Advisory Committee on Heritable Disorders in Newborns and Children

Meeting Summary
November 1-2, 2018

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) meeting was convened on November 1-2, 2018 and adjourned on Nov. 2. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

Committee Members

Mei Baker, M.D.
Professor of Pediatrics
University of Wisconsin School of Medicine and Public Health
Co-Director, Newborn Screening Laboratory
Wisconsin State Laboratory of Hygiene

Susan A. Berry, M.D.
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Department of Pediatrics and Genetics
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University of Minnesota

Joseph A. Bocchini, Jr., M.D. (Chairperson)
Professor and Chairman
Department of Pediatrics
Louisiana State University

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Professor of Clinical Pediatrics
University of Miami School of Medicine
Department of Pediatrics
Deputy Secretary, Children's Medical Services
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Cynthia M. Powell, M.D.
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Director, Medical Genetics Residency Program
Pediatric Genetics and Metabolism
The University of North Carolina at Chapel Hill

Annamarie Saarinen
Co-founder, CEO
Newborn Foundation

Scott M. Shone, Ph.D.
Senior Research Public Health Analyst
RTI International

Beth Tarini, M.D., M.S., FAAP
Associate Director
Center for Translational Science
Children's National Health System

Ex-Officio Members

Agency for Healthcare Research & Quality
Kamila B. Mistry, Ph.D., M.P.H.
Senior Advisor
Child Health and Quality Improvement

Centers for Disease Control & Prevention
Carla Cuthbert, Ph.D.
Chief, Newborn Screening and Molecular Biology Branch
National Center for Environmental Health

Food and Drug Administration
Kellie B. Kelm, Ph.D.
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Health Resources & Services Administration
Laura Kavanagh, M.P.P.
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National Institutes of Health
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Eunice Kennedy Shriver National Institute of Child Health and Human Development

Designated Federal Official

Catharine Riley, Ph.D., M.P.H.
Health Resources and Services Administration
Genetic Services Branch
Maternal and Child Health Bureau

Organizational Representatives

American Academy of Family Physicians
Robert Ostrander, M.D.
Valley View Family Practice

American Academy of Pediatrics
Debra Freedenberg, M.D., Ph.D.
Texas Department of State Health Services

American College of Medical Genetics
Michael S. Watson, Ph.D., FACMG
Executive Director

American College of Obstetricians & Gynecologists
Britton Rink, M.D., M.S.
Mount Carmel Health Systems

Association of Maternal & Child Health Programs
Jed Miller, M.D.
Director, Office of the Office for Genetics and People with Special Health Care Needs
Maryland Department of Health Maternal and Child Health Bureau

Association of Public Health Laboratories
Susan M. Tanksley, Ph.D.
Manager, Laboratory Operations Unit Texas Department of State Health Services

Association of State & Territorial Health Officials
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Department of Defense
Vacant – representative to be determined.

Genetic Alliance
Natasha F. Bonhomme
Vice President of Strategic Development
Genetic Alliance

March of Dimes
Siobhan Dolan, M.D., M.P.H.
Professor and Vice Chair for Research
Department of Obstetrics & Gynecology and Women's Health
Albert Einstein College of Medicine and Montefiore Medical Center

National Society of Genetic Counselors
Cate Walsh Vockley, M.S., CGC
Senior Genetic Counselor Division of Medical Genetics Children's Hospital of Pittsburgh

Society for Inherited Metabolic Disorders
Shawn E. McCandless, M.D.
Section Head, Genetics and Metabolism
Children's Hospital Colorado

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I. Administrative Business — November 1, 2018

Joseph A. Bocchini, Jr., M.D.
Committee Chair
Professor and Chairman
Department of Pediatrics
Louisiana State University

Catharine Riley, Ph.D., MPH
Designated Federal Official
Health Resources and Services Administration

A. Welcome and Roll Call

Dr. Bocchini welcomed participants to the fourth meeting for 2018 of the Advisory Committee on Heritable Disorders in Newborns and Children.

Dr. Bocchini conducted roll call. Committee members in attendance were:

- Dr. Mei Baker
- Dr. Susan Berry
- Dr. Joseph Bocchini
- Dr. Jeffrey Brosco
- Dr. Carla Cuthbert (Centers for Disease Control and Prevention)
- Dr. Kellie Kelm (Food and Drug Administration)
- Dr. Melissa Parisi (National Institutes of Health)
- Dr. Cynthia Powell
- Ms. Annamarie Saarinen
- Ms. Joan Scott (Health Resources and Services Administration)
- Dr. Scott Shone
- Dr. Beth Tarini
- Dr. Catharine Riley (Designated Federal Official)

Organizational representatives in attendance were:

- American Academy of Family Physicians, Dr. Robert Ostrander
- American Academy of Pediatrics, Dr. Debra Freedenberg
- American College of Medical Genetics, Dr. Michael Watson
- American College of Obstetricians & Gynecologists, Dr. Britton Rink
- Association of Maternal and Child Health Programs, Dr. Jed Miller
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health Officials, Dr. Chris Kus
- Genetic Alliance, Ms. Natasha F. Bonhomme
- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Ms. Cate Walsh-Vockley
- Society for Inherited Metabolic Disorders, Dr. Shawn E. McCandless

B. Vote on August 2018 Meeting Minutes

By roll call vote, the minutes were approved by all Committee members who were present.

C. Opening Remarks

An announcement soliciting nominations for new Committee members in 2019 and 2020 will be issued soon. Self-nominations and nominations by colleagues will be considered. Information on the application process and the application deadline will be posted on the Committee's website and on various listservs. A call for nominations to fill three organizational representative openings will be issued soon as well.

Dr. Bocchini reiterated decisions made during the August meeting, including a Committee review of the process for nominating conditions to the Recommended Uniform Screening Panel (RUSP), the evidence review process and the matrix, and consideration of developing a method for recommending removal of a condition from the RUSP.

The Committee is also undertaking two additional projects. The first is a study of progress made to date on timeliness in newborn screening, led by Alex Kemper and K.K. Lam. The second project will assess how adding the recently approved conditions to the RUSP has impacted the newborn screening system.

Dr. Bocchini announced the formation of a new Ad Hoc Workgroup to address overlapping issues identified through the Committee's discussions regarding assessing risk based newborn screening test results. The workgroup will encompass education efforts and possibly policy considerations for stakeholders, including as states and clinicians. The Ad-hoc Workgroup will include members of the Committee, the Laboratory Standards and Procedures Workgroup and the Education and Training Workgroup.

The Committee's February 2019 meeting will be held in person and by webcast, as will the April meeting, the dates for which have been changed from April 22-23 to April 23-24.

II. Public Comments

A. Dr. Robert Steiner, clinical professor at the University of Wisconsin

Dr. Steiner introduced himself as a pediatrician, geneticist and researcher. He is providing comments as a private citizen, advocating before the Committee for people with CTX, including patients with the condition whom he has treated. He explained that the treatment for CTX, chenodeoxycholic acid (CDCA), has been documented in journals for 40 years and is being used to treat nearly 100 patients with this condition. He indicated that chenodeoxycholic acid is safe, and is effective for treatment of CTX when the condition is diagnosed in its early stages, but has little benefit once the patient suffers serious complications such as autism, dementia and cataracts. Other adverse clinical outcomes of CTX include diarrhea, loss of cognitive skills, seizures and ataxia; symptoms, which can be irreversible and may overlap with other conditions, making CTX difficult to diagnose. Dr. Steiner stated that newborn screening will reduce the time to diagnosis and pointed out that Dr. Andrea DeBarber and other colleagues have developed an accurate, reliable screen for CTX using dried blood spots and mass

spectrometry that are already used in newborn screening. Confirmatory testing through genetic sequencing and measurement of cholestenol is widely available.

B. Dr. Andrea DeBarber, research associate professor, Oregon State Health and Science University

Dr. DeBarber is the lead for the team that nominated CTX for addition to the RUSP. She has been working with others to conduct pilot studies on using tandem mass spectrometry to screen newborn dry blood spots for CTX. Dr. Michael Gelb at the University of Washington has screened 30,000 de-identified dried blood spots and compared them to dried blood spots from CTX patients with no false positive results. The goal of this study is testing 100,000 dried blood spots. She also described other large-scale pilot studies being conducted in Israel, New York State and the Netherlands. She noted that her laboratory has confirmed the identity of a primary tetrol glucuronide disease marker in dried blood spots in newborns with CTX. This information has been shared with the Centers for Disease Control and Prevention's (CDC) Newborn Screening and Molecular Biology Branch to inform the development of external quality assurance materials. She requested that the Committee recommend that CTX move forward in the review process.

C. John Wolf, board member, United Leukodystrophy Foundation and father of a daughter with CTX

Mr. Wolf explained that his 24-year-old daughter, who began exhibiting symptoms of CTX at birth, starting with chronic diarrhea, was diagnosed when she was 10 years old. Over time, but before diagnosis, she began showing signs in school of attention deficits and memory loss followed by progressive disintegration in vision resulting from cataracts and weight loss. She was referred to a geneticist who diagnosed CTX. She started treatment immediately, began doing better in school and gained 70 pounds. She now lives independently, works, drives and recently had her first child. Mr. Wolf said the gene mutation that causes CTX affects multiple systems in the body, making it easy to misdiagnose. He called for the Committee to move the CTX nomination forward.

D. Kent Richter, spouse of a patient with CTX

Mr. Richter introduced his wife, who was also in attendance. Mrs. Richter now uses a wheelchair for mobility. He described the long and frustrating process prior to receiving a diagnosis. First, there was what he referred to as "bumps" on her legs, and then problems with her Achilles tendons, and severe pain that affected her mobility in her 20s and 30s. She was diagnosed as an adult and continues to suffer from severe complications of the disease.

E. Susan Stewart, mother and legal guardian of a 27-year-old patient with CTX

Ms. Stewart said that her son, Eric, was not diagnosed with CTX until he was 16 years old. By 16 months old, he showed a desire to play by himself for long periods of time and began losing vocabulary he had mastered. He was diagnosed with a communication disorder as a toddler, then with a seizure disorder, and at age 6 was diagnosed with a probable immune system disorder. MRIs showed decreased gray matter in his brain. Over the years, he was identified as intellectually disabled, developed bilateral cataracts, became nonverbal, could not bathe or dress himself, relied on a wheelchair, had an IQ of 40 and exhibited significant energy decline. Ms. Stewart learned that disorders involving the inability to break down certain forms of cholesterol are often linked to autism and cataracts and that Oregon Health

and Sciences University was studying disorders with these characteristics, which is where Eric received a correct diagnosis. Since receiving treatment, he has regained the ability to dress himself, walk, and buckle a seatbelt; but he continues to have a severe language disorder and moderate-to-severe autism. He lives in a group home for developmentally delayed people, receives Social Security, Medicare and Medicaid and receives more than $9,000 per month from Oregon to pay for necessary care.

F. Robert Rauner, president, United Leukodystrophy Foundation and father of a patient with CTX

Mr. Rauner noted that he has been associated with the United Leukodystrophy Foundation since his son was diagnosed with CTX in 1994; he became a board member in 2000 and has been president for the past four years. He lauded the Committee for recommending that X-ALD be added to the RUSP and participated in adding the condition to the Nebraska Newborn Screening Panel. The Foundation has worked with Manchester Pharmaceuticals to win orphan drug status for CDCA to treat CTX and has worked to make funds available to families to help pay for treatment and provide support in other ways, such as holding meetings and providing travel grants for affected families. He expressed confidence in Dr. DeBarber's and Dr. Steiner's work in support of seeing CTX considered for addition to the RUSP.

G. Ron Bartek, ALD Foundation

Mr. Bartek provided the Committee with an update on the RUSP roundtable they held. Participants included state laboratory directors and representatives from the pharmaceutical, clinical care, policy, legislative, patient advocacy and relevant technology communities. One of the discussion topics centered on the tensions between state labs and the federal committees that determine processes and recommendations. He acknowledged that it is difficult to reach the requisite level of certainty when it is difficult or impossible to diagnose the condition until patients become symptomatic. Delays in state decision-making and implementation may be more tied to the certainty of benefit than to funding levels. Also discussed was the potential for reauthorization of the Newborn Screening Saves Lives Act, which could include additional funding, and what aspects of newborn screening might be funded. The next roundtable will be held in April in conjunction with the Committee's meeting; participants will discuss how technological advances and other developments might alter the newborn screening landscape over the next five years, concerns about long-term follow-up challenges and shared experiences. A report on this roundtable meeting will be posted online at www.newbornscreening.us.

III. Condition Nomination for Cerebrotendinous Xanthomatosis (CTX)

Scott M. Shone, Ph.D.
Senior Research Public Health Analyst
RTI International

The Committee received a nomination package on CTX from a team of nominators led by Dr. DeBarber. The Nomination and Prioritization (N&P) Workgroup, a subgroup of the Committee consisting of Drs. Shone, Bocchini, Cuthbert and Tarini reviewed the package to determine whether it contained all of the elements required.

Dr. Shone explained that CTX, a progressive metabolic leukodystrophy, causes the body to store lipids. It is an autosomal recessive inheritance—a deficiency of mitochondrial enzyme coded by the CYP27A1 gene—but has variable phenotypic expression. More than 57 disease-causing variations occur in the gene and thus far, no phenotype/genotype correlations have been described. The onset of symptoms, which can include infantile onset diarrhea and childhood onset cataracts, can range from birth to adulthood. Young adult patients can develop tendon xanthomas and deterioration of neurologic function, which may later manifest as dementia and seizures but different symptoms can occur even among members of the same family.

The N&P Workgroup considers key questions:

Q. Is the nominated condition medically serious?
A. Yes. CTX is a progressive neurologic disorder. When left untreated it is very serious but it is very rare with only 300 cases identified in the last 70 years.

Q. Is the case definition and the spectrum of conditions well described to help predict the phenotypic range of the children who will be identified based on the population screening?
A. No. The case definition is not well described. Although the most serious phenotype is clear, there is a lack of genotype/phenotype correlation and there are minimal data on clinical subtypes. In addition, the case definition in the nomination packet lacked biochemical markers/profile to help identify CTX cases.

Q. Are there prospective pilot data from a population-based assessment available for the disorder? Dr. Shone reiterated the Committee's criteria for prospective pilot studies.
A. No, there is a lack of pilot study data that meet the Committee's criteria for newborn screening pilot studies. Several pilot studies have been conducted or are in process; however, true positive cases have not been identified. An Israeli study on a population with a higher prevalence of CTX has been conducted, but it is not comparable to the U.S. population.

Q. Does the screening test have analytic validity?
A. The analytical validity and characteristics of the screening test were unclear. Although the data were good, they are not thorough enough for a complete evaluation. A manuscript describing assays contained data that had limited analytic validity and supplementary data referred to in the manuscript were not included. Accuracy and precision data were incomplete and linearity and interference results and matrix effects were discussed but data were not presented.

Q. Are the characteristics of the screening test reasonable for the current newborn system (among other aspects, is there a low rate of false negatives)?
A. It was unclear whether the proposed screening tests, which use quarter-inch punch rather than the one-eighth punch used in U.S screening systems, would be suitable. In addition, the type of mass spectrometry used varied from lower to higher end. The assays are not multiplexible with current mass spectrometry methodology; also, the availability and stability of free agents is unknown. The false positive rate was acceptable but the false negative rate is unknown. In addition, other disorders are likely to be detected through screening but were not effectively discussed.

Q. Is there a widely available CLIA and/or FDA-approved confirmatory and diagnostic process?
A. A CLIA FDA-approved confirmatory test is widely available. The measurement of elevated cholesterol and elevated bile alcohol glucuronides in urine is well established, as is the measurement of ketosterol

bile acid precursors in the blood as well as genetic testing. Multiple CLIA-certified laboratories are conducting these types of confirmatory tests.

Q. Do the results bear clinical utility? Given the broad spectrum of disease, will the screening and/or diagnostic test identify who is most likely to benefit from the treatments that have been discussed?
A. The clinical utility is unclear. There is a broad spectrum of disorder phenotypically with a few cases. Although the most serious phenotypes are clear, the progression of others is uncertain and there are little data on variance. Although a suspicion index has been established, it is unclear how cases that rate high on the index would be handled when there are limited clinical findings.

Q. Are defined treatment protocols and FDA-approved drugs widely available?
A. Defined treatment protocols are widely available; however, CDCA treatment, while low risk, is associated with hepatic toxicity and has not been FDA-approved for marketing. However, it has been granted orphan drug status. Cholic acid is a possible alternative but may not be as effective.

The N&P Workgroup recommended the Committee provide guidance to the nominators regarding additional information needed to complete the nomination packet as well as additional areas that require clarification.

Dr. Bocchini indicated that based on the N&P Workgroup's findings, the Committee would not vote on whether to advance CTX to evidence review. More work is needed to produce the level of data needed to meet the pilot study criteria and clarification is needed in some areas.

A. Discussion

- How often does CTX present in neonates rather than later onset? Dr. Shone said that the N&P Workgroup did not address this question.
- Early onset symptoms, such as diarrhea, are easy to attribute to other causes, in part because the condition is rare and, as a result, the full spectrum of disease is not yet well understood. For example, equivalent mild versions of CTX have not yet been identified.
- Early detection through newborn screening and treatment would limit the number of patients who exhibit the full spectrum of CTX symptoms.
- Once effective screening is introduced, it will lead to identification of previously undetected cases or asymptomatic disease; as a result, early screening and treatment, could result in an increase in prevalence.
- More data on both early detection and treatment would be helpful.

Dr. Bocchini stated that the Committee would transmit this and other advice to nominators and those conducting pilot testing and collecting data on CTX cases, screening and treatment.

IV. Baby's First Test

Natasha F. Bonhomme
Vice President of Strategic Development
Genetic Alliance

Ms. Bonhomme discussed the development, implementation and impact of Baby's First Test, a national newborn screening resource center, which also served as a Newborn Screening Saves Lives Act-mandated clearinghouse for newborn screening information from September 2011 through August 2018. The center collects and disseminates information on 79 conditions detectable through newborn screening and on the types of screening each state conducts. About 80 percent of those who visit the center's website, babysfirsttest.org, do so to access these two categories of information.

Ms. Bonhomme noted that many health care providers check the website to learn what conditions are being screened for in other states, especially when they are dealing with patients from those states, to determine what type of follow up those patients might need. The site features interactive maps to provide context, such as when a particular condition was added to the RUSP. The clearinghouse targeted a broad range of audiences but Baby's First Test's primary target audiences are existing, new and expectant families. The resource center contains information that people can order. The materials were free until last August. All of the materials provided through Baby's First Test have been reviewed and approved by a Community and Consumer Workgroup to ensure the information is relevant and accessible.

In 2015, the resource center also began providing Baby's First Test information on a separate website in Spanish. Although visitors to the English version site are split almost evenly between families and health care providers along with newborn screening advocates or industry representatives, most visitors to the Spanish site are families.

Genetic Alliance has been working with RTI to evaluate Baby's First Test in terms of its contributions to user knowledge and awareness and development and use of partnerships. To evaluate the website's effect on parents, information was collected from 777 couples who were planning or undergoing pregnancies. They visited a Baby's First Test website page on nutrition or were part of a control group that visited another popular pregnancy website. Those who visited Baby's First Test scored higher on a knowledge test than the control group and visits to that page alone increased their knowledge about that topic. Those who visited the Baby's First Test website expressed increased confidence in their ability to make informed decisions about newborn health, discuss such issues with their doctors and to find useful information on this topic.

Ms. Bonhomme drew attention to the fact that two thirds of participants, before visiting either site, said they had heard of newborn screening but only one third selected the right definition from a multiple choice list; these misconceptions extend to many health care providers as well, which indicates the importance of taking the intended audience's perspectives and assumptions into account. About 30 percent of the questions that Baby's First Test fields are not about newborn screening per se but about maternal and infant health. Most questions asked whether infants are drug tested and whether a positive test would cause the mother to lose custody of her baby—questions they should, but may be afraid, to pose to their health care providers. Despite the nature of these questions, it is clear that people want to learn about screening procedures, state specific information, and condition-specific information. Families want a copy of the results and they want to know what issues they should raise with their health care providers, who, themselves, want effective communication tools.

A. Discussion

- A Committee member asked how Genetic Alliance weaves in topics and messages that the newborn screening community thinks parents and health care providers need to know; for example, he felt the issue of specificity—how specific the public should expect screening's results to be—ought to be addressed. Another Committee member agreed, saying that it is important to convey that the test is sensitive but not conclusive and that a positive result should lead to confirmatory testing. However, it is also important not to overwhelm families with too much complex information that they cannot understand or remember. More information can be conveyed over time and potentially by more than one practitioner. Ms. Bonhomme responded that right now, the focus is on ensuring families know why screening is important but there has been no effort to influence where newborn screening should fall into a family's priority list (among the need to impart information on breastfeeding, sleep schedules, etc.). No approach is right or wrong; it is just important to know what you are trying to achieve.
- A Committee member asked whether Genetic Alliance maintains contacts with state newborn screening programs, which might, in some cases, be better positioned to answer some of the questions that Baby's First Test receives. Ms. Bonhomme confirmed they refer questions to health care providers or state follow-up programs.
- An organizational representative asked how Baby's First Test might handle a parent's decision to decline a newborn screen. Ms. Bonhomme indicated that parents may contact the site's "Ask the Expert" about how to arrange for a private company to do it, rather than the state program, more so than how to decline a screen. Ms. Bonhomme indicated the approach of the program in the Philippines is geared toward ensuring that every child is screened, but if the objective is to help parents make an informed decision about whether to screen their infants, the approach to achieve that would be different.
- A Committee member suggested that Baby's First Test could help parents of infants with specific conditions by either giving them or pointing them to a platform to engage with families with similar experiences.

V. Education Activities in Newborn Screening – Panel

Beth Tarini, M.D., M.S., FAAP (Moderator)
Associate Professor and Division Director
General Pediatrics & Adolescent Medicine
University of Iowa Hospitals & Clinics
Chair, Education and Training Workgroup

Jackie Seisman, M.P.H.
Assistant Director of Maternal & Child Health
Genetic Alliance

Debra Freedenberg, M.D. Ph.D.
Medical Director, Newborn Screening and Genetics
Texas Department of State Health Services

Susan Berry, M.D.

Professor and Director, Division of Genetics and Metabolism
University of Minnesota

Kimberly Noble Piper, RN
Executive Officer, Center for Congenital and Inherited Disorders
Iowa Department of Public Health

Dr. Bocchini introduced the panel and indicated the Committee believes it would be helpful to know what types of newborn screening educational activities are being conducted in the field and, toward that end, assembled a panel to describe some of them. Their perspectives will inform the work being done by the Education and Training and Ad Hoc Workgroups.

Dr. Tarini further introduced the panel and highlighted the critical role education plays in newborn screening. She explained that simply providing someone with information does not mean that the person will absorb or use it, which illustrates the complexity involved in the education process. She referred to two examples of education materials: a hand-out from the Minnesota Department of Health containing an infographic that shows and explains each step in the newborn screening process and a handout in Spanish produced by Baby's First Test. The latter to indicate the importance of conveying this information in a variety of languages and cultural contexts and to a variety of stakeholders. She reminded participants that the American Academy of Pediatrics (AAP), in calling in the early 2000s for a national agenda on newborn screening programs, stressed that education should be a part of every step in newborn screening: screening, short-term follow up, diagnosis, treatment and management and evaluation. She also referenced the Committee's recent education products: 1) the communication guide the Education and Training Workgroup produced that is designed to providing a starting point and framework for providers as they speak with parents about out-of-range screening result and 2) the Newborn Screening Education Planning Guide, which is meant to be used as a resource by people who are creating newborn screening educational materials.

Ms. Seisman provided an overview of the Beyond the Bloodspot Education Engagement Summit, which was hosted by Baby's First Test in June 2017 and received support from HRSA. The event drew 90 people including 30 representatives from 22 states as well as, members of health care associations, public health organizations and maternal and child health and family-led associations. The diversity of participants—ranging from newborn screening and genetics experts to maternal and child health groups and families—and their ability to network were singled out as highlights of the summit. Among the topics covered were how to engage families through priority target populations, how to educate in a crisis and priority setting in education. Attendees learned about key newborn screening touchpoints and the difference between education and education engagement. Attendees gained a better understanding of both the need for but also the challenges associated with education, how to engage with target audiences and disseminate information. They also became aware that there are many different groups involved in education engagement and it is possible to adapt what they have done or produced rather than creating educational resources from scratch. They also found that Baby's First Test is an important way for stakeholders to connect over education efforts and challenges. Attendees said that the summit made them feel more confident in making educational engagement an organizational priorities and through networking with a variety of stakeholders they saw more potential for connection and collaboration with other partners, especially at the national level. They also learned the importance of engaging consumers in materials development and evaluation. Participants expressed a desire to see more opportunities like the summit to develop materials and resources and technical assistance to support educational activities. The summit highlighted the need for resource and strategy sharing, a

process to devise best practices and a more guided approach to education. A meeting monograph is being developed that provides an overview of what was learned during the summit and information on educational and health communication models and frameworks. It will also cover the Baby's First Test Newborn Screening Educational Best Practices Framework for creating newborn screening educational materials and will adapt existing foundational knowledge on health education and communications frameworks to meet newborn screening needs; it will be produced and disseminated by December.

Dr. Freedenberg discussed the creation of X-ALD education materials in Texas in preparation for implementing X-ALD screening in September 2019 if funding is available. The first step in preparing educational materials was to examine what other programs had already done. New York State's newborn screening program provided some information. Through a project funded by the Association of Public Health Laboratories (APHL), a group of relevant Texas-based physicians and national experts convened to discuss clinical aspects of X-ALD and newborn screening laboratory methodology and algorithms. A year later, Texas clinicians attended another meeting during which laboratory and follow-up flows, algorithms and protocols were refined. A genetic counselor also attended to provide educational sessions on the types of challenges families with children who screen positive for X-ALD face. From this background, a brochure for families was developed in English and in Spanish. To help educate providers about the screening, Dr. Freedenberg offered grand rounds at various medical societies and medical schools and a national expert's Texas newborn screening grand rounds on X-ALD has been archived. One of the department's educators staffs a booth at professional meetings around the state and X-ALD training is offered online for CME credit. In an effort to beta test the Educational Best Practices Framework developed by Baby's First Test, the NBS program retrospectively compared their process with the framework. The department found that many "what" and "why" questions were addressed by adding X-ALD onto the state's newborn screening panel but they were still unsure how to implement education because of the many different audiences and potential timeframes for dissemination. They were cognizant of the fact that printed information should be delivered in plain language (i.e. at a sixth-grade level of comprehension). To cover "when" and "how," they developed a timeline working backward from the anticipated implementation date timeline. The Texas Department of Health received a CDC grant to assist with implementation of screening for new conditions, capacity building and quality improvement through data harmonization, and is planning an X-ALD webinar. In addition, an X-ALD tutorial is being developed for the state's Medicaid program, Texas Health Steps, which is being offered as a free training that offers CME credits.

Dr. Berry spoke on behalf of the Midwest Genetics Network, which conducted a project to determine what types of information on newborn screening results families want to receive. As a first step, medical student Whitney Thompson surveyed families about how results were conveyed and how well they understood them. The survey revealed that more than half of the families did not receive results or know whether they had. Most clinics returned few results and many had returned none. The network worked with the Provider Education Workgroup, which is part of the Midwest Genetics Network and consists of primary providers, families and specialists, to educate providers on how to return newborn screening results. They are completing a training activity, which includes a three-module virtual learning package on newborn screening and return of results. The modules focus on: 1. What newborn screening is; 2. Return of normal results; 3. Return of positive or borderline results. This was developed as a Maintenance of Certification 4 (MOC4) offered through the American Board of Pediatrics. So far, 82 physicians enrolled, and other health professionals will be encouraged to take it. In addition, Minnesota developed a newborn screening fact sheet, which, coupled with education provided to clinics about newborn screening, resulted in a much higher number of parents who received and believed they understood their infants' newborn screening results. The third module, which is being prepared, will

discuss how to present high-anxiety-inducing results to parents. They also hope to offer an 'advanced practices in newborn screening' information module.

Ms. Piper discussed the recommendations the Iowa Department of Health (IDH) gleaned from participants in a "Deliberative Community Engagement Project" focused on communicating newborn screening information and reporting results. Deliberative community engagement gives participants time to consider an issue and discuss it in depth before making a decision or reaching a consensus on it. Iowa's leadership wanted to hear from people who are not invested in newborn screening programs and are not confronting the challenges of dealing with late onset conditions—which can have expensive treatments with severe side effects. Through this project, 28 Iowans gathered to discuss newborn screening issues in connection with Pompe, MPS 1 and X-ALD. IDH was interested in how it can improve communication with families. Participants agreed that information should be provided to pregnant women, not just after birth and said that all—not only positive—results should be reported to families, preferably by phone or in person. Hard copies of information should be made available and an information checklist might be helpful to the family as well. Having a support person present or available when difficult news is delivered is also advisable. They also said they wanted to understand what early versus late onset means, what false positives are and to discuss opting out so that families could decide whether to participate in newborn screening. Participants also called for information on the availability, efficacy and cost of various treatments. They stressed the importance of conveying information more than once and inviting parents to ask questions and called for those providing this information to document questions they received and relevant follow-up conversations. Several people said that newborn screening should be discussed in high schools or even in middle schools and online, through social media, videos and interactively as well as through brochures. An app option was less popular because there are already so many. Referrals to support groups on Facebook, when warranted, would be helpful as well. It was also suggested that the topic should be discussed throughout hospitals and health organizations, including settings such as outpatient labs. Respondents also said they want to hear about positive or abnormal results from their primary care providers with whom they already have therapeutic relationships with back up consultations with a specialist if needed but the initial information should come from one source and should be conveyed compassionately. Other questions for which they wanted answers included: what an abnormal result means for the family, the risk for late onset, whether treatment will be initiated before confirmatory testing is done and what resources are available to help a family navigate the system or obtain information about a condition. In response, IDH is enhancing its newborn screening web page with information for parents and families as well as providers and making the information viewable on mobile apps. The department will also give health care providers business-sized cards with the QR code and the url for its website that can be given to patients and discussed with them during a subsequent visit.

A. Discussion

- A Committee member asked whether IDH is working with communication scientists to develop messages to families or the public about newborn screening, rather than public relations experts. None of the presenters were aware of this type of consultation but several agreed that it was warranted.
- A Committee member asked whether there is evidence to show what the best practices are about conveying newborn screening results. Ms. Piper said she was pleasantly surprised to see that although the participants in the deliberative process came from all walks of life and different educational backgrounds and levels, they were able to reach consensus on a range of questions, which could be useful in developing a best practice.

- A Committee member observed that despite careful efforts to develop and disseminate expertly crafted or vetted information on newborn screening that providers could share with their patients, they still just told patients to Google a condition to learn more about it. One possible suggested solution was to teach people how to search discerningly online. Another alternative is to add information as a pop up to electronic medical records so that the provider has it readily at hand. Another possible solution is to ensure that solid information destinations, such as Baby's First Test, is linked widely to other sites that parents, providers or relevant organizations visit frequently.
- An organizational representative said that UptoDate, a software system that serves as a point-of-care medical resource, which has a newborn screening section written by Alex Kemper, is a good resource, which has links to Baby's First Test and the ACT sheets.
- An organizational representative stressed the importance of repeating messages up to seven times to ensure they "stick" and that health care providers are using language similar to that employed by Genetic Alliance/Baby's First Test.

VI. Administrative Business — November 2, 2018

Joseph A. Bocchini, Jr., M.D.
Committee Chair
Professor and Chairman
Department of Pediatrics
Louisiana State University

Catharine Riley, Ph.D., MPH
Designated Federal Official
Health Resources and Services Administration

D. Welcome and Roll Call

Dr. Bocchini welcomed participants to the second day of the November 2018 meeting of the Advisory Committee on Heritable Disorders in Newborns and Children.

Dr. Bocchini then conducted the roll call. The Committee members in attendance were:

- Dr. Mei Baker
- Dr. Susan Berry
- Dr. Joseph Bocchini
- Dr. Jeffrey Brosco
- Dr. Carla Cuthbert (Centers for Disease Control and Prevention)
- Dr. Kellie Kelm (Food and Drug Administration)
- Dr. Melissa Parisi (National Institutes of Health)
- Dr. Cynthia Powell
- Ms. Annamarie Saarinen
- Ms. Joan Scott (Health Resources and Services Administration)
- Dr. Scott Shone
- Dr. Beth Tarini

- Dr. Catharine Riley (Designated Federal Official)

Organizational representatives in attendance were:

- American Academy of Pediatrics, Dr. Debra Freedenberg
- American College of Medical Genetics, Dr. Michael Watson
- American College of Obstetricians & Gynecologists, Dr. Britton Rink
- Association of Maternal and Child Health Programs, Dr. Jed Miller (did not attend afternoon session)
- Genetic Alliance, Ms. Natasha F. Bonhomme
- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Ms. Cate Walsh-Vockley
- Society for Inherited Metabolic Disorders, Dr. Shawn E. McCandless
- American Academy of Family Physicians, Dr. Robert Ostrander
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health Officials, Dr. Chris Kus

VII. Genomic Sequencing in Newborn Screening: Ethical, Legal and Social Implications – Panel

Cynthia Powell, M.D. (Moderator)
Professor of Pediatrics and Genetics, Director, Medical Genetics Residency Program
The University of North Carolina at Chapel Hill
Co-chair, Education and Training Workgroup

Barbara Koenig, Ph.D.
Professor of Medical Anthropology & Bioethics and Director of Bioethics
University of California at San Francisco

Josephine Johnston, M.S.
Director of Research
The Hastings Center

John Lantos, M.D.
Director of Pediatric Bioethics and Professor of Pediatrics
University of Missouri-Kansas City School of Medicine

Dr. Bocchini introduced the panel, focused on the ethical, legal, and social implications of genomic sequencing, both in the context of newborn screening and in clinical settings for sick and healthy babies. In August 2018 the Hastings Center published, "The Ethics of Sequencing Newborns: Reflections and Recommendations," in collaboration with the University of California, San Francisco's Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) Ethics and Policy Advisory Board.

Dr. Powell opened with a history of, and rationale behind, genomic sequencing. The potential to do whole genome sequencing is complex and it is not always clear which variants are pathogenic. She

explained that there are many ethical issues associated with the discussion of which genes should be sequenced—all of them or only those that are associated with specific conditions—and what type of information should be provided to patients. A workshop was held in 2010 with representatives from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Human Genome Research Institute, the Office of Rare Disease Research and other invited guests, who noted that sophisticated and increasingly cost-effective techniques for DNA-based sequencing may make it possible to expand newborn screening and increase its clinical and public health value, including in newborn screening. The meeting summary of the workshop is available at https://www.genome.gov/pages/policyethics/staffarticles/newborn_screening_meeting_summary.pdf. This could lead to a trans-NIH research agenda that could help to shape the application of new genomic concepts and technologies to newborn screening and health.

A request for applications was issued in August 2012 to examine how genomic sequencing could replicate or augment existing methods to screen for disorders in newborns, how sequencing could add to knowledge on conditions that cannot yet be screened for and what additional information it could provide that is relevant to clinical newborn care. Four sites participated in the NSIGHT project: Brigham and Women's and Boston Children's Hospital, Children's Mercy Hospital in Kansas City (later moved, with the researcher to Rady's Children's Hospital in San Diego), the University of California, San Francisco and the University of North Carolina (UNC) at Chapel Hill. Each awardee conducted a sequencing project, a clinical project and an ethics project. The Boston project involved healthy newborns and those in the neonatal intensive care unit (NICU). The Children's Mercy Hospital-Rady's Children's Hospital group focused on the speed of sequencing and its effect on clinical aspects (this project showed that the time needed to get results from a whole exome sequence could be reduced from 6-12 weeks to under 24 hours). The San Francisco group used dried blood spots from anonymized patients with metabolic conditions that were identified through standard newborn screening. This group also examined selected immunodeficiency genes in patients with immune function disorders that are not detected through traditional newborn screening. The project used cohorts of patients with known conditions and healthy newborns whose parents were recruited during pregnancy. UNC also examined more than 450 genes that are part of what they call the next-gen sequencing newborn screening group. UNC researchers were also interested in learning how parents' decision making about sequencing their children's genomes.

Dr. Koenig and Ms. Johnston introduced the Hasting Centers Report "The Ethics of Sequencing Newborns: Reflections and Recommendations". At the University of California, San Francisco, they convened a local group to discuss ethics issues with newborn screening ethics experts from all four NSIGHT teams and other selected people from around the country, thus forming the NSIGHT Ethics and Policy Advisory Board. The board held three meetings over three years and workshopped the draft analysis and recommendations at various meetings, including the June 2017 Ethical, Legal and Social Implications (ELSI) Congress. The work resulted in 12 essays for the Report.

In their article, "Sequencing Newborns: A Call for Nuanced Use of Genomic Technologies, they considered a number of questions: Which contextual forces shape our discussion of the utility of sequencing in newborns? Under what circumstances should newborns be sequenced? How should state-mandated newborn screening programs use sequencing? What role should parents play in determining how sequencing information about their infants is used and stored? Should sequencing be part of routine pediatric practice? With an assumption that newborn gene sequencing would be used for screening and diagnosis, they focused on two types of sequencing technology: sequencing for specific genes or variants that are associated with conditions and whole exome/whole genome sequencing or

analysis. The advisory board was most concerned with the just distribution of benefits, including those that could extend to the families of newborns. It also focused on the need to consider protections from harm, such as the risk of increases in expenses, unnecessary follow up and health-uncertainty-related harms that information gleaned through sequencing could trigger. It was not as clear that sequencing should be used as a screening tool in the clinical context; this would apply more to routine pediatric care rather than to asymptomatic infants. Concerns were expressed about storing results and other data and the potential for discriminatory or insurance use of the data. Negative results could also lead to unnecessary distress and, therefore, the need for counseling and could also trigger unnecessary follow up care and monitoring. These concerns were also expressed about using targeted or whole exome sequencing as a sole screen to improve public health. Dr. Johnson noted that such screens do not detect every condition. The board did conclude that sequencing would be useful as a secondary test to confirm a positive screening result or as a primary screen to detect conditions that meet all screening criteria on newborn screening panels, especially those that cannot be detected adequately using existing technology. The board also concluded that direct-to-consumer use of sequencing is not advisable.

Dr. Lantos worked with Stephen Kingsmore at Children's Mercy Hospital and later at Rady's Children's Hospital on a project to examine whether rapid genome sequencing in sick infants in the NICU could improve their care management. He reported that 50 to 60 percent of such tests led to a molecular diagnosis and, among these, 38 percent affected clinical care management, but he added that the results' clinical utility were vague. He added that the ambiguity of the meaning of test results might lead to clinical decisions that are harmful. He also noted that one of the most common changes in clinical management associated with genomic sequencing was the decision to shift care goals from life-prolonging treatment to palliative care. He warned that efforts to see whether adding whole genome sequencing to standard care would affect the quality or length of clinical care or lower costs have been problematic because doctors are unwilling to participate in randomized controlled trials comparing standard care alone to standard care and genome sequencing. They would rather receive all of the clinical data on each patient that is obtainable for treatment purposes.

Dr. Lantos also reported on a study to identify Krabbe disease among 2 million babies. He explained that this is a life--threatening condition for which the only treatment is a stem cell transplant, which often causes serious complications. Fourteen were identified with low enzyme levels and a genetic diagnosis of Krabbe disease. This group was followed for up to 10 years; five became symptomatic, four received stem cell transplants, two died within a few months of complications of the transplant, and two survived and experienced developmental delays. Dr. Lantos said that this example illustrates the potential harm in receiving false positive results but also true positive results that lead to treatment that can kill patients earlier than they would have otherwise have died or lead to an outcome that is no more favorable than those associated with the disease. He expressed concern that infants in the NICU incorrectly diagnosed with Krabbe disease through genomic testing might be moved from clinical to palliative care, despite the fact that many babies with those results would remain asymptomatic for much or all of their lives. In short, ambiguous results could lead to harmful clinical management decisions.

Dr. Koenig reported on a study comparing whole-exome sequencing with tandem mass spectrometry (MS/MS). The project team found that, due to the potential for missed cases and the high rate of false positive results associated with whole-exome sequencing, it should not be a stand-alone test to detect inborn errors of metabolism among the general population. The research, which involved examination of 1,200 false negative or false positive cases from the California newborn blood spot collection, showed, however, that, genomic sequencing of positive results revealed by MS/MS provided

information that did or might have informed diagnosis. In short, DNA testing can play a key role as a second-tier test but its efficacy depends on the disorder, the gene or even the particular variant. She stressed that it will take many years before genetic testing can truly predict an infant's likely medical future. She also mentioned several other risks to genome sequencing, particularly in the public health realm. It is an unconsented practice, which could be challenged legally. In California, samples are stored and made available for research, which raises privacy and other concerns, and sequencing would identify conditions that do not meet legal and ethical justification for state mandated screening and for which states cannot provide follow-up care.

In addition, state newborn screening programs listed a series of concerns about the burden discovery of genome sequencing could reveal including:

- Workforce and cost burdens;
- The difficulty of explaining the technology and the results to parents;
- The potential for private companies to push for implementation, which could place a burden on parents to follow through;
- Incidental or unexpected findings, potentially from the discovery of variants of uncertain significance, that result from sequencing;
- The discovery that other family members may be carriers, which can affect reproductive and other decisions; and
- The dilemma of whether to return results to a child or family, knowledge that might affect the parents' view of the child or the child's autonomy or do psychosocial harm, which must be weighed against the patient's right to know about one's—or family members'—immediate or future health status and risks.

Other concerns that were raised included the lack of large and thorough databases to study all disease variants, a process that is also hampered by a deficit of data sharing, and uncertainty in interpretation, especially among ancestral-diverse populations. The general conclusion was that, to date, whole-exome sequencing has proved to be useful only in clinical populations in which diagnostic uncertainty is a barrier to good care.

A. Discussion

- A Committee described the "messiness" of clinical medicine and the challenge of trying to come up with general rules about the role of genomic sequencing in newborn screening when various contributing factors are not clear cut. The difficulty with getting clinicians to do a randomized study to test the efficacy of genomic sequencing and MS/MS speaks to this point as well. Dr. Lantos said that the question of whether a genomic test result should lead to a change in management is a key question to pose and pointing out when such testing might be used appropriately or inappropriately is useful. An organizational member said that DNA tests are complex but they *are* tests that provide information and, as such, should be viewed and treated as any other medical test.
- Dr. Lantos reminded the Committee that diagnostic tests conducted in the NICU are not typically subjected to randomized controlled trials; doctors decide what tests to conduct based on their clinical judgement so the argument could be made that genetic testing is being held to a higher standard than other tests. Several organizational representatives pointed out that genetic testing will not be paid for unless there is published documentation indicating its clinical utility and usefulness in determining care options.

- Another Committee member warned against summing up medicine as "messy" because it may dissuade practitioners from "demessifying" it; in this case, viewing genomic sequencing as "just a test" whereas, such a test could be construed as an intervention because it might lead to an action that may or may not be well informed. This is the danger in not randomizing the test because choosing to conduct genomic sequencing on every infant—in the interests of getting as much information on every patient as possible—could fail to reveal a harm.
- A Committee member said that there needs to be an examination of whether secondary findings should be shared with families if they could, not only shed light on the newborn's future health, but benefit other family members as well. Whether and when such a step should be taken should be flexible; decisions should be subject to possible change, over the lifetime of the person who was screened.
- A Committee member pointed out that, even if genomic sequencing in the Noonan syndrome case did not reveal information leading to a life-saving change in care, in some cases, such testing could help to rule out the possibility a treatable condition might yet be revealed, thus offering "closure."
- Dr. Johnston said that it is important to help consumers understand the risks and potentially unintended consequences of genetic testing and ensure they understand fully its benefits and limitations.
- A Committee member pointed out that the direct-to-consumer medical tests regulated by the FDA is only authorized for use for and by people 18 years old and older.

VIII. Ethical, Legal, Social & Policy Considerations for Newborn Screening Pilot Studies

Jeffrey Brosco, M.D., Ph.D.
Professor of Clinical Pediatrics
University of Miami School of Medicine
Department of Pediatrics
Deputy Secretary, Children's Medical Services
Florida State Department of Health
Chair, Follow-up & Treatment Workgroup

Dr. Brosco began by pointing out that ELSI questions have been raised since newborn screening was introduced in the 1960s and focused initially on reducing false negative results, which was the impetus for making this screening a public health mandate. There was little concern then about parental consent or, until the 1970s about genetic exceptionalism, even though PKU had already been identified as a genetic disease. After a million babies underwent newborn screening, ELSI issues began to come to the fore, such as whether to treat based on indeterminate results and what treatment was appropriate. The unnecessary anxiety false positive results can trigger among families was discussed as well. ELSI issues are relevant to conditions added to the RUSP and/or state panels and these concerns help to inform decisions. There are also condition specific questions that can arise. For example, with regard to Duchenne muscular dystrophy, which is X-linked, is it useful to report carriers?

To encourage researchers to include ELSI research in their pilot studies and ensure that clinicians, advocates and those conducting pilot studies for candidate conditions had tools to decide what ethical issues to consider, the authors listed some questions and hypotheses that a researcher might include in

a more general pilot newborn screening study. One example might be in connection with the ELSI issues that might arise from a positive screen for a disease that could remain asymptomatic for many years or life-long and for which the intervention is fairly drastic. As the pilot study continues, the family could be asked to answer a survey that explains how they felt about getting a positive screening result under such circumstances. Did they appreciate the information or did it cause undue anxiety? The same types of questions could be asked about false positive results. Did the initial screen change how parents viewed the child? Did it trigger more doctor visits and a commensurate rise in medical fees? Early research indicates that this is not the case, which would be helpful for the Committee to know because some conditions it reviews have high false positive rates. Another possible question is whether families want to know about a child's carrier status? If the answer is yes, such reporting could become commonplace.

In terms of ELSI issues that affect the newborn screening system, questions about resource allocation would be relevant, as would equity in health care. Some populations are more likely than others to be stigmatized in connection with a screen for an infectious disease, for example. Also worth monitoring is the extent to which the public might begin to lose faith in the newborn screening program because the condition is rare or the perceived benefits of it are subtle. Other questions might touch on parental consent—whether it is necessary and the challenges to obtaining it—and ethical or social justification for population-based screening. Asking such questions ahead of time could help to avoid the need to address them when a candidate condition for the RUSP comes before the Committee.

A. Discussion

- A Committee member said that health disparities are an important consideration in connection with molecular genetic testing because half of the people in her state are covered by Medicaid, which does not cover this type of testing. She added that it is important to have this type of test as part of the newborn screening process rather than relying on outside sources to do it. Dr. Brosco agreed, saying that it could easily be added to the MS/MS screen that is already being done rather than expecting families to bear that burden.
- An organizational representative said that multiplexing rare disorders may increase the likelihood of identifying them. He also said that as states seek to add rare disorders about which little is known and for which there is no treatment, it may be advisable for the Committee to split the RUSP into one group of disorders that are clearly beneficial to detect early and another for those that are unfamiliar but may still warrant parental notification. Dr. Brosco asked what the informed consent process would look like in the perinatal period under such a scenario; he said that researchers have studied whether adding new conditions to a newborn screening panel confuses parents but, given enough education, they are able to distinguish between them.
- A Committee member asked what Dr. Brosco meant by the term "pilot study"; she asked whether it refers to studies that are conducted before a condition is added to the RUSP, or to those conducted by states that are early or relatively late in adding a condition to their newborn screening panels. She pointed out that the CDC provides funding to states in all of these cases. Dr. Brosco said it refers to all three; he cited as an example, Florida's consideration of whether to add Pompe to its screening panel. He said it would be useful through a pilot study to ask parents who got an indeterminate result how they might react to the news to hearing that the condition might be late onset—would it cause anxiety or make them feel better prepared for what might come? Would it make them view their children differently in any way? Such information could inform the state's decision regarding whether to add the condition to the panel.

- A Committee member said that it is important to distinguish between the types of pilot study that is being conducted. The example Dr. Brosco mentioned focuses on whether to implement an existing screen, which is different from one that is being conducted to try out a new test.

IX. Education and Training Workgroup Update

Beth Tarini, M.D., M.S., FAAP
Committee Member
Chair, Education & Training Workgroup
University of Iowa Hospitals & Clinics

Dr. Tarini described current activities being conducted by Workgroup members.

- Ms. Yvonne Kellar-Guenther from NewSTEPS is working on a video tutorial to train midwives on how to discuss newborn screening with their clients.
- Dr. Powell discussed a voluntary screening project in North Carolina for Fragile X and SMA she is helping to conduct.
- Ms. Walsh Vockley is working on educational materials for the National Society of Genetic Counselors.
- Ms. Bonhomme is working on a project to educate parents on newborn screening issues.
- Dr. Berry and Amy Gaviglio in the Midwest region developed an MOC module for newborn screening and Ms. Gaviglio has a genetic counseling student working on a master's thesis on redesigning the newborn screening report and content to improve parent/provider education.
- Mr. Jeremy Penn is working on a master's thesis on parents' newborn screening result communication preferences and how to structure delivery of that information.
- Dr. Tarini will study post-screening harms from false positive newborn screening results.
- Dr. Aaron Goldenberg presented data from one of his student's master's thesis, "Content Analysis of State Newborn Screening Education Materials, which compares current educational materials to those published in the past.

The Workgroup's communication guide is available on the Report section of the Committee's website and the education guide will be posted the week after this meeting. The Workgroup also discussed issues to be covered by the new Ad Hoc Workgroup, which includes four members of this Workgroup, including the need to examine the definition of and harmonize terminology laboratories use in describing newborn screening results to providers; an additional focus on how providers communicate this information to parents will be considered later.

X. Follow-Up and Treatment Workgroup Update

Jeffrey Brosco, M.D., Ph.D.
Committee Member
Chair, Follow-Up and Treatment Workgroup
University of Miami School of Medicine and Florida State Department of Health

Dr. Brosco thanked Kathryn Hassell and Sylvia Mann for participating on the Workgroup and welcomed new member Dr. Jed Miller of the Association of Maternal and Child Health Programs. The Workgroup

hopes to publish its medical food report, which the Committee recently accepted, in the journal *Pediatrics*. The Workgroup is focusing on devising a roadmap of what a multi-level—federated—system to ensure that every child with a newborn screened condition receives high-quality, evidence-based, family-centered care. Over the course of about 10 years, the Workgroup began examining what long-term follow up means and entails. This discussion led to a variety of perspectives on the topic leading to the development of a framework for sharing good outcomes (e.g., decreased mortality and morbidity, increase in function, disparity reduction). NewSTEPS and the Newborn Screening Translational Research Network have been working on developing a core set of long-term follow-up quality measures and data resources, which is moving the field forward.

The Workgroup has been encouraged the large data collection efforts through the National Survey of Children's Health (NSCH) or the Healthcare Effectiveness Data and Information Set quality improvement activities. HRSA's Maternal and Child Health Bureau has added a question about newborn screening to the NSCH. Dr. Brosco said that yesterday's discussion revealed that "follow-up" can have different definitions; to some it means checking on a patient's status while, to others, it means data collection and reporting. They also discussed whether treatment implies equity—is there an obligation to ensure that every child is identified, gets treatment and improves? There is also the question of who is responsible for long-term treatment and improvement and to what extent are state newborn screening programs responsible for this? The Workgroup's 2011 charge says that it should identify barriers, develop recommendations and provide guidance on who is responsible for long- and short-term follow up, including treatment for all children who have newborn screened conditions. Based on this, the Workgroup asked the Committee for permission to explore possible options for incorporating long-term follow-up care and treatment plans into the process for considering conditions for the RUSP.

A. Discussion

- A Committee member asked what period of time "long-term" covers; some interpret it as three months after a blood spot is discarded while others may view is as during the life span. An organizational representative referred to a paper that refers to it as provision of management and treatment over the patient's life-span. Dr. Bocchini said that it is worth examining how short-term and long-term follow up is used in publications in connection with newborn screening to see whether they remain valid or need clarification.
- A Committee member pointed out that the reason for doing follow up can vary by organization. A state newborn screening program may do it for program quality assurance purposes whereas a Title V director would want to know how a child is faring over time but another organizational representative said that ensuring the best health outcomes for the child is what is important.
- Dr. Bocchini said that the issue regarding the RUSP could be considered during the Committee's planned re-evaluation of the nomination packet and the evidence review process.
- A Committee member suggested that the Committee could engage nominators on the follow-up issue to stress that their participation does not end with a successful campaign to add a condition to the RUSP. Another Committee member pointed out that family advocacy and research organizations are interested in outcomes and how to improve them.

XI. Laboratory Standards and Procedures Workgroup

Kelli Kelm, Ph.D.

Ex-Officio Committee Member
Chair, Laboratory Standards and Procedures Workgroup
Food and Drug Administration

Dr. Kelm said that the Workgroup has spent the past few meetings focusing on risk assessment and cutoffs with APHL to develop a framework and provided input to a draft guidance document. The Workgroup received an update from APHL on this document - an overview of cutoff determinations and risk assessment methods. The document has been finalized and posted on APHL's website; it is considered a living document but there are no plans to modify it now.

The Workgroup is also charged with examining the role of next-generation screening and timeliness data to gauge states' progress in the areas of early specimen collection and unforeseen costs and other consequences of focusing on timeliness. The Workgroup also discussed some topics the Ad Hoc Workgroup could address:

- Improving screening specificity by adding variables such as weight and age into risk assessments to improve specificity and see whether it improves screening.
- New second-tier tests, such as molecular mass-spectrometry tests and using reference labs for second tier tests.
- Unifying definitions for newborn screening—should a negative test be referred to as "normal" for example, or "unaffected in range" to add clarity and should it be a risk-based description?
- What is the target for screening and what might be found in addition to the condition for which states are screening? Is there a need for the Committee to revisit its list of primary and secondary conditions and assess their clarity and transparency?

A. Discussion

- Dr. Bocchini said that the fourth topic is important because it is relevant to the Committee's plan to review conditions recently added to the RUSP to determine their respective impacts on laboratories and on short-term and/or long-term follow up. This Workgroup could help ensure that the right questions are asked and help to evaluate the process.
- Dr. Bocchini also suggested that the Workgroup could help examine APHL's data on timeliness, which involves several states.
- A Committee member pointed out that NBSTRN supports regular calls among clinicians, laboratories and screeners who have early adoption experience with conditions on the RUSP and representatives from states and other organizations can participate in them.
- An organizational representative predicted that it will be necessary to revisit the breadth of phenotypes and genotypes that are being targeted with treatments, as it continues to grow and will affect workforce capacity. Dr. Bocchini said it would be helpful to capture how states are addressing this. Dr. Watson is working on a manuscript about this topic.

XII. Ad-Hoc Workgroup – Interpreting NBS Results

Mei Baker, M.D.
Committee Member
Chair, Ad-Hoc Workgroup
University of Wisconsin School of Medicine and Public Health, Wisconsin State Laboratory of Hygiene

Dr. Baker explained that the Ad Hoc Workgroup is a collaboration between members of the Laboratory and Standards and the Education and Training Workgroups. The Workgroup has two charges. The first one is to address newborn screening result interpretation. A great deal of work has been done to educate primary care physicians that newborn screening is a risk assessment but it is actually a tool. The goal is to embed all of the concepts inherent in newborn screening into these physicians' day-to-day practice; for example, that there are positive, negative (normal) and indeterminate results. It is also important to convey these concepts in the right type of language. It is important to explain what "normal" means. The second charge is to review cutoffs and to develop recommendations for states on how to establish and do ongoing evaluation of cutoffs.

This Workgroup also hopes to develop recommendations regarding evaluation of cutoffs, present recommendations at local conferences and develop a white paper. Dr. Baker hopes that a work plan will be developed by early next year and recommendations and a white paper completed between February and April with the goal of finishing this project by August.

A. Discussion

- An organization representative pointed out that trying to engage primary care physicians on the specifics of how to incorporate newborn screening concepts into their practices may be challenging because they tend to spend most of their time focusing on conferences they attend on daily challenges rather than on conditions they rarely see. The best approach may be to engage them during a conference or training they are already attending.

XIII. New Business

Joseph Bocchini, M.D.
Committee Chair

No suggestions for new business were forthcoming.

XIV. Adjourn

Dr. Bocchini thanked everyone for their participation and adjourned the meeting. The next meeting will be held at HRSA headquarters on February 7-8, 2019.