Advisory Committee on Heritable Disorders in Newborns and Children

Meeting Summary
April 23-24, 2019

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) meeting was convened on April 23, 2019 and adjourned on April 24, 2019. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

Committee Members

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

Susan A. Berry, M.D.
Professor and Director
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Department of Pediatrics and Genetics
Cell Biology & Development
University of Minnesota

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Professor and Chairman
Department of Pediatrics
Louisiana State University

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Professor of Clinical Pediatrics
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Department of Pediatrics
Deputy Secretary, Children's Medical Services
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Associate Professor of Pediatrics
University of Louisville School of Medicine

Jane M. DeLuca Ph.D., R.N.
Associate Professor
Clemson University School of Nursing

Cynthia M. Powell, M.D.
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Director, Medical Genetics Residency Program
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Co-founder, CEO
Newborn Foundation

Scott M. Shone, Ph.D.
Senior Research Public Health Analyst
Center for Newborn Screening, Ethics, and Disability Studies
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Associate Director
Center for Translational Science
Children's National Health System

Ex-Officio Members

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Kamila B. Mistry, Ph.D., M.P.H.
Senior Advisor
Child Health and Quality Improvement

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

Food and Drug Administration
Kellie B. Kelm, Ph.D.
Deputy Director,
Division of Chemistry and Toxicology Devices
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National Institutes of Health
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Designated Federal Official

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

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Robert Ostrander, M.D.
Valley View Family Practice

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

American College of Medical Genetics & Genomics
Michael S. Watson, Ph.D., FACMG
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American College of Obstetricians & Gynecologists
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Association of Maternal & Child Health Programs
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Department of Defense
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Genetic Alliance
Natasha F. Bonhomme
Vice President of Strategic Development

March of Dimes
Siobhan Dolan, M.D., M.P.H.
Professor and Vice Chair for Research
Department of Obstetrics & Gynecology and Women's Health

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

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

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

Catharine Riley, Ph.D., M.P.H.
Designated Federal Official
Health Resources and Services Administration (HRSA)

A. Welcome and Roll Call

Dr. Bocchini welcomed participants to the second meeting in 2019 of the Advisory Committee on Heritable Disorders in Newborns and Children.

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

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

Organizational representatives in attendance were:

- American Academy of Family Physicians, Dr. Robert Ostrander
- American Academy of Pediatrics, Dr. Debra Freedenberg
- American College of Medical Genetics and Genomics, Dr. Michael Watson
- American College of Obstetricians and Gynecologists, Dr. Britton Rink (webcast)
- Association of Maternal and Child Health Programs, Dr. Jed Miller
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health Officials, Dr. Chris Kus (webcast)
- Genetic Alliance, Ms. Natasha Bonhomme
- March of Dimes, Dr. Siobhan Dolan (webcast)

- National Society of Genetic Counselors, Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders, Dr. Shawn McCandless

B. Vote on March 2019 Meeting Minutes

The Committee members received a draft of the minutes of the March meeting to review prior to this meeting. Revisions submitted by Committee members were incorporated into a final draft, which was also distributed to the Committee before the meeting. Dr. Bocchini asked whether any additional edits were needed; hearing that there were none, the Committee voted unanimously to approve the minutes in their current form. Dr. DeLuca and Dr. Brothers abstained.

C. Opening Remarks

Dr. Bocchini introduced new Committee members: Dr. Jane DeLuca, Ph.D., R.N. and Dr. Kyle Brothers, M.D., Ph.D. They will serve until June 30, 2023.

Dr. Bocchini thanked all the organizations that applied to appoint organizational representatives to the Committee. Two have been selected and will join the Committee during its August meeting.

The Committee received a new condition nomination for the RUSP, congenital cytomegalovirus infection, nominated by a team led by the National Cytomegalovirus Foundation. The submission is undergoing initial review.

The next in-person meeting will be August 1-2, 2019. All the meeting dates have been set up through 2023 and can be found on the Committee's website.

II. New Disorders Readiness Tool

Yvonne Kellar-Guenther, Ph.D.
Senior Research Scientist
Center for Public Health Innovation
Clinical Associate Professor
Colorado School of Public Health

On September 1, 2016, NewSTEPs received funding from the Health Resources and Services Administration (HRSA) to help support states in implementing three disorders recently added to the RUSP: Pompe, MPS-1 and/or X-ALD. As the Program Evaluator for New STEPs, Dr. Kellar-Guenther developed and administered the Readiness Tool to track newborn screening programs' readiness for screening for new disorders. Using the tool, they examine statewide implementation readiness in four phases: 1) approval or authority to screen; 2) laboratory set up and follow-up logistics (includes lab, follow-up and IT readiness); 3) education for the general public, families and providers; and 4) implementation (e.g. pilot screening, screening for selective populations, or statewide implementation).

By using prospective data, the team sought specifically to learn how long it takes to implement statewide screening for a new disorder from the first activity to statewide implementation. The length of time to achieve readiness was of most interest. The team obtained data from 39 states (39 states provided data on Pompe, 38 on MPS1 and X-ALD, and 7 on SMA).

Three to four years after a condition was added to the RUSP, 50 to 58 percent of the states that provided readiness data were preparing for implementation, while 10 to 15 percent of states had not started preparations. For the 13 states that implemented screening for Pompe, MPS-1 and X-ALD, it took a median of two years and four months to do so.

The team sought to learn how long each readiness phase took. For the first phase, obtaining authority to screen, 25 of the 39 states had started at least one activity in obtaining authority to screen. Seventeen had received approval for funding. Other states were working toward, or had obtained, authorization to screen. Some states require additional approval for funding to screen. It took a median of 18 months to complete this phase. Mandated approval times by several different states lengthened the time to implementation, but also provided the state newborn screening program time to get ready (laboratory set up, education, and follow-up readiness).

Lab readiness had the longest median time at 21 months. Identifying lab space, obtaining and installing equipment took a median of 12 months. Other steps that were time intensive included: 1) identifying medical specialists or treatment centers; 2) developing and gaining buy-in for short-term follow-up protocols; and 3) staffing. Half of the states that provided data had started at least one IT activity. IT readiness took a median of six to nine months, much of which was focused on developing specifications for the laboratory information management system (LIMS) software. In terms of education for families and the general public, it took states a median of 10 to 14 months for this activity and only 16 of participating states have started at least one activity. This involved identifying and modifying materials and measures to track their impact, including obtaining input from stakeholders.

Discussion

- A Committee member asked what are some of the elements or lessons learned by states that were able to implement rapidly that could be offered to others to facilitate implementation? The presenter responded that many of the leaders that are farther ahead did not provide data. Insight at this point is based on about a third of states that provided data. An interesting observation was that half of the states that provided data benefitted from an outside mandate to screen.
- A Committee member asked if readiness involves multiple aspects and things do not happen sequentially, how is the timeline defined? The presenter responded that the date on which the first activity is initiated is the start date, which is usually the granting of approval to screen. The last date is the date of implementation. The states that have not yet implemented screening use the last date they received updated data.
- A Committee member asked why didn't the team use the date a condition was added to the RUSP as the start date? The presenter's response was that the median time to implementation differed for each of the three conditions. Programs were asked how long it would take them to implement after getting approval in their state to screen. Time to implementation data, with a start time tied to when the condition was added to the RUSP, could be produced.
- A Committee member asked if they looked at opportunity costs? Are there any opportunity costs or things that did not get done in order to make it possible to bring on a new condition? Do you have any data on that? The presenter responded that the biggest reported cost was loss of staff or negative effect on staff morale. It is difficult for staff to train on how to screen for a new condition because they are so busy working on other components.

- A Committee member asked if there had been an assessment of the role of champion within states that help push things forward? Also, what can we control and how much does the process change? Dr. Guenther responded that people who start earlier show optimal median time rates, so it is something to consider. In terms of what can be done, connection to other states is important and should not be minimized. There are education resources available for states to take and use, but not everyone is using them. There are also things missing with regard to education, such as a way to measure the impact. Obtaining authority to screen is where you have the least room. There can be some support for that, but it is the lab readiness, the development of follow up and the IT and education components where there is the most room to help the process along.
- A Committee member pointed out that even with a law in place and a mandate, implementation may still take a long time. What could the Committee and other champions suggest to improve the process? The presenter indicated that programs that start earlier show the best median time rates to implementation but pointed out that if a follow-up system is not up and running when implementation starts, labs are less prepared to respond adequately to a positive screen and the risk of false positive results may rise as well. Time is needed to develop and encourage wide-spread use of educational materials as well.
- A Committee member asked what the committee could do to share this information and streamline the process for others? Dr. Guenther hopes that states that have provided data will continue to do so as they continue to implement screening but acknowledged the danger of data submission fatigue. She would also like to publish these data.
- Comment - this leads to our discussion this afternoon. The Committee does not include all of the variables in our decisions about the RUSP. States may want to know about cost effectiveness or public health opportunity costs.
- Comment - these data would also be helpful for people outside this room who are making decisions about whether to add conditions to newborn screening panels.
- Comment - a state legislator will add things to their state panels that the next state over has not added to its panel, creating an equity problem for families based on where they live. On the other hand, some states have to seek legislative approval for a condition that has been vetted thoroughly through the RUSP process, and that can take years.
- Comment - the amount of complexity of equipment needed can hamper implementation of screening for some conditions. Some states contract a laboratory service to another state that has more capabilities and that must be factored in as well.

III. Public Comments:

A. Dean Suhr, MLD Foundation and Rare Army

Mr. Suhr reported on the most recent meeting of the RUSP Roundtable, held April 22, 2019. The group discussed the following: reauthorization of the Newborn Screening Saves Lives Act; pilot studies; long-term follow-up; and improving clinical care. The group will meet again in November and will update the Committee thereafter.

B. Danae Barke, Elizabeth Carter and Margie McGlynn, Homocystinuria Network America

Homocystinuria Network America is a patient advocacy and patient/family support group co-founded in 2016 by Ms. Barke, who is also its executive director. Newborn screening for homocystinuria (HCU) is conducted nationwide but at least 50 percent of patients with classic homocystinuria are missed. Methionine is used as the biomarker instead of homocysteine. Studies have shown that cut-off levels are set too high to avoid false positives or the infants do not have high enough levels at day one or two to be detected by this biomarker. She asked for the Committee's support in helping to improve screening so that all patients could be identified early and receive life-saving treatment.

Ms. Carter recalled when her two-year-old asymptomatic son, who screened negative at birth for HCU, began having seizures. He was diagnosed with HCU 11 days after entering the ICU. Ms. Carter hopes that medical advancements will be developed to ensure that he can live as normal a life as possible.

Ms. McGlynn highlighted a publication from the *European Network and Registry for Homocystinuria* that recommends a second-tier test involving a lower methionine cut-off level and use of a second-tier test to assess both homocysteine and methylmalonic acidemia. The same dried blood spot could be used to detect CBS-deficient homocystinuria, methylation disorders and cobalamin defects. The Centers for Disease Control and Prevention has been working on methods to detect both homocysteine and methylmalonic academia (MMA) and is supporting the adoption of second-tier screening methods through both hands-on training as well as technology transfer.

Dr. Bocchini thanked everyone for his or her testimony and for bringing these findings to the Committee's attention. The Committee will look into them right away.

IV. RUSP Condition Nomination and Evidence Review Process: Draft Approach and Timeline

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

Dr. Bocchini reminded participants that the Committee embarked on a review of the current processes for nominating a condition, conducting evidence-based reviews, and decision-making. The discussion will start regarding the systematic evidence-based review process. In August, the Committee will continue to examine the evidence-based review process and discuss the potential for incorporating values and possibly modifying the approach to cost assessment, population-level modeling, and public health system assessments. In November, the Committee will discuss the decision matrix and possible review of the conditions that are on the RUSP. At the February 2020 meeting, the Committee will review the nomination form to determine whether it needs to be revised.

In the discussion to follow, Dr. Bocchini asked the Committee to think about how the methods for conducting the evidence review process or the type of data included could be modified to better inform the Committee's deliberations and decision-making. He also asked those present to discuss what case

definition should include, how outcome measures could be identified and graded, what types of treatment should be considered in the evaluation, and what is the best way to use gray literature. He also asked workgroups to discuss these topics at their afternoon meetings.

V. Evidence Review Process (Part 1 – Case Definitions)

Alex R. Kemper, M.D., M.P.H., M.S.
Lead, Evidence-based Reviews
Division Chief, Ambulatory Pediatrics
Nationwide Children's Hospital

Cynthia M. Powell, M.D., M.S., FACMG, FAAP
Professor of Pediatrics and Genetics
Director, Medical Genetics Residency Program
Pediatric Genetics and Metabolism

Dr. Kemper stated that today's objective is to think about ways to strengthen the evidence review process, while keeping in mind the evidence review process must be completed within nine months. The presentation focused on case definitions and explained that a challenge during previous reviews was determining how to define a condition. It is important to understand what is being screened for, so the incremental benefits or harms of identification through screening can be clear. He noted the Committee's case definition for a condition recommendation for the RUSP directly affect what state newborn screening programs look for to meet reporting requirements. Dr. Kemper proposed standardizing the terminology used to identify the primary target—the specific condition that is being targeted—and secondary targets, which are those that it would be useful to identify and consider through evidence evaluation. There are also incidental findings, which are not targeted, but are conditions that could be identified in the process of screening.

Dr. Powell moderated the discussion.

- A Committee member said there is much confusion about secondary targets; she understood them to be indications that appeared unexpectedly and for which there was limited evidence. An example would be discovering children with Down syndrome and T-cell immunodeficiency in the course of screening for SCID. She expressed concern about the possible tendency to mistake secondary targets as primary targets, when they could be "ride alongs."
- Another Committee member said he believed the focus should be entirely on primary targets, which should be set at the federal level, so that the states can comply with the federal mandate.
- A Committee member said that "secondary target" means something you were actually looking for, not those that are "incidental" or "unintended" findings.
- A Committee member said that a clean break between primary and secondary needs to be delineated.
- An organizational representative reminded those present that, outside the genetics world, screening tests are not diagnostic—diagnoses require a confirmatory workup. Part of the evidence review should be determining if there is a potential condition that could be confirmed through a workup, which would result in a case definition.
- An organizational representative pointed out that a number of what are being referred to as secondary targets or conditions, could be fatal to newborns and, if detected, require life-saving

treatment. At least one state expanded its focus to include secondary targets, which allows children who have these conditions to receive treatment. She also noted that the natural history of some conditions has changed and they are not as clear as they used to be.

- Another organizational representative said that this debate illustrates how much education is needed for the public in discussions because the terminology is confusing even to professionals in the field.
- An organizational representative said that the decision on whether to conduct evidence review on a condition should be predicated on whether there is a test that can identify it in a presymptomatic phase and whether there is a treatment that can be initiated presymptomatically that alters the outcome. It is also important to stress that what's being discussed here is a condition, not a marker. First you identify the condition as being suitable for newborn screening; then you look at the marker you're using. This gives you the opportunity to define secondary markers to enhance the specificity of the newborn screening test and reduce the false positive rate.
- A Committee member said that it may be important, not only to do case definitions but also for states to indicate what they are screening for along with the methods used, which can change.
- An organizational representative pointed out that since some of the tests are mandatory they can have an impact on families. There are issues of mortality, quality of life and morbidity, which a health care provider may view differently than a family member. For example, who determines quality of life and is it in terms of the patient or the family? The state will probably have to give input to that, since they are providing funding.

Dr. Kemper concluded by indicating this discussion is important in regard to the nomination package, in particular with regard to case definitions and whether they reflect primary or secondary targets. The evidence review team can continue to focus on identifying both primary and secondary targets as they have been, while also continuing to catalogue incidental findings as they are described in research studies, but without focusing on the effects of those incidental findings.

Evidence Review Process (Part 2 - Outcomes)

Dr. Kemper indicated the Committee's goal has traditionally been to pre-specify what the expected outcomes of interest are to ensure that they are identified and catalogued while remaining open to new outcomes. Examples of benefits, particularly for the most recently added conditions, are improvements in mortality, some components of morbidity, length of life, ventilator-free survival, neurologic and motor function. Harms related to screening include pain and other adverse effects from screening or diagnostic testing, earlier exposure to treatment, adverse effects and the psychosocial harms of uncertain outcomes. He noted that it can be difficult to detect a link between intermediate outcomes, such as lipid screenings and MRIs and patient-centered outcomes, such as how a patient physically feels. He asked how the intermediate outcomes, which can affect quality of life, and are often poorly understood and under-reported, should be pre-specified. He noted the need to avoid the diagnostic odyssey.

He asked whether the Committee should have a list of outcomes that it always looks for, as other evidence systems do. This would consist of lists of outcomes that are most or least significant in decision making. Alternatively, the Committee could continue to convene experts to examine the nomination package and determine at that point what types of outcomes should be targeted.

Dr. Powell moderated the discussion.

- A Committee member said that a mandatory test has a specific legal standard, which needs to be taken into account when discussing the rationale for why the Committee decides to recommend a screen. Clinicians and families could view outcomes of interest and quality of life measures differently. This is an important consideration when you're removing parental rights in testing the child. Dr. Kemper noted that quality of life can vary between the affected child and his/her family.
- Another Committee member said that one solution is to determine what outcomes are most important, followed by a second and third tier of outcomes. It would also be useful for groups that are submitting a condition for RUSP consideration to have surveyed affected families to find out what their high-priority outcomes are and the Committee would then determine where those fall in its tiered system. Another Committee member said that the first tier could consist of morbidity and mortality—which are universally recognized—while the second tier could consist of complications or concerns that are specific to a condition and whose frequency can be measured; followed in the hierarchy by quality of life, as reported by the parent.
- An organizational representative said that it is important to remember that the treatment administered to prevent mortality or intellectual disability can cause significant deterioration in quality of life. Also, given the mandatory nature of newborn screening programs, it might be best to keep the decision making simple by setting the primary goal of a screening program to permit intervention pre-symptomatically when it will prevent death, intellectual disability or permanent physical disability. Dr. Kemper said that this approach would argue for having a pre-specified list of outcomes that investigators, advocacy groups and funders could examine when setting up outcomes for newborn screening studies they are initiating.
- An organizational representative said that approval of a screening should not be based on family and quality of life measures but it could be worthwhile for the Committee to, between now and 2020, convene parent partners to discuss benefits and harms related to reducing the diagnostic odyssey, a concern that is very important to families. He has heard that getting the family connected to a medical home, with people who understand parent's expertise but also what they are going through, can offer effective support. The Committee would be doing these parents a disservice if it failed to learn what benefits they think are most important and take them into account.
- A Committee member noted that the National Academy of Medicine and the Vital Signs project, among others, are researching quality of life issues and some are disease-specific (asthma, for example).

Based on this discussion, Dr. Kemper concluded that, from an evidence review standpoint, the Committee will continue looking at the full range of benefits and harms as it has in the past but there is the potential to develop a list of tiered outcomes. However, it is also important, when talking about differences in morbidity or mortality, to what those differences are being compared. He also asked, whether there is a minimum amount of time to wait before learning what the outcomes will be.

Evidence Review (Part 3 - Treatment)

Typically, the Committee has focused on recently FDA-approved therapies (e.g. nusinersen) but he wondered whether therapies under development, and supportive therapies for patients or their families

should be considered as well. Or should the availability of therapies be considered? If yes, when in the review process should these things be considered?

He also asked about the use of gray literature and unpublished data from local or national databases or by reaching out to others who have been conducting studies.

Dr. Powell moderated the discussion.

- Several members cautioned about using the unpublished data before it is proven effective and FDA-approved.
- A Committee member noted that clinical trials do not always have positive results—which is why they are done in the first place—and cautioned it would not be wise to make decisions about newborn screening based on therapies without confirmation of their efficacy, although that does not necessarily limit them to those that are FDA-approved.
- A Committee member said the group has to consider whether approved therapies are available to all from a cost, geographical or genetic standpoint. She asked whether some therapies might be available only to those with a specific mutation.
- An organizational representative pointed out that many therapies cannot be assessed for long-term efficacy because, typically, only short-term data are available. The Committee has to rely on some short-term data, as there isn't much long-term data yet available. It is possible that treatment is turning a condition from a severe form to one that is more chronic.

Evidence Review (Part 4 – Availability of Evidence)

Dr. Kemper turned the discussion to the evidence review team's process for assessing peer-reviewed published evidence with regard to applicability to newborn screening and the overall strength of the evidence presented, including an examination of their structure and the consistency of results. The evidence review group could implement *Grading of Recommendations, Assessment, Development and Evaluation* (GRADE), a standardized process for literature quality evaluation, or something similar. However, GRADE does not have a process for assessing the types of small case series that the evidence review team often uses. As a result, it may be necessary to assess quality in a quantitative rather than assigning them quality ratings.

The evidence review team has also examined gray literature, focusing on screening accuracy and the process used for diagnostic confirmation as well as literature covering therapies that are still being developed. Sources include information submitted to the FDA, conference and abstract proceedings, discussions with authors and sponsors and examination of data registries. Dr. Kemper believes that information collected directly from newborn screening programs has the lowest risk of bias due to its algorithmic approach. He envisions mirroring the process that developed for GRADE to develop a standard way of collecting relevant information from the field.

Dr. Powell moderated the discussion.

- A Committee member pointed out that much of the literature and drug trial information only releases positive results, which makes it difficult to gauge its quality. Dr. Bocchini said that studies submitted to the FDA for vaccine licensure but have not yet been published are sometimes made available to the Advisory Committee on Immunization Practices on request; he

wondered if that courtesy could extend to drug trial data that would be of interest to the Committee.

- A Committee member expressed concern that it may be difficult to assess the quality or quantity of information that is provided in gray literature, especially in connection with ongoing trials, not all of which is submitted to peer review.
- An organizational representative said that it would be unwise to use data on a novel therapy until the FDA has approved it in case the agency ultimately decides to withhold approval. Dr. Bocchini confirmed that the data that might be requested from the FDA would be for a drug that has been approved—therefore, the compound is licensed—but the data have not yet been published.

VI. Acknowledgement of Dr. Bocchini as Chair of ACHDNC

Members of the Committee and organizational representatives past and present expressed their appreciation of Dr. Bocchini's leadership of the Committee as its chairperson, since 2011. Many other people from outside agencies and health care and advocacy organizations that have worked with the Committee during his tenure saluted him, as did members of families with relatives who have newborn conditions and benefited from his kindness. The Committee DFO Catharine Riley was the first among many to thank him for his many years of service as the Committee's chair. HRSA Staff member Alaina Harris, who has worked with Dr. Bocchini since he took the helm, explained the Mardi Gras beads distributed to attendees is in honor of Dr. Bocchini being a native of New Orleans. Ms. Joan Scott, director of HRSA's Division of Services for Children with Special Health Care Needs stood in for Dr. Michael Warren, associate administrator for HRSA's Maternal and Child Health Bureau. She praised Dr. Bocchini for leading "the Committee through many important but difficult discussions, not only about conditions that are added to the RUSP but how newborn screening could be improved throughout the nation to benefit all children and for doing so with compassion, wisdom and kindness."

HRSA presented Dr. Bocchini with a plaque that reads: "The Advisory Committee on Heritable Disorders in Newborn Children, as the Chair from 2011 to 2019, you have made a difference in the lives of newborns and their families with your wisdom, compassion and generous spirit. Thank you for your many years of service and leadership to help the nation's infants and children."

Dr. Bocchini thanked everyone for their kind words and singled out Dr. Howell and Michelle Puryear for establishing the way the committee would operate. He said that one of his most important priorities has been to develop collaborations and build on relationships and work together to accomplish what the Committee wanted to be over time. He added, "When something happens and it's good and then you get something extra, that's lagniappe. And so, these eight years have been lagniappe."

VII. Administrative Business — April 24, 2019

A. Welcome and Roll Call

Joseph A. Bocchini, Jr., M.D.
Committee Chair
Professor and Chairman

Department of Pediatrics
Louisiana State University

Catharine Riley, Ph.D., M.P.H.
Designated Federal Official
Health Resources and Services Administration (HRSA)

Dr. Bocchini welcomed participants to day two of the second 2019 meeting of the Advisory Committee on Heritable Disorders in Newborns and Children.

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

- Dr. Mei Baker
- Dr. Susan Berry
- Dr. Joseph Bocchini
- Dr. Kyle Brothers
- Dr. Jane DeLuca
- Dr. Carla Cuthbert (Centers for Disease Control and Prevention)
- Dr. Kellie Kelm (Food and Drug Administration)
- Dr. Kamila Mistry (Agency for Healthcare Research & Quality)
- Dr. Melissa Parisi (National Institutes of Health)
- Dr. Cynthia Powell
- Ms. Annamarie Saarinen
- Ms. Joan Scott (Health Resources & Services Administration)
- Dr. Scott Shone
- Dr. Beth Tarini
- Dr. Catharine Riley (Designated Federal Official)

Organizational representatives in attendance were:

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

VIII. Newborn Screening Pilot Studies

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

Dr. Bocchini explained that the Committee adopted the Newborn Screening Pilot Study Workgroup's 2016 recommendations regarding the minimum pilot study data required to move a nominated condition into the evidence review process. Dr. Watson and a team of experts have been conducting a comprehensive review of the necessary components of newborn screening pilots and presented some of the team's results.

The team's work is being done largely from a Newborn Screening Translational Research Network (NBSTRN) perspective. The workgroup is examining new technologies, conditions, treatments and management approaches to obtain unbiased information.

Dr. Watson, and Drs. Sue Berry, Piero Rinaldo, Amy Brower, and Bob Currier serve on the NBSTRN Steering and Pilot Study workgroup and have drafted a manuscript covering much of this discussion, which is working its way through the NBSTRN Steering Group; the steering group and will be published as a "white paper" The workgroup is trying to determine valid measures of progress and whether the results of the pilot are likely to be reflected in the real world. They have identified many challenges that need to be addressed to collect the right types and amounts of pilot study data and ensure that they are relevant to newborn screening.

One of the challenges is to know how large a pilot needs to be to be able to measure its success. When the pilot for SCID began, 25 genes were associated with the condition. That number has risen to 50. Although the incidence of SCID is now estimated to be about 1 in 45,000 to 50,000, the pilot study had screened close to 800,000 babies when the first true positive case was identified. The size of pilots is going up to ensure that enough patients get a particular treatment to measure the outcome and thus justify the decision to add a condition for newborn screening.

There is a strong need to understand statistics around rare diseases at the population level and how to meet the capacity needs, but the system is strained. The R&D pipeline—research ranges from new conditions to new types of testing, to new treatments—is full. The world is moving toward an era of molecularly targeted drugs, for example, which will be targeted at specific subgroups of patients. Meanwhile, newborn screening and medical genetics workforces are overwhelmed, funding for new research is limited, and the targets of newborn screening are changing.

The workgroup is finding that many conditions that were on the uniform screening panel in 2005 are more common than had been previously thought. The variability in duration of treatment and disease onset will require longer-term data collection than a pilot study can provide. There also needs to be more curation of genetic variations to weed out the large number of variants of uncertain significance that are being identified. The Clinical Genetics Genomics Resource Initiative (ClinGen) is addressing this need. False positive results need more attention as well. Collaborative Laboratory Integrated Reports (CLIR) tools and second-tier biochemical tests perform well in this area.

Other challenges Dr. Watson mentioned are the difficulty in:

- Calling on the clinical world to increase capacity in newborn screening laboratories, especially in dealing with off-target cases—because electronic health record systems focus heavily on the business side of medicine and are too variable to permit centralized data sharing;
- Encouraging data sharing, which is being done through registries started and supported by people who are clinically affected but attracts far less participation from asymptomatic people.
- Introducing new drugs expeditiously, although the FDA's provisional approval process has

helped to address this issue in certain cases and;

- Reimbursement for testing: how do you incentivize people to make their data available? Coverage with evidence development is one possible avenue.

A. Discussion

- A Committee member noted that the FDA has given approval for the use of ClinGen determinations of clinical significance of molecular variants, paving the way for their use by newborn screening programs when molecular testing is part of their screening algorithms and asked Dr. Watson, who is a co-principal investigator in the ClinGen project, to describe some of its work. Dr. Watson explained that ClinGen is clinically curating the magnitude of gene relationships to disease and determining the pathogenicity of variants within the genes that are parts of disease sets. The difficulties come with phenotype-driven types of screens because many genes that were assumed to be closely associated with some types of diseases are not. ClinGen is studying and curating gene-phenotype associations, and genetic variants that are not closely associated with diseases are being eliminated. He also noted that the FDA is going to recognize the ClinGen-curated parts of the ClinVar database that NIH maintains as clinically validating whether a variant is benign, uncertain or pathogenic in the context of FDA pre-market submissions. This work could encourage pharmaceutical or device companies to develop test kits for rare diseases that it can sell to labs to reap a return on investment for doing such research. Labs have been developing their own tests to fill the current void. A Committee member noted, however, that Congress only allows companies to recoup the money used for R&D, not to make a profit. In any case, some states are doing small retrospective studies along these lines. Dr. Watson noted that Congress is considering legislation to bring labs that are acting as manufacturers under regulatory oversight.
- Dr. Watson explained that virtual pilots can use data from pilots that have already been conducted which helps them to make decisions about what to include, on an ongoing basis, in their screening programs. The data will be reanalyzed because it may not have been used originally to identify a particular condition, and because the data may be coming from subjects who may have been identified clinically, not through newborn screening initially, they would not have necessarily been diagnosed already with a rare disease. A Committee member offered as an example, the Mayo Clinic's decision to inform Minnesota's newborn screening program when it found screened newborns with low methionine, though this was not a routinely reported range for metabolite results, which led the newborn screening program to identify children with Cobalamin C deficiency and other low methionine-associated forms of homocystinuria.
- A Committee member asked how to ensure that this type of data—and data collection—is captured so that, through evidence review, the condition that is found is an appropriate screening target. System-based prospective pilot studies are needed to ensure that the entire newborn screening system is working together to identify a child with a condition. That approach is not reflected in the example just described. Dr. Watson said that the approach would probably involve collecting and using data in connection with a screen and ensuring that the screen is conducted at the pilot study stage and in a post-market surveillance environment to ensure that the test is performing as expected. Dr. Bocchini said that the same parameters might be applied to examination of conditions that are already on the RUSP.

IX. Ad-hoc Workgroup - Interpreting Newborn Screening Results

***Mei Baker, M.D*.**
Chair of the Ad-Hoc Workgroup
Professor of Pediatrics
University of Wisconsin School of Medicine and Public Health

Dr. Baker reminded the Committee of the Workgroup's two charges: The first one was to make a report to the Committee on interpretation of newborn screening results and then publish the results in a peer-reviewed journal and preparing a slide deck or other tools for clinicians. The other charge was to examine and make recommendations regarding cut-offs. The workgroup decided to table the cut-offs discussion for now so that the workgroup can concentrate on it exclusively later.

In the report's introduction, the workgroup hopes to explain—to newborns' families and the public as well as physicians—newborn screening's benefits but also its limitations. Terminology needs to be consistent so that providers, organizations and families understand what screening is and is not. The group also plans to explain that, compared with other medical screening programs, newborn screening is done in newborns and turn-around-time is critical for some conditions. The types of technologies that are used will also have some differences between screening and diagnosis. Dr. Baker noted that the workgroup can draw on existing literature to explain these distinctions.

The next part of the document on current practice will describe risk assessment evidence and explain that results are threshold based and categorical. It will explain that the results interpretation focuses on establishing the risk for and indications of a condition and resulting in associated recommendations—which screening results will trigger a second newborn screening or confirmatory testing or no further action. The fact that clinical symptoms take precedence over screening results will also be emphasized.

The workgroup will also encourage discussion and request recommendations and suggestions, including input from the Education and Training Workgroup, regarding

- how to make the language on risk assessment and newborn screening results interpretation more explicit;
- how to clarify terminology and ensure its use is more consistent;
- strategies for communicating newborn screening results to families; and
- strategies for improving newborn screening performance.

Dr. Bocchini asked anyone with questions or comments about the presentation to pose them to the workgroup directly or through HRSA.

X. Cystic Fibrosis Registry

Dr. Bocchini explained today's presentations on two specific registries are intended to help the Committee determine the role they may plan in providing data for evidence reviews and to states for long-term follow up.

Bruce Marshall, M.D.
Senior Vice President of Clinical Affairs

Cystic Fibrosis Foundation

Dr. Marshall explained that about 35,000 people in the U.S. have cystic fibrosis (CF); there are about 100,000 cases worldwide; it is the most common inherited life-shortening disease among Caucasians. The main cause of death is chronic lung disease. Comorbidities include diabetes, psychosocial issues, and allergic bronchopulmonary aspergillosis. Sweat chloride is still an important diagnostic test.

The foundation conducts a broad scope of activities ranging from basic research to direct contact with people with cystic fibrosis (CF). Its CF registry is an IRB- approved, patient consented, observational study and all of the care centers must participate in it to be accredited. About 5 percent of the care centers do not offer consent. The registry collects data on diagnosis, demographics, treatment and other types of care, measurements in screening tests and other conditions and events. Centers receive financial support to enter data and support is given to the users. Edit checks within data entry fields ensure quality—if the data entered is outside the limits, a waiver must be requested and key metrics (e.g., deaths, transplants) are validated. The data are processed annually, specifically to erase duplications, in particular; some selective, usually random, audits are also conducted; for cause, audits occur as necessary. The major problem is adherence to the informed consent process, which is run by clinical, not research-oriented people, and this is policed through the accreditation process.

Registry data are used to track the national levels of CF's natural history and the impact of delivered therapies. About 10 years ago, the foundation added post-marketing studies, which helps to bring in revenue and drive improvements in care. A detailed annual report on each center that is posted online and distributed to the center shows where they stand in regard to a process and outcome measure vis-à-vis their peers and trends over time. The CF Smart Report, a new idea to get registry data more quickly involves vendor collection of data, which is transferred nightly to the foundation's data warehouse for limited processing and then to the centers within 24 hours. The CF Smart Reports contain patient summary reports and graphical trends on key metrics as well as key information that may not be available in the electronic medical record. It tracks hospitalizations and home IVs and overlays it with trends in pulmonary function. Centers are encouraged to use the data in pre-visit planning. The report also contains a tool to identify patients who may be eligible for clinical trials; this information is available to a center that is selected to participate in a study. It is also possible to conduct observational studies through the registry. One important finding data examination revealed, for example, is that IV antibiotic-treated exacerbations had an unexpectedly negative effect on survival; this type of finding indicates the type of research the data can support and shows where more research is needed. It is also possible to conduct observational studies through the registry. Through surveys of clinicians, patients and families, for example, the foundation was able to design a randomized control trial, involving up to 60 centers and 1,000 subjects, to determine the optimal duration of treatment, all of which tracks back to the registry.

Dr. Marshall explained that the registry is used to assess newborn screening performance, in particular, false negatives. It can also track the time from birth to entry into one of the care centers and the time to clinical follow up of those who fall into the CF screen-positive, indeterminate diagnosis category CFTR-Related Metabolic Syndrome (CRMS) because they have intermediate sweat chloride values.

A. Discussion

- A Committee Member asked whether policy had changed to begin identifying centers, which had previously been de-identified and, if so, whether centers resisted this change. Dr. Marshall

confirmed the change, pointing out that the foundation was started by patients and families—it is not a medical society—so this seemed appropriate. He said that it has not led to a mass-migration of patients to another center and that high-profile institutions monitor the metrics to improve their performance and decisions regarding where to invest resources.

- Another Committee Member said that there is the potential for up to 20 percent of CRMS diagnoses to change to CF and asked whether the registry captures such diagnosis changes over time. Dr. Marshall said that it does but is not sure that all are being captured.
- A Committee member asked whether the registry accepts outside requests for data. It does; this is associated with a peer review process and the foundation asks requesters to contact one of the care center physicians to help provide context about CF. He also noted that the registry earns revenue by selling data to organizations that are conducting post-approval research in connection with EMA- or FDA-mandated studies.
- A Committee member asked whether the foundation has explored the feasibility of connecting the registry to EMRs or of mining data from these records to populate the registry with that data. Dr. Marshall that this is technically feasible but dealing with each of the 180 medical centers' compliance and IT officers is becomes resource intensive. He said they would like to get more lab data, which is fairly standardized.

XI. Primary Immune Deficiency Treatment Consortium: (PIDTC); Severe Combined Immunodeficiencies (SCID) Data Collection

Jennifer Puck, M.D.
Principal Investigator, Primary Immune Deficiency Treatment Consortium
Department of Pediatrics
University of California, San Francisco

Dr. Puck described the Primary Immune Deficiency Treatment Consortium's (PIDTC), efforts to gather data on severe combined immunodeficiency (SCID). PIDTC is part of the NIH-funded Rare Diseases Clinical Research Network (RDCRN), a group of consortia and a Data Management and Coordinating Center that stores the data. The consortium, which has included patient advocacy groups since its inception, conducts natural history studies in SCID, Wiskott-Aldrich syndrome, and Chronic Granulomatous Disease. Sites around the country and in Canada apply for membership; those that underperform are excused and each year new sites are invited to apply. There are 44 centers in the United States and Canada that have enrolled 1,749 subjects with various immune deficiency conditions. Two of four current protocols focus on SCID. As of last December, all 50 states were screening for this condition.

The PIDTC operates with a central IRB—which NIH mandates for multi-center clinical studies that it supports, although the Canadian sites do not have to participate. PIDTC devised definitions for SCID for eligibility purposes: typical SCID, leaky or atypical SCID, Omenn syndrome and a variant form, which is poorly defined. The Center for International Bone and Marrow Transplant Research collects all U.S. transplant data and a significant amount of transplant data as well. There are two levels of data collection forms. One is simple, the other is more detailed; it includes data about the donor and recipient HLA type, conditioning and all data related to transplant. The consortium also collects samples for study in specialized centers.

The PIDTC also conducts a variety of pilot studies such as one on T-cell exhaustion in patients in which transplants are losing efficacy. The consortium is also conducting a quality of life study, using the PROMIS Pediatric Assessment Tool because survival is the only measure that has been widely published.

If the consortium continues to receive funding beyond August, it hopes to undertake other studies, including incorporating genetic and pathogenic evaluations of new SCID patients to catch the 10 percent of cases that are currently missed. PIDTC will also develop candidate variants for study in specific laboratories with expertise. One of these could involve known cases involving defects, not in the bone marrow but in the thymus, which prevents the manufacture of mature T-cells. To try to determine why 40 percent of infants with SCID develop pre-transplant infections, including cytomegalovirus, which can be transmitted through breastfeeding, the consortium will conduct a prospective natural history study to examine which mothers are CMV-positive and will try to do a PCR in breastmilk samples to study viral excretion. This could lead to a clinical trial for prophylaxis with newer anti-CMV agents.

A. Discussion

- A Committee member asked what the consortium is doing to be sustainable. Dr. Puck said that it hopes to receive five years of additional support from NIH, is working with its patient advisory group partners and hopes to enlist corporate participation because it hopes to evolve from a data collection center to a clinical trial network for primary immune deficiency conditions. The PIDTC hopes that gene therapy will lead to standard-of-care treatment for various types of SCID, which will need corporate partners. The consortium wants to conduct clinical trials for the development of substitutions for chemotherapy as well.

XII. Public Comment

A. Dr. Emmanuele Delot, DSD Translational Research Network (DSDTRN)

The DSDTRN is an NIH-funded national network of clinics and research centers dedicated to improving management of and service to patients with disorders of sex development. Congenital adrenal hyperplasia (CAH), which is caused by 21 hydroxylase deficiency, is the most common disorder of steroid synthesis and is recommended as part of newborn screening in all U.S. programs. The current screening method is to test the level of 17 hydroxyprogesterone. However, prematurity, low birth weights or critical illness are known to have falsely elevated results and reduce the test's positive predictive value; these findings were included in the new clinical practice guidelines for management of CAH that the Endocrine Society published last year. A survey of state protocols revealed that each state has a different procedure for identifying and reporting positive newborn screens and the process needs to be standardized.

B. Ms. Brittany Hernandez, Director of Advocacy for the Muscular Dystrophy Association (MDA)

MDA is an umbrella organization covering over 40 different types of neuromuscular conditions and supports the Neuromuscular Observational Research Data Hub called MOVR, MDA's new clinician data registry. MOVR tracks ALS, Duchenne, SMA, and is working to develop a RUSP nomination package for

Duchenne Muscular Dystrophy to have it added to the RUSP. She acknowledged concerns about using creatine kinase (CK) to detect Duchenne because it would lead to detection of other conditions but the MDA care clinic network provides care to all patients with neuromuscular conditions, including those that could be identified through a CK test for Duchenne.

C. Ms. Annie Kennedy, Parent Project Muscular Dystrophy (PPMD)

In 2009, PPMD received funding from the CDC to convene a task force to increase clinicians' awareness of peripheral neuromuscular disease as a cause of developmental delay in young children and help them identify the early symptoms. The task force developed training tools, diagnostic and clinical algorithms, and clinical support tools, all of which are housed on the website, childmuscleweakness.org. In 2016, PPMD, the American Academy of Pediatrics (AAP), and the CDC partnered to develop a motor delay assessment tool for parents through a program called Learn the Signs, Act Early, which is housed on AAP's website. In October of 2018, the AAP dedicated a supplement of their journal to a series of 13 publications featuring expanded care guidelines in Duchenne entitled Specialty Care for the Patient with Duchenne Muscular Dystrophy. The ICD-10 code for Duchenne and Becker MD was implemented within the CMS addenda, an effort led by PPMD with support from the CDC, CMS, and AAP. Despite these efforts, surveillance data continues to reflect unnecessary delays in access to care that affects outcomes. A pilot study in New York is being funded through consortia of biopharmaceutical industry partners, with a commitment to early diagnosis and intervention in Duchenne. The pilot is being guided by a Steering Committee comprised of representatives from federal agencies, provider groups, and representatives from key Duchenne stakeholder communities.

D. Ms. Rebecca Abbott, Deputy Director of Federal Affairs, March of Dimes

Ms. Abbott explained that she spearheads a group of more than a dozen organizations, which began laying the ground work last year for Newborn Screening Saves Lives Act reauthorization by developing a set of shared principles to guide reauthorization that they shared with congressional champions. The Newborn Screening Saves Lives Act Reauthorization of 2019 would raise authorizations for programs at CDC and HRSA and makes targeted refinements to language governing activities of these agencies and NIH. The legislation will also commission a report by the National Academy of Medicine, to examine the future of newborn screening and extend the Committee's charter for another five years.

XIII. Follow-Up and Treatment Workgroup Update

Christopher Kus, M.D., M.P.H.
Associate Medical Director
Division of Family Health
New York State Department of Health

Dr. Kus presented on behalf of Dr. Brosco. Dr. Amy Brower delivered a presentation on the Longitudinal Pediatric Data Resource (LPDR) tool, which is part of the NIH-funded NBSTRN and enables clinicians, researchers, parents and patients to enter health information in a secure centralized system. The workgroup has been working with NewSTEPs to determine what type of long-term follow-up data could

be collected from states. The goal is to create a minimum set of questions and answers (whittling 2,500 questions down to four) from the LPDR that state newborn screening programs could use.

Dr. Marci Sontag from NewSTEPs has been working with NBSTRN to develop a minimum set of long-term follow-up questions for public health. Proposed questions include: 1. diagnosis; 2. date of appropriate first intervention; 3. is the patient alive?; and 4. did the child receive care and treatment specific to the diagnosis and type of care provider? Dr. Sontag also presented on work by the states in terms of long-term follow-up. Twenty-eight of 53 newborn screening programs reported doing some type of long-term follow-up, classified as:

- Basic (up to three years with collection of data on basic health status, access to care and specialist feedback);
- Intermediate (up to five years with some clinical outcomes, potentially patient surveys and specialist management information); and
- Comprehensive (five to 15 years or more, with more detailed outcomes and ensured access to care, including formula).

The workgroup discussed consent and confidentiality, which included a discussion of the risk of potential harm of identifying patients, which is a significant concern in small states.

XIV. Education and Training Workgroup Update

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

Dr. Tarini described several presentations that were delivered to the workgroup.

- Natasha Bonhomme described the newborn screening family education project Genetic Alliance is working on and a needs assessment of 500 parents to ascertain their health information preferences and usage that is also underway. She will provide the workgroup with the results when they are available.
- Workgroup members Aaron Goldberg and Keri LeBlanc led an initiative to develop an education best practices framework that will support the development of educational resources; it is available on babysfirsttest.org. It provides a newborn screening implementation pathway and examples.
- Yvonne Kellar-Guenther discussed a video tutorial NewSTEPs is working on that focuses on midwife-client discussions about newborn screening, which should be finished by the fall.
- Cate Walsh Vockley talked about training programs for midwives in Pennsylvania with an emphasis on critical congenital heart disease (CCHD) screening and the universal donation of pulse oximeters.
- Michigan Newborn Screening Program Manager Mary Kleyn described a general information sheet for primary care providers to give to parents whose infants had a strong positive screen; this would accompany an existing disease-specific fact sheet.

The workgroup discussed the condition nomination evidence review process from an education and training standpoint and felt that the discussion focused mainly on terminology, which must be shared and consistent if educational efforts surrounding it are to be effective. Members also discussed the Ad-Hoc Workgroup's project, which, it was noted could pull information from other initiatives. They agreed that a long-term deliverable could be templates that stakeholders could use to address the educational issues the workgroup is tackling.

XV. Laboratory Standards and Procedures Workgroup Update

Kellie B. Kelm, Ph.D.
Chair, Laboratory Standards and Procedures Workgroup
Deputy Director,
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics and Radiological Health

The Workgroup discussed the impact of broad phenotypes in a laboratory setting, for example, lessons learned related to identifying late-onset Pompe or SMA. APHL also updated the workgroup on its new conditions implementation project, which includes developing informational webinars for the states. APHL has funded 16 states to conduct implementation projects and designated three states as Peer Network Resource Centers that will provide technical assistance to other states.

Dr. Anne Comeau, Deputy Director of the New England Newborn Screening Program, described a new SMA screening procedure and results from Massachusetts, which is doing a single-plex assay separately from SCID, which, thus far, has yielded no positive results. The state reported one false positive, which appears to involve a specimen with an inhibitor. Utah is multiplexing SMA with SCID. The state has identified two confirmed cases and two false positive cases. The number of false positives has increased with the multiplex approach.

In its discussion about the condition nomination evidence review process, the workgroup agreed on the need to define terminology and prefers the term "case definition" or "condition" rather than "target." The condition needs to be defined so that the lab knows what it is supposed to find. The workgroup would also like to see an improved assessment of the availability of a confirmatory test, turnaround time, assurance that information is available on how those tests perform, and on the availability of specialty care.

XVI. RUSP Condition Nomination and Evidence Review Process: Follow-up Discussion

Joseph A. Bocchini, Jr., M.D.
Professor and Chairman
Department of Pediatrics
Louisiana State University
RUSP Condition Nomination & Evidence Review Process

Dr. Bocchini invited those present to continue the discussion of Dr. Kemper's and Dr. Powell's discussions of the examination of the evidence review process that was conducted the day before.

- A Committee member asked whether anything has been done regarding newborn blood spot screening in the NICU. One issue in the NICU is blood drawn from different sources being used for NBS blood spots.
- Another Committee member commented that nurse education is a challenge, in part because of the high turnover rate. The Joint Commission was approached about the potential to add a standard on this but was not receptive to the suggestion.
- An organizational representative noted that it can be more useful from an educational perspective not to just tell someone what he or she should do but explain the consequences. In this case, what are the implications for the infant and their family if correct action is not taken?
- A Committee member noted that issues were raised about homocystinuria and CAH. These may be two conditions in which it could be helpful for the Committee to re-examine the methodology used to screen for them, as the Committee has done for tyrosinemia.
- Another Committee member said that there is an issue of false positive and false negative results for CAH. CDC has been working with Minnesota to develop an assay in connection with this.

XVII. On the Horizon

Cynthia Powell, M.D.
Incoming Chair
Professor of Pediatrics and Genetics
Director, Medical Genetics Residency Program
Pediatric Genetics and Metabolism
The University of North Carolina at Chapel Hill

Dr. Powell reviewed the Committee's charge and the Workgroups' charges and described the challenges she sees the Committee facing in the future and asked the Committee whether there is a need for additional ad hoc workgroups or expansion of scope for existing workgroups.

She stressed the need for increased transparency and, in connection with that, suggested that more time be allotted for public comment on the Committee's work. Another move toward transparency would be to have more access to information on outcomes through peer reviewed publications rather than relying on the gray literature. Dr. Powell noted that the pace at which conditions will be nominated for the RUSP is likely to accelerate, which will be a challenge for the Committee. One possible solution is to look at groups or panels of conditions rather than considering them separately, which may require a high-throughput review process.

Registries that are accessible and sustainable are necessary to examine the long-term outcomes of newborn screening conditions in patients and a single registry that encompasses all rare conditions would be ideal. The challenge of providing appropriate long-term follow-up for conditions that may not be immediately symptomatic is also important but patients are difficult to follow when they move from one state or region to another so the Committee needs to consider what it can do to encourage states to support their registries.

To address timeliness issues in newborn screening, it may be time to start working toward prenatal screening, especially for conditions in which early diagnosis is extremely important, such as urea cycle disorders. More input is needed from clinicians and families to collect necessary treatment information but also to understand what families with rare conditions confront. Establishing medical homes is important to ensure continuity of care but also to help families cope.

There are barriers to address as well, such as: specialists being in short supply; the need patients have for additional services, such as therapy services; and navigating insurance and Medicaid (which doesn't cover genetic testing in some states). Other constraints include: rising health care costs; impact of introducing more newborn screening conditions on labor and resources; ethical issues, such as inequities in access to care; funding for research, including pilot studies; and the time and labor involved in conducting evidence reviews and tracking long-term outcomes.

Despite all of these challenges, Dr. Powell believes that the future is bright and plans are already underway for the Committee's next meeting. In August, the CDC will update the Committee on the work it is doing to address the false negative rate for homocystinuria and how the screening methodology can be improved.

She thanked Dr. Bocchini and others for their support and guidance during this leadership transition.

Dr. Bocchini said it is clear that he is leaving the Committee in excellent hands. He then passed the (virtual) gavel to Dr. Powell.

XIII. Adjourn

Dr. Bocchini adjourned the meeting at 1:55 p.m.