue and came up with common sense recommendations that are now being adopted by the secretary.

- Dried Blood Spots

    - The Advisory Committee advised that states develop policies related to access, disposition, education, and documentation regarding blood spots. It has encouraged a national dialogue and explored the usability and feasibility of a national repository.

    - On April 13, 2011, a letter from the Secretary to SACHDNC stated that those particular recommendations were not ready for adoption, but referred the issue to the Interagency Coordinating Committee on Newborn and Child Screening.

- Dr. Kemper noted that an important aspect of this Advisory Committee has been to help others in the community think about some of the more complicated issues surrounding newborn screening.

- In summary, Dr. Kemper noted that the Advisory Committee has developed a sound model of success. The subcommittees develop reports under the guidance of the larger Advisory Committee, and these reports are used to inform recommendations to the Secretary.

Dr. Calonge suggested that, due to the large turnover in members, this is a good time to examine the subcommittees and their scope and work. He recommended adding a methods subcommittee.

D. The Role of Engaging Parent/Consumers to Weigh-in/Acknowledge Viewpoints

Jana Monaco
Former SACHDNC Member

Ms. Jana Monaco brings the perspective of a consumer on where the Advisory Committee has been, where it is today, and where it hopefully will go.

- Ms. Monaco defined a consumer as one who acquires goods or services for direct use or ownership rather than for resale or use in production. A patient is a person who requires medical assistance. Medical consumers are people seeking a service; in the context of newborn screening a consumer seeks a service to save their children's lives.

  - From the Advisory Committee perspective, a consumer is a member of the public with special expertise about or concern with heritable disorders. Those coming to the table as consumers have distinct areas of expertise.

- Consumer advocates of newborn screening take on various roles: (1) patients and families, who are considered the experts; (2) parents of affected children who were not screened; (3) parents of deceased children who were not screened; (4) parents of affected children who were detected early; and (5) adult patients.

- Ms. Monaco used the analogy of a consumer report to describe the progress and activities of the Advisory Committee.

  - At the time of the Advisory Committee's inception, many states were not screening newborns, supplemental information was not provided to families, many disorders were diagnosed only when the child was in crisis, there was one consumer member on the Advisory Committee, and the public comment period was the only opportunity for outside input.

  - Today, at the Advisory Committee's 25th meeting, all states have expanded newborn screening, a recommendation was made to states to inform them about supplemental screening (made following this Advisory Committee's first meeting), babies are now diagnosed with screening instead of in emergency rooms, there are several consumer members on the Advisory Committee and integrated into all three subcommittees, the consumer voice is included in RCs, the Newborn Screening Saves Lives Act was passed, and the public comment section of this meeting is vital to giving voice to the interests of consumers.

- Advocacy groups are a critical entity of Advisory Committee discussions. They have distinct needs and concerns related to newborn screening, and they bring first-hand experience to the table.

- To increase consumer involvement, consumer representation on the Advisory Committee must be increased. Ms. Monaco listed several ideas for getting consumer involvement from across the country, including expanding the public comment session to a "time for dialogue," providing scholarships for consumers to attend these meetings, partnering Advisory Committee initiatives with advocacy groups, and encouraging providers to link their patients with advocacy groups.

- Advocacy groups are an excellent resource for submitting nominations for the screening panel and for participating in the evidence review workgroup discussions. Children, families, and advocacy groups of conditions not yet included on the panel are the consumers who are not being serviced, and they are losing their children. These stakeholders understand the difficulties in the numbers.

The Committee was invited to comment and ask questions.

- Drs. Howell and Fleischman expressed gratification in seeing the advocacy community incorporate the Advisory Committee's recommendations into their plans at the local level.

- Dr. Fleischman further noted that, given the current fiscal environment, the participation of the advocacy community is critical. The Advisory Committee should consider attempting to understand the implementation constraints of its recommendations at the state level because states are working very hard simply to maintain the work they do and expanding it can seem unreasonable. The advocacy support will be critical in the state-by-state fights for implementation.

- Dr. Howell acknowledged the extraordinary activity and support of Michele Puryear who was the original executive secretary of this committee and served in that role through the 24th meeting. She is now in the Office of Rare Disease at the National Institutes of Health, and he wished her well there.

III. PRESENT WORK OF THE COMMITTEE

A. NBS Awareness Campaign—A Report on the Media Scan

Jennifer Nichols
Porter Novelli

Dr. Howell explained that the Advisory Committee charged the Subcommittee on Education and Training to start a newborn screening awareness campaign. To do that, the subcommittee decided the first step would be a scan to determine the current status. A media scan was completed by Porter Novelli under the guidance of HRSA and Altarum Institute.

- Ms. Jennifer Nichols explained that the purpose of the environmental scan was to assess the field readiness for a campaign to raise awareness about newborn screening. Porter Novelli explained their three-step process.
    - The first step was to conduct an environmental scan that broadly determined what is on the Internet, what providers are saying, and what is reaching consumer.
    - The second step is to convene a strategy summit with newborn screening stakeholders for strategic planning and consensus building.
    - The third step will be a set of recommendations regarding future steps to build consumer awareness.
- Since the Internet is the most popular place people go when seeking health information, besides seeking health information directly from physicians, Porter Novelli used a Web-based approach to search standard terms that parents-to-be would use when searching for information about newborn screening on the Internet. They used Style Survey, a proprietary database licensed by CDC and other HHS agencies that annually surveys consumer perspectives on health services.
- Porter Novelli examined what initial information people are finding on the Internet. Porter Novelli reviewed Google, Yahoo, WebMD, and Wikipedia using a standard set of search terms, such as "newborn screening" and "heel prick test," to determine what people find on the first four pages of a search. The most frequently referenced sites were CDC, AAP, and March of Dimes. Other frequent sites included NIH, Cystic Fibrosis Foundation, Wikipedia, and WebMD. The most referenced sites consistently had an educational orientation, providing definitions and describing health impacts for the child and society, benefits of diagnosis and treatment, variations from state to state, and how procedures work. The information appeared to be neutral (no positive or negative bias).
- Porter Novelli then reviewed newborn screening information available from hospital and physician websites. Pediatricians generally have links to the AAP and the ACMG, but hospitals, in addition to such links, provide specific information on different conditions being screened for as well as explanations of how the screening varies from state to state.

- A media audit spanning the past 5 years was concluded on August 30, 2011. Out of 300 articles identified through search terms from the Web, newswires, newspapers, and medical journals, only 88 proved to be relevant to newborn screening. The articles tended to have an educational focus and had neutral or positive messaging; there was very limited press on the perceived negative aspects of newborn screening. Many of the articles were disease specific.

- Porter Novelli then conducted a targeted search for organizations and campaigns that provide information and resources on newborn screening. The American Academy of Pediatrics, Genetic Alliance, March of Dimes, National Newborn Screening and Genetics Resource Center, Save Babies through Screening Foundation, National Healthy Mothers, and Healthy Babies Coalition provide specific information for consumers. One general campaign, Saving Babies Through Newborn Screening, and two disease-specific campaigns, SCID Newborn Screening Campaign and CARES Foundation, provide newborn screening messaging.

- Porter Novelli conducted a brief review of the literature to better understand the attitudes and perspectives of consumers. The literature findings show that parents are generally positive about screening and perceive it as part of the process in hospitals. They have some anxiety about what happens in the care of a false positive or a false negative result, they are not familiar with most of the conditions screened for, and they have limited understanding of the issues around residual storage and research.

- Porter Novelli concluded that, while there is information about newborn screening online, it is only moderately accessible and it has not been optimized so as to be readily available to the average parent. Indirect exposure to information through the media and campaigns is very limited. The messages are neutral or trending towards the positive aspects of screening. In summary, Porter Novelli feels that more information is needed with regards to how providers share information with their parents, since what is posted on their websites is a limited slice of their interaction with their patients.

- Before embarking on an awareness campaign, more understanding of the consumer perspective is needed. The missing pieces include an understanding of where the consumer is starting from and what is already happening that could be folded into the campaign.

Dr. Howell invited comments and questions.

- Dr. Botkin commented that there is some literature out there that defines what parents want to know about newborn screening. For example, Dr. Terry Davis's group held several focus groups 5–6 years ago on this topic. A key outcome of that research was that parents do not want to know detailed information, such as a list of conditions. He asked if part of this project is to assess sites by those levels of criteria. Do they meet what we think we know about parents educational needs about these topics, or are those elements embedded in a more complicated data field that might be challenging for people to navigate?

    - Ms. Nichols responded that a standard Google search brings up a lot of irrelevant information mixed with information that is delivered in formats difficult to digest. Consumers go to Wikipedia and WebMD because they are digestible.

- Dr. Fleischman noted that most families do not come into meaningful contact with pediatricians and hospitals before labor and delivery, and the obstetrics community does not engage in newborn screening educational activities. While the AAP has done its job, the information is not getting to parents at the time they need it. The obstetricians and nurses are an important part of our educational arm. There is probably no way to empirically measure universal exposure to such education.

- Sharon Terry commented that using websites for the scan is like looking at a snapshot of the past because parents are now seeking and consuming information in different ways. How will Porter Novelli stay ahead of the curve if we go into campaign mode?

    - Ms. Nichols noted that it is difficult to justify the need to raise awareness when 95% of the media is neutral or positive. We will have to figure out where the campaign fits. We will need to talk more with parents to determine how they get their information and how we put the information there.

- Dr. Alexis Thompson asked about what consideration had been given to reaching families and communities that do not speak English as a first language or do not use the Internet as a source of information, specifically, communities with a high rate of poverty, African-American communities, and Hispanic communities.

    - Ms. Nichols conceded that this environmental scan is based on the population that has access to the Internet, which is a safer representation of the public now than it was 2–3 years ago. She noted that recent trends indicate that many who do not use computers are now receiving Internet information downloaded to their mobile phones; this is especially prevalent in the Hispanic community. These types of environmental scans are very secondary. Phase 2 will involve direct conversations with people to determine where else they get information.

- Tracey Trotter offered some background to this project. The Advisory Committee has been discussing an awareness campaign since 2004, and Coleen Boyle and Angie Colson, through the Subcommittee on Education and Training, picked up the banner about a year ago. The Advisory Committee conceived a four-phase approach that would attempt to replicate the successful autism, back-to-sleep and immunization campaigns. The Advisory Committee approved phase 1, and this environmental scan is the beginning of phase 1. The second part is to bring together as many stakeholders as possible to get a more real-life view.

- Because newborn screening is already very successful and nearly universal, Dr. Frederick Chen asked if part of the analysis could include potential negative effects of an awareness campaign.

    - Ms. Nichols gave examples of campaigns where community awareness already existed. In an early autism campaign, they did not get out ahead of the message and found themselves addressing the information that was already out there. Although a public health success, vaccinations were threatened with many messages coming from the media and literature. With newborn screening, we will need to determine what might potentially change in the messaging and how to address that.

- Ms. Katherine Harris said that NYMAC and Genetic Alliance are spearheading a program to provide newborn screening information to parents-to-be through childbirth educators, doulas, midwives, etc.

- Dr. Bailey suggested that in the next phase the Advisory Committee devise clear objectives that lead to the change Advisory Committee members want to accomplish as a result of the campaign.

B. Tour of Baby's First Test

Sharon Terry, M.A.
Organization Representative

Natasha Bonhomme
Genetic Alliance

- Ms. Sharon Terry noted that this project engages multiple communities and audiences in numerous ways. She delineated three questions for Advisory Committee members to consider as they tour the site. She also noted that it is critical to understand that the communication tools we are using are evolving at a rapid pace.
  - How should issues around the universal screening panel and other conditions be included in the site's educational efforts?
  - How can terminology be harmonized to represent all states?
  - What are our key messages? Are we looking for awareness or informed decision making?
- Ms. Natasha Bonhomme presented a tour of the site: www.BabysFirstTest.org, which is operational. It is designed to be the nation's newborn screening clearinghouse of information.
  - The "about newborn screening" tab provides general information about newborn screening—basic facts, resources, genetics, and family history. An important aspect of this site is that people can get as little or as much information as they need. Those who need more can easily navigate into detailed information.
  - Under the "what to expect" tab, parents are encouraged to become informed before the birth. Based on information from a HRSA project, it includes a discussion of the seven things parents want to know about newborn screening. It goes into detail about screening procedures, talks about results and different screening outcomes, and discusses what happens to the blood samples.
  - The "living with conditions" tab helps families navigate after receiving a diagnosis. The issues addressed in this section were brought to light during the research of the consumer-focused newborn screening project, which partnered with the Johns Hopkins Genetics and Public Policy Center and the University of Maryland. Key messages of the site are that it is important to get follow-up and speak with your health care provider and that there *is* life after diagnosis.
  - From the "about newborn screening" tab, visitors can access information on state programs. In an effort to show uniformity across states, the conditions listed at this time for each state are those on the recommended uniform screening panel. The intention of the site is to highlight the good work of the state programs in newborn screening. The states pages will continue to evolve. An important element on the state pages is the description of how newborn screening is paid for; this message is key to preserving screening in the state budgets.
  - "Find a condition" allows viewers to access extensive information about specific conditions that concern them. All conditions are cross-referenced with variants that the searcher may use. The

condition-specific pages provide tiers of information, from an at-a-glance overview to detailed scientific descriptions of the condition. All the condition pages were sent to the appropriate advocacy organizations for their input.

- From the home page, site visitors can access a variety of current information on major events in newborn screening. The site also posts a weekly blog, for which different partnerships are in the works including a blog to come out in October by the American College of Nurse-Midwives. The site also attempts to engage people in conversation through social media and has a link to Twitter.

- The site is laid out with very long pages and a lot of information. It was done this way because, when people are not sure what they are looking for, they will often skip material that is collapsed under a heading, not realizing it is key information. On the side of most pages, additional key resources and key facts are listed, giving people an opportunity to educate themselves, but not bombarding them with links. A usability test of the site's layout will be done.

Dr. Howell opened the floor for questions.

- Dr. Bocchini asked what the targeted reading level of the site is and whether the site would be available in other languages.

  - Ms. Bonhomme reported that the current reading level of the primary and secondary navigation pages is 8th grade. There are plans to bring that down to 5th or 6th grade. This will be difficult to accomplish on condition-specific pages which necessarily use complex medical terminology. By the end of project year (August 2012), the site should be available in Spanish. Because it will need to be professionally translated, the translated version may be implemented in phases. Ms. Terry added that, since the site's funding does not include translation costs, they are seeking funders interested in the interpretation and translation of this site.

- Dr. Nancy Greene asked whether the site has been optimized to rise to the top of the list in searches.

  - Ms. Terry reported that they are working on optimizing the site for search engines, but noted that so is every other website. Because of the relationship built from Ms. Terry serving on Google's health board, www.BabysFirstTest.org is being vetted to be one of Google's trusted sources. As a trusted source, the site would appear at the top of the search returns, along with Mayo Clinic and other similar sites.

C. Newborn Screening Translational Research Network

Michael Watson, Ph.D.
Organization Representative

Dr. Michael Watson reminded the group the Newborn Screening Saves Lives Act also established the Hunter Kelley research program at NICHD, which is broadly the newborn screening translational research network activity. The American College of Medical Genetics (ACMG) operates the coordinating center for this activity and is now ready to integrate grantees and contractors into the infrastructure and resources that have been under development.

- The Act lays out the goals of the NBSTRN: (1) Capture the evidence around newborn screening activities, particularly for conditions that are candidates for screening and for conditions that are already screened for but not fully understood. The NBSTRN research assess new technology and new conditions that are candidates for newborn screening, and it supports rare disease pilot studies across states in order to provide more robust information.

- The first wave of grants awarded in the program were in the area of developing clinical histories of newborn screening conditions. Outcome studies are also important, as they provide the longitudinal health care information that captures interval visits to physicians and treatment and long-term outcomes progress. As new therapeutics are developed, clinical trials will provide insight into the broad population impact around clinical interventions for these conditions.

- The NBSTRN Standing Committee oversees four major workgroups that define areas of activity. (1) The Clinical Centers Workgroup identified the datasets that define diagnosis and follow-up of patients in newborn screening. This was done early so a standardized terminology could be integrated with the National Library of Medicine; thus, it would become part what manufacturers and EMR systems build into their systems and ultimately allow EMR rather than independent capture of data. (2) The Laboratories Workgroup addresses a critical component of the translational research network, newborn screening laboratories and programs. This workgroup connects newborn screening and public health with the specialty and primary care providers. (3) The Bioethics and Legal Issues Workgroup look at unresolved issues of conducting this research. (4) The IT Workgroup crosscuts the other committees because of the need to factor in gaining permission and other elements when building an infrastructure that aggregates study data from widely distributed researchers.

- Several projects have been developed or are nearly complete.

    - The NBSTRN developed a website, www.nbstrn.org, which opened in June 2011 that includes both public and investigator content. Great care was taken to secure the privacy of information in the databases, and it is fully HIPAA-compliant. Guidelines were developed for researchers to assist in newborn screening understanding and knowledge.

    - As a research tool, a virtual biospecimen repository is being developed with dry blood spots and should be available in the spring or summer of 2012. The virtual repository allows researchers to gaze into the resources held by participating states. Information from other repositories will be added. A possible source of growth for the repository are the unique cohorts generated by industry investigations.

    - R4S, a region 4 collaborative for improving their test performance by capturing data from the newborn screening process, has been adapted to bring in pilot data as new tests are developed. In this way, everyone is working together and getting more robust data.

    - Tools to capture diagnosis at the point of care and to move data into warehouses or back to institutional EMR systems are being developed. These tools will also determine how to display data tools that allow investigators to analyze their data.

    - The next step will be to develop a method to bring public information about the studies back to the public and communicate it with the partnerships that make it possible.

- Dr. Watson explained some of the website's features. The site has a lot of information explaining its resources and how to use them. It allows extensive parsing of database queries and makes it possible to "clean up" the study populations. The site has resources that show available grant opportunities, describe issues around state IRBs, and allow investigators to questions.

- R4S is a Web-based database for the collection and display of data from true positive patients found in newborn screening. In addition to improving the quality of newborn screening, it allows discovery of new markers for screened conditions and prospective collection of data in pilot tests for new conditions and technologies. Several grantees are using it, including new Advisory Committee member Dietrich Matern who is creating a lysosomal storage disorder component. We also used the database for SCID studies. The database serves regional collaboratives, state programs, and translational research networks.

- The four areas of interest for the repository are surveillance, public health, patient care, and knowledge generation. There are 88 data elements in 24 data categories, which include demographics, SES, family history, prenatal history, newborn screening, and emergency management. Survey results show broad interest in each data element of all four interest domains. As new grantees come in, they add their standardized terminology through NLM.

- Dr. Watson explained that NBSTRN provides a centralized data warehouse to capture data from the multiple providers and investigators. Its infrastructure uses a REDCap database, a commonly used system evolved out of work at Vanderbilt work and used by 45 of the clinical translation science awardee institutions. This keeps the network compatible with multiple research infrastructures. There is no personal health information in the NBSTRN databases, but there are mechanisms to get back to the local physicians if required.

- The NBSTRN relates to the Advisory Committee on several levels. It facilitates evidence development that can support nominations to the Advisory Committee. At this juncture the mandates often are made before the evidence comes into the database, but that will turn around. It also provides a resource for post-market surveillance. By capturing data longitudinally, the Advisory Committee will be able to review how things are developing. Bioethical issues are also a critical aspect of current screening.

Dr. Howell invited questions and comments.

- Dr. Calonge asked if, in light of the inherent potential for misinformation that has come out of the genome-wide association studies (GWAS), there are opportunities for statistically significant but not clinically important, and potentially incorrect, associations looking across multiple metabolic markers in this method.

    - Dr. Watson responded that newborn screening is not ready for most things found in GWAS. Whole genome analyses are going to take us to a point where we can begin to interrogate the genome for other genes that are altering the outcome of the patient with that very strong genetic factor, and this will be one of the areas of research that brings the next generation of genome sequencing into newborn screening. It will take a long time, though, to aggregate enough factors to make this useful in newborn screening.

- Dr. Lorey countered that this is already taking place. It causes a dilemma because most grant applications require the sequencing data to be shared.

- Dr. Watson concurred that the field is changing quickly. Whereas at one time genetics research took place outside of practice, it is now moving into the point-of-care as translational medicine; something is learned from every patient that informs us on the next patient. The databases are important for learning, and how physicians can access these databases to improve the way they care for their next patient is under development. We want to build models to learn from day-to-day care how to better care for the next patient. This is a significant paradigm shift for NIH.

- In closing this session, Dr. Howell commended the Eunice Kennedy Shriver National Institute of Child Health and Human Development for funding this expensive and very valuable network.

D. Regional Genetic and Newborn Screening Services Collaboratives: Cross Regional and National Projects

Barry Thompson, M.D.
National Coordinating Center

Dr. Barry Thompson explained that the heritable disorders program's cooperative agreements, outlined and administrated by HRSA, allow the National Coordinating Center (NCC) and the seven RCs to act on procedures developed and recommended by SACHDNC.

- The central goal of the RCs is to ensure individuals have access to appropriate quality of care and genetic expertise in the context of the medical home. The overarching goals follow:
  - Building bridges between public health, medical home, geneticists and specialists, patients and families, and the MCHB;
  - Facilitating the movement of quality genetic and newborn screening services to local communities; and
  - Enhancing the activities of the RCs by providing the infrastructure, coordination, technical assistance, and resources necessary to address issues of universal importance, thereby avoiding duplication of efforts and allowing the regions to focus on their unique areas of need.
- There are seven NCC workgroup initiatives that assist the RCs by working on definitions, identifying and sharing practices, and improving communication between the RCs.
  - The action sheets (ACT sheets) are constantly under review and revision as clinical decisions support tools for the care providers.
  - Major progress has been made in evaluation measures for identifying areas of collaboration and technical assistance.
  - A minimal dataset with emphasis on surveillance and public health measures for long-term follow-up and research is under development.
  - The medical home concept continues to evolve. The goal is to achieve uniformity among RCs of its definition and application.
  - The publications workgroup coordinates efforts between RCs to develop abstracts and session proposals, increase participation, and reduce submission duplications at national meetings.
  - The telemedicine and telegenetics workgroup helps develop infrastructure in RCs that do not have it yet. A publication is coming out soon on telegenetics policy.
  - An interregional project on transition and opportunities for linkages with other centers and national partners works to increase the uniformity and approach of the transition model to facilitate linkages between genetic experts and primary care providers.

- The NCC pushes national issues to the local level by sharing information through the following emerging topics: health care reform and financing, health insurance, and workforce development. The NCC collaborates with seven national centers. In this way the RCs have connectivity with national centers and their information.

- National and cross-regional education and training programs

  - ACT sheets serve as clinical decision support tools for primary care providers with information around disorders on the newborn screening panel. Dr. Thompson acknowledged the AAP for subcontracting the Quality Improvement Innovation Network (QUIN) project to the NCC and ACMG. This project reviews the utility of Act sheets through feedback solicited from practices.

  - Funds from the NCC subcontract sponsor genetics and medical home visiting professorships that provide medical home providers to enhance their education. There have been eight professorships in the past 2 years.

  - The quarterly newsletter *NCC Collaborator* showcases activities of the NCC and RCs.

  - A recently completed hearing loss brochure for parents highlights the importance of genetics as an aspect of hearing loss during the newborn period.

  - To develop an increased degree of cultural competence, the ACMG sponsored relevant sessions at the past two annual meetings: (1) native American perspectives from the Navajo Nation and (2) a look at CPT1A screening among First Nations in the peoples of British Columbia and Alaska.

  - The *Genetics and Your Health* brochures address specific needs. Collaborations between the NYMAC and the Genetic Alliance Clearinghouse have enhanced the NCC's efforts at education. Dr. Thompson highlighted two successful training programs: the Sickle Cell Peer Educators Training program and the Genetic Metabolic Nutrition and Expanded Newborn Screening course.

- National and cross-regional long-term follow-up and treatment programs

  - Dr. Thompson provided a slide showing the long-term follow-up goals. The project is a bridge between the national centers funded by NIH and HRSA. It coordinates and accelerates efforts by engaging in health informatics technology and standardization efforts and by identifying the intersection of effective follow-up from newborn screening grantees and other follow-up activities.

  - There are many cross-regional projects in long-term follow-up. The HIPAA-compliant registry of diseases under the IBEM-IS recently shifted from HRSA to NICHD support. Developed by region 4, MyEIF is a Web-based tool for sharing current information about children with special health care needs involving family specialists and primary care providers. A region 1 project, going on since 1999, uses common data elements shared across a long-term follow-up system with national and local partners and interregional participation. The Southeast Regional Collaborative has a specific requirement for long-term follow-up systems and is working on a business plan for that type of activity. A Mountain States consortium implemented a survey on medical foods and nutrition management guidelines. New England collaborative has a quality improvement program and genetics assistance program developed in collaboration with heartland, mountain states, and western states.

- National and cross-regional laboratory projects

- The laboratory emergency preparedness exercises highlight the importance of genetic patients' needs when natural disasters occur. A specific example was the difficulty patients had during Hurricane Katrina in getting critical medical foods. This project has conducted scenario-driven tabletop exercises with state newborn screening and confirmatory laboratories through the RCs.
- In 2004, Region 4 started an MS/MS data project, now called R4S, to improve lab quality by comparison and clinical validation of tandem mass spectrometry cutoff values. It involves states from all seven regions and several countries, and it continues to expand.

- The regional collaboratives are our feet on the ground, made up of people involved in clinical activities and research labs. They facilitate cross development of projects that meet professional and personal success and encourage sharing of information.

E. Laboratory Quality Program

Carla Cuthbert, Ph.D.
CDC Newborn Screening and Molecular Biology Branch

Dr. Carla Cuthbert is chief of the newborn screening and molecular biology branch of the CDC. She talked to the Advisory Committee about the laboratory quality program in the CDC that has been operating for 30 years. The CDC, acting through this branch, has been given a congressional mandate through the Newborn Screening Saves Lives Act to provide quality assurance for labs involved in screening for newborns and children.

- The branch provides quality assurance for laboratories and tests, performance evaluation services, technical assistance, technology transfer, assistance to ensure analytic validity and utility of screening tests, and appropriate quality control and test materials to evaluate the performance of new screening tools.

- The branch's Newborn Screening Quality Assurance Program (NSQAP) team has the only comprehensive quality assurance program using the dried blood spots for newborn screening. The team provides filter paper evaluation for new lots, DBS reference and quality control materials, a system for proficiency testing, an Internet reporting site for laboratories, subject matter experts who follow up with states and labs on false-negative results, and training, consultation, and network resources. Many of the activities provided by the team are coordinated through a cooperative agreement with the Association of Public Health Laboratories.
  - This is a voluntary process on the part of states, and as of the end of 2010 all of them participate, as do 67 countries. At the end of 2010, 463 labs were enrolled and there is a waiting list to join.
  - Dr. Cuthbert showed a slide of the conditions for which the NSQAP provides quality assurance materials in dried blood spots. The list includes the recently added SCID.

- The Newborn Screening Translation Research Initiative is a smaller team that represents an ongoing collaboration between the CDC Foundation and the Molecular Biology Branch. The team's mission is to assure that the translation of research methods into routine laboratory tests for newborn screening leads to sustainable high-quality testing and healthier babies worldwide. The team develops new screening methods, so they can provide technical support for labs as they enroll in the program. The team interacts with state public health labs in the translational process, and adapts innovative technologies for screening and quality assurance.
    - One of the most important laboratory projects for this team at the moment is SCID, for which they have produced materials for TREC assay and developed a TREC assay specifically for dried blood spots. In addition, the team has ongoing work in lysosomal storage disorders and new and emerging technologies in newborn screening.
- The Biochemical Mass Spectrometry Laboratory team's mission is to work with public health partners to develop new mass spectrometry-based assays to detect and monitor metabolic disorders, and enhance newborn screening laboratory performance through innovative approaches to biochemical marker detection. Two of their highest priorities are to develop new methods for analysis of dried blood spots and to develop other pilot programs for tandem mass spectrometry analyte ratios.
    - In terms of their public health impact, the team has full coverage of the primary biomarkers for the 43 disorders, a quality control program for lysosomal storage disorders screening, and quality assurance materials to enhance analytical specificity.
- The Molecular Quality Improvement Program is a high priority of the branch. It was developed in response to the Secretary's acceptance, in May, of this committee's recommendation to add SCID to the panel. It is recognition of the need to provide support for public health laboratories as they bring molecular testing into their routine practices. Molecular screening brings new technologies into the newborn screening laboratory creating a need for new resources.
    - At the end of 2010, 36 states offered a molecular test, but not necessarily statewide. Now, these states are seeking to incorporate SCID into statewide testing.
    - The activities of this group include establishing a newborn screening molecular network that brings together APHL, public health laboratories, and our branch to share common knowledge and to identify gaps. They are also identifying best practices and making sure labs are well equipped to provide this testing. It is also implementation the NBS Molecular Assessment Program, which is a site visit to labs to review how they are doing with molecular implementation and to identify best practices (two visits have taken place). They are providing quality assurance research for the development of materials to identify and develop quality molecular methods for the DBS matrix. They are conducting a molecular characterization of quality assurance materials, and they are conducting other translational research to address needs identified by the newborn screening community and quality assurance protocols.
- The branch has three main priorities.
    - Sustain and strengthen existing quality assurance programs through two conditions

        - The branch is focusing on improving the number of samples and increasing the population variation from which samples - for cystic fibrosis DNA in California – are being tested.

        - The branch is collaborating with Ghana, which has high rates of sickle cell disease, to expand the proficiency of testing for hemoglobinopathies. With the assistance of Dr. Kwaku Ohene-Frempong, Ghana will provide samples for use in our program and in return we will provide Ghana with technical assistance.

    - Implement quality assurance programs for recent additions to the panel

        - The most recent addition was SCID. This branch has funded SCID screening implementation in Wisconsin, Massachusetts, and the Navajo population. Within the month, funding of another two states will be announced.

    - Identify gaps in newborn screening implementation regarding molecular testing

        - The branch established the Molecular Quality Improvement Program, the Newborn Screening Molecular Network, and the Molecular Assessment Program. (Initial outcomes will be presented at the November meeting of APHA in San Diego.) The branch also conducts collaborative laboratory research to assure quality molecular testing.

F. State of NBS in the Military

Mary Willis, M.D., Ph.D.
Organization Representative

Dr. Mary Willis is a clinical geneticist who works for the U.S. Navy and is the Department of Defense's (DOD) representative on this Advisory Committee. Her presentation focuses on the ways screening for military babies is different from screening in the non-military population.

- Dr. Willis informed the group that 120,000 babies are born to military families every year, and half of them are born in military treatment facilities (MTF). MTFs are bound by federal, not state, law, so they are not obligated to report to state laboratories; yet, many attempt to comply with state law. Both military families and military physicians are very mobile, so care providers change frequently, often within days of birth. It is of note, also, that military births take place worldwide.

- The first official newborn screening action in the military took place in 2002 when the army published a policy that required screening for four disorders and required MTFs to have written policies and procedures in place. In 2004, The ACMG approved universal screening of this panel, and the AAP and March of Dimes endorsed the panel. The TRICARE manual dictates AAP guidelines be followed, so their endorsement of newborn screening is critical.

    - The first to act, the U.S. Navy's Perinatal Advisory Board recommended immediate adoption of the expanded panel. In November 2004, they agreed to a subcontract with a single lab (then Pediatrics, now PerkinElmer Genetics) and the TRICARE Management Activity (TMA) initiated a

military-wide cost analysis study for subcontracting the lab work. A month later, the TMA endorsed the centralized funding.

- In 2005, at a time when there was a lot of disparity in what was offered state to state, the Integrated Process Team was formed to facilitate military-wide implementation of newborn screening. The DOD recommended three tasks for the military IPT: education plan, newborn registry, centralized contract availability.

- The IPT developed an educational plan targeted at provider groups that were involved in newborn care. They also developed ancillary educational tools for parents. The plan and tools are available at https://www.qmo.amedd.army.mil/Newborn/index.htm.

- Plans for a newborn registry were put on hold until a laboratory subcontractor was identified. Since that has happened, the registry plans will move forward.

- The contract solicitation was carefully considered to ensure that everything needed was included—centralized contract, worldwide service, HIPAA compliant, portable between MTFs, available 5 days per week, include materials and specimen delivery, immediate notification of abnormal results, and link with the DOD birth registry for metabolic data. The contract, which went into effect May 2011, was awarded to PerkinElmer Genetics, which has a strong history of working with the Navy. The action memo (marching orders) was signed July 1, 2011.

- Dr. Willis explained details of the 5-year contract. The cost is $33.64 per baby in the continental United States and $32.09 outside the continental United States. The latter price does not include shipping of samples. The contract specifies time limits for receipt of specimens, how to report results, and rescreening and confirmatory testing requirements. For abnormal results, the contract requires that reports include quantitative results for abnormal metabolites, detailed interpretation of the results, and the name and phone number of a laboratory representative. All results are to be reported by PerkinElmer Genetics to the appropriate state government. The consultative services requested and received include round the clock access to genetic counseling staff, interpretation of test results, recommendations for further evaluation and initial management, educational support, and patient referral management support. A final element of the contract is training and education on how to take a proper blood spot sample.

- Each MTF must decide how to comply with second screens. Since reporting public health data is part of the contract, the military needs to maintain contact with the states to ensure the data are received as they want it. Public health data are reported to the states, not the individual positives. Physicians may assume the state is taking over a positive result, but actually the states are not responsible for follow-up of PerkinElmer Genetics screens. Instead, the baby should be referred for follow-up according to regular channels. Referral patterns will vary by MTF and will depend on where the baby is and what the disorder is. There are few metabolically trained geneticists working in the military, so the vast majority will have to be referred out.

- Because the TRICARE manual requires AAP endorsement of conditions screened for, they will be able to renegotiate the contract for CCHD, but not yet for SCID.

IV. PUBLIC COMMENTS

A. Seth Morris, Child Who Has PKU and Has a Brother Who Died from Krabbe

"My name is Seth Morris and I have PKU. PKU is a disorder that makes me unable to process certain proteins, like meat and beans. Luckily, I was diagnosed at 11 days old and treated. Untreated, I would not be the young man you see before you today.

I am a cornerback on my school's football team. I am a catcher on the baseball field. I am an A student. I am a big brother. I wish my little brother Greyson could have had the chance to be what I've become. Greyson had Krabbe disease and died six days before his first birthday.

Texas does not screen for Krabbe like they do for PKU. Why is my disease so much more important than my brother's? Why should his life be any less important than mine? Why me?

This summer I saw kids with Krabbe for the first time, kids who were screened and treated. They were running and laughing and playing. But my brother didn't get that chance. He never even crawled.

Everyone should get a chance at life. My life should be no more important than Grey's. I will have to live with that thought every day for the rest of my life. But you have the power to change that. Please help me make a difference."

B. Sharon Terry, Genetic Alliance

"I want to thank you, Dr. Howell and members of the Advisory Committee. It is my pleasure to provide comments today on behalf of Genetic Alliance and Baby's First Test. During the past 7 years, the Advisory Committee has made a very significant and lasting impact on the welfare of newborns and children across this country. I did write about all the accomplishments, but I am going to skip them all, since we have heard today about how wonderful the Advisory Committee has been.

These advances have enjoyed your exceptional leadership, Rod. Your passion, your drive, and your wry wit has driven this ambitious agenda. You have a grace that allows you to navigate the rapids with aplomb and also still face the hard questions.

Thank you for guiding the Advisory Committee for all these years. I have witnessed the urgency with which you have led the committee to grapple with emerging topics and create frameworks to better strengthen and support state newborn screening programs.

Due to the solid foundation developed during the past 7 years, this committee is poised to address the emerging issues facing the entire spectrum of population-based screening, including whole genome sequencing, the public trust, incidental findings, and much more. Even as technology advances and new priorities emerge, the leadership of this committee has kept the interest of children and their families central to decisions and recommendations. As a mother of two children diagnosed with a rare condition, I appreciate that piece above all.

To Dr. Howell and to the other departing members of the committee who are rotating off this year, the advocacy community and the 4.2 million babies born each year thank you for your vision and your commitment. Thank you."

C. Katherine Harris, NYMAC

"NYMAC welcomes this opportunity to thank Dr. Howell for his longstanding support of programs serving people with special health care needs. Under his leadership, the Secretary's Advisory Committee has set standards for newborn screening never before thought possible. Finally, in this national forum newborns, regardless of the state in which they are born, have the same chance to be diagnosed with so many devastating conditions and receive the treatment they need to live healthy and productive lives. The members of this committee and its subcommittees have engaged in thoughtful and intelligent discussions around guidelines and availability of screening, medical care, and treatment that are bettering the lives of so many. I personally am grateful to have worked with Dr. Howell for over 20 years, first through the regional networks and now the regional collaboratives to bring to the national stage the issues of uniformity of screening and evidence-based care. I also am grateful that Dr. Howell was able to participate in last spring's NYMAC summit, bringing his insight and wisdom to many people who had not yet heard of his work. As the project manager of NYMAC and personally, I want to wish Dr. Howell well as he steps away from this committee. I hope that he leaves knowing that it will continue doing well the job he has set before it."

D. Christine Brown, National PKU Alliance

"I am the mother of two children with PKU as well as the executive director of the National PKU Alliance. I would like to thank Dr. Howell and the committee for your leadership and vision in making sure that the voices of children and adults with heritable disorders are heard.

As we all know, PKU is one of the most prevalent diseases among the heritable disorders, but the National PKU Alliance is still a newcomer to the national rare disease space, and we are still learning to navigate federal policy and the players involved. The guidance, the insight, and the relationships that Dr. Howell and others on the committee have helped me to foster have been integral and critical to our success and our work.

I do not know where I would have turned, without having this committee in place. Your work, in particular the work on medical foods and the issues around access and reimbursement of medical foods, has been paramount in our success to bring that to the attention of both state and federal legislators. As Alex alluded to earlier today, that fight is not over.

We are currently waiting for the essential health benefits package to come out of HHS. We hope that will happen by the end of the year. If medical foods are not included as essential health benefits, that means that states that still want to cover, or have insurance cover, medical foods are going to have to do so at their own expense. That possibly could put 34 current state laws in jeopardy.

I would like to thank you for making a difference in the lives of the 15,000 Americans living with PKU in this country. Thank you, Dr. Howell, very much for your leadership and support

and insight. We hope that the committee will continue to welcome and count upon the voices of children and adults in this country living with heritable diseases."

E. Jill Levy-Fisch, Save Babies Through Screening Foundation

"I am the president of the Save Babies Through Screening Foundation. We are the only advocacy group in the country solely dedicated to newborn screening.

In honor of Newborn Screening Awareness Month, we have launched a redesigned website and an educational video titled "One Foot at a Time." Our user-friendly site provides quick references for people in various circumstances: practitioners, expectant families, families whose baby has had an initial positive screen, and families whose child has a confirmed diagnosis. There will be an interactive area where experiences and information can be shared.

We also include an FAQ section regarding newborn blood spots. The information for both the website and the video was developed by our network of parents with firsthand experiences with newborn screening supported by the knowledge of a medical advisory panel with vast combined experiences in newborn screening as well.

In order to help parents become more informed, we developed the educational video to give families a new way to learn about why testing is recommended, when and where it will be done, how to obtain results, and how the process can be more comfortable for parent and child. The video was designed for use during pregnancy or even before, where parents can learn in a more relaxed setting. It can be viewed on our website and on YouTube; DVDs are available at no charge. We also have a Spanish version. We are pleased to announce at this time that we have signed an exclusive licensing agreement with the state of California for the use of the video, which makes California a true leader in newborn screening education. One of our advisors on the video was Dr. Howell.

Dr. Howell, you wove together a successful collaborative effort after your appointment to this landmark position as committee chair. Through your chairmanship the babies in our country today fare far better than they did before you arrived. A sea change has occurred.

You set sail with your motivated crew through uncharted waters, determining an effective path forward. It was not long after you stood at the helm that this committee had a uniform panel for newborn screening and a plan as to how the panel should be expanded. Prior to this accomplishment, it was each baby for itself in the states, some faring better than others. Through your vision and unmatched efforts, we have sailed to smoother waters, erasing many of the discrepancies in the states, thereby minimizing the negative effects on our American families.

For more than 7 years, I have attended these meetings along with my colleague, Nicky Gartsky. We have listened, questioned, studied, and been inspired by you on so many levels. Your patience to be available to answer questions means only one thing to us: the well-being and improved health of American families are at the top of your mind.

To explain how much we appreciate the support you have given us when answering all of our questions can be summed up in one word: priceless. Your patience and availability has also enhanced our principles and knowledge to do our part to create the very best possible ave-

nue for advocating greater awareness of newborn screening so that more education is possible for all American families.

Your words and wisdom will continue to inspire us as we move forward in this new era of newborn screening. You will be sorely missed here, but we know you will continue your good work in many ways. We look forward to continued work with you on our efforts. Thank you".

F. Annamarie Saarinen, 1 in 100 Newborn Screening Coalition

"In the past few months, those of us who have been working on this critical congenital heart disease issue have met with nearly 80 congressional offices to share information that has been learned and developed and provided via this committee and the evidence review process and the workgroup process. An additional dozen or so informational briefings were provided to HHS, HRSA, and other stakeholders that, I do think, moved the needle on an issue that had a lot of divisiveness. Information overcomes a lot of things.

We have also worked with the New Jersey Department of Health and their implementation workgroup and established pilot projects that not only get more hospitals adopting newborn screening for heart disease, but are encouraging the meaningful use of electronic health information exchange. So hopefully, we are accomplishing multiple things through this wonderful screening.

In the year since this committee voted to recommend newborns be screened for heart disease, more than 100 additional hospitals have implemented the screening around the country. Pennsylvania has introduced legislation since we last met in May. New Jersey's governor signed their bill into law, within days after we met. Starting on August 31, that state started screening every newborn for critical congenital heart disease. That all happened in 8 weeks' time. The reporting piece and the infrastructure piece is still being worked on.

To give a state credit for being able to put together a program, look at the evidence that has been provided and the guidance that was provided out of many key people in this room, and how a state can translate that into an operational program that is screening babies has been inspirational. The commissioner and assistant commissioner have been wonderfully supportive in that state. I hope it is a model for others.

In Minnesota, we are now screening a population of what will be 15,000 babies in the coming year. We have translated our educational materials into three languages, and we are working with IT at the Minnesota Department of Health to support electronic results reporting. In fact, we are meeting in the next couple of weeks. We hope to have the system up and running very soon. That will make it even easier for hospitals, not just to screen, but to track their results, which is going to be really important for this committee to know about.

I hope this effort has reinforced something very important—that the work here reaches beyond metabolic screening. Today 11,000 babies are going to be born in this country, and 110 of them will be diagnosed with some sort of a heart problem. Eleven of them will die before their first birthday.

I know, not just in my heart but on paper, that what you have done here is going to change that number. More babies will survive because of the work that you did and the leadership that has now been provided at the federal level.

My dad was diagnosed with stage four cancer 2 weeks ago. No daughter wants to hear from the doctors at Mayo Clinic or anywhere that we would have had more options had we known sooner. No parent wants to hear that, either. Please know that the work being done here helps so parents do not have to hear that as often.

On behalf of my family, 1in100, the CHD community, the Newborn Coalition, I thank you all for your important work. Chairman Howell, the work you have done will be recognized by generations. You leave some very, very big shoes to fill, Kobe Bryant-sized shoes to fill.

I hope those who come after you can follow in your wonderful footsteps. Thank you all. It has been a pleasure."

G. Dean Suhr, R.A.R.E. Project

"Good afternoon, committee and Chairman Howell. I wear three hats today, that of the parent of two children with a rare disease, one of whom passed away about 15 years ago, the other who I gave up her birthday to be here with you this afternoon; she is still with us. That is metachromatic leukodystrophy. My wife and I formed the MLD Foundation 10 years ago, and we focus in on that particular rare disease.

Today I want to start my comments in a new role that I have as the COO for the R.A.R.E. Project, a global genes initiative. I also want to acknowledge the work that this panel has done and the chairman has done for rare diseases since its existence.

Twenty-five meetings, 7 or 8 years—I didn't come to the first meeting, so I don't know when that was— you have come a long, long ways in that timeframe. It has been something that I have observed and now have some responsibility to be more engaged in. I want to acknowledge that. The committee, under your leadership, but, certainly, with a lot of individual and group contributions outside of the scope of the people we see around this table, needs to be acknowledged. You have established the process. You have established standards. We heard about evidence-based review. You have a methodology for making decisions going forward. Certainly, it is not perfect. Certainly, you will get pressure from all different directions as we look at the evidence, but you do have a process and a procedure.

I think the results of that are validated by the 50 states and where we have come over these past 7 years. The fact that those states, that have their own ability to make decisions, have honored what you have said and respected what you said and learned, based on that, I think, is a validation.

Clearly, parents are all for screening—there is no question about that—but when we get a little less emotional about that, I think the states say it for us.

Specifically, for Dr. Howell, I've had occasion to meet him, talk with him, and videotape him at a number of venues other than this. He is just a wonderful. You are accessible. You are open. You communicate well. Somebody already alluded to your sense of humor. You have a

way of dealing with very complex issues in a very, very concise and friendly way. That is really important, literally, to the millions of families out there that are the beneficiaries or are anxious about what this committee decides. I want to acknowledge that.

On behalf of the MLD Foundation and metachromatic leukodystrophy, we are not on the docket. We are not at the point where we have a diagnostic screen. There is much debate about the effectiveness of therapies. We have a lot of challenges in front of us. We are going to be the beneficiaries, I hope, at some time in the relative near future of the process and the procedure you have put together. When we can show the evidence, when we can deal with and wrestle with the issues and the waiting that you have built into an evidence-based system that includes, in essence, variations of the ethics, the trade-offs that are not quite all numbers based, and the waiting, we are going to be the beneficiaries of that, as are many, many other diseases.

I want to thank you for all your work, those of you who are going off. I challenge those who are stepping onto the committee. Dr. Howell, particularly, thank you for your leadership."

H. Celia Kaye, Mountain States Genetics Regional Collaborative Center

"Thank you, Dr. Howell and committee, for this opportunity to say a few words to thank you all for the service that you have been rendering. On behalf of the Mountain States, particularly, I would like to thank all of you, and especially Rod, for the leadership that you have shown.

I think we all are extremely conscious of the impact that the approval by this group of the uniform panel and the expansion of the uniform panel that happened through this group has made a tremendous difference in the way that newborn screening is thought of and taught throughout our various venues. As an on-the-group person, a Mountain States person, I want to emphasize that in my few remarks.

What this group does really matters to the states, to the public health departments, to the community clinics, and, as a medical school person, to our medical students, our nurses, our physician assistants. They actually know what this group is doing. I think a good example is the going viral of the ACCCHD recommendation. I have had multiple e-mails about that since it happened 24 hours ago, because people are interested in what is happening. They know that it makes a difference, and that it will impact lives. So, again, from the regional collaborative perspective, from the on-the-group perspective where people work every day and where differences are made in lives every day, I want to thank you for what you have done.

Rod, in particular, we so much appreciate your calmness, your humor, your focus, and all that you have done for all of us in the Mountain states. We appreciate your visits. It was wonderful to have you come and spend time with us, interact with geneticists, family members, pediatricians, laboratorians. That matters. It makes change happen when people take their time and use their influence to actually see that change happens on the ground level.

So thank you to all of you and looking forward to all the good things that are coming."

I. Lori Williamson Dean, Heartland Genetics

"Chairman Howell and distinguished committee members, my name is Lori Williamson Dean. I am the Program Manager of the Heartland Region. Both Drs. Klaas Wierenga and Brad Schaefer send their regards to you.

The Heartland Genetics and Newborn Screening Collaborative thanks you, Chairman Howell, for your leadership and dedication to the work of this committee since its inception. The eight Heartland states have screened for the core panel of conditions since July 2008, and states are adding the LSDs and SCID disorders in the coming months.

Without the hard work of those who envisioned the regional collaboratives as a way to reduce disparities in access to quality genetics in newborn screening services across this nation and without your leadership to implement that vision, I know that the great states of North Dakota, South Dakota, Nebraska, Kansas, Oklahoma, Arkansas, Missouri, and Iowa would not be where they are today in terms of access to high-quality newborn screening and genetic services.

You have made a real difference in the lives of families across this country and in public health genetics. Thank you, Dr. Howell."

J. Jennifer Miller, Mother of Logan Miller

"Thank you for giving me the opportunity to talk to you today. I would like to introduce a new disease to your list of heritable diseases. It is called adrenoleukodystrophy, otherwise known as ALD.

Logan Miller is 9 years of age. We need the standard procedure for health care for children 0 to 10 years of age to change. It should be made the standard procedure for small-town PCPs to ask for genetic screening called blood spotting. We live in Bellwood, Pennsylvania, a very small community, and this is a very rare disease. One in 20,000 children, actually, have it, but 1 in 100,000 are being diagnosed correctly with it.

We would like to have this happen, and it is wonderful to hear that your committee is already tackling blood spotting and all the wonderful things that I have heard today that you do.

Logan's story began on August 23, 2010. He was struck by a truck in Bellwood, Pennsylvania. He was with his babysitter. Due to the multiple facial fractures, he was flown to Children's Hospital in Pittsburgh, Pennsylvania, where an MRI was done coupled with a chain of fatty acids. They discovered, in addition to this life-changing event, that he was diagnosed with adrenoleukodystrophy. That was on September 22, 2010.

This is an X-linked chromosome disorder. It is hereditary, and he had been born with this. You can imagine how devastating that was for us, within a month's time, to realize this disease and not really understand it, but then, also to be—where do we go from here? What are his life expectancies?

Until this point, we knew nothing. We just thought that he had ADHD. Logan had been asymptomatic, of course. He just had the minor behavioral disorders when in school. So, imagine how these educators feel when they have to deal with a child who has something as

devastating as this disease. I would like to tell you a little bit about the disease and what it actually does, that we have learned in a short amount of time. But what is meant when it is asymptomatic is that it is presenting on an MRI.

Adrenoleukodystrophy is a disease that is hereditary and a genetic X-linked chromosome disorder. It is passed down. My biological father had it; however, I never really knew my biological father. This is a common story. We went to the Mayo Clinic in Minnesota in our travels in a short amount of time to try to get a transplant. It had progressed too far, this disease, so we went to Kennedy -Krieger Institute in Baltimore, Maryland.

In order to stop this, we need to have the blood spotting genetic testing starting at 0 to 10 years of age. In order to watch the progression of the disease, we need to couple that with an MRI and very long chain of fatty acids blood tests to be done as well. These children are being diagnosed with ADHD, bipolar, Addison's, multiple sclerosis, which is, in fact, what my father had. All his life he thought he had it, but he really had AMN, which is actually the muscular version of adrenoleukodystrophy. His brother also had it.

In the time that we learned, in this short period of time, the school district wanted to get me involved with a support group. I said yes to that, wanting to learn a little bit more about their experiences. The numbers didn't add up in Bellwood. Bellwood is such a small town; how could there be two children in that town with the same disease? The only way that can happen is if you are related. Turns out that that person was my first cousin, and that child died in 2005. So it is very important, and it is a wonderful thing that your committee is actually offering to take this role and do this in all the states. So we appreciate that.

In my situation, my insurance would not allow us to have an MRI for Logan unless there was a traumatic reason to have it. So, in our area, the child that was before Logan actually did not even have it diagnosed until after he passed on; he had been diagnosed with all the things that I had mentioned prior to this.

So we are here to introduce the ALD Foundation. We put it in Logan Miller's name. I have a picture that I gave them from the Caring Bridge website from Minnesota. I also have literature from Dr. Westin Miller, who works for the Mayo Clinic in Minnesota. I have literature on the disease from Dr. Gerald Freeman. He worked under the Mosers at Kennedy-Krieger Institute and Johns Hopkins in Baltimore, Maryland. I would like to enter that literature for you as well.

In our travels, we went to Minnesota in hopes of stem cell transplant. Then, last year, in October to November, it actually progressed too far, so he was ineligible for that procedure. They gave him 18 months to 2 years on September 22 of last year. Thank you for your time today, and thanks for all your good work.

Dr. Howell followed up Ms. Miller's comments saying that in one of the earliest Advisory Committee meetings Dr. Hugo Moser, a leading ALD researcher, discussed this disease. Since then a lot of progress has been made in diagnosis and therapy for ALD. Dr. Howell expressed hope that the condition be formally nominated in the near future".

K. James Bialick, 1 in 100 Newborn Screening Coalition

"We were thrilled with the Secretary's letter yesterday and how much it was picked up. Politico ran with it. That is always really good to see.

I want to talk about how, with this recommendation, we are starting to see some convergence of worlds here, where you are seeing something like a point-of-care examination which has a lot of resonance in the process, within HHS for a lot of electronic health records development, even to the point where public health reporting can qualify for the lab reporting requirements of certain hospitals and providers.

I want to point out, though, that in this ecosystem that we are developing there are a lot of blind spots. One of those that I see frequently has to do with public health. Recently, there was a big HHS press event around Blue Button, which is this ability for insurers and hospitals to provide an entire patient's record all at once.

Another announcement they made got overshadowed, but I think it has a lot of relevance here. HHS announced the Advanced Notice of Proposed Rulemaking. It would require that all individuals have direct access to their lab results. I know that this is going to have an interesting impact on newborn screening, and I know this is going to have an interesting impact on a lot of state laws.

So, I suggest that, maybe through your associated organizations or through this body, comment be made on that, because I think that the thinking is that this is information coming from the labs directly. So, especially with newborn screening, especially with something that has had a lot of debate about that, a lot of standards about that, it is going to become increasingly important that there be a consensus on how that information is managed.

So I wanted to put that on the radar as well as talk about how these things are starting to converge a little bit. It is really an interesting, exciting time, but I think that it is going to take the input of a lot of the knowing people that we have around this table".

Friday, September 23, 2011

On behalf of the March of Dimes, Dr. Fleischman thanked Dr. Howell for his service on the Advisory Committee as chair and presented him with plaque inscribed with the following words "Rodney Howell has led the transformation of modern newborn screening and saved countless lives. A charismatic leader, a marvelous political, clinical, scientific, and dramatic person who has helped the women and children of America and across the world."

V. SUBCOMMITTEE REPORTS

A. Subcommittee on Laboratory Standards and Procedures

Gerard Vockley, M.D., Ph.D.
Committee Members

- Dr. Gerard Vockley noted that Dr. Dietrich Matern, who will join the full committee at next meeting, will join this subcommittee. Dr. Fred Lorey will assume the role of chair of this subcommittee.

- During the subcommittee meeting, members reviewed the progress of the past 4 years. The subcommittee charge includes implementing a mechanism for the periodic review and assessment of the conditions included on the panel. This is about to become a major focus of the work. The subcommittee was also charged to define and implement infrastructure services for screening and laboratory procedures for testing of conditions on the panel.

- Dr. Vockley reviewed the subcommittee's accomplishments.

    - The second screen project is almost ready.

    - The Health Information Technology Workgroup, in which the subcommittee collaborates with the National Library of Medicine in the assessment of new medical language (specifically LOIN codes) in regards to newborn screening results and the medical record, has evolved into an important role of the Advisory Committee.

    - The subcommittee has evaluated novel molecular technologies, a transformative piece of newborn screening in the past few years. There has been a shift from using molecular-based testing as a follow-up of a metabolite or analyte test to using it as a primary test.

    - The subcommittee has had ongoing dialogue with the CDC over their development of quality assurance and quality control materials for SCID testing and lysosomal storage disease (LSD).

    - The subcommittee has reviewed the technologies for the LSD newborn screening market and recommended a project for direct comparison of these alternative techniques. The Mayo Clinic now has a project funded by the NICHD to compare competing technologies directly to see whether any has a clear advantage in the newborn screening arena.

- The subcommittee made a formal recommendation to the Advisory Committee that its name be changed to "Laboratory and Information Technology Subcommittee" to better reflect its evolving pattern of responsibilities. This name recognizes the increasing role of information technology in the subcommittee's work.

- The subcommittee members recognize that, in terms of scope of work, the Advisory Committee will be consumed in the near future with work on newborn screening.

- As an initial agenda for the immediate future and success of the Advisory Committee, the subcommittee came up with three areas of focus: (1) The Advisory Committee should continue to aggressively monitor and review new enabling or disruptive formative type technologies and bring in speakers to stay abreast of those technologies. (2) The Advisory Committee should provide states with guidance in making decision about implementing new screening tests by providing comparative performance metrics and an overview of technologies. (3) The Advisory Committee should have an ongoing discussion about the point of origin versus traditional laboratory-based newborn screening type tests.

- The subcommittee identified four goals from these focus areas.

- As one of the Advisory Committee's charges is to review the standard panel as it goes forward, the subcommittee could take a lead role to establish processes for regular review and revision of the standard panel. This would include mechanisms to remove some disorders and to alter the status of targets from secondary to primary when appropriate.

- The subcommittee will recommend specific changes to technology as appropriate. Members believe that the use of tyrosine levels to identify Tyrosinemia 1 is in need of adjustment at this time. It has been superseded by succinylacetone. Tyrosinemia 1 is a disorder already on the panel, but there is a new technology that eliminates almost all the problems associated with the original methodology. There should be a mechanism for updating the type of screening recommended.

- The subcommittee's IT component will continue to be important, so members want to maintain collaborative interaction with the IT Workgroup.

- Monitoring of new technologies will be important going forward.

Dr. Vockley opened the floor for comments and questions

- Dr. Christopher Kus asked where tests that do not rely on laboratory technology, such as pulse oximetry and hearing, fit into the subcommittee's work. Dr. Vockley responded that that was the implication of "point-of-care testing," it covers all other technologies.

- Dr. Howell asked about the status of second screening. Dr. Harry Hannon explained that they are done collecting the data and are now cleaning it up. They expect to have a report compiled for the Advisory Committee by the next meeting.

  - Dr. Howell expressed the opinion that either everybody should be doing a second screen or nobody should be doing a second screen.

  - Dr. Vockley commented that the project has struggled with IRB issues due to working with multiple states. The Advisory Committee may want to recommend alterations to the procedure.

- Dr. Howell believes that the issue of whole exome sequencing will be before the Advisory Committee soon. One of its biggest issues will be ethical and legal issues. He asked if the subcommittee had discussed technology and sequencing in the real world.

  - Dr. Vockley responded that the subcommittee did not bring this procedure to the table because, while that technology is looming, the application of it to a high throughput newborn screening environment is probably a few years away. He is sure the Advisory Committee will eventually wrestle with it, and at that time it will probably cut across more than one subcommittee. The ethical issues will be outweighed only by the IT issues.

  - Dr. Botkin: The Bioethics and Legal Workgroup of the Newborn Screening Translational Network is planning a small meeting in November that will focus on unanticipated findings, secondary results that generate results on conditions that are not the primary target, and the ethical and legal obligations of disclosing that information to families and clinicians. Current problems will be much bigger once we get DNA-based platforms.

- Dr. Howell asked for confirmation that the primary screening analyte for tyrosinemia type I is generally agreed to be succinylacetone.

- Dr. Vockley confirmed, but added that it is not implemented uniformly across states and a specific recommendation from the Advisory Committee would be helpful. The issue raises the question of how the Advisory Committee re-evaluates conditions: Is a full evidence review needed or can the technology subcommittee submit a statement to the Advisory Committee at large regarding preferred technologies?

- Dr. Howell noted that the Advisory Committee does not ordinarily make recommendation of exactly what is measured when a condition goes on panel, but it seems worthwhile for the Advisory Committee to look at the data and deliver a recommendation.

- Dr. Lorey concurred because otherwise the provider can say they are screening for the condition, even if they are not using the best available technology.

- Dr. Howell suggested that the Advisory Committee develop a process whereby the subcommittee can make specific recommendations to the larger Advisory Committee based on a review the evidence.

- Dr. Jane Getchell believes that the reason states have not implemented succinylacetone screening is due to its higher cost. There is one commercial manufacturer of the succinylacetone assay, so many laboratories use a "homebrew" assay that requires two separate processes, increasing the cost. Cost aspects should be considerations in the Advisory Committee's specific recommendations. Dr. Matern noted that it is not necessary to double the equipment fees given revised methods of processing the samples. Dr. Howell noted that this is the kind of thing the Advisory Committee would review in details prior to making a recommendation.

- Dr. Anne Comeau noted that the second screen is meant to determine whether babies were missed by one or another method. Having two screens with a particular algorithm or using one screen with different algorithms produces screens with the same sensitivity and specificity. It is good for states to use different assays and algorithms, so long as sensitivity and specificity of predictive values of any particular assay and algorithm are assured.

- Dr. Alan Zuckerman reminded the Advisory Committee that Dr. Sharon Terry and he chaired an ad hoc HIT workgroup which has since disbanded. Their recommendation was that HIT workgroup activities move within the standing subcommittees because of the importance of ongoing activity in HIT laboratory data reporting and exchange.

- Dr. Sara Copeland suggested the Advisory Committee develop a formal operating procedure, using succinylacetone and tyrosinemia 1 as the example, for reviewing the screening technology of conditions on the screening panel. Dr. Howell noted that this is the first time this has come up, and a systematic way of handling such situations should be developed.

- Dr. Howell asked if the subcommittee wanted a formal vote on their name change. Dr. Dougherty voiced and the subcommittee members generally agreed that such a vote was premature.

B. Subcommittee on Education and Training

Tracy L. Trotter, M.D., F.A.A.P.
Don Bailey, Ph.D., M.Ed.
Committee Members

- Dr. Tracy Trotter offered a brief history of the subcommittee. It was established in 2005 and held its first meeting in April of that year. Its charge was to review existing educational and training resources, identify gaps, and make recommendations regarding newborn screening to health professionals, parents, screening program staff, hospital and birthing facility staff, and the public.
    - Accomplishments of the subcommittee include establishing an ongoing dialogue with professional organizations about newborn screening; expanding the subcommittee membership to include parents, counselors, nurses, and screening staff members; compiling a list of vetted websites on newborn screening; facilitating the establishment of a repository of educational materials; and providing input and getting feedback from organizations developing educational programs.
    - In June 2009, the subcommittee participated in a workshop on genetic education topics and developed a blueprint for genomic education of primary care physicians. A summary of the blueprint was published by Dr. Alex Kemper in February 2010, and from its recommendations the Subcommittee on Education and Training was authorized to develop a training institute plan.
    - The Genetics in Primary Care Institute contract was recently awarded to the AAP. The goal of the 3-year program is to improve genetic-based medicine and services across the lifespan. It will pair genetics experts with 20 practices.
- Reports on current activities were made at the meeting. The BabysFirstTest.org website is live. Applications for the Consumer Task Force will be available soon. The first Challenge Awards were announced last spring (they will be posted on BabysFirstTest website in a week) and applications for the next round are due October 30.
- The subcommittee is working on future activities. The Advisory Committee has already heard a report from Ms. Nichols on phase 1 (environmental scan) of the proposed national newborn screening awareness campaign. The next step is to assign a workgroup to facilitate phase 2, a strategy summit to define our goals, determine if it is appropriate to go forward, and if so how.
- As the incoming chair of the subcommittee, Dr. Don Bailey assumed the microphone to comment on future directions. He noted that the role of this subcommittee continues to grow in importance.
    - Subcommittee members deliberated on the extent to which they should address education and training issues regarding follow-up and implementation after the newborn screening. Members are unsure whether the long-term follow-up subcommittee is addressing issues of education around follow-up and treatment.
    - The subcommittee recommended developing a mechanism whereby all the subcommittee chairs meet periodically to discuss the overlap areas of their charges.
    - Members feel the subcommittee would benefit from increased participation by American Congress of Obstetricians and Gynecologists, and they would like a nurse representative on the subcommittee. They will confer with Dr. Copeland about the formal process to do this.
    - The subcommittee recommends that information on newborn screening become part of genetics training initiatives.

- The subcommittee's charge is currently limited to education and training on newborn screening. Members will further contemplate the need for an official modification to the charge to encompass all the work of the Advisory Committee.

- The subcommittee suggested developing a blueprint for advocacy groups to make panel nominations. The blueprint would not only include instructions on completing the nomination form but also offer examples and strategies to help them provide the Advisory Committee with the evidence it needs to make a decision.

C. Subcommittee on Follow-Up and Treatment

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

Dr. Botkin thanked Ms. Jill Shuger for the document she prepared for the subcommittee to work from and expressed hope that the document will become part of the record.

- Previous work of subcommittee members include two articles in *Genetics in Medicine*, "What questions should newborn screening long-term follow-up be able to answer?" (in electronic form ahead of June 2012 publication, Dr. Cynthia Hinton lead author), and "Long-term follow-up after diagnosis resulting from newborn screening" (2008, Dr. Alex Kemper lead author).

- The subcommittee fostered many meetings, discussions, and presentations in the general categories of health policy reform and its implications for the care of children (with an emphasis on medical foods) and health IT.

- The subcommittee has several important works in progress that are near completion.

  - Led by Dr. Nancy Green, a paper that emerged from the CCHD recommendation and is relevant to conditions like bilirubinemia, "Hospital-based point of care screening," illustrates changes in screening modalities. The paper is in early draft form. It will be presented to the Advisory Committee in the next 6–9 months.

  - While the topic of Dr. Brad Therrell's paper, Improving data quality and quality assurance in newborn screening by including the bloodspot screening collection device serial number on birth certificates, addresses a narrow issue, it is very important to follow-up and data collection. The paper has been finalized and will be ready for submission to the full Advisory Committee for evaluation at the next meeting.

  - Lead author Susan Berry's paper, "Parent's experience with limited insurance coverage for medical foods used for treatment of inherited metabolic disorders," is almost in final form. It needs to be reviewed by several federal agencies, and then it will be ready for submission for publication.

- The subcommittee has clear consensus that the complex issues of services available to children upon diagnosis need further attention and evaluation. There was a general sense that the Advisory Committee would benefit from additional attention to issues in the trenches, especially implementation issues. This is ambitious and, thus, worthy of collaboration with other subgroups.

- The subcommittee suggested the following revised charge, making it broader than the original charge. The revisions highlight implementation issues and add treatment, which is in the name of the subcommittee, as an area of concern.
    - Identifies barriers to post-screening implementation and short and long-term follow-up, including treatment, relevant to newborn screening results.
    - Develops recommendations for overcoming identified barriers in order to improve short and long-term follow-up, including treatment, relevant to newborn screening results.
    - Offers guidance on responsibility for post-screening implementation and short and long-term follow-up, including treatment, relevant to newborn screening results.
- After discussion, the subcommittee determined that long-term follow-up care begins at the time of diagnosis and ends at 21 years of age. Adult transition is important, but the purview of this Advisory Committee limits activity to sending the child into adulthood.
- Regarding additions to the subcommittee, the members felt that they would benefit from a neonatologist (point-of-care issues), a nurse practitioner (issues of children receiving long-term follow-up care), and an adult clinician (adult transition issues).
- Subcommittee members discussed several areas of work for the future.
    - Given that regional collaboratives are tightly linked with the trenches, it seems beneficial to collaborate with them. This subcommittee could serve as an avenue between the larger Advisory Committee and the RCs to exchange information and gather feedback.
    - After a discussion of roles and responsibilities, the subcommittee changed "accountability" to "responsibility" in its charge. In this way, the Advisory Committee can now discuss whose responsibility it would be to do the long-term follow-up.
    - The subcommittee places a lot of importance on medical foods and will continue to highlight the issues as the federal process for determining minimal care elements moves forward.
    - Members expect health IT issues to become increasingly important.
    - The subcommittee discussed the possibility of giving specific focus to long-term follow-up of children with sickle cell disease. Although the efficacy of early intervention is unquestionable, data indicates that many children are falling through the cracks and long-term follow-up for this disease could be improved. This is a tentative direction for further exploration.

Dr. Howell invited comments from the Committee.

- Dr. Calonge suggested that the future Advisory Committee chair consider diversifying the outcomes or products of the recommendations of the Advisory Committee. As it stands, the pathway is that a condition ends up or does not end up on the uniform panel list, which creates public health mandates by state governments. Sometimes, but not always, this is the correct action. Despite the large majority of medicine being unmandated, we manage to have consistency, quality improvement, and population based roll-out of many services. Other routes used include professional guidelines, hospitals (Joint Commission), and medical standards of care. This Advisory Committee should consider broader implementation strategies for its recommendations. Dr. Calonge expressed an interest in having this task assigned to a workgroup or subcommittee.
    - Dr. Calonge responded to a question from Dr. Howell about what the charge would be for such a workgroup or subcommittee. The charge would be looking at the way other recommendations, guidelines, and standards are implemented in population-based medicine across other organizations and then determining the criteria for adding a condition to the panel versus rolling it out through a different route. Additionally, he urged the Advisory Committee to consider provisional recommendations.

- Dr. Frederick Chen commented that his subcommittee also discussed implementation in context of new technologies that move screening beyond dried blood spots. The new methodology requires that we think differently about implementations.

- Dr. Vockley noted that the importance of the evidence-based review is not captured in any of the subcommittees, but should be. Due to the difficulty in researching large numbers of patients with rare diseases, the Advisory Committee could do a lot of good by promoting the process of evaluating such disorders, and the various components of the subcommittees' individual charges could reflect this.

- Dr. Botkin noted that none of the subcommittees are charged with addressing ethical, legal, and social issues. He asked that the Advisory Committee explicitly consider developing a formal mechanism in this area. If not a subcommittee, perhaps the Advisory Committee could develop a relationship with the bioethics and legal workgroup of the translational network.

VI. THE FUTURE OF THE COMMITTEE

A. New Steps in the NBS Consent Conversation

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

Dr. Botkin reported on a 2-day meeting recently held in Utah under the auspices of the bioethics and legal workgroup of the NBSTN. About 30 people were in attendance, including many in today's audience. The meeting was prompted by an NIH project at the University of Utah (Kathryn Swoboda, principal investigator) that is doing a pilot study to screen newborns for spinal muscular atrophy.

- The meeting's goal was to reach consensus on key ethical and regulatory issues in the conduct of population-based screening research. The key question was: Under what circumstances might newborn screening pilot studies qualify for a waiver of traditional informed permission (signed consent form) from parents?
    - The parental permission process sometimes impairs recruitment and timely completion of population-based research.
- The ethical issue involves the conflict between longstanding respect for parental decision making, in clinical care and research and the need to move forward in collecting data and complete research for the welfare of children.
- The group arrived at some general conclusions.
    - There is strong support for evidence-based newborn screening and research.
    - A pilot study in newborn screening mimics the newborn screening system. The newborns should be screened with identifiable samples that can be returned when the results are positive. Issues of long-term follow-up fall outside the parameters of parental permission for screening.
    - When supporting evidence is incomplete for the introduction of new tests on a state or uniform panel, pilot studies should be conducted under a research paradigm.
- Under federal research regulations, waiver of traditional consent must meet four criteria: the research must be judged to be no more than a minimal risk; there has to be no abridgement of the rights and welfare of the participants; the research must be judged impracticable if traditional informed consent is used; and research participants must be informed later about the research, when appropriate. After walking through each criteria in context, the group drew further general conclusions.
    - Issues of minimal and greater than minimal risk include the quality of the test itself (analytic and clinical validity), availability of treatment that appears to be beneficial for children, and the burden of further diagnostic procedures.
    - Regarding the rights and welfare of the participants, screening for certain sensitive conditions might make a pilot ineligible for a waiver. This could be related to a cultural sensitivity. There may also be a particular discrimination or stigma associated with screening.
    - Impracticability factors include the size of the population that needs to be screened, the number of birth facilities involved, the number of individuals responsible for obtaining the informed consent, and birth facilities with ongoing research and "in-house" IRBs.
    - Not reaching consensus, the group highlighted the importance of ethical questions about the return of results. Is it ethically necessary or appropriate to return negative results in this context? What are the risks of doing so through a primary care physician? What are the benefits to families, and do parents have a right to that information? What are the implications for the project in general? It requires a big effort to deliver results in an interpretable fashion, and that may impair the ability of a project to be successful.

- A high priority was placed on the education and engagement of parents, regardless of their consent. Parents must be aware that there is a research protocol going on and that they have the ability to opt out of it. A waiver of traditional informed consent may be appropriate in some circumstances; an opt out or other method may be appropriate in other situations. The assumption is that there is meaningful parental education and readily available mechanism to opt out of the study.

- The meeting group plans to prepare a manuscript publication in the next few months with all participants (except Dr. Sara Copeland) as authors. The paper is hoped to have an effect on the field and IRBs with oversight of these types of proposals.

- Dr. Howell invited comments and questions from the Committee.

- Dr. Frederick Chen asked about implementation beyond publishing a paper. He also asked if, given that we are still in the public comment period, the proposed rule-making changes to the common rule might provide an implementation pathway for this group's work.

    - Dr. Botkin said the announced notice of proposed rulemaking would have significant impact in this domain. If prospectively acquired specimens for clinical purposes are to be used for research purposes, written informed consent would be required. Yet, what the common rule anticipates as the informed consent process is a very simple form with a signature gathered at the clinical interface, which does not fulfill the traditional values that we want to promote with informed consent.

- Dr. Christopher Kus expressed concern that this study pilots screening and short-term follow-up, but leaves out the important long-term follow-up element.

    - Dr. Botkin replied that each project will have to be designed around its own specific aims. With respect to the SMA project, if it is determined that an opt out is appropriate at the time of screening, that opt-out would not carry forward after the identification and further study of affected children.

- In response to a request from Dr. Howell to provide a status update of the SMA project, Dr. Botkin explained that it is in active discussion about feasibility of the protocol with the states of Utah and Colorado. The study has been funded, but there are complications with sample handling, permissions, and finalizing the testing format. The laboratorians who have developed the DNS-based platform indicate that the test is not only inexpensive but also highly sensitive and specific, giving clear information about the type of SMA. The barriers, in this case, are the screening protocol, permission issues, and transfer of samples. The study will require the birth cohort of both states over 3 years in order to have adequate numbers for follow-up.

- Dr. Michael Watson noted that there were representatives from both institutional and state IRBs at the meeting seeking guidance on how to interpret the rules for this type of situation. Dr. Botkin added that federal regulations governing research weren't designed with large population-based research in mind. Another aspect that can become a barrier is state health departments that do not have research as a primary goal.

- Dr. Nancy Green commented on the considerable discussion at the meeting of the difference between previous pilots which were generated from state health departments and this one which is led by academics with a federal grant. She noted two points of contention to consider for the report: (1) regardless of who leads these projects, there needs to be partnership because the project requires infrastructure and activities of the public health department and (2) the project cannot interfere with the mission of the public health newborn screening activity.

- Dr. Anne Comeau commented that there were many issues discussed at the meeting that will need to be revisited. She noted that there was general consensus that pilot programs in newborn screening require an extra level of consideration to make sure the newborn screening program is not undermined by the research.

- Dr. Susan Tanksley of the Texas Department of State Health Services shared Texas' experience with informed consent on a SCID pilot program. Since October 2010, they have received a mere 1,800 consents out of more than 200,000 births. The main concern of hospitals has been who will do the consent. They are a very expensive process for the facility, and they appear to be limiting the study considerably.

    - Dr. Lorey reinforced the Texas experience, explaining that when California tried a consent process, many people were missed and many others did not get off of the consent when they wanted to. That was the reason they sought (and were granted) a waiver review from the IRB with SCID.

    - Dr. Botkin brought up an example of a successful population-based study. Studies in Massachusetts used an opt-in that waived documentation but also gave hospitals the opportunity to defer to the health department. Dr. Comeau explained that the Massachusetts pilot programs for tandem mass and cystic fibrosis engaged and educated parents. Having established the mechanism, the state was able to move ahead with the SCID pilot. The opt-in is a 5-minute process, and parents receive a copy of what they verbally say to the clinical provider who asks for consent. It is accepted by the hospitals, and there have been very few complaints. The success is in large part due to the educational groundwork done by the state health department and medical school IRBs to get OHRP agreement and in educating the hospital IRB. This way there is no need to go through all the individual institutional IRBs. It has been in place since 1999.

- Dr. Bailey opined that the Advisory Committee needs to address these important topics more systematically, perhaps through a subcommittee or a link to an outside workgroup, so that it can make responsible recommendations. The topics are the (1) intersection of ethics and data and the need for information and (2) how you ask for consent and what happens when you ask for it.

- To highlight the variation across the country, Dr. Alan Fleischman suggested convening OHRP with the organizations of health commissioners and territorial leaders in a discussion of these issues. Knowing what other states are experiencing would help individual state leaders approach their legislatures.

- Dr. Rebecca Buckley suggested the Advisory Committee develop a stance on performing preliminary studies, perhaps changing the word "pilot" to "limited study" or "initial study" to remove the research connotation. A statement from this Advisory Committee would have a lot of influence.

B. Moving the Evidence Review Process Forward

Alex Kemper, M.D., M.P.H.
External Evidence Review Workgroup

Dr. Alex Kemper explained future plans for the evidence review process in the Advisory Committee, asking that group provide input and advice for improving the process. He explained that the core principles of the reviews are that they be comprehensive, prepared in as unbiased and transparent a fashion as possible to provide a fair presentation of information on which the Advisory Committee can base its decisions.

- Dr. Kemper quickly reviewed the well-known challenges faced in preparing evidence review reports for this Advisory Committee. (1) Inconsistent case definitions across reports make it difficult to combine reports. (2) Some studies follow individuals for short others for long periods of time. (3) There are variations in reported outcomes. (4) Proxy outcome measures are common, making it difficult to get to real health outcomes in terms of improvement in life. (5) The traditional evidence review process is not built for single case reports, which is where much of the knowledge of rare diseases rests. (6) Individual cases can appear in multiple reports, making it difficult to confirm whether the review covers the same individual repeatedly or unique individuals. (7) The harms of screening and treatment seem underreported.

- To improve the evidence review process, the workgroup participated in a 1-day meeting with experts who work with the U.S. Preventive Services Task Force, AHRQ, and other large systematic review efforts. The workgroup uses standards for the conduct of high-quality systematic reviews put out by the IOM and the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.

- To incorporate new processes, the work plan needs to be refined and developed, data abstraction needs to be improved, and data needs to be synthesized for presentation. A feature that allows for easy future updates as new evidence becomes available needs to be incorporated. A mechanism to assist SACHDNC with the collection of missing data also needs to be added.

- In refining the process of the work plan, the workgroup's reports have all used a similar analytic framework to develop key questions and case definitions.

    - Future refinements should include tailoring the analytic framework to address the length of time we should follow people for the benefit of screening, comparing newborn screening to standard clinical care in given environments, and determining upfront the specific outcomes we want to consider. Well defined case definitions and analytic frameworks will be used to develop key questions, search strategies, rules for study design inclusion, and a list of experts for interviewing.

    - Some input from other Advisory Committee members thus far include peer-review of the evidence by a technical panel, a forum for a public comment period, and a review by SACHDNC liaisons. Dr. Kemper encouraged further input for ways to improve the process.

- Improving data abstraction, which traditionally requires multiple rounds of extraction and is prone to introducing error, in such a way that allows for easy updating will significantly improve the evidence review process. The group is moving toward using a Web-based systematic review software, Distiller (systematic-review.net), to track reports and articles and facilitate putting reviews into formats developed by the user. With it, we can extract what we want from the reports and automatically populate evidence tables in many different ways. It can develop a wide range of reports, such as the reliability between different reviewers, and it keeps track of reasons for exclusion.

- As we develop more specific key questions and use Distiller for developing evidence tables, we will be able to provide more detail in our data synthesis and presentation. We will also be able to expand the grading and evaluation of individual studies and the body of evidence as a whole for the key questions. We are interested in including the risk of bias in studies, the consistency both within the study and across studies, issues of precision, the directness with which the body of evidence addresses the key questions, and reporting bias. By developing more rigorous evidence tables, we will be able to manipulate them to get a better sense of reporting bias across a number of domains.

- Decision modeling provides a quantitative assessment of the findings which can be linked directly to the analytic framework. The model complements the narrative summary and evidence tables and addresses areas of uncertainty to help inform decision making. It can also help identify important areas for new research.

- Dr. Kemper emphasized a need to protect the evidence review from external pressure.

- Thus far, the workgroup has generated full systematic reviews that have helped inform the Advisory Committee's decision making. There is an opportunity to develop other products, including summaries that are more accessible to the general public.

- The workgroup's next steps are to work with members of the Advisory Committee to formalize these processes.

Dr. Howell invited the Committee to ask questions and offer comments.

- Commending the workgroup for its excellent work, Dr. Fleischmann counseled that public comments and liaison members from the Advisory Committee are not appropriate for an external workgroup because it changes its relationship with the federal committee.

    - Dr. Calonge expressed concern that total separation of the Advisory Committee membership from the evidence review leads to disconnects when the evidence review is presented and the Advisory Committee works through the process of translating the synthesized evidence into a recommendation. Finding a way to have Advisory Committee members involved enough to avoid a disconnect while avoiding the potential influence or bias that could be introduced by involvement with the Advisory Committee is critical.

    - Dr. Bocchini commented that, in his experience with the Advisory Committee for Immunization Practices (ACIP), having a workgroup formed in part by ACIP members, experts in the area, appropriate liaisons interested in the subject, and both internal and external CDC individuals significantly informed the Advisory Committee.

- Dr. Fleischman pointed out that the Advisory Committee membership is intentionally made up of people with varying expertise that is different than the very focused expertise of those who sit on other kinds of committees. Were the Advisory Committee made up of experts, other members might defer to them. As it is, the process of teaching the Advisory Committee members about a subject is an important part of the process.

- Based on past roles with the American Academy of Pediatrics and the U.S. Preventive Service Task Force, Dr. Charlie Homer thinks that having a liaison between the committee which needs to use the information to make recommendations and the evidence groups is very helpful, specifically in terms of framing the questions. For example, at the AAP, the committee received a report that did not address the questions the committee most needed answered. He also thinks it appropriate to give the advocacy community the opportunity for public comment on the questions. It allows greater buy-in from those communities when the final report comes out.

- Dr. Calonge said that one of the very important facets of having an Advisory Committee member in the working group is establishing ground rules for the role. It should be clear the Advisory Committee member is not there to influence the work, and there should be a mechanism for reining that person in should the boundaries be overstepped.

- Dr. Kemper concurred, explaining that it is important to have a written document that outlines all these steps and how to implement them.

- While Dr. Calonge supports transparency, he cautioned that public comment periods require synthesizing and responding to the comments without allowing them to bias the science of the review.

C. Evidence Evaluation and Methods Workgroup: Update on Developing a Decision Analysis Model

Alex Kemper, M.D., M.P.H.
External Evidence Review Workgroup

Lisa Prosser, Ph.D.
External Evidence Review Workgroup

Dr. Lisa Prosser discussed some of the limitations of evidence review with respect to the methods workgroup meeting held in April. She also gave a brief introduction to decision analysis, using a case study in which a decision analysis modeling approach was applied to newborn screening for MCADD. She concluded by discussing how to apply this modeling to hyperbilirubinemia.

- The SACHDNC Evidence Evaluation Methods Working Group, convened in April, was charged with considering new evidence review methods to supplement the work of the evidence review group, with particular attention to modeling to assist in evidence synthesis and generation when data is sparse. The application of modeling to hyperbilirubinemia is expected to create a process or framework that can be used for evaluating future conditions.

- It was noted by representatives from the U.S. Preventive Services Task Force, AHRQ, and other decision making bodies that the way modeling has been used in other contracts is different from how it is going to be used here. Decision analysis modeling is usually used as a

structure for developing cost-effectiveness analyses, but here the decision analysis model is being used to project health outcomes as an end point.

- Decision analysis is a systematic approach to decision making under conditions of uncertainty; it provides a framework for evaluating the available alternatives. For example, in this group's case, it would evaluate universal screening compared with not screening.
    - The analysis provides a range of potential outcomes, providing information about the level of projected outcomes for screening relative to not screening.
    - An advantage of modeling is that evaluation of both existing and untested alternatives can be made with the available data.
    - It requires an explicit definition of the assumptions, which provides documentation and transparency in the decision making process.
    - Once a model is up and running, it can be used to identify future research.
    - A primary benefit is that data from randomized clinical trials that lasted only 3–5 years can be extended into the future to project what the long-term data would be. Projections using available data are supplemented by expert opinion.
- The decision analysis modeling will be used to project long-term health outcomes but not cost effectiveness.
- In general, ACIP's decision analysis models have developed economic information. As the decision analysis modeling approach goes forward, there will be an opportunity to incorporate costs into the model and project cost-effectiveness information. That will require another level of data collection.
- The general approach here is to incorporate modeling into the evidence review process by using simple models to project health outcomes. The initial goal is to use a model to project health benefits and potential harm.
- Dr. Prosser presented a case study example of modeling, expanded newborn screening for MCADD, from the early 2000s. The decision analysis model was developed to estimate the costs of screening (incremental test costs and follow-up and screening costs) and the long-term costs of treatment for MCADD.
    - The MCADD model had three types of inputs: costs, outcome probabilities, and health data values.
    - The model projected economic, screening, and clinical outcomes. It was able to project health outcomes, short-term screening outcomes, the number of false positives, how many newborns required follow-up, clinical outcomes, the number of cases identified, the number of hospitalizations both under a no-screening option and screening, the number of averted hospitalizations, the number of averted deaths, under-screening versus no screening, and the economic outcomes.

- The intent is to make the models a completely transparent process. Other goals are that there be understanding and agreement about assumptions, outcomes, and inputs used for the decision analysis model to generate additional data for the Advisory Committee.

- The newborn screening simulation model has two sub-models, one that simulates a hypothetical cohort of newborns undergoing newborn screening and an identical cohort that does not experience screening.

- The model was able to project the number of false-positive screens (20) and provide projected cost data. Using a cost-effectiveness ratio, the model indicated that screening for MCADD was not cost-saving, but would be considered cost-effective by many metrics ($21,000 per quality-adjusted life year gained).

- The importance of this modeling is its ability to look at projected long-term outcomes throughout the life course. For the 100,000 cohort of hypothetical newborns, we can see, over time, what the cumulative number of deaths would be, what the incremental deaths averted at each time point would be, and the number of cases that would end up with intellectual disability.

- Using this model, we determined that the number of hospitalizations would be higher under screening than under no screening. A closer look at the model's projected outcomes indicated as screening saves newborns and children from dying, those children are at risk for hospitalization.

- Modeling provides the very useful opportunity to study sensitivity analysis by varying the inputs.

- Dr. Prosser presented a model of how the cost-effectiveness ratio for hyperbilirubinemia affects specific health outcomes. Change in the cost of the initial screen was found to be very sensitive. Most of the other parameters had very little effect on the outcome of cost-effectiveness ratios.

- This is the key element of what can be done when evidence available in the literature is used as inputs into a model supplemented by expert opinion to create some projected health outcomes.

  - For MCADD, we are able to project the screening tests, follow-up results, short-term outcomes, the number of children with the condition, cases of developmental delay, hospitalizations, and deaths. We are also able to project short- and long-term costs as well as quality-adjusted life years.

  - For hyperbilirubinemia, we plan to create a simple decision analysis model as a way to synthesize this evidence into tangible short- and long-term health outcomes. An expert panel has reviewed the structure of the model, and the next step is to supplement the data to develop assumptions around the missing data. There will be a screening sub-model and a clinical assessment comparison sub-model. Each step will be documented and vetted by the expert panel, possibly with input from the Advisory Committee. An important part of the modeling will be to process what is happening in practice now, because that will be the analysis comparator. The intent is to be able to project health outcomes and screening outcomes, comparing clinical assessment to universal screening. A base case estimate and a range over which those estimates are likely to vary will be developed from these projections. There are no plans at this time to develop a cost-effectiveness analysis.

- Other models have been built on data from randomized clinical trials, large cohort studies, and retrospective databases, and the validation of the models has hinged on matching to actual available data and then projecting from that point. In contrast, this is a decision modeling approach that is geared towards a method for evidence synthesis. It is an alternative to meta-analysis, because the evidence base needed for that is not available.

Dr. Prosser opened the floor for discussion.

- Dr. Botkin asked how, in the MCADD modeling, circumstances in which there is a spectrum of disease are dealt with.
    - Dr. Prosser replied that this is a nice example of how modeling can provide useful information. The variables of the disease can be included in the model and then, the assumptions around what happened to the children can be varied.
- Dr. Vockley noted that, based on the historic literature, there are probably some MCADD costs that are not being captured. He added that this modeling provides an excellent opportunity to review some of the better-characterized screening disorders.
- Dr. Prosser addressed the notion of cost-saving versus cost-effectiveness. It cannot be assumed that a situation in which there is immediate death is cost-saving. When doing cost-saving analyses, we look at the relative value of that. So, we are never looking just at costs, but at what the health is that is being purchased for that.
- Dr. Chen asked how the time variability in terms of risk for hyperbilirubinemia would be incorporated into the decision analysis. He also asked how the significant racial and ethnic variables associated with hyperbilirubinemia will be addressed.
    - In response to the first question, Dr. Prosser explained that they will probably identify specific time points for the base case analysis and then vary the time points. Regarding the second question, she thinks, because there are many variables, they will have to stratify the cohort.
- Dr. Homer noted that, while the sought-after outcome from screening for hyperbilirubinemia is encephalopathy, the linkage between the two remains enigmatic. He asked how the model will account for that uncertainty.
    - Dr. Prosser explained that they will make an assumption about what that translation is and then will vary it to evaluate how good of a marker it is for ABE and then CBE.
- Dr. Kemper noted that the purpose of this modeling is not to replace the full evidence report; rather it is additive. In this case it should point out where the important gaps are. Few data exist around the relationship between hyperbilirubinemia and acute bilirubin encephalopathy and kernicterus. Reasonable guesses can be made and boundaries can be established to get a sense of what is going on.

D. Committee Related Work, Preparing for Transition

Joseph Bocchini, M.D.

Committee Member, Incoming Committee Chair

To discuss upcoming transitions of the Advisory Committee, Dr. Howell welcomed the incoming Advisory Committee chair, Dr. Joseph Bocchini, to present. Dr. Bocchini thanked everyone present for undertaking the important work of the Advisory Committee. He drew special attention to the hard work of Dr. Rodney Howell and Dr. Michelle Puryear. He proceeded to lay out ideas about where the Advisory Committee is and where it needs to go.

- Dr. Bocchini started by reviewing the Advisory Committee's charter and duties. The Advisory Committee was chartered in 2003 with Section 1111 of the Public Health Services Act. The charter was updated in the Newborn Screening Saves Lives Act of 2008, and was in the reauthorization of the Public Health Service Act that year. This extended the operation of the Advisory Committee for a 5-year period beginning in April 2008, so reauthorization of the Advisory Committee is required in 2013.
    - The Advisory Committee provides advice to the Secretary about aspects of newborn and childhood 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, health care services for newborns, and children with or at risk for heritable disorders. The Advisory Committee's focus has been on newborn screening because of its ability to have the greatest effect.
    - The Advisory Committee's duties are three-fold: to establish operating procedure bylaws, to review and report on screening practices, and to recommend improvements in the national newborn and childhood screening programs. There is no doubt that the Advisory Committee has adequately met these duties.
    - There are a number of activities from the 2008 act that affect and complement the work of the Advisory Committee. Section 1112 established the clearinghouse for newborn screening, section 1113 established the program for laboratory quality, section 1114 established the Interagency Coordinating Committee on Newborn and Child Screening, and section 1116 established the Hunter Kelly Newborn Screening Research Program at NICHD. As these move ahead they will continue to inform the Advisory Committee's work.
    - Section 1109 of the Children's Health Act of 2000 established grant programs to improve the ability of states to provide newborn and child screening for heritable disorders. The Advisory Committee provides advice, recommendations, and technical information to the Secretary concerning those grants and projects.
    - Further specific duties are outlined in the Newborn Screening Act of 2008.
        - One was to make systemic, evidence-based, peer-reviewed recommendations that include the heritable disorders that have the potential to significantly impact public health, for which all newborns should be screened. The Advisory Committee has been remarkably successful in this area.

        - Another duty was to develop a model decision matrix for newborn screening expansion, including an evaluation of the potential public health impact of such expansion, and periodically evaluate and update the recommended uniform screening panel based on such a matrix. It is clear that the decision matrix has been made for newborn screening expansion and we are looking at ways to strengthen the evidence on which that is based.

        - The above two areas could benefit from more focus on the public health impact for the individual. Re-evaluation and updating, based on a time period as well as new data, is also important for the Advisory Committee's future.

        - Another duty is considering ways to ensure that all states attain the capacity to screen for conditions chosen. This helps to inform how to provide grants through section 1109.

        - Another is to provide recommendations, advice, and information as necessary to enhance, expand, and improve the ability of the Secretary to reduce the mortality or morbidity from heritable disorders. This may include follow-up activities; implementation (a big issue in two of the subcommittees), monitoring, and evaluation of screening activities; diagnostics and technology used in screening.

        - Another duty evaluating the availability and reporting of testing for conditions for which there is no existing treatment and conditions not included in the recommended uniform screening panel that are treatable with FDA-approved products or other safe treatments as determined by scientific evidence and peer review. This leads us to conditions that might not be considered for universal screening but might be targeted for specific activities or specific individuals.

        - Other duties include developing minimum standards and policies for state screening programs; recommending quality assurance oversight and evaluation of screening (this was brought up in the laboratory standards subcommittee); creating public and provider awareness and education; looking at costs and effectiveness of newborn screening and medical evaluation systems and intervention programs conducted by state-based programs (this is something the Advisory Committee will need to address); identification of the causes of, public health impacts of, and risk factors for heritable disorders; and the coordination of surveillance activities (a concern of the laboratory standards subcommittee).

    - The Advisory Committee is required to submit an annual report on peer-reviewed newborn screening guidelines.

- The Advisory Committee's three standing subcommittees have made suggestions for better interaction and modification of titles and charges. Dr. Copeland and Dr. Bocchini will consider the suggestions and determine how to integrate them smoothly.

- The Advisory Committee has several workgroups that address specific topics. Additional workgroups will be needed for the development of subsequent Advisory Committee assignments.

- Dr. Bocchini expressed his view of the current items that need addressing.
    - Due to recent changes in the membership, the Nominations and Prioritization Workgroup has no members. The group needs to be repopulated.
    - The structure and function of each standing workgroup needs to be reviewed.
    - The Advisory Committee needs to prepare for the 2013 reauthorization.
    - The Advisory Committee needs to determine whether its standard operating procedures and activities match the charter and the legislation.
    - The Advisory Committee needs to develop a formal matrix for evaluation of the public health impact. The Advisory Committee needs to know how states can include or implement the decisions it makes. The Secretary has told the Advisory Committee it needs to conduct a thorough evaluation of the public health impact of screening for CCHD, and she indicated that it would help the states to have information about these impacts.
    - In addition to modeling health outcomes, the Advisory Committee should begin to look at modeling cost effectiveness.
    - The Advisory Committee needs to develop a system of follow-up for policy decisions in terms of implementation, surveillance, patient outcome data, and evaluation. Sharing feedback with states about the results of the initiated policies is important.
    - This is also a good point in time to review the structure and function of the Advisory Committee's workgroups as well as to look at the structure of workgroups for individual nominated disorders.
    - The Advisory Committee should consider the appropriate process to review, endorse, or use relevant work done outside of the Advisory Committee. The group should think about how it can enhance the role of the Advisory Committee or help others who are working in a similar field by being involved in the development or support of those products.

Dr. Bocchini closed his presentation by emphasizing the quality of professionals at the table, noting that five excellent new members will join the table at the next meeting. He invited comments from the audience.

- Dr. Calonge asked what the process for reauthorization is.
    - Dr. Copeland responded that HRSA's Office of Legislation is already aware of the need and has started working on it. It is called an A-19 process. Part of the process is making sure that the charter is in line with the legislation and making sure that there is minimal controversy.
- Dr. Botkin asked about the charter and the Advisory Committee's name. Although the heritable condition phrase is in the name, that has not limited the Advisory Committee from looking at congenital heart disease, which is congenital but not heritable, and hyperbilirubinemia, which is heritable only in some cases. He wondered if the Advisory Committee needs to rethink the charter in that respect.
    - Dr. Bocchini expressed the hope that a congenital infection would be under the purview of the Advisory Committee.

- Dr. Howell noted that the name of the Advisory Committee changed between the first and the second authorization. During the first iteration, the name included "genetic."
- Dr. Copeland explained that this will depend on the OGC's interpretation of the legislation, because the charter has to reflect what is in the legislation.
- Dr. Vockley warned against mission creep. There are other groups that oversee these important issues, and this group has a legislative mandate to tend to. The group of disorders this group oversees has traditionally had no other home or advocates. The heritable component is a focus worth keeping.

VII. PASSING THE GAVEL

R. Rodney Howell, M.D.
Outgoing Committee Chair

Dr. Howell made parting comments about his wonderful privilege to serve as chair of the Advisory Committee since its inception. The Advisory Committee was formed at a time when there was rapidly-developing technology in the area of mass spectrometry so we were able to see a dramatic expansion of newborn screening.

- The Advisory Committee has had an outstanding and diverse membership. Dr. Howell mentioned a few by name. Dr. Dwayne Alexander, the former director of NICHD, was extremely supportive of the activities of the Advisory Committee as it got underway. Dr. Alan Guttmacher, his successor, continues to be highly supportive and interested. Dr. Tiina Urv is toiling away at the NIH to oversee a portfolio of situations that relate heavily to the Advisory Committee. He extended a personal thanks to Dean Pascal Goldschmidt at the University of Miami, for being flexible and supportive of the work that we do in the Advisory Committee. Dr. Michele Lloyd-Puryear, of HRSA, worked hard during the inception of the Advisory Committee until very recently; the Advisory Committee would not be where it is today without Dr. Puryear on the firing line. Ms. Alaina Harris, Dr. Sara Copeland, Ms. Carrie Diener, all of HRSA, continue to support the work of the Advisory Committee. Dr. Howell acknowledged Dr. Michael Watson and the American College of Medical Genetics for overseeing a HRSA contract that laid the groundwork of the Advisory Committee.
- Dr. Howell also acknowledged the advocacy groups that have contributed to the Advisory Committee's work. He specifically singled out the March of Dimes for its persistent support of our activities and for helping to educate Congress about the Advisory Committee's work.
- Dr. Howell passed a figurative gavel to incoming chair, Dr. Joseph Bocchini.

VIII. ADJOURNMENT

On behalf of HRSA, Dr. Mary Wakefield (HRSA's administrator), and Dr. Peter Van Dyke (retired from the Maternal Child Health Bureau), Dr. Sarah Linde-Feucht thanked Dr. Howell and

all the Advisory Committee members who are rotating off the Advisory Committee for their tremendous work.

MOTION #2 PASSED: To adjourn the meeting. Dr. Gerard Vockley moved and Dr. Tracy Trotter seconded the motion. The motion was approved unanimously with 15 yes votes, no abstentions, and one absence (Dr. Alan Guttmacher).

- The meeting was adjourned at 12:35 p.m.

Appendix A. Written Public Comments

1. Jennifer and John Garcia, College Station, Texas, SCID Screening

Jennifer & John Garcia; 3701 Night Rain Dr., College Station , Tx
(979) 690-0630

2011

Testimony for Universal Newborn Screening for SCID
(Severe Combined Immunodeficiency)

On behalf of Cameron, our family and all families living with the affects of SCID we would like to ask for a few minutes of your time to hear our story. We are Cameron's parents. Cameron passed away from complications of SCID on March 30, 2011, at 9 months old.

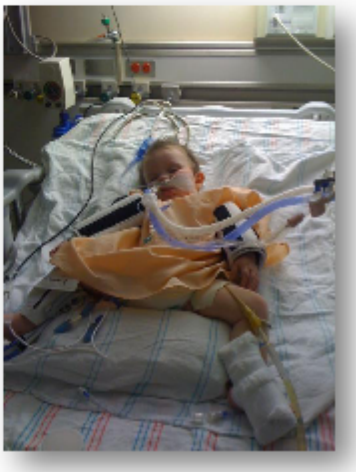
Cameron was born on June 30, 2010 in Texas. Cameron underwent state newborn screening, and was discharged from the hospital as a "normal newborn." Little did we know that Texas does not screen their newborns for everything nationally recommended. If we had lived in Massachusetts or Wisconsin, Cameron would have been screened at birth for SCID. If that newborn screen had been available for Cameron then his journey, our journey, and our lives would have been much different.

Brothers...

Cameron has an older brother, Gavin, who is now 5. Gavin has been healthy all of his life. We expected nothing less from Cameron. We considered ourselves blessed to have two beautiful, healthy boys.

Months passed and Cameron thrived, met milestones, was usually in the 90% in both height/weight, and at time s even exceeded his brother at the same age markers. Cameron's only ailment was recurrent ear infections, not unlike many babies including his brother. Like Gavin, Cameron got tubes in his ears at 7 months, but he continued to have cold symptoms. Cameron would be hospitalized for pneumonia shortly after he received his tubes.

February 24th 2011 would be the beginning of our journey, changing our lives forever...



Hospitals...

After a week at our local hospital being treated for pneumonia with only minimal improvements, we were transferred to Houston on March 3rd, 2011. Within 4 hours of arriving at Children's Hermann Memorial Hospital in Houston, Texas, Cameron was intubated and put into an induced coma for what was thought to be seizures.

We would not get to hold Cameron in our arms again for over 4 weeks, until the last moments of his life, and he passed away.

Cameron endured many tests: CAT scans, MRI's, EEG's, spinal taps, blood transfusions and massive doses of antibacterials, antivirals, and antifungals, just to list a few. Eight teams worked on him daily: Critical Care, Pediatrics, Neurologists, Epileptologist, Toxicologists, Immunologists, Infectious Disease, and Respiratory Therapists.

It took 10 days after arriving at a major medical center before Cameron was finally diagnosed with SCID on March, 13th 2011. Cameron was 8 months old.

SCID…

SCID occurs in approximately 1 out of every 33,000 live births. Some states currently screening are finding that it could be as frequent as 1 in 22,000 in the Hispanic community. The expected occurrence of infants born in Texas with SCID each year is 11-12. Most cases of SCID have no previous family history. There was no history of SCID in our family.

If SCID is identified in the first months of life, such as through newborn screening, and before severe infections occur, 94% of infants are successfully treated by a bone marrow transplant. For many, this is a **cure**. If SCID is not diagnosed before infections, survival rates drops dramatically. Unfortunately for Cameron, he was not diagnosed as a newborn because Texas does not screen newborns for SCID. Each day that passed Cameron's chances at survival were diminishing.

Treatment costs for infants before severe infections occur can be as **low as $50,000** Cameron's medical treatments have totaled **almost $1,000,000** date. In addition to the stress of medical bills, our baby's funeral expenses were over $3,800. The national estimated cost of the newborn screening test for SCID is a **mere $5 - $7 per infant.**

Screening…

SCID was added to the National Recommended Uniform Newborn Screening panel in 2007. Texas, however, has failed to act. Texas is the home state of David Vetter, the "Bubble Boy", and the most famous SCID case known. Texas has a special place in history for SCID, yet some 30 years later we have not started screening our newborns for SCID.

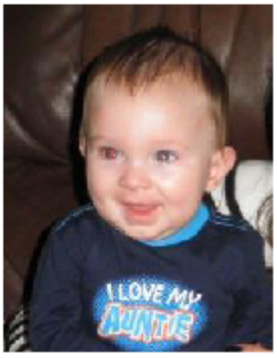
After his death we requested his newborn bloodspot be screened for SCID in a small pilot program currently being conducted in only a few Texas hospitals through the Texas DSHS for research purposes.

We were informed that Cameron did test positive for SCID at birth after his blood spots were screened.

We found out 9 months too late for Cameron.

With SCID newborn screening, Cameron's life could have, and would have been saved.

Please support newborn screening for SCID; it is an identifiable and treatable condition!



A. 2. David and Molly Altobelli, Houston, Texas, SCID Screening

David and Molly Altobelli, 2410 A Dorrington, Houston, TX 77030

Testimonial for Universal Newborn Screening for SCID

(Severe Combined Immune Deficiency)

Luke's story

On behalf of Luke, our family, and all families living with the effects of SCID, we would like to ask a few minutes of your time to hear our story. Our son Luke passed away from complications of SCID on March 2, 2011, at 7 months old.

A happy, healthy baby boy

Luke was born on July 17, 2010 in Houston, Texas. He was a beautiful, healthy baby boy for the first three and a half months of his life, and we had such joy watching him grow.

Just as we were getting into our new family groove, Luke got sick with what we thought was just a little stomach virus. I tried to be a calm pediatrician mom and not worry too much about it. But then on November 10 he got a high fever, wouldn't eat, and turned yellow. The rest happened so quickly. Suddenly Luke was in the ICU at Texas Children's Hospital.

Months of fear; a ray of hope

We spent the next four months with Luke in the hospital. He was so sick during those first weeks he wouldn't even smile. We still remember the day in December when he finally cracked a smile – Luke was back! It was clear, however, that something was very wrong with his immune system. It took over a month to diagnose the problem.

We learned that Luke had Severe Combined Immune Deficiency (SCID) in January. We were devastated, but there was a ray of hope: a total, life-saving cure was possible: a bone marrow transplant. However, children with SCID have much better chances of survival (94%) when they are transplanted prior to three months of age and infection-free; Luke was now almost six months, with a serious viral infection. His chances of survival had already dropped dramatically.

A parent's worst nightmare

Just weeks away from transplant, Luke developed a terrible form of pneumonia that was too much for his weak immune system to fight. He couldn't breathe and was in terrible pain. Luke went back to the ICU and spent the last month of his life sedated, on a ventilator.

On March 2, we had the dreaded discussion with Luke's doctors. Luke was never going to make it to transplant. We made the awful decision that no parent should have to make. We let Luke die in as much comfort as possible. We got to hold our baby as he exited this life, just as seven months and thirteen days earlier we had welcomed him into it.

Early identification of babies with SCID is critical to their survival. Luke had a pediatrician for a mom, lived five minutes from the world's largest medical center, and was cared for by some of the world's SCID experts at the very hospital where David Vetter, the famous "bubble boy" with SCID, was treated. But it was not enough.

But there is hope for others with SCID

There is a way to diagnose babies with SCID before they get sick, and other states are already screening babies for this life-threatening disease. SCID was added to the National Recommended Uniform Newborn Screening panel in 2007, but Texas has not added SCID to state screening. After Luke died, our immunologist went back and performed the proposed test on the Luke's newborn screening card bloodspot. Sure enough, Luke tested positive for SCID.

Luke's hospital bills totaled over $1.4 million. Treatment costs for infants before severe infections occur can be as low as $50,000. The national estimated cost for the proposed newborn screening test for SCID is just $5 – $7 per child.

So many lives could be saved with newborn screening for SCID.

It is too late for our precious Luke, but other babies have the right to benefit from this life-saving screening test.

Please support newborn screening for SCID.