Advisory Committee on Heritable Disorders in Newborns and Children

Summary of Fourth Meeting
February 11-12, 2016

Please note: These minutes are pending formal approval by the Committee. Corrections or notations will be incorporated in the final minutes.

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) was convened for its fourth meeting on Thursday, February 11, 2016 and adjourned on Friday, February 12, 2016. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

COMMITTEE MEMBERS

Don Bailey, Ph.D., M.Ed.
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RTI International

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(Committee Chairperson)
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Associate Vice President for Research
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Acting Director
Eunice Kennedy Shriver National Institute of
Child Health and Human Development

DESIGNATED FEDERAL OFFICIAL
Debi Sarkar, M.P.H.
Health Resources and Services Administration
Genetic Services Branch
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LIAISONS AND ORGANIZATIONAL REPRESENTATIVES

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

American Academy of Pediatrics
Beth Tarini, M.D., M.S., F.A.A.P.
University of Michigan Health System

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

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March of Dimes
Edward R. McCabe, M.D., Ph.D.
Senior Vice President and Medical Director

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

Society for Inherited Metabolic Disorders
Carol Greene, M.D.
University of Maryland Medical System
Pediatric Genetics

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I. Administrative Business: February 11, 2016

Joseph A. Bocchini, Jr. MD
Committee Chair
Professor and Chairman
Department of Pediatrics
Louisiana State University
Shreveport, LA

Debi Sarkar, M.P.H.
Designated Federal Official
Health Resources and Services Administration
Rockville, MD

A. Welcome and Roll Call

Dr. Joseph Bocchini welcomed the Committee members and other participants to the fourth meeting of the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) and took roll. Voting members present were:

- Dr. Don Bailey
- Dr. Joseph Bocchini
- Dr. Jeffrey Botkin
- Dr. Fred Lorey
- Dr. Dietrich Matern
- Dr. Stephen McDonough
- Ms. Catherine Wicklund

Ex Officio members present were:

- Agency for Healthcare Research and Quality: Dr. Kamila Mistry
- Centers for Disease Control and Prevention: Dr. Carla Cuthbert
- Food and Drug Administration: Dr. Kellie Kelm
- Health Resources and Services Administration (HRSA): Ms. Joan Scott (for Dr. Michael Lu)
- National Institutes of Health: Dr. Catherine Y. Spong (Dr. Tiina Urv morning of Day 1)

Organizational representatives present were:

- American Academy of Family Physicians (AAFP): Dr. Robert Ostrander
- American Academy of Pediatrics (AAFP): Dr. Beth Tarini
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- American College of Obstetricians and Gynecologists (ACOG): Dr. Joseph R. Biggio, Jr.
- Association of Maternal and Child Health: Dr. Debbie Badawi
- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Department of Defense (DoD): Dr. Adam B. Kanis
- Genetic Alliance: Ms. Natasha Bonhomme
- March of Dimes: Dr. Edward McCabe
- National Society of Genetic Counselors: Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders: Dr. Carol Greene

B. Secretarial Correspondence

Dr. Bocchini reported on the Committee's correspondence submitted to the Secretary of Health and Human Services (HHS), Sylvia Mathews Burwell. He informed participants that both the MPS I and ALD recommendations are currently under review.

A letter was sent letter to the Secretary about the Newborn Screening and Informed Consent

Recommendations. The Secretary accepted the Committee's Recommendation Number 5, which recommended the creation and distribution of targeted materials on the importance of newborn screening options for parents to participate in newborn screening research. To support this recommendation, the Secretary asked the Centers for Disease Control and Prevention (CDC), the Health Resources Services Administration (HRSA), the U.S. Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP) to work with states in this endeavor. These agencies and office will work together with states to develop specific guidance and educational materials.

Although the Secretary did not adopt Recommendations 1 through 4, she did forward them to OHRP so that they may consult with states as needed to develop guidance in the areas specified in the these four recommendations. The Secretary did not adopt Recommendation 6, which asked for Federal funding for states to conduct translational research activities. However, the Secretary will encourage HHS agencies to use discretionary funding to fund research.

The Committee also submitted comments for the NPRM on federal policy for the Protection of Human Subjects as discussed in the Committee's last meeting.

Committee Discussion

- Dr. Bailey asked if the recommendations were not accepted because they were not under the purview of the Committee or if the Secretary disagreed with the recommendations or perhaps thought they would be best handled in a different venue.
- Dr. Bocchini said that OHRP was working on this matter and that the information related to the Committee's concerns was relayed to them to review and address, and that it was not under her purview to address.
- Dr. Matern asked about the 120-day rule that states that the Secretary has to make a decision on the Committee's recommendations within that timeframe.
- Ms. Sarkar explained that MPS I was voted under the Discretionary Committee charter, so the 120-day rule doesn't apply. However, for X-ALD the rule does apply and we should be hearing soon about the Secretary's decision.

C. Approval of November Meeting Minutes

Committee members offered no comments or recommended changes to the meeting minutes for the November 2015 ACHDNC meeting. Dr. Botkin made a motion to approve the minutes, which was seconded by Dr. Bailey. Dr. Bocchini took a roll call vote for the approval of the minutes. The Committee members present approved the minutes unanimously.

D. Other Business

Dr. Bocchini reviewed the meeting agenda and informed participants that there are three additional meetings scheduled for this year:

- May 9-10, 2016 (Webcast and In-Person)
- July 25-26, 2016 (Tentative)
- November 3-4, 2016 (Tentative)

Dr. Bocchini said they had increased the number of organizational representatives for the Committee but had not yet received any applications from organizations to fill those slots. He informed participants that there are three vacant slots and that applications are currently being accepted. He also said that two Committee members will be ending their term on July 2016. In addition, three other members will also be ending their terms in 2017. A call for applicants will be released in the near future to fill these slots.

Ms. Sarkar reviewed the ethics and conflict of interest recusal requirements for voting members and outlined the process for participating in the webinar for Committee members, organizational representatives,

and the public. She also reviewed the provision of interviews by Committee members and key portions of the Federal Advisory Committee Act that guides the operation of the Committee, including the role of public comment and participation by non-Committee members.

Dr. Bocchini turned the meeting over to the first presenter which discussed ACHDNC's work in long-term follow-up.

II. Newborn Screening Long-Term Follow-Up (LTFU) Panel

A. ACHDNC's Work in Long-Term Follow-Up: A History

Amy Brower, PhD
American College of Medical Genetics and Genomics

Cindy Hinton Ph.D., M.S., M.P.H.
National Center on Birth Defects and Developmental Disability
Centers for Disease Control and Prevention
Atlanta, GA

[Note: While the majority of the presentation was covered, broken audio limited the complete coverage of this presentation].

Dr. Amy Brower stated that newborns who screen positive undergo a series of screenings and ultimately receive a diagnosis. Screening and short-term follow-up is undertaken within the state-based health system, while long-term follow-up occurs in pediatric care centers.

The leaders of this Committee implemented several key efforts related to long-term follow-up. In 2004, it established its three standing subcommittees focusing on treatment protocols, evaluation of new treatments, and reimbursement.

In 2005, the Follow-Up and Treatment subcommittee (LTFU) was asked to engage in a multi-step process that identified barriers to both short- and long-term follow-up and treatment, develop recommendations for overcoming the identified barriers, and recommend mechanisms for establishing accountability for newborn screening guides.

In 2006, the Committee held a one-day expert meeting which eventually led to the development of a report stating that it would be helpful to define what is meant by long-term follow-up for newborn screening, the goals of long-term follow-up, and the key elements of long-term follow-up. In 2007, the LTFU provided a definition for these three items. The summary was published as an article by Kemper et al. in *Genetics in Medicine* (2008:10(4):259-261). The Kemper article defined long-term follow-up as being comprised of the assurance and provision of quality chronic disease management, condition-specific treatment, and age-appropriate preventive care throughout the lifespan of individuals identified with a condition included in newborn screening.

The principal goal of long-term follow-up is to assure the best possible outcome for individuals with disorders identified through newborn screening. The essential elements of long-term follow-up were identified as care coordination through a medical home, evidence-based treatment, continuous quality improvement, and new knowledge discovery.

In 2011, Hinton et al. published an article which summarized the September 2009 stakeholder meeting and harmonized discussions on long-term follow-up. Another article by Hinton et al., to be published in 2016, will build off the overarching questions, essential elements, and stakeholder groups defined thus far. It will establish a framework to build a common understanding.

Previous key efforts also include a CDC four-state pilot to track long-term follow-up across all the conditions that are part of the Recommended Uniform Screening Panel (RUSP). HRSA has funded projects through the regional collaborative including efforts in Massachusetts, NYMAC diagnostic guidelines, Region 4 efforts, and other activities. And NIH has funded natural history studies that focus on long-term follow-up and collect basic information for understanding the trajectory of these conditions.

B. California Newborn Screening Long-Term Follow-Up Data Collection

Lisa Feuchtbaum, Dr.PH., M.P.H.
Chief, Program Development & Evaluation Section
Genetic Disease Screening Program
California Department of Public Health
Berkeley, CA

Dr. Feuchtbaum discussed long-term follow-up newborn screening efforts in California. The state defines long-term follow-up for newborn screening as a "Systematic evaluation to determine if newborn screening is meeting its goal." The goal is to assure that condition-specific treatment and age-appropriate preventive care is available for individuals identified with a condition included in newborn screening.

In 2002, a framework for LTFU was created as part of a HRSA-funded pilot study to examine the efficacy of tandem mass spectrometry screening. A computer-based Screening Information System was developed in 2005, which supports all aspects of lab results reporting, mailer creation, patient referral tracking, and coordination with about 65 specialty care follow-up centers.

Dr. Feuchtbaum explained that they also develop an Annual Patient Summary (APS) Report, which is a one-year survey that is conducted right after the birth date of the child each year and lasts until age 5. It primarily gathers data for program evaluation purposes, although it also has other uses. The data are provided by specialty follow-up centers under contract with the states. The APS started with metabolic disorders in 2005 and over time has included other conditions on the RUSP.

In the past 10 years the program has screened over 5 million babies in California. It has diagnosed 1,500 infants with metabolic disorders and collected over 5,200 Annual Patient Summaries on those children. These long-term data have been used in various collaborative studies with CDC, UCLA, and NIH-funded studies. More specifically, the data have been used to answer the following questions:

- What percent of children with diagnosed disorders are in care through age five?
- What percent become lost to follow-up?
- What percent have disorder-related complications?
- What percent died and for what reasons?
- What percent have developmental delay?
- What percent have high rates of ER visits and in-patient hospitalizations?
- What percent have more frequent visits to the specialty care follow-up centers?

During the 10-year period, 448 patients with one of the RUSP primary metabolic disorders were diagnosed. Of the 448 children diagnosed, 56 percent were still in active care by age five. There are various reasons why children are not reported as being in active care: some are lost to follow-up, or parents refuse follow-up, or they move out of state, or in some children treatment is no longer deemed necessary, or some of the children unfortunately die.

It is important to note that active follow-up status varies by disorder. For example, for PKU 90 percent of the children were still in active care at the end of five years. Work is ongoing to further explore why patients are becoming lost to follow-up. One of the ideas being explored is to use GIS mapping systems and determine the distance families have to travel clinics to determine if this is a contributing factor. Insurance status may also be examined as well as the impact of the Affordable Care Act on service utilization.

In conclusion, long-term follow-up data has been very helpful to obtain an assessment of the impact of the screening program and how well parents and families have been able to access care in California. It is also a valuable resource for clinical collaborations as well as for program evaluation.

Committee Discussion

- Ms. Scott asked if parents are invited to participate in the follow-up.
- Dr. Feuchtbaum explained that through state regulations they are allowed to collect data from contracted centers for program evaluation and research purposes. The California Human Subjects Committee has provided them with an exemption to evaluate the program's data.
- Ms. Wicklund said the data collection is currently going through year 5. She asked if for ALD they will follow-up individuals until they are 21 years old.
- Dr. Feuchtbaum explained that they track the children until the time that they start school. At that time the school system kicks in and a Department on Developmental Disabilities begins collecting data on those children. She added that they have looked into trying to partner with those centers as data sources in order to create data linkages.
- Ms. Wicklund asked if the school system is indeed tracking those data.
- Dr. Feuchtbaum said that one of their research scientists, who unfortunately is no longer with the program, had established in the past a kind of agreement to get those data but she never was able to start working on the project. Dr. Feuchtbaum said this offers an interesting and worthwhile opportunity for long-term tracking by linking to other data systems in the state.
- Dr. Urv asked how aggressively they were able to track down parents given their limited funding. Will someone be trying to reach them by phone to try to find them [if they are lost to follow-up]?
- Dr. Feuchtbaum said the burden is on the Center to provide those data. If a Center knows a child is moving from Northern to Southern California, they will make the transfer and notify the new center that the family is moving. This is then entered into the computer system as a "transferred care." She added that 70 percent of the children indicated as "transferred" were still in the system the following year and reported as active and in care at the new location. If the family is in California, they are part of the long-term follow-up system unless they move out of state.
- Dr. McDonough asked if they had any discussions regarding point-of-care testing for long-term follow-up (eg newborn hearing screening and congenital heart disease).
- Dr. Feuchtbaum said that in many states the newborn screening program has picked up the responsibility for monitoring the implementation of point-of-care services for hearing and congenital heart disease. But in California that hasn't happened and the genetic disease screening program follows up on the more traditional diseases. In California the hearing and congenital heart disease programs are run by a different department. She added that over the years she has encouraged a physician who is in charge of the congenital heart disease screening program to work with this Committee.
- Dr. Botkin said that some past observations had suggested that there was a broad spectrum of treatment approaches to individual conditions, perhaps due to difficulties in developing large-scale comparative research protocols to figure out what really works best. He asked if the system is able to make those kinds of comparisons to guide clinical care for outcomes for the children.
- Dr. Feuchtbaum replied that one of the intentions was to gather evidence. She said they know in general what kind of treatments the children are receiving and also ask whether the family is adhering to the treatment regimen. She added that they are examining these simple data to hopefully be able to make some kind of broad generalizations. She said she has been able to put together a team of epidemiologists that will be specifically devoted to newborn screening outcomes and evaluation. In the future, the data will be mined to determine what kind of useful information can be obtained.
- Dr. Bailey asked if they are collecting data on families such as information on the satisfaction of services or adaptation to having a child with a disability.
- Dr. Feuchtbaum said that would be a wonderful project but they don't have any direct contact with families. They are simply working through the specialty care centers which report if there is an issue with adherence to care. Data are collected in some clinics on families missing appointments.

She added that the new grant opportunities have come out, particularly on long-term natural history projects. They are considering such opportunities to perhaps connect with families directly but it hasn't been done yet.

- Dr. Matern asked if they knew, for the children that had died, if the children had died as a result of the screened condition or complications thereof.
- Dr. Feuchtbaum said they need to carry out a more detailed analysis of the deaths and the reasons why those deaths occurred. Some questions that could be addressed are, for example, if the children neonatal intensive-care unitwent home or if they never left the hospital. She added that looking into the mortality and morbidity associated with those deaths could be a manuscript in and of itself.
- Dr. Greene said that fundamentally long-term follow-up has been defined by the Committee as the assurance and provision of quality chronic disease management, condition-specific treatment, and age-appropriate preventive care throughout the lifespan of the individuals identified with the condition found through newborn screening. She respectfully requested to keep in mind that this is really long-term tracking. Long-term follow-up means the children are treated first and then one carries out the outcomes evaluation.
- Dr. Feuchtbaum replied that treatment unfolds over the years and also that treatments change. Even disease diagnosis can change. She added that their definition [of long-term follow-up] is taken from the Kemper article.

C. Long-Term Follow-Up after Newborn Bloodspot Screening: Why, How, and What Next?

Sue Berry, M.D.
Professor and Director
Department of Pediatrics and Genetics, Cell Biology & Development
University of Minnesota
Minneapolis, MN

Dr. Berry described the development and current work of the Inborn Errors of Metabolism Collaborative (IBEMC), which involves about 25 centers. The goals of the IBEMC are to improve knowledge about the clinical history of persons with IBEM on a long-term basis and to gather evidence about effective management and treatment strategies for persons with IBEM.

Work began around one suggested disorder, MCAD, which has an incidence of 1:10,600 in Minnesota. Funding was provided by HRSA through a Region 4 Genetics Collaborative LTFU. A subsequent Region 4 HRSA Priority 2 Workgroup grant was awarded followed by an NIH natural history grant, which formally established the IBEMC.

Although efforts began with one disorder (MCAD) others have been added since then. Currently close to 40 conditions are covered and a wide variety of data elements are gathered under the following broad categories: Demographics, Presentation, Initial Care Plans, Follow Up Status, Laboratory Testing, Emergency Care and Hospitalizations, Developmental Evaluation, Care Coordination, Pharmacotherapy, and Nutrition Intervention.

Dr. Berry explained that the Inborn Errors of Metabolism – Information System (IBEM-IS) was initially developed and implemented through the HRSA-funded Region grant in 2004-2007. The IBEM-IS is currently supported through the NIH-funded IBEMC and includes all inborn errors of metabolism in the Recommended Uniform Screening Panel (RUSP).

She explained they began using an off-the-shelf web-based system for data collection, but through collaboration with other centers the IBEMC developed the Longitudinal Pediatric Data Resource which collects data using the REDCap data system. Currently there are close to 2,000 enrolled subjects.

The IBEM-IS currently contains 7,299 unique data elements. Patient demographics is comprised of 3,404 data elements while special situations—such as pregnancy and transplants—have 1,744 data elements.

Longitudinal clinical data contains 2,515 data elements. In all, there are 544,838 completed data fields. The overall goal is to create an evidence base to improve outcomes.

The original intent was to include conditions for which early treatment existed and made a difference, but this may not be completely the case for newly added conditions. Other differences between the original and newly added conditions include: the timing of therapies, their effectiveness and cost, and the timing of onset of manifestations of the conditions. Some of the conditions added have late-onset and poorly characterized long-term interventions. There is also limited knowledge of timing and utility of early interventions for some of these conditions.

Dr. Berry explained that there is current no infrastructure for true long-term follow-up (i.e. lifespan). She added that keeping up with persons identified with late onset disorders will require a new and complex infrastructure.

Committee Discussion

- Dr. Botkin asked Dr. Berry if it would be possible to combine their data with the data from California in an effective way to answer some of the questions raised. Also, would it be necessary for every collaborative to do something similar or is it enough for one collaborative to do the work in combination with one or more states to answer the questions raised?
- Dr. Berry explained that the marrying of the data is something important they would like to accomplish. They are still working on the data exchange.
- Dr. Urv said that she e-mailed Dr. Brower asking the same question who said that the California data is at a higher level (i.e. less detailed), but that one could be able to map some of the data.
- Dr. Berry added that there is another important project going on in the Newborn Screening Translational Research Network (NBSTRN) to create a public health data set, which is a subset of the elements in the Longitudinal Pediatric Data Resource (LPDR). The idea would be to map the data so that public health could use it at a higher level and clinicians could be involved at a more detailed-oriented level. Dr. Berry said, with respect to Dr. Botkin's question, that in order to have representative data one would need to include the Southwestern states, Texas, California, and other locations with diverse populations. It is also important to consider that outcomes could be different and distributed differently depending not just on socioeconomic factors but other factors as well. She added that to obtain data on some rare diseases [where the numbers are small] there would be a need to collaborate even more effectively.
- Dr. Watson said that data storage is incredibly expensive for this magnitude of data, so one needs to ask how much statistical power is needed to answer the questions raised and stop collecting data when one can. Eventually the long-term data will reside in Electronic medical records (EMR) and we'll eventually figure out how to talk through systems and databases, but we are not quite there yet. He added that discussions have begun with states about interfacing in these long-term follow-up efforts. Over the next months there will be five states that will initiate pilot studies for fairly narrow studies of one or two conditions, just to see how they can fit into the LPDR system of data collection. One of the nice things about the IBEMC studies is that several of the institutions do work very closely with their states.
- Dr. Ostrander said one needs to keep in mind that a long-term follow-up system is currently in place and one doesn't need to be built from scratch. The approach to change and improvement requires good measurement at the front end to identify if there is a problem and determine where the problem is—rather than assuming that a problem already exists. Finally one needs to decide which areas one wants to intervene on, and then be able to do an intervention and test the intervention. Once the system is in place, creating a measurement has to be the first step.
- Dr. Matern said that for some disorders there are registries out there already. He wondered if there are any ongoing discussions about how they could be combined and made accessible.
- Dr. Berry said that many clinicians neither participate nor want their data handled and controlled by industry. There are NIH-funded long-term follow-up projects, or at least newborn screening history projects, that are looking at some disorders and they have been working actively to develop datasets for those conditions that would be deployable in the LPDR. She added that although they would like to find ways to reconcile the data from the registries, they will also move

forward with collecting data about those disorders irrespective of this because not everybody participates in registries.

- Dr. Matern said that some registries are for patients that are diagnosed and have the disease, whereas in newborn screening now moving forward one finds some patients that are of uncertain significance. He said it would be extremely helpful if there was a way for this group, or for patient advocates, to get these registries to be more open so one can compare diagnostic results through genotypes or enzyme activities in newborn screening.
- Dr. Berry agreed and said that more data would support those children.
- Dr. Watson said there is a bit of a financial disconnect because the registries for the four LSDs that Genzyme operates is a system that costs $15 million a year to operate and has more FTEs associated with it than does the NBSTRN . He said they are looking at mapping, so that when a clinician or the states enter data into a registry one could map across those systems so the data are entered once but can be exchanged.
- Ms. Wicklund asked if the presenters could speak a bit more about public/private partnerships and thinking about how that could work if funding is so difficult to obtain from grants to keep things going.
- Dr. Watson said they have thought about it and one of the challenges is that some registries go back 20 years, so there is a retrospective aspect that is extremely expensive to get a handle on, while [industry] has gone through probably two or three iterations of their data systems which further complicates integration.
- Dr. Berry said that an honest broker is needed to make sure the data are freely accessible to researchers because industry might have a proprietary interest in their data.

D. Parent Perspective on Long-Term Follow-Up

Christine Brown
Executive Director
National PKU Alliance
Tomahawk, WI

Ms. Brown spoke as the Executive Director of the National PKU Alliance and also as the parent of two children born with PKU. She explained that there are 15,000 Americans with PKU. Nearly 8,000 are in clinical treatment, but 7,500 have been lost to follow-up. In the 1970s and 1980s, when no real long-term follow-up existed, the medical community believed that by the time children with PKU reached ages 7 or 8 their brain would be fully developed and there would be no detrimental effect to have them discontinue their PKU treatment.

However, two studies: the *National Collaborative Study (*1976-1984) and the *Effects of Maternal PKU on Pregnancy Outcome* study (1984-2002) showed otherwise. These were some of the first long-term follow-up projects and showed that those children taken off their diet had a loss of IQ, decline in school performance, increase in behavioral and psychosocial issues, pareses, epilepsy, tremors, and other impacts.

These early initiatives and long-term follow-up projects led to the recommendation that patients stay on PKU dietary therapy for life. In the meantime, because this recommendation was not in effect, there was a negative impact in at least two generations of adults with PKU.

In 2015, the Alliance decided to conduct a survey of PKU patients. A total of 625 individuals responded: 53 percent of them were parents and 47 percent were adults. Nearly 86 percent of the patients reported having visited a metabolic clinic to receive PKU care in the last year while 8 percent said they had not visited a clinic in more than two years.

Nearly 68 percent of individuals less than 18 years of age reported having blood levels within the recommended range, while 25 percent did not. In addition, almost 62 percent of adults reported that their blood phenylalanine levels were above the recommended range.

When asked about new PKU treatments, 91 percent agreed that new treatments were important. When considering new treatments participants listed the following as the top three most desired results: a drop in phenylalanine blood concentrations, attention span and ability to focus, and executive function skills. This is important because dietary therapy does not always control phenylalanine levels within the recommended range for some PKU patients and controlling these levels can become more difficult as patients age.

Research is also showing there are differences in the white and gray matter in the brain of people with well-controlled PKU when compared to their non-PKU siblings. Some long-term follow-up data also shows that even in well-controlled children there still is a slight decrease in IQ as well as issues with executive function, processing speed, and emotional regulation when compared to siblings. There also is a higher incidence of anxiety, ADHD, and depression in the PKU community versus the general population.

Committee Discussion

- Dr. Botkin asked Ms. Brown for her feedback about children of adult women who have PKU and whether there is long-term follow-up and data about the impairments that those children are experiencing.
- Ms. Brown replied that there is a project that was funded by the National PKU Alliance looking at children that were born of adult women with PKU. Some of that research shows that even for those that were well controlled, there are still issues in terms of head size and some developmental delays. She added that the Alliance runs an emergency assistance program for adult women with PKU who are pregnant and can't get access to medical foods during their pregnancy. The outcomes have not been good because their phenylalanine levels were too high. She said she is not aware of any national statistics that show how often maternal PKU syndrome is occurring.
- Dr. Greene asked how many people are having trouble keeping levels in control because of difficulties with access to formula. She said people don't have health insurance coverage that covers treatment. This is a fundamental issue related to long-term follow-up.
- Ms. Brown agreed and said that whenever she speaks before this Committee she always stresses the importance of medical foods reimbursement.
- Ms. Wicklund emphasized the importance of trying to look for some other treatment in addition to what is currently available.
- Ms. Brown agreed and said this is another reason why long-term follow-up is so important. Advancement in knowledge is what long-term follow-up is about.
- Dr. Bailey pointed out that in the study's sample half of the individuals were parents or caregivers. He said it seemed like the data presented were primarily from the people who had PKU themselves. He asked if parents and caregivers were asked a different set of questions.
- Ms. Brown said that everyone was asked the same questions.
- Dr. Ostrander said that moving forward it would be interesting to look into the more subtle neurocognitive behavioral health issues, to try to tease apart the contribution of the substrate related to the condition itself and the contribution of nurture—that is, how the early childhood of these individuals is different. Early childhood exposure increases long-term substrate in the domains that relate to anxiety, mood, concentration, etc., so it's important to remember that substrate is modified not just by the disease, but by also the disease experience in people.

III. Panel Discussion – Challenges and Best Practices

Joseph A. Bocchini, Jr. MD
Committee Chair
Professor and Chairman
Department of Pediatrics
Louisiana State University
Shreveport, LA

- Ms. Scott asked about potential data systems that we should be looking at (or building) that can answer the questions about the children (diagnosed through screening) as well as other children with special complex needs.
- Dr. Berry said we need to be creative and thoughtful about ways to create linkages. Several things are needed including common languages, ways to share information, fair and comprehensive access to the data, and the ability to pay for entering the data and storing it. Entering the data is expensive and takes time, so we should be actively pursuing any possibility of finding ways to automate the gathering of that information, such as using electronic records.
- Dr. Feuchtbaum said they have done some interesting and creative linkages and were able to develop profiles of the population of people living with sickle cell disease in California—not just newborns, but across the age span. But from a technical standpoint, it can be hard to get those linkages done and de-duplicated at the individual level. In terms of the new disorders on the horizon, Dr. Feuchtbaum said they have explored the idea of partnering with primary care providers and have been experimenting with that idea through a HRSA grant that funds primary congenital hypothyroidism efforts. Also, engaging primary care providers seems to be a natural way to go using REDcap for data entry. One of the questions is how to provide incentives for providers to get on the computer and report lab results. She added that maybe working directly with families is ultimately the way to go. One should also consider data linkages that already exist in the system.
- Ms. Scott said it is important that patients have access to those data because it helps answer some of the quality of life issues as well as to any data that are going to help provide a picture of what the child may or may not be challenged with in the future.
- Dr. Greene asked if there had been discussions about working with Enterprise Data Warehouses or health information exchanges in different states.
- Dr. Feuchtbaum said there is a lot of talk about doing those things. She added that in California they are trying to do some very fundamental things such as reporting out the results of newborn screening electronically using electronic health information exchanges. She said it is very challenging to set up these systems and that being able to collect that level of detail electronically may be a long way off in the future.
- Dr. Berry said they have created common Epic templates because most of their groups use Epic. She added that others have created strategies to have families participate in entering the data. Those data elements are complementary to the ones gathered by clinicians and provide a critical complementary perspective. She added that it's important, when planning, to always make sure that families are engaged so researchers are answering the questions they want to know the answers to, in addition to any other questions.
- Dr. Brower said the Data Linkage Project which she mentioned in her presentation aims to survey public health to determine what kind of information they routinely collect such as whether children are in Medicaid, are in care, are getting medical food, have received their immunizations, etc. There may be some systems in place in public health where one can harvest the data to answer some of those questions.
- Dr. Hinton said that there are outcomes besides clinical outcomes that are also important. Ms. Brown asked the question "How will my son with PKU do in school?" It is a key outcome people are interested in but a hard dataset to get access to. Having access to data or having that kind of follow-up to show that people are doing well or what needs to be done to help them to do better is part of the whole system approach.
- Dr. Bailey said that there is an immediate focus on the baby and a little bit on the immediate family, but there is also a much broader family community that is important. A number of disorders have consequences for families, such as cascade testing of other family members or conditions where there is carrier status being detected, like cystic fibrosis. Therefore, research that requires interactions with families to truly understand the cascade effect of some of these conditions in families is an important gap in the literature and an important gap in the newborn screening field.
- Dr. Berry agreed that while there is some cascade, the impact will not be as profound as with X-ALD, which has a multi-generational impact. X-ALD changes the current paradigm in terms of exchanging information with families and providing a new level of responsibility of care.

- Dr. Feuchtbaum said that for sickle cell, cystic fibrosis, hemoglobinopathies, and other conditions they offer follow-up counseling for individuals determined to have carrier status. However, the uptick has not been huge and it is not known exactly why. The larger issue is making genetic services a priority and integrating them into general practice medicine so that the knowledge is readily available to the families.
- Dr. Botkin asked the presenters if they had any specific recommendations for the Committee based on the work they are doing.
- Dr. Berry said that what has not yet been addressed are practical and thoughtful ways to actualize some of the activity discussed. For example, there isn't a larger impact assessment of longer-term follow-up.
- Dr. Feuchtbaum said that one of the barriers is that sometimes there is a lack of trust and also a need to recognize public health as an honest data broker. She said they have encountered barriers that seem to have a lot to do with trust or families feeling that big government should stay out of their private business or not wanting their data or specimens shared. But her experience is that having a conversation with the parents about what is being done can really turn them around. Perhaps the Committee could help by supporting policies or programs to encourage more discussion between the public and [professionals in] public health genetics about why all of this is important, why there is a need for trust, and the fact that one is really trying to serve the interests of the public. In other words, policies that will promote more dialogue and discussion in an open way about how advances in genetics could positively impact people's lives.
- Ms. Brown said there seems to be a disconnect because newborn screening is covered by health insurance companies and the Affordable Care Act, but when it comes to access to treatment to treat the conditions that were screened for, there isn't the same commitment to ensure that those children have access to the treatments they need to alleviate the most serious consequences of the condition they have. The other point is that the committee looks at this through age 21 but PKU doesn't go away at age 21.
- Dr. Berry said that in the short-term it would help to encourage participation in projects like the one in the National Coordinating Center, which is trying to put together where data are obtained at the 10,000-foot level. Even taking a baby step towards having more uniform information available from states would be a tremendous advancement.
- Dr. Feuchtbaum said that perhaps the Committee can recommend that medical foods be mandated through medical coverage. She didn't believe this had been dealt with properly in the Affordable Care Act since it is not considered an essential coverage item. Also, if one is going to screen for a condition one should also have treatment for that condition in children up to the age of 21 and beyond.
- Dr. Hinton asked if the Committee could play a role in helping to broker discussions with some of the datasets mentioned in the discussion, such as the Genzyme dataset. It is important for the newborn screening community to [be able to access] such datasets.
- Dr. Greene said it is important to consider what to do with the data we already have as well as how to get more as well as better data in the future. We also need to think about ways to tag data. We need to pay attention to the quality of the data and, as data are merged, we have to tag where those data came from along with any assumptions and limitations.
- Dr. Watson said the questions about educational outcomes will be important in chronic diseases so it would help to get a better understanding of how Family Educational Rights and Privacy Act (FERPA) may constrain getting that information. He added that the National Library of Medicine (NLM) put together an entire coding manual that gave uniformity to the communication of information from newborn screening programs. The results of tests were standardized so they could be communicated across states and also provided in a standardized way to providers. As projects are developed it might be helpful to talk to the NLM. They also fund SNOMED and LOINC, which are the programs that establish the way EMRs collect data and how that information is standardized. So ultimately EMR vendors have to accept those standards and they become part of their systems. It would be helpful to get a better understanding of standards for either data or systems that can be applied to newborn screening.

- Dr. Badawi said it might be helpful to think about partnering with Title V to bring resources from a couple of different sectors because children with special health care needs are facing the same types of barriers to care such as inadequate insurance, care coordination, geography, etc.
- Ms. Bonhomme explained that as new screening conditions are added—even if we don't necessarily know for sure what the long-term follow-up would look like for that condition—it is important to think of the questions we need to start asking. She asked presenters if they knew of any examples of doing this well for conditions that have been added.
- Dr. Feuchtbaum said that the ALD screening program has forced them to think differently because normally metabolic centers address metabolic diseases, endocrine centers address endocrine diseases and so on. But a large percent of the children with ALD will have symptoms of an endocrine disorder even before they have neurological symptoms, which would require partnering with endocrinologists in the short term. Eventually, there will also be a need to partner with neurologists and primary care providers because those children will need an MRI every year. As the data systems are designed they are putting a lot of thought into having conversations with all the specialists, and even primary care doctors, to make sure the right questions are being asked in order to obtain useful information to evaluate the impact of an ALD screening program.
- Dr. Berry said that, generally speaking, things are added on without a plan. The public health follow-up programs do their very best to be respectful and to get that information but they don't always have resources to do it. One of the things that this Committee could entertain as they add conditions is thinking very thoughtfully about the long-term implications. As conditions are added one could think about answering the following question: *Are we not only able to implement the test but also do the things we owe the families afterwards so that they get what they need from the newborn screening?*
- Dr. Comeau said that what the Committee can do is to emphasize staging and quality. Staging is the kind of public health data that California and Massachusetts collect such as whether the children are they still in care, how they are doing in general, whether any have died, etc. She emphasized that good case definitions are also needed. Without good case definitions 5 or 10 years from now all we are going to have is a bunch of data about children—some of which might have died and some of which might have done well—but we may not necessarily know why. She said that if we want to improve clinical outcomes we have to be comparing "apples to apples."

IV. Public Comment

Mr. Jon Miller, Network of Tyrosinemia Advocates: Mr. Miller spoke as the President and Founder of the Network of Tyrosinemia Advocates as well as a parent. The Network covers tyrosinemia 1, 2, and 3. Of these, type 1 is the most common. He said his son was born in 2009 in New Jersey and was given a newborn screening panel but the newborn screening panel did not come out positive. His son was given a clean bill of health but his child started getting sick. Fortunately, his condition was eventually diagnosed and he is alive and doing well with treatment.

Mr. Miller said there was a void in the panel because tyrosinemia was tested by using tyrosine as the primary marker. It was recommended by this Committee that succinylacetone be used as the primary marker. However, Connecticut, Delaware, Maryland, Georgia, Illinois, and Oklahoma are not acting on the Committee's recommendation. Because of this, there is a risk of losing, or damaging more children before they can be treated, in those states.

Mr. Miller said this was unacceptable and dangerous because if one tests only by using tyrosine, the children can be sent home without a diagnosis, but will get sick. By using succinylacetone as the primary marker many more cases can be diagnosed correctly. Mr. Miller proposed that the Committee reach out to states that are not currently in compliance with their recommendations and ask them to update their systems.

Ms. Annie Kennedy, Parent Project Muscular Dystrophy: Ms. Kennedy is a Senior Vice President at the Parent Project Muscular Dystrophy (PPMD). Duchenne Muscular dystrophy is one of the most common fatal genetic disorders diagnosed in childhood, affecting 1 in 5000 live male births.

In September of 2014, she informed this Committee that their Duchenne research pipeline was both robust and hopeful. Because of that, PPMD launched a national newborn screening effort in December 2014 and in January 2015 PPMD enlisted the expertise of Dr. Michele Lloyd-Puryear to help lead the organization's Duchenne newborn screening efforts. A National Newborn Screening Steering Committee was convened which conducted an analysis of current readiness for a public health program and for newborn screening and began to map out an action plan to address identified gaps.

Six Work Groups were then created to address the priorities identified by the action plan. They have also supported the development of a refined screening test for Duchenne. A pilot in Ohio tested 43,000 babies and found 7 confirmed cases of Duchenne. The pilot used an enzyme assay for creatine kinase as the first-tier screening tool. Work is ongoing to further refine the first-tier screening and develop a potential new newborn screening test method for Duchenne.

In August of 2014, the EU granted marketing authorization for the use of a treatment of a nonsense mutation in Duchenne muscular dystrophy. It is estimated that nonsense mutations cause Duchenne in approximately 13 percent of patients, which accounts for about 2,000 people living in the U.S. This treatment will be reviewed in the second quarter in the U.S. An FDA Advisory Committee will also review a therapeutic approach that could potentially benefit another 13 percent of boys in whose disease may be modified through the exon skipping of a targeted exon 51.

Mr. Dean Suhr, MLD Foundation: Mr. Suhr is President of the MLD foundation. He reported on discussions of the RUSP Roundtable which is an MLD foundation initiative that is not specific to MLD. The roundtable, which met yesterday, provides a forum for a broad variety of perspectives from industry, clinicians, academia, ethics, advocacy, technology, and other groups.

Mr. Suhr said there were several important discussions at their roundtable meeting. These included the benefit to the child, the benefit to the family, viable therapies, repurposing and building upon existing toolkits, and specific diseases where genomic sequencing may offer an opportunity to screen children. Mr. Suhr said MLD will formally reach out to the Committee with some questions in the future.

V. Committee Business: February 12, 2016

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

A. Welcome and Roll Call

Dr. Bocchini welcomed the Committee members, organizational representatives, and other participants to the second day of the meeting and took the roll. Voting members present were:

- Dr. Don Bailey
- Dr. Joseph Bocchini
- Dr. Jeffrey Botkin
- Dr. Fred Lorey
- Dr. Dietrich Matern
- Dr. Stephen McDonough
- Ms. Catherine Wicklund

Ex Officio members present were:

- Agency for Healthcare Research and Quality: Dr. Kamila Mistry

- Centers for Disease Control and Prevention: Dr. Carla Cuthbert
- Food and Drug Administration: Dr. Kellie Kelm
- Health Resources and Services Administration (HRSA): Ms. Joan Scott (for Dr. Michael Lu)
- National Institutes of Health: Dr. Catherine Y. Spong

Organizational representatives present were:

- American Academy of Family Physicians (AAFP): Dr. Robert Ostrander
- American Academy of Pediatrics (AAFP): Dr. Beth Tarini
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- American College of Obstetricians and Gynecologists (ACOG): Dr. Joseph R. Biggio, Jr.
- Association of Maternal and Child Health: Dr. Debbie Badawi
- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Department of Defense (DoD): Dr. Adam B. Kanis
- Genetic Alliance: Ms. Natasha Bonhomme
- March of Dimes: Dr. Edward McCabe
- National Society of Genetic Counselors: Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders: Dr. Carol Greene

VI. Subcommittee Updates

A. Laboratory Procedures and Standards Subcommittee Update

Kellie Kelm, Ph.D.
U.S. Food and Drug Administration
Silver Spring, MD

Susan M. Tanksley, Ph.D.
Texas Department of State Health Services
Austin, TX

Dr. Kelm thanked all subcommittee members for their work. She began by reviewing the subcommittee's charge which is listed below.

Subcommittee's Charge
Define and implement a mechanism for the periodic review and assessment of:

- The conditions included in the uniform panel
- Infrastructure services needed for effective and efficient screening of the conditions included in the uniform panel
- Laboratory procedures utilized for effective and efficient testing of the conditions included in the uniform panel

Dr. Kelm suggested a small revision to the charge for clarification. She swapped the last two bullets and modified the third bullet to read "Infrastructure *and* services…" as per below:

Proposed Subcommittee's Charge
Define and implement a mechanism for the periodic review and assessment of:

- The conditions included in the uniform panel
- Laboratory procedures utilized for effective and efficient testing of the conditions included in the uniform panel
- Infrastructure and services needed for effective and efficient screening of the conditions included in the uniform panel

Dr. Kelm then proceeded to review potential projects that the subcommittee could address. Broadly speaking, the subcommittee could address the following projects:

1. Develop a process to periodically review data for conditions on the RUSP
2. Evaluate current methods to determine if improvements are needed to enhance sensitivity or specificity
3. One screen vs. two screens
4. Timeliness initiatives

She said that implementing a mechanism for periodic review of conditions to be included in the RUSP could be an interesting project as NewSTEPs delivers new data. This could be an ongoing process that the subcommittee can undertake periodically. It could be done for one or more conditions at a time.

The subcommittee could also evaluate current methods to determine if improvements are needed to enhance sensitivity and/or specificity for some of tests already being done. For example, determining if there is a better analyte to identify a particular condition (e.g. Tyr vs. SUAC or T4 vs. TSH). Work could also be done to assess the utility of additional data to determine call outs, such as gestational age or birth weight.

Dr. Kelm said that second tier testing to improve specificity is also something that many labs are considering along with cutoffs that might be used, such as percentile cut-offs, floating cut-offs, or multiple of the mean. More specifically, the subcommittee could discuss whether or not it makes sense to have a discussion about how cutoffs are set and used for certain cases.

Another project the subcommittee could discuss is the issue of "one screen vs. two screens." More specifically, it could discuss case definitions and also whether babies identified on the first screen as normal could be identified by a single screen model targeted rescreening. Another area of discussion is how to establish a study design to assess the "one screen vs. two screens" issue. One of the questions to answer in that area is: *Would it be easier to do retrospective studies or do we need a prospective design which would be harder and require time and money?*

Dr. Kelm said there is growing interest in the role of Next Generation Sequencing (NGS) in newborn screening. NGS raises a lot of questions for discussion such as: *How do we accumulate data to identify a correlation between phenotypic and genotypic data? Are there conditions for which sequencing is the only screening method? What does one gain or lose by using NGS? Which data should be reported and what should one do with variants of unknown significance? When does one report carrier status? Are there particular conditions where reporting carrier status is important? and What new infrastructure needs to be built for NGS?*

Dr. Kelm added that once data are available from NewSTEPs, it could be reviewed as part of the timeliness initiative. The subcommittee could also discuss the implications of earlier specimen collection (less than 24 hours) and any unforeseen consequences and costs related to timeliness. She also asked the Committee which subcommittee should address point of care issues since more tests seem to be moving to point of care.

Dr. Kelm closed her presentation by asking an interesting question: *What happens if we want to consider moving a condition off the panel or promoting conditions from the secondary to the core panel? How would this be done? Is it mostly through another evidence review?*

Committee Discussion

- Dr. Bocchini thanked the presenters. He said that unless there are any concerns by members of the Committee, they would like to accept the subcommittee's recommendation for minor changes to the charge. [No concerns were raised].
- Ms. Scott asked if there were projects that had a higher priority than others. She also asked the presenters if they believed they had the right individuals in the subcommittee, or if any more

needed to be added. Ms. Scott asked what would be the advantage to having the projects done under this setting as opposed to any other setting.

- Dr. Kelm said that in some ways the easier ones to do would be reviewing the screening data and assessing the timeliness, because data will be available from NewSTEPs, whereas the other projects would involve more work from the subcommittee or others. In terms of having the right subcommittee members, regarding the project reviewing the timeliness data, some of the existing subcommittee members would be great to assess those data. The same may be true for assessing existing conditions.
- Dr. Tanksley said that, with respect to lab procedures, there are many questions around current methods or ways to improve current screening. The goal would be to focus on one project. She added that they have spent years discussing "one screen vs. two screens" with no convincing evidence for changing to one side or the other. Next Generation Sequencing (NGS) is more of an exploratory project and the subcommittee could bring in experts to discuss the topic and start formulating ideas. The question is whether the subcommittee is at a place where they could begin to think about all the issues surrounding NGS in newborn screening.
- Ms. Wicklund asked if the approach would be to obtain information from experts and then try to determine if the [Committee has] a role there, as opposed to maybe taking the lead and developing guidelines.
- Dr. Tanksley agreed and said it would be a starting place to begin to assimilate information that is already out there.
- Dr. Botkin said he was concerned about giving too much attention to the idea of whole genome sequencing in the context of a public health program. He said that idea is different than thinking about the role of DNA-based platforms for testing, which seems to be a more productive area to think about, or potentially sequencing in the context of affected children to better understand genetic background and why some children respond to a specific treatment, which is currently being addressed by existing NIH grants. He expressed caution about going down a road that would suggest that the Committee is taking seriously the notion that every baby being sequenced in the near future.
- Dr. Kelm said the goal of the subcommittee would be to "keep their finger on the pulse" of what's going on and share that with the Committee. This is especially true for some efforts such as determining where targeting sequencing would be appropriate, examine how laboratories are using it, and discuss challenges related to analytical and clinical validity.
- Dr. Matern said that Dr. Piero Rinaldo is working with several states on congenital hypothyroidism and how to incorporate birth weight, gestational age, and age and collection to help determine which children are affected and which are not. Perhaps this person, or someone from the subcommittee, could provide an update on the matter at the next meeting. With respect to "one screen vs. two screens" Dr. Matern agreed it is a discussion that has been going on for many years without a conclusion. The problem is that it puts states that do not do two screens in the uncomfortable position of not really knowing whether they are providing the screening they want to provide and also puts two-screen states into a position where they may be duplicating efforts. In other words, it puts the two-screen states in a position of not knowing whether two screens are really required. Dr. Matern said it costs a lot of money to do two screens and this would be even more expensive if there is indeed duplication as states are eventually going to add Pompe disease and other conditions to their screening. Dr. Matern said it would be important to come to a resolution because the subcommittee was put in place to ensure uniformity for screening babies across the country and we currently do not have such uniformity. He suggested looking retrospectively at the data from R4S . The Committee couldfree ourselves of the typical cutoffs and looking at patients identified by those states and putting them through the system to determine whether the first screen data would not have been sufficient to pick up all the cases that were picked up with the second screen and presumably not with the first. This approach could clarify this in a very short time.
- Dr. Watson said that whole genome sequencing would be awful at this time as a first-tier test. He added that grantees have looked carefully at genes involved in newborn screening and one could easily look at them and do assessments of the pathogenicity of the variants that are found in those genes.

- Dr. Greene agreed with Dr. Matern on the "one screen vs. two screen" issue. Some of the questions to be addressed include: *Do we need to do everything on the first screen? If two screens are being done, and if one provides appropriate education to recognize critical aspects of timeliness, could one put for example Krabbe on the second screen along with some onus of responsibility on the family so the test doesn't have to be done twice?* For example, CF could be done on the second screen so as to not scare parents with a positive first screen when the child is too young to undergo a sweat test. In other words, to address issues surrounding duplication and cost [we may need to determine] what belongs on a first screen and what belongs on a second screen and what belongs on both. She suggested not dropping the timeliness issue because changes are currently being made and there is a need to determine whether those changes worked and also whether there were any unintended side effects.
- Dr. McDonough asked if there was any discussion about linking the birth certificate to the newborn bloodspot. He said it was recommended a number of years ago, but they were told it couldn't be done because birth certificates would not be changed until 2020. He suggested that perhaps the subcommittee might want to revisit the issue and the timetable of when to discuss this (e.g. right now, a year from now, two years from now, etc.). He also suggested inviting someone from the Center for Vital Statistics to discuss the issue with the Committee.
- Dr. Kelm said they discussed this in the Timeliness 2.0 Workgroup, primarily in suggesting that the states find ways to realize those linkages. She agreed that the topic might be of interest to the Committee and it might make sense to determine if someone could provide an update on the [birth certificate] issue.
- Dr. Ostrander said that, with respect to whole genome sequencing, there might be the possible threat of it being mandated by a state legislature, outside of the purview of labs. He added that it may be helpful if the subcommittee could keep their finger on the pulse regarding this issue.
- Dr. McCabe said the March of Dimes echoes Dr. Ostrander's concern. He added that if this happened it could be a huge mistake because the correlation between genotype and phenotype is not well known for all disorders. He agreed it would be helpful as a community to keep abreast of the issue.
- Dr. Comeau said that multiple markers make sense. It is something that many state laboratories are already using and such data should be investigated further. With respect to standardization, she encouraged caution from the Committee. She said that what should be standardized is standardized quality and not so much a standardized laboratory test or method. With standardization one risks a manufacturer running out of a particular reagent for an assay or quashing innovation. She added that some of the best algorithms have come about because state laboratories use a variety of methods and have learned from each other. She reminded participants that next generation sequencing is a platform, and how it is used—whether it is used for sequencing or as a multiplex genotyper—is yet to be determined, but the responsibility should be to standardize quality. She added that NGS is a topic that the APHL's Molecular subcommittee is putting a lot of work into.
- Dr. Bailey said he is one of the four Insight funded projects related to the potential implications of whole genome sequencing for newborn screening. He added that whole genome screening is a technology, like tandem mass spectrometry was a few years ago, that could be a potential disruptor for newborn screening. Rather than ignoring it, one should explore it and try to understand its different ramifications. He said that each of the Insight projects has a clinical component, a sequencing component, and an ethics component. He suggested that the Insight group provide the Committee with an update and said he would be happy to work with Dr. Urv to organize such a presentation.
- Dr. Botkin informed the Committee that there is a Virginia hospital that provides pharmacogenomic screening or testing in newborns—about 20 different variants relative to a whole host of drugs that newborns are highly unlikely to be taking, such as anti-depressants, opioids, anti-chemotherapeutic agents, etc. He said this is an example of technologies moving into the newborn screening domain outside health programs that perhaps have not yet been fully evaluated.

B. Education and Training Subcommittee Update

Cathy Wicklund, M.S., CGC
Northwestern University
Chicago, IL

Beth Tarini, M.D., M.S., F.A.A.P.
University of Michigan Health System
Ann Arbor, Michigan

Ms. Wicklund began by discussing the broad charge given to the subcommittee which is to:

- Review existing educational and training resources, identify gaps, and make recommendations regarding the following five groups: health professionals, parents, screening program staff, hospital/birthing facility staff, and the public

Dr. Tarini explained that Ms. Bonhomme provided the subcommittee with an update on the nomination and education process. The Genetic Alliance and the NBS Clearinghouse are currently collaborating with Dr. Kemper and his team on providing educational guidance to groups who might be interested in preparing a nomination packet. The work is expected to be completed by December 2016 and the Education and Training Subcommittee will be available to provide suggestions and review the materials.

The subcommittee also discussed previous priority issues from 2015. One of them was workforce issues. Ms. Wicklund explained that this issue is now being covered by other organizations, such as NSGC, which is looking specifically the genetic counseling workforce. Other priority issues discussed included: helping legislators better understand NBS issues and program needs, educating OB/GYNs regarding their role in NBS (particularly in discussing NBS with prenatal parents), and improving the initial communication between clinician and parents regarding a positive finding.

Dr. Tarini presented the following project ideas:

1. Create an ACMG companion piece to the ACT Sheets that provides primary care providers with guidance and tips for discussing positive NBS results with parents

2. An Educational Outreach Project in collaboration with NBS Clearinghouse/Baby's First Test

3. Create a summary of educational initiatives among states

Dr. Tarini explained that while ACT Sheets are valuable, they are clearly focused on management from a pathophysiologic and medical perspective. They tend not to focus or emphasize the discussion a provider might have with a parent around process, emotional and psychological aspects, next steps, the child's health, and other issues the parents may raise. This companion piece would be something brief that the physician or health care provider would have as a guide on the issues that might come up.

For the second project idea, the goal would be to provide a visual representation of an educational web to determine who is in the field, what their missions are, and what they are doing. Also, instead of developing more content, it may be helpful to leverage the dissemination of existing educational resources. The third project idea would be to create a summary of educational initiatives among state programs that can be disseminated among members of the community.

Committee Discussion

- Dr. Spong said that the second point [Educational Outreach Project in Collaboration with NBS Clearinghouse/Baby's First Test] could be very useful given the new requirements around research and newborn screening. She added that NIH held a workshop to try to determine how to address those requirements utilizing existing resources and recognizing that ACOG [may be a partner as well].

- Ms. Wicklund said that one of their initial ideas was to determine how to get OB/GYNs more engaged in the newborn screening arena. She said they are hearing back from a lot of primary care physicians about challenges regarding the limited amount of time [in a consultation] as well as limited resources. She added that they did have a discussion about partnering with ACOG to increase awareness
- Dr. Tarini said that, as a health services researcher, she was aware that having ACOG (or any other organization) endorse something doesn't always mean that it will flow down to the providers and that providers will actually use it. However, there are organizations that when they speak, their membership stands up a little straighter and takes a little more notice and ACOG is one of them. So perhaps ACOG might be a good place to start if we understand that it may have a trickledown effect but perhaps not a massive [impact].
- Dr. Spong agreed that ACOG would be a good place to start, although this may go beyond ACOG since individuals have children through many different kinds of providers. She said the NIH workshop addressed time limitations and all the items providers are trying to address during a prenatal visit. She added that having the information provided in a nicely packaged way for the provider is helpful.
- Dr. Urv said the NIH brought together OB/GYNs and nurse-midwives and other representatives who are interested in the educational component. That is, how education can be added into their materials as well as materials they recommend to patients. They are looking for input from the Committee as well as other groups to help them develop materials they can use for education. Dr. Urv explained that they will be holding more meetings with these groups as they move forward.
- Dr. Tarini said they had a discussion with ACOG representatives yesterday, which they found helpful. She said they are not asking to have a discussion about consent with patients, but simply to start having a conversation about newborn screening. If couched this way, the message may be more appealing and have more traction.
- Dr. Botkin said that ACOG already has a statement about obstetricians addressing newborn screening issues by making information available. He said that research clearly shows that handing patients a brochure is not very effective. He suggested thinking creatively, perhaps considering smartphones and videos or other ways to take the burden off the clinician. He suggested using the interest patients have in their babies in the obstetric context to promote innovative educational strategies.
- Dr. Ostrander said he is part of the workgroup that develops the ACT Sheets for primary care physicians. He said that how to deliver bad news is something that physicians usually learn in training, and primary care doctors might not really need a script to do that. They may need information, but not a script. Dr. Ostrander read from the PKU ACT Sheet which provides various clinical considerations. The sheet provides physicians with information they can relay to parents as they are making the immediate referral to the specialty center. He said that he believes that when it comes to information "less is more" but that he is open to any other thoughts and perspectives.
- Dr. Tarini said that patients would love to have a doctor who discusses the disorder and its consequences as well as attends to parent issues. However, if there's a trade-off, parents tend to appreciate more a physician who attends to parent issues. For example, a physician who may say "I don't know this area, but this is what I understand about PKU and I will access the specialist and then have deeper discussions about your concerns, thoughts, and worries moving forward." Dr. Tarini said there are scripts and simple word choices available that some physicians may or may not be using. She said that physicians often think they are doing a better job than they actually are when talking to patients. She added that there have been studies about oncologists providing individuals with a cancer diagnosis and it turned out that they weren't doing it very well. She said the information provided doesn't have to be long, but it has to be attentive.
- Ms. Wicklund said that, from the perspective of a genetic counselor, it's not so much the information but how it is communicated as well as the impact it has on the individual and family. She added that even though the clinical aspects of each diseases may vary, the psychosocial issues are similar in each case.It is important to determine how the provider can help them cope emotionally with the information.
- Dr. Greene said that when she talks to primary care providers what they universally want to hear most from her is not the details about the disease—which they can obtain from the ACT Sheet—

but how likely the disease is, whether it is likely to be a false positive or a real positive, and what they should tell the family. She said that what she hears from families are statements like "nobody told me I needed a referral, nobody told me I had to go somewhere, nobody told me how long it would take, nobody told me it would be a blood test, etc." Dr. Greene said she carried a multi-step process where she met with families and heard from them about what they wanted their pediatrician or family practice doctor to know and say. This information was then distilled down into about 20 lines. In other words, it is not about getting into too much detail but more about "What questions do I need to anticipate and how do I address them?"

- Dr. Tarini said they have created a provider guide for cystic fibrosis. The guide has bullets for the primary care physician about what to do next, who to call, etc.
- Dr. Greene read from a sample document for pediatricians "as you prepare to wait for results have the parents consider how they cope with stressful situations, including whether they want to talk to somebody else or search for more information, or if they would rather wait…"
- Dr. Bailey agreed with Dr. Tarini. He said there is well-established literature on family centered practices that cuts across many different settings, not just newborn screening, but also pediatric care, nursing, etc. He said the literature is clear on three things: 1) There is a clear understanding of the specific components of family centered practices—we know what the components are and we can define them, operationalize them, and measure them; 2) It is clear that providers think they do family centered practices, but not everyone who thinks they are doing it actually do it [well]; and 3) If a provider follows family centered principles and practices they get better outcomes in terms of families adapting to their child's condition, to the information they get, and follow-up on specific recommendations. He added that it is under the auspices of the subcommittee to enhance family centered practices in the context of more screening and not just in informing of families.

C. Follow-up and Treatment Subcommittee Update

Stephen McDonough, M.D.
Sanford Health Bismarck
Bismark, ND

Dr. McDonough thanked Dr. Mistry for her efforts in supporting the subcommittee meeting. He discussed some of the subcommittee's potential priorities for 2016 and 2017.

One of the priorities discussed was access to long term follow-up and treatment. He said it was frustrating for him to hear that even after all the changes made in health care [with the Affordable Care Act] many parents still have the burden of expensive treatments being denied by their health insurance. This is an issue that the subcommittee has attempted to address before and there is strong interest in revisiting this again. This would mean not only discussing medical foods, which are very important, but also treatments for conditions in the RUSP that currently have treatments. He explained that access also involves access to health care specialists, specialty clinics, and access in rural areas of the country.

Another priority discussed was the need for standardized clinical quality measures to promote long-term follow-up, which would be of great benefit for clinicians. This would not necessarily be for all conditions in the RUSP. It might involve looking at funding for developing measures where there is evidence and also looking at existing measures (such as National Quality Forum (NQF), discussing quality vs. performance measures, and the issue of quality measures public health vs. clinical quality).

Dr. McDonough said there is also the issue of long-term follow-up vs. lifetime follow-up. The Committee has been restricted in terms of age, but there is obviously a need to make follow-up lifelong, so if the Committee can't address the issue perhaps someone else could.

There was also discussion about state infrastructure for long-term follow-up. This raised several questions including: *How are states doing this? Whose job is it to achieve or assess long-term follow-up? How are different states doing this differently? Could we assess state efforts for long-term follow-up? What are the barriers for improving long-state follow-up? Would increasing fees by a dollar help states with long-term follow-up? Could the APHL survey be leveraged in this area?*

There has also been some information on barriers that states have faced in implementing new conditions and it might be interesting to learn more about barriers that states have in improving their long-term follow-up. Two additional issues discussed were documenting best practices and prioritizing what can be done with existing data. There is interest in publishing a framework paper from the group and also to prioritize what is needed with respect to increasing data collection.

Committee Discussion

- Dr. Matern pointed out that it is not only about collecting data, but also about using it and finding a mechanism to fund its collection. He said that Dr. Berry explained that in her project physicians who submit data are being paid. He asked if this [collection] could be turned into a billable [coded] service.
- Dr. Bocchini said this was a question that could be pursued, but that he doubted there was a mechanism to accomplish that.
- Dr. Matern explained that for laboratory tests one goes through AMA, but he wasn't sure whether clinical services are different.
- Dr. Bocchini said it would still go through AMA and there would be a coding caucus reviewing it.
- Dr. Botkin said there were discussions as to whether data could be collected directly from families as opposed to only from clinicians. He informed participants that the Precision Medicine Initiative is getting started and one of its characteristics is to be fully engaged with the participants on an ongoing longitudinal basis. There may be valuable tools developed to help engage families in a longitudinal fashion to collect various sorts of data and that may be something that could be transported into this domain as a way of helping families participate in long-term follow-up.

VII. Discussion and Prioritization of Projects

Joseph A. Bocchini, Jr. MD
Committee Chair
Professor and Chairman
Department of Pediatrics
Louisiana State University
Shreveport, LA

Dr. Bocchini said they had heard from all three subcommittees and their projects. He informed participants that Committee members had voted on the projects so that they would be prioritized. Dr. Bocchini proceeded to read out the results of the voting session. The resulting priorities for each subcommittee are listed below.

Laboratory Procedures and Standards Subcommittee Update

- Define and implement a mechanism for periodic review and assessment of laboratory procedures utilized for efficient and effective testing of conditions included in the uniform panel (Explore the role of next generation sequencing in newborn screening)
- Define and implement a mechanism for periodic review and assessment of infrastructure and services needed for effective and efficient screening of conditions (Review data related to testing, the implications of earlier specimen collection (< 24 hours) and the unforeseen consequences and costs of timeliness)

Education and Training Subcommittee Update

- Create an ACMG companion piece to the ACT Sheets that provides primary care physicians with guidance and tips for discussing positive newborn screening results with parents
- An Educational Outreach Project in collaboration with the Newborn Screening Clearinghouse/Baby' First Test

Follow-up and Treatment Subcommittee Update

- Promoting the role of clinical quality measures to promote long-term follow-up, not just data collection
- Examine state infrastructure for long-term follow-up

Dr. Bocchini thanked all subcommittee members for their work. He said that while the above projects will take priority, it does not mean that other projects would fall by the wayside. They would still be kept in the hopper and potentially be selected to be worked on in the future.

He said the next step would be to review the membership of each subcommittee to ensure it has all the people needed to cover all the necessary areas and make the subcommittee function effectively. He asked the Committee if there was any additional discussion. Hearing none the Committee proceeded to hear the workgroup updates.

VIII. Workgroup Updates

A. Timeliness Workgroup Update

Kellie Kelm, Ph.D.
U.S. Food and Drug Administration
Silver Spring, MD

Cathy Wicklund, M.S., CGC
Northwestern University
Chicago, IL

Dr. Kelm started the meeting by thanking all members of the workgroup. She said that the group's charge is to:

- Optimize successful strategies to address newborn screening specimen collection and transport
- Collect and disseminate timeliness specific practices from state newborn screening programs including programs that have implemented efficiencies in collection, transport, screening and follow-up
- Investigate strategies for improved standardization of communication of newborn screening results to providers and families

The workgroup continues to gather success stories from states, their programs, and hospitals. Each of the states operates differently, so the goal would be to write a white paper that includes success stories that others may choose to use in their programs. She said they have heard from Iowa and Michigan and other programs that are excited to share some of their success stories.

It would also help to partner with stakeholder groups, such as the American Heart Association and American Nurses Association, to raise awareness by disseminating success stories. There is also interest in working together with The Joint Commission and possibly their hospital membership.

It would be helpful to get updates on what other groups are doing—for example, The March of Dimes and NewSTEPs 360. The latter does quite a bit of data collection. Looking at the data that NewSTEPs releases would be useful to get a better view of what parts of the process may need more attention.

Regarding strategies for improved standardization of communication of newborn screening results, it might be helpful to wait until the data from NewSTEPs is released. The new timeliness data will be the first available to include metrics from collection through 12 months of age, including results to primary care providers and confirmatory diagnosis. Several projects could be developed in this area but they would depend on both the data to be released and areas of need.

Committee Discussion

- Dr. Greene raised a concern about new legal developments that may impact timeliness. She informed the Committee that there is a new bill in the Maryland legislature. If passed, it would allow parents or guardians of a newborn infant to perform initial tests on specimens collected to screen for hereditary and congenital disorders, including the tests that the department of public health laboratory would otherwise perform, to a laboratory of their choice. She said this could be a very serious threat to timeliness. This is happening in multiple states and perhaps the Committee might be interested in commenting on the matter.
- Ms. Scott asked Dr. Greene if there are additional tests that are being offered on top of what would generally be part of newborn screening. Also, is there any evidence behind the other tests that may be performed?
- Dr. Greene replied that the bill would allow a parent or guardian to ask for the sample to go to another laboratory. The bill does not direct any hospital to send the sample to another laboratory.
- Dr. Bocchini asked if it was proposed by single member of the legislature and whether it still needs to go before the health and welfare committee for review.
- Dr. Greene said that delegate O'Donnell introduced the bill in February 2016 and it has been assigned to health and government operations.
- Dr. Badawi said they are in the process of responding to this bill. It was proposed by one legislator and is now scheduled for hearing on February 23. The intent of the legislation was to allow parents to have their infant's newborn screen sent to a lab to do a broader panel, including lysosomal storage disorders. Dr. Badawi said that while it is understandable that a parent may desire to have that broader panel, they agree with Dr. Greene in opposing this bill because the test would not be in addition to the public health laboratory newborn screening. It is in lieu of the screening, which creates multiple barriers with regard to timeliness and accurate reporting of a result.
- Dr. Bocchini said the best approach would be to bring in experts during the hearing to make people understand the negative implications of going ahead with such a bill.
- Dr. Greene explained that Maryland is not the only state facing this challenge and even if experts are able to be marshaled fairly expeditiously, it does not necessarily mean the bill will get stopped or modified. She added that if this Committee were to make a statement, it would be useful to other states facing the same issue.
- Dr. Bocchini said this is more of a local issue that could have a national implication. He asked if anybody had been able to talk with the legislator who put the bill forward.
- Dr. Badawi said the bill came out after their deputy secretary had a conversation about another bill related to newborn screening and they have not yet had an opportunity to have a conversation. The process is such that once they put in their position, there will be discussions between their legislative office and delegate O'Donnell.
- Ms. Bonhomme said that, when speaking to legislators, in addition to bringing in experts it would also help to bring in families who know about the experience of newborn screening. Those families would know all the benefits of going through the public health channels. For other states facing this, one should really think about bringing in parents and the family perspective because there are some situations in which experts are only on one side of the issue. Thus bringing [a varied] perspective—specifically a perspective of those of being directly affected—would be very valuable.
- Dr. Bocchini agreed and said that perhaps the Maryland chapter of the American Academy of Pediatrics might be interested in being a partner on this as well.
- Dr. Greene agreed that they might be interested and The March of Dimes may be interested as well. She added that a simple fix would be to change the language so that families are required, as they are in some other states, to be educated about the option of supplemental screening. There are plenty of states that have a requirement for educating people about the availability of a supplemental screen.
- Dr. McCabe asked if Dr. Greene could send him a summary of the situation via email.
- Dr. Greene said that Ms. Sarkar had already sent out the email.

- Dr. Badawi said they don't have information on what prompted the bill to be introduced, but they had a discussion at an advisory council meeting about educating families about the possibility of requesting supplemental testing, so it is possible that this grew out of that discussion. Dr. Badawi agreed with Dr. Greene and said their recommendation would be that families be offered supplemental testing but not in lieu of sending the baby's first specimen to the public health laboratory.
- Mr. Jelili Ojodu from the Association of Public Health Laboratories said this not only affects timeliness but also the fracturing of newborn screening systems as a whole, especially follow-up. He added that they do have a policy statement on the role of state public health programs in newborn screening that addresses this particular issue. He said he agreed with Ms. Bonhomme about the need to build a coalition of individuals, not just experts, to be able to help them understand what's going on.
- Dr. Bocchini said that he and Dr. Badawi would try to determine what potential role the Committee could play. He added that the Committee's policies certainly support the need of the primary series of testing to go through the state system.

B. Cost Analysis Workgroup Update

Alex Kemper, M.D., M.P.H., M.S.
Duke Clinical Research
Institute and Department of Pediatrics
Durham, NC

Dr. Kemper began the meeting by thanking all members of the workgroup. He said that the group's charge is to:

- Consider methods to assess the "cost of newborn screening expansion" as required by the newly reauthorized legislation

Dr. Kemper explained that the workgroup's deliverable would be a report with recommendations to the ACHDNC on how to incorporate cost assessments into the decision-making process. The general objective is to determine the budget impact on states. This would be done through a various methods including interviews, surveys with programs that are screening (or considering screening), discussions with vendors and technical experts, and the literature

The goal is to determine the cost incurred to the state to add newborn screening for a particular condition. The workgroup will examine screening and laboratory costs through short-term follow-up and also look at a two-year time horizon (annualized over two years). Other outcomes may also be considered.

Dr. Kemper said that their draft approach is to assess the feasibility and effectiveness of proposed cost assessment methods. The target condition selection for pretest would consider three conditions: Pompe disease, MPS I, and X-ALD. These conditions have been reviewed and added/recommended to the RUSP.

Dr. Kemper explained that there are a wide variety of variables that impact the cost of screening for particular condition including birth rate, geographic issues, whether there are existing laboratory facilities and personnel, shared resources with other states, how newborn screening is funded, and more. Modeling the cost estimations would also incorporate specific assumptions which Dr. Kemper reviewed. Because of these multiple variables, Dr. Kemper thought it would be wise to provide the Committee with a general overview by providing cost ranges.

Primary cost categories would include laboratory equipment, supplies, installation and maintenance, space, utilities, staffing, and laboratory information systems. There would also be costs for staff training and education, as well as for outreach and referral for confirmatory testing and short-term follow-up. Dr. Kemper also reviewed some secondary cost categories which included state costs for long-term tracking and monitoring, educational outreach, reporting, LT surveillance, and family treatment and long-term care.

Dr. Kemper presented the workgroup's timeline. The goal would be to report cost estimates to the Committee by the May 2016 meeting. He said the immediate next steps would include: scoping out the costs from MPS I and Pompe disease, identifying states that are either screening or preparing to screen, gathering state costing templates to confirm cost categories, gathering state costing estimates, and finally presenting the results to the Committee.

Committee Discussion

- No items were discussed by the Committee following Dr. Kemper's presentation.

C. Pilot Study Workgroup Update

Jeff Botkin, M.D., M.P.H.
Professor of Pediatrics and Medical Ethics
Associate Vice President for Research Integrity
University of Utah
Salt Lake City, UT

Dr. Botkin introduced all members of the workgroup and said the workgroup will submit their report by the next meeting. The workgroup's charge is to:

- Recognize and support current efforts regarding pilot studies and evaluation
- Identify other resources that could support pilot studies and evaluation
- Identify the information required by the Committee to move a nominated condition into the evidence review process (i.e. define the minimum pilot study data required for a condition to be accepted for evidence review)

One of the fundamental questions to be considered is to determine what data are the minimal necessary to move a nominated condition to the evidence review process—rather than trying to determine what evidence is necessary to approve a condition for the RUSP. One of the items for discussion is how high to set this threshold. On the one hand, if it is set too high there will be a lot of good data to review, but it may be so high that it will turn people away from the process. On the other hand, having the bar too low might result in deficient proposals that might not be successful. The challenge is to strike a critical balance.

Dr. Botkin explained that currently for a nominated condition to be considered it must meet the following three core requirements:

1. Validation of the laboratory test
2. Widely available confirmatory testing with a sensitive and specific diagnostic test
3. A prospective population based study

He walked participants through a broad outline of the subcommittee's report, which would include the following items:

- The charge given to the workgroup
- The ACHDNC evidence review process
- Types of data necessary to support an evidence review
- Changes in federal policy (NBS reauthorization Act)
- Definition of pilot studies
- Models of parental permission
- Experience of ACHDNC with pilot studies and their existence/adequacy
- Recommendations for the Committee

Dr. Botkin explained that the government had received more than 2000 comments on the proposed changes to the law. Once the review process is finalized, which will happen this fall, those requirements will

supersede the newborn screening reauthorization act. These changes may have an impact on the design of pilot studies in the next few years.

The report will identify the information required by the Committee to move a nominated condition into the evidence review process. In the area of feasibility studies, the report will provide recommendations regarding the minimum criteria for an adequate evaluation of test modalities for analytic validity and clinical validity. The report will also discuss benefit and provide recommendations regarding prospective population-based screening of identifiable newborns as well as their net benefit to children and families.

The report will recognize current efforts regarding pilot studies carried out by a variety of federal agencies such as CDC, HRSA, FDA, NIH as well as the NBSTRN and states. The goal is to both recognize and seek opportunities to see how the Committee could suggest to the Secretary how to provide different kinds of support for this enterprise.

The report will provide recommendations regarding the identification of other resources that could support pilot studies and evaluation and also try to better define what kind of "system" should be in place to support newborn screening projects.

Dr. Botkin reviewed the report's draft recommendations. In terms of the recommendations regarding the minimum criteria for the test, for analytic validity it must fulfill both Clinical Laboratory Improvement Amendments requirements and FDA verifications. The test must also be scalable to a high-throughput platform to move forward.

Regarding clinical validity, for sensitivity the test must be evaluated through analysis of NBS bloodspots from known true positives, carriers, and from clinically relevant variants. For specificity, the test must be evaluated through the analysis of known true negatives.

Regarding recommendations about prospective population-based screening of identifiable newborns, a sufficient number of newborns needs to be screened to identify a case. Studies showing the efficacy of early intervention are necessary but they can be separate from a population-based study. Also, the population-based study should be conducted using a newborn screening system similar to the US system.

The workgroup is still discussing the above items and several questions have been raised such as: *How many babies does one need to have screened in a pilot in order to be considered an adequate pilot? If the known frequency is 1 in 10,000, should one have a pilot study that has screened at least 10,000 children? Does it matter at the threshold stage that different populations may have a different phenotypic expressions of a particular condition?*

The workgroup will also provide recommendations in the following two areas: 1) Recommendations to recognize and support current efforts regarding pilot studies and evaluation; and 2) Recommendations regarding the identification of other resources that could support pilot studies and evaluation.

Committee Discussion

- Dr. Bailey said that one of the challenges is that when the workgroup sends a condition to the Evidence Review Group it is important that enough review has been performed so that one is not wasting the Evidence Review Group's time. He added that this workgroup's task is primarily with regard to the pilot study component, although obviously there are other pieces as well. Dr. Bailey said they have not come up with recommendations yet because these are complicated issues, but he said he believes that in the next couple of months they will be able to work through some of them.
- Dr. Bocchini said he was very pleased with the process and thought they are moving in the right direction.
- Dr. Urv agreed the bar should not be too high, but she also said that the science needs to be rigorous. She emphasized the need for rigorous science.

- Dr. Cuthbert said it is critical to be mindful of the volunteers' time—those who volunteer on the Prioritization and Nomination Committee. They do a lot of good work and it is important to make sure there are enough good data available. She said that CDC has started putting together quality materials, particularly about the dried bloodspot tests. Dr. Cuthbert added that they need to be informed ahead of time and have good lead time to make good quality materials and also start developing in-house methods.
- Dr. Bocchini agreed with Dr. Cuthbert.
- Dr. Botkin said this would also be an opportunity to work with Dr. Kemper and his group in terms of thinking about the nomination process and what the nomination process would look like if the elements presented today were to become acceptable.
- Dr. Kemper said there are a lot of pieces to the puzzle: the nomination process, the evidence review, and the decision-making process. It might help to take a step back and think about how all the pieces work together. He said they are working with Ms. Bonhomme to determine how to structure the nomination form in a way that somebody who is not steeped in the arcane world of evidence review can put it together. He said that if it becomes clear that there is a critical gap in evidence, they should be able to stop at that point and communicate that to the Committee. It is important for the nominators to be aware of critical gaps so they may work with NIH or other potential funders to resolve such gaps.
- Dr. Bocchini said it is important to know what issues on the "cost side" need to be in the nomination packet.
- Dr. Lorey made a comment about the harms of informed consent, which were learned from the California tandem mass spectrometry pilot. He said that within the pilot period, when informed consents are required, there could be two sources of human error. One is the hospitals. He said that many of them refuse to participate because they are understaffed and it is difficult for them to take the time to present an informed consent. The second is families that requested the supplemental testing for a child that was not caught because they were not offered testing and the child became permanently impaired. He asked if there was going to be mention about the harms of informed consent in the pilot.
- Dr. Botkin said they will indeed talk about the barriers that the informed consent process offers. He said there are also substantial advantages with the trust element it brings to the whole process, so there are both pros and cons to consider about informed consent. He said the group will describe the experience to date and how different consent models have either made pilot studies more or less feasible.
- Dr. Berberich from the State Hygienic Laboratory at the University of Iowa said one may want to consider the consequences of allowing nominations to go forward into the evidence review knowing that the bar is set at a height where some will be rejected and not be added to the RUSP. He asked if as part of the nomination process if the bar is set lower that there will be some guidance provided so that they will move forward with that condition based on the evidence review.
- Dr. Bocchini said the Committee has done so in the past both at the nomination prioritization level when the committee has chosen not to proceed to evidence review, and also following evidence review when it has provided feedback for those conditions that have not been accepted. Dr. Bocchini said this is important and will continue to be done.

IX. New Business

Joseph A. Bocchini, Jr. MD
Committee Chair
Professor and Chairman
Department of Pediatrics
Louisiana State University
Shreveport, LA

The Committee did not discuss any new business.

X. Adjournment

Dr. Bocchini thanked all committee members for their participation in the meeting as well as all subcommittee and workgroup members for their work. He also thanked the organizational representatives and all attendees for their participation. In addition, he thanked Ms. Sarkar for all her efforts and contributions in organizing a successful meeting.

With no additional business to address, Dr. Bocchini adjourned the meeting.