# Advisory Committee on Heritable Disorders in Newborns and Children

Meeting Summary
August 1-2, 2019

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) meeting was convened on August 1, 2019 and adjourned on August 2, 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.**
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**Jeffrey P. Brosco, M.D., Ph.D.**
Professor of Clinical Pediatrics
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**Kyle Brothers, M.D., Ph.D.**
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**Jane M. DeLuca, Ph.D., R.N.**
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**Cynthia M. Powell, M.D., M.S., FACMG, FAAP (Chairperson)**
Professor of Pediatrics and Genetics
Director, Medical Genetics Residency Program
Pediatric Genetics and Metabolism
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**Annamarie Saarinen**
Co-founder, CEO
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**Scott M. Shone, Ph.D., HCLD (ABB)**
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**Beth Tarini, M.D., M.S., FAAP**
Associate Director
Center for Translational Science
Children's National Health System

**Ex-Officio Members**

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

**Centers for Disease Control & Prevention**
**Carla Cuthbert, Ph.D.**
Chief, Newborn Screening and Molecular Biology Branch
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**Health Resources & Services Administration**
**Michael Warren, M.D., M.P.H., FAAP**
Associate Administrator,
Maternal and Child Health Bureau

**National Institutes of Health**
**Diana W. Bianchi, M.D.**
Director
*Eunice Kennedy Shriver* National Institute of Child Health and Human Development

**Designated Federal Official**

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

**Organizational Representatives**

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

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

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

**American College of Obstetricians & Gynecologists**
Steven J. Ralston, M.D., M.P.H.
Chair, OB/GYN
Pennsylvania Hospital

**Association of Maternal & Child Health Programs**
Jed L. Miller, M.D., M.P.H.
Director, Office for Genetics and People with Special Health Care Needs
Maryland Department of Health
Prevention & Health Promotion Administration

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

**Association of State & Territorial Health Officials**
Christopher Kus, M.D., M.P.H.
Associate Medical Director
Division of Family Health
New York State Department of Health

**Association of Women's Health, Obstetric & Neonatal Nurses**
Jaqueline Rychnovsky, Ph.D., R.N, CPNP, FAAP
Vice President, Research, Policy and Strategic Initiatives

**Child Neurology Society**
Jennifer M. Kwon, M.D., M.P.H., FAAN
Director, Pediatric Neuromuscular Program
American Family Children's Hospital
Professor of Child Neurology, University of Wisconsin School of Medicine and Public Health

**Department of Defense**
Jacob Hogue, M.D.
Lieutenant Colonel, Medical Corps, US Army
Chief, Genetics, Madigan Army Medical Center

**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
Albert Einstein College of Medicine and Montefiore Medical Center

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

**Society for Inherited Metabolic Disorders**
Georgianne Arnold, M.D.
Clinical Research Director
Division of Medical Genetics
UPMC Children's Hospital of Pittsburgh

# Table of Contents

# I. Administrative Business — August 1, 2019

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

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

## A. Welcome and Roll Call

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

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

- Dr. Mei Baker
- Dr. Susan Berry
- Dr. Kyle Brothers
- Dr. Jane DeLuca
- Dr. Carla Cuthbert (Centers for Disease Control and Prevention)
- Dr. Kellie Kelm (Food and Drug Administration)
- Dr. Michael Warren (Health Resources & Services Administration) (morning only)
- Ms. Joan Scott (Heath Resources & Services Administration) (afternoon only)
- Dr. Cynthia Powell
- Dr. Melissa Parisi (National Institute of Health)
- Ms. Annamarie Saarinen
- Dr. Scott Shone (webcast)
- 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 (webcast)
- American College of Medical Genetics & Genomics, Dr. Michael Watson
- Association of Maternal & Child Health Programs, Dr. Jed Miller
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Child Neurology Society, Dr. Jennifer Kwon
- Department of Defense, Ms. Theresa Hart
- Genetic Alliance, Ms. Natasha Bonhomme
- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Ms. Amy Gaviglio
- Society for Inherited Metabolic Disorders, Dr. Georgianne Arnold

### B. Vote on April 2019 Meeting Minutes

The Committee members received a draft of the minutes of the April meeting to review prior to the meeting. Revisions submitted by Committee members were incorporated into a final draft, which was distributed to the Committee before the meeting. A change to page 14 was received after the final draft was sent out and will be incorporated into the final version of the minutes. Dr. Powell asked whether any additional edits were needed; hearing that there were none, the Committee voted unanimously to approve the minutes.

### C. Opening Remarks

Dr. Powell introduced two new organizational representatives joining the Committee's group of organizational representatives that provide expertise to the Committee: Jacqueline Rychnovsky, Ph.D., R.N., CPNP, FAAP representing the Association of Women's Health, Obstetric, and Neonatal Nurses, and Jennifer Kwon, M.D., M.P.H., FAAN representing the Child Neurology Society.

Additionally, three of the current organizations identified new representatives. Dr. Powell thanked the outgoing organizational representatives and introduced the new representatives: Dr. Steven Ralston, M.D., M.P.H. from the American College of Obstetricians and Gynecologists, Dr. Georgianne Arnold, Ph.D. from the Society for Inherited Metabolic Disorders, and Lt. Jacob Hogue, M.D. from the Department of Defense.

The next meeting will be November 7-8, 2019. All the meeting dates have been set up through 2023 and can be found on the Committee's website.

## II. Improving Detection of Newborns at Risk for Homocystinuria and Congenital Adrenal Hyperplasia

***Carla Cuthbert, Ph.D.***
Ex-Officio Member
Chief, Newborn Screening and Molecular Biology Branch
Division of Laboratory Sciences
Centers for Disease Control & Prevention

The Newborn Screening and Molecular Biology Branch (NSMBB) works on developing methods to detect newborn screening conditions, creates quality assurance materials, evaluates current or new screening methods, provides technical assistance, and offers education and training. Biochemists and molecular biologists are currently working on developing screening methodologies to improve newborn screening for congenital adrenal hyperplasia (CAH) and homocystinuria (HCY). The inclusion of additional biomarkers could allow for the second-tier testing for HCY or CAH. Currently the NCMBB is developing four different approaches to enhance detection of HCY and CAH in newborns. The first method is a second-tier test using reverse phase liquid chromatography to evaluate various biomarkers for homocystinuria, methylmalonic acidemia, propionic acidemia, GAMT, and MSUD. The second method is a second-tier test using reverse phase liquid chromatography to assess a steroid panel for CAH. The third method is a Universal NBS Panel, which is a second-tier screening test that expands on the biomarkers used by separating out amino acids, acylcarnitine, LPCS, organic acids, and steroids The

fourth method includes both a first- and second-tier biomarkers on a single platform using an ultra-high throughput mass spectrometry approach. A more in-depth presentation on these methods can be provided at a future meeting.

In addition to developing and testing methodologies, NCMBB provides financial and technical support to state newborn screening programs to enhance existing screening methods and implement screening methods for conditions added to the Recommended Uniform Screen Panel (RUSP). The NSMBB also hosts a MS/MS training course once a year for 10 to 12 trainees; approximately 30 applicants apply each year. The training is a combination of classroom sessions and hands-on laboratory components. CDC worked with Minnesota on a molecular approach to enhance detection of CAH in newborns to address the number of false positive and false negative results. To increase sensitivity, while maintaining specificity, the 17-hydroxy progesterone cutoffs were reduced and a second-tier molecular test was added. Over a period of one-year, 72,000 samples were tested. The new screening algorithm identified the known true positive case and two cases missed by previous assay. The CDC anticipates more state/federal/academic collaborations moving forward.

## A. Discussion

- A Committee member asked if you put isoleucine on a first-tier screening would you potentially not need a leucine isoleucine? The presenter responded that that is correct, as allo-isoleucine is the biomarker you want to look at for maple syrup urine disease.
- Another Committee member asked in terms of assays ability to be very specific, if there were any potential barriers with states and programs being able to combine assays with readily available commercial or FDA-cleared assays running as a first tier and are vendors looking at bringing on a second-tier commercial tests? The presenter stated that one of the reasons the NSMBB wants to publish testing methods is so vendors can see the methods and choose. In terms of anyone doing this, the answer is no. As we look to the future of newborn screening, we need to consider ways to combine these markers and identify markers that are more relevant. Implementing new screening methods is difficult, so CDC works with the states to make sure these efforts can result in the best outcomes for the states.
- A Committee member stated the study on molecular testing for CAH reflects that 70 of the 72,000 samples were identified with at least two variants and there were only three true positives within that 70. This may reflect our need to learn more about this gene, the variants, and their pathogenicity. Are there plans in the works to define that molecular analysis to make it more robust? The presenter responded yes, in one case there were many variants on one allele and one chromosome. Finding a variant or two does not mean that person is at risk for this disease so it will require a lot of thought on how it is done.
- An organizational representative asked if there was any interest in opening this to genes for low methionine homocystinuria like cobalamin disorders? The presenter responded that yes, the ability to detect low levels will be improved and thus the cutoffs could be lowered. The organizational representative followed up by asking if the lower cutoffs with DNA testing would be something they would work on. The presenter responded yes, these are the types of things they are thinking about but everything is dependent on resources.
- Another organizational representative asked if there has been a comparison of the two CAH second-tier assays, the molecular versus the LC-MS/MS, and how they fared? The presenter deferred to Amy Gaviglio who worked on the study in Minnesota, who answered that they did look at performance between the two methods. The carrier frequency was 1 in 13, which was higher than expected. You do see a shift from finding the most false positives in the low birth

weight NICU population to finding the single variants primarily in the well-baby population given that their 17OHP in the NICU is not because of CAH.

- A Committee member asked a fellow Committee member to say something about the pseudo-allele and how that impacts detection for CAH. The answer was that the assay takes care of it. The gene is in an exceedingly complex region, so it causes a host of issues, which is why a multistep assay is needed.
- A Committee member asked the presenter if they foresee any differences in utilization and implementation in these newer methods between one-screen and two-screen states? The presenter was unsure and indicated they would need to partner with one-screen and two-screen as they develop these methods to determine that.

# III. Public Comments – Condition Nomination and Evidence Review Process

## A. Margaret McGlynn, Homocystinuria Network America

Ms. McGlynn is the co-founder and President of the Board of Homocystinuria Network America and is following up on comments she made during the April Committee meeting. She believes the best solution is to enable first-tier screening of homocysteine and ongoing screenings past the newborn stage to detect older children and adults who may not have elevated levels at birth. She urges the Committee to consider a two-tiered screening approach. She has provided contact information for three experts who are willing to provide more information to the Committee.

## B. Joseph Schneider, M.D., University of Texas Southwestern Medical Center

Dr. Schneider is a practicing pediatrician in the Newborn Nursery of Parkland Hospital at University of Texas Southwestern. Dr. Schneider urged the Committee to consider three things: 1) create a learning healthcare system starting with newborn screening patients; 2) standardize data collection, reporting and analytics nationally so it can be done more efficiently; and 3) get patients and parents involved and provide them with affordable and easy to use tools. He hopes the committee will create a vision of the future of newborn screening that includes these points.

## C. Heidi Wallis, Association for Creatine Deficiencies

Ms. Wallis serves as Vice President of the Association for Creatine Deficiencies and is a parent and advocate for children affected by GAMT deficiency. She stressed that the best outcomes are only when a child receives treatment soon after birth. Ms. Wallis' daughter was diagnosed with GAMT when she was five and at 16 she is intellectually disabled. However, her son was diagnosed and treated since birth and is a healthy 7-year-old. Ms. Wallis wants to shed light on the seriousness of the Committee's decisions and asked the Committee to consider removing the requirement of one perspective find from the requirement for a disorder to be moved forward.

# IV. RUSP Condition Nomination and Evidence Review Process

## A. Approach and Timeline

***Cynthia M. Powell, M.D., M.S., FACMG, FAAP***
Committee 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 provided a recap of discussions at the April meeting and reminded the Committee of the four areas of the review: nomination, systematic evidence-based review, the decision matrix, and review of the current conditions on the RUSP. Dr. Powell asked the Committee to focus discussion at this meeting on cost assessment, population-level modeling, assessment of the public health system, and assessing the values within the evidence review process. In November, the plan is for the Committee to discuss the decision-making process. Then, in February of next year, the Committee will review the nomination process.

## B. Analysis of Committee Procedures:

***Alex R. Kemper, M.D., M.P.H., M.S.***
Lead, Evidence-based Reviews
Division Chief, Ambulatory Pediatrics, Nationwide Children's Hospital
Professor of Pediatrics, Ohio State University College of Medicine

Dr. Kemper provided an overview of the upcoming presentations focused on the systematic evidence-based process used to inform the Committee about conditions nominated for addition to the RUSP. He introduced the presenters and the topics they would cover: Dr. Lisa Prosser will discuss modeling, Mr. Jelili Ojodu will discuss the Public Health System Impact (PHSI) assessment, and Dr. Scott Grosse will discuss the cost analysis. Currently, there are three components in the decision-making process: the evaluation of evidence for clinical effectiveness and net benefit, the public health impact assessment that looks at newborn screening programs in terms of feasibility and readiness, and the cost of expanding newborn screening. Dr. Kemper recapped previous discussions on streamlining case definition, establishing clear health outcomes, clarifying treatments, either pharmaceutical or non-pharmaceutical, and making sure interventions are identified early enough within the process to be evaluated within the appraisal process.

## C. Population-Level Decision Modeling

***Lisa A. Prosser, Ph.D., M.S.***
Director, Child Health Evaluation and Research Center
Professor, University of Michigan
Adjunct Professor, Harvard School of Public Health

In 2011, numerous nominated conditions lacked sufficient evidence to move forward, so other methodologies were evaluated that could be incorporated into the evidence review process to develop broader knowledge on these conditions. This prompted the decision to incorporate decision analytic

modeling, also referred to as decision modeling or simulation modeling, which is a systematic approach to decision making under conditions of uncertainty. This approach can simulate randomized controlled trials for new interventions, project beyond trial timeframes, or compare treatment protocols that are not compared in head-to-head trials. It can also characterize uncertainties of long-term outcomes or data gaps.

An evaluation of all the available evidence with the goal of identifying alternatives or strategies to yield the most public health benefit is summarized into a report that is provided to the Committee. For example, decision analytic modeling has estimated the range of health outcomes (e.g. number of deaths averted or number of cases of ventilator dependence avoided) expected for conditions when detected through universal newborn screening compared to clinical detection.

Evaluation of the conditions since 2011 have included decision analytic model, which is done collaboratively with a panel of technical expert and Committee members that are a part of the Evidence Review Group. Developments for these models include its structure of the model, the input parameters, what the key outcomes are, and the assumptions from available literature or expert recommendations starting with a very complex model that is reduced to reflect the available evidence. This is used to project population-level health outcomes and to identify what that range is given the best available evidence.

Within the context of the evidence review process, there were issues raised by the expert advisory panel (EAP) on the understanding of availability and type of evidence on conditions before evidence review, the scarcity of published literature, and having a systematic method for including and assessing unpublished evidence. Some conditions nominated for the RUSP have had a lower evidence base at the time of nomination. This has prompted a discussion on what the criteria would be to determine if the evidence available is sufficient to conduct modeling. It is difficult to define specific criteria due to the variability of types of evidence. Should there be an insufficient amount of evidence a conversation on foregoing modeling would then be needed.

## D. Public Health System Impact (PHSI) Assessment

***Jelili Ojodu, M.P.H.***
Director, Newborn Screening and Genetics
Project Director, NewSTEPs
Association of Public Health Laboratories

Dr. Ojodu explained that the purpose of the Public Health System Impact (PHSI) is to inform the Committee, stakeholders, and advocacy groups about challenges, and other kinds of implementation barriers facing states when adding new conditions as well as describing the overall feasibility, and costs of adding a new condition. This begins with gathering all the available information regarding testing, implementation, and treatment to create informational fact sheets for states.

The process of gathering this information for the PHSI begins with gathering information from early adopter states that are already screening for a given condition. Online surveys are distributed to all of the state newborn screening programs to get a sense of feasibility of implementation. This process takes about four to six weeks. An in-depth review of early adopters' processes is done in order to have a full understanding of their newborn screening system. All information is then anonymously provided to every program.

During the February EAP meeting, the following concerns were raised concerning the PHSI: lack of communication to the Committee regarding the difficulties of new condition implementation, lack of consideration of the increased burden on providers for true positives and false positives, concern of the type of respondents for questions on specialist availability, uniform long-term follow-up plans for each condition, and uncertainty of how the Committee weights the survey data during the decision-making process. Limitations concerning hypothetical survey questions, OMB survey approval process, and funding pose challenges to address potential issues raised by the EAP. A new resource is the NewSTEPs Readiness Tool, which captures information about states overall readiness to expand newborn screening. Moving forward it is very important to understand the challenges and opportunities that face state newborn screening programs and how long it may take for them to add new conditions.

## E. Cost Assessments

***Scott Grosse, Ph.D.***
Research Economist
National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention

A Cost Assessment Workgroup met and came up with recommendations for an approach to cost assessment in the context of newborn screening. The tool that was developed asks states that have started screening, or are about to screen one of the proposed conditions, to come up with costs for staff time, equipment, reagents and other disposables, and facility overhead and space. The information from those states is then pulled and reported with a focus on the direct costs of screening and confirmatory testing.

There are many challenges when estimating cost. Estimates are projected costs and not the actual costs, so the costs may be substantially lower than what states calculate. Additionally, other cost components may be needed, or cost assumptions are made, such as administrative costs, short-term follow-up costs, equipment costs, or laboratory costs. Costs can also widely vary if it is multiplex or a standalone test, which may also have a short shelf life due to changes in technology. These factors cause difficulties when trying to standardize estimates state to state.

Dr. Grosse asked a number of hypothetical questions, which may be useful when getting feedback from the state programs. An issue raised by the EAP is the concern of cost estimates needing to be both internally valid and generalizable across states. Another issue is the question of which costs are the most important and how do we measure these costs, keeping in mind that some important costs cannot be measured. Additionally, follow-up costs such as quality control, contractual issues, support levels from NIH or sponsors, as well as staff and monitoring need to be included as cost assessments.

Dr. Grosse provided the following potential solutions and recommendations: create a consistent cost assessment tool; request that pilot studies funded by HHS agencies report costs using common data elements; collect all data from screening programs; and for that data to be analyzed to create a cost function that varies based on annual numbers of births in the state, number of screenings per infant, and the number of tests by screening laboratories. He also recommends that the cost assessment be broadened in scope

## F. Discussion

***Cynthia M. Powell, M.D., M.S., FACMG, FAAP***
Committee 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 moderated the discussion:

- A Committee member asked in what circumstances would modeling not be possible and how would that affect the information provided to the Committee to make a decision. Dr. Prosser stated that this circumstance has not happened. However, it has been discussed that if there is a time frame or sample size for which modeling is not possible, it would come back to the Committee to discuss whether a nomination can proceed.
- A Committee member commented that suggesting that implementing a disorder will only cost $3 a sample is not taking into consideration the whole system. The Committee member went on to ask if information gathered from the Readiness Tool could be combined with the impact assessment? To preface the response, Dr. Kemper wanted to be clear on what is seen as a decision versus a data-gathering point. To answer the question, Mr. Ojodu agreed that there can be a partial combination of some of the information collected using the PHSI surveys.
- The same Committee member asked if it was possible to bring in genetic counselors, SIMD, or other groups to help gauge the impact on stakeholders. An organizational representative responded that absolutely, that is something we need to be doing.
- A Committee member stated that it was mentioned in a presentation that therapy and follow-up costs should be added to considerations, which has not been previously done. Dr. Grosse clarified that the EAP members suggested it be included. It is not feasible to include within the present process.
- An organizational representative asked if adding a condition under less than ideal circumstances has been considered and if that could provide a sense of timing for the addition of new conditions. Mr. Ojudu responded that he likes the idea of making sure a number of subspecialty groups are able to provide more information on the system impact, but it is important to consider how that information is used to make a final decision.
- An organizational representative commented that they like the idea of using the organizational representatives to gather information from their perspectives, as it would be very helpful to have the broader perspective represented.
- An organizational representative asked about the recommendation to include standard pre-specified outcomes along with the condition specific. Have those been defined yet or will those be defined? Dr. Kemper responded that it is surprisingly straightforward to figure out the ones that we should pre-specify across all the conditions as it is about survival. If there was a good measure of survival and a need for mechanical ventilation and neuro or cognitive development, it would be great to have quality of life measures.
- An Organizational representative stated, in regard to qualitative representation of cost, that if instead of pre-specifying qualitative categories to think about it as a confidence interval, you could say it is between $0.50 and $2.35.When there is a contractual requirement and you are not allowed to provide the cost, that may be exactly the kind of disclosure the company would want. A Committee member suggested that it is more an issue of confidentiality [vs. being

proprietary]. Dr. Grosse mentioned that the entire U.S. healthcare system has a lack of price transparency. Another Committee member mentioned that there are circumstances when proprietary information cannot be held back. Dr. Comeau noted that there are a variety of contractual kinds of things that have begun to be addressed. She asked what a state might expect to get back from contributing granular data and if the granular data is going to drive companies to offer the same price for a particular reagent. Mr. Ojodu responded that what Dr. Comeau suggested is something that has begun to be incorporated into the information that is being collected relating to costs.

## G. Stakeholder Values in Decision-Making

***Alex R. Kemper, M.D., M.P.H., M.S.***
Lead, Evidence-based Reviews
Division Chief, Ambulatory Pediatrics, Nationwide Children's Hospital
Professor of Pediatrics, Ohio State University College of Medicine

Dr. Kemper began by stating how challenging it is to discuss the topic of values. He explained the three notions within the Evidence Review Processes and the challenges they present during decision-making. The first being the notion of competing options. The option to either add a condition to the RUSP, to test for a particular condition, or deciding to not include the condition as there can be alternative strategies for newborn screenings. However, as the decision is being made within public health programs, it affects individuals and their families.

The second notion involves characterization of the various outcomes of newborn screenings. This includes the immediate number of positives or negatives and how many of those turn out to be true-positives or false-positives, as well as the individual level of health impact, and the impact on newborn screening systems. This presents challenges concerning the variation of benefits and harms across the population and the knowledge of those benefits and harms being available at different times. There is also the challenge of equality—ensuring everyone has access to newborn screening—along with decisional regret regarding what could have been done instead.

Finally, the third notion being uncertainty outlined during the Evidence Review Process. For example, there are ranges of accuracy within screenings and gaps within pilot studies, however, discussions focus on the gaps within that evidence. There are often significant challenges due to the fast pace in which advances within screenings and treatments are being introduced, paired with insufficient evidence on their benefits or harms. However, by implementing more pilot screening or broader screenings, this may resolve some of the uncertainty.

Dr. Kemper then read a quote about values from the guidelines GRADE and explained how they focus on patients' perspectives and individual clinical decision-making as opposed to public health. GRADE does a lot of what the Committee does, such as looking at the magnitude of estimates on important health outcomes and the confidence in those estimates. However, it also considers estimates of typical values and preferences and the confidence in those estimates, the variability of values and preferences, and resource use.

We need to think about values in terms of perspective, whose values do we value and how are the values we are interested in determined. Are we enabled within the process to understand the values of stakeholders? There also needs to be an understanding of the variability of those values and what

drives them so that it can be incorporated within the context of what is done as part of the Evidence Review Process.

Dr. Kemper then presented the concept of a Quality-Adjusted Life Year with a reference of one Quality-Adjusted Life Year equated to living one year in perfect health. Quality-Adjusted Life Years is a standardized measurement of health outcomes that can facilitate comparisons across health conditions and populations. It is calculated as a function of time and utility, with utility ranging from zero (death) to one (perfect health). Some of the strategies to measure this concept are time trade-offs, standard gambles, visual analog scales, and the use of conversions from other quality-of-life instruments can also be used. Beyond the challenge of variability, there is the challenge of figuring out utilities. To do so, there needs to be a full understanding of the health condition, awareness of the perspective, as well as consideration of any contextual factors.

An alternative method of discovering utility is through the use of a citizens' jury which is the selection of up to 20 people to form a group which represents the public, much like a Grand Jury or focus group. The citizens' jury is provided with an extensive amount of information and substantial time to deliberate and produce a range of values or what their thoughts are. Another alternative method involves issuing public surveys. This is more feasible on a national level and they provide that ability to assess preferences using sophisticated approaches, much like those use in marketing strategies.

Dr. Kemper introduced a study by Dr. Tarini and Dr. Prosser that was done on adults which asked them about characteristics related to newborn screening and what they think is important. Dr. Prosser stated that one of the conclusions from this process was the extreme amount of difficulty there is to frame survey questions in a way that the public could answer in a reasonable manner and that the survey really did not work well. Additionally, it was concluded that a citizens' jury approach for newborn screening would a better approach to the extreme complexity of the process.

Dr. Kemper presented a multi-criteria decision analysis method called EVIDEM. This method determines the value of an intervention by the need for the intervention, its comparative outcomes and economic consequences, the knowledge about the intervention, and then by the population's priorities. This is done in a way to ensure systematic thinking of all the considerable components, such as the alignment of priorities, environmental sustainability, system capacity, and the political, historical, and cultural context. EVIDEM also provides a framework for explaining the various values of the intervention which are the need for intervention, the comparative outcomes, what the types of benefits are, any economic consequences both medical and nonmedical, the knowledge about the intervention including the degree of evidence and expert consensus, and finally does it have a scoring system that has been adapted for rare diseases. Applications of EVIDEM can be provided for both therapeutic interventions and preventative interventions.

## H. Discussion

Dr. Powell moderated the discussion:

- A Committee member asked if a citizens' jury would include people who have some familiarity with the condition or people who have no familiarity with newborn screening or the condition. The presenter was not sure but believes they are supposed to be broadly representative. A Committee member responded that ideally it would incorporate both the patient and family perspective as well as the public perspective to enhance the process while another Committee

member stated the possibility of two citizens' juries, which could provide some interesting crosstalk among those groups.

- A Committee member reminded members of the Committee that the Iowa Newborn Screening Program held a citizen jury about their newborn screening program that was led by Kim Piper and Dr. Michelle Gornick.
- A Committee member commented that it is great to discuss ways to incorporate the public perspective with the perspective of those who are affected by conditions, but those tend to be lumped into public or advocacy groups, but there may be others out of that context.
- A Committee member wanted to discuss the meaning of assessing value and the decision-making process in a mandatory program as the concept of decision-making is that there is a decision to be made and what that means in this context. Another Committee member responded that an important point that came up during the EAP meeting was that patient/family preference and public preference groups were not being included. The presenter followed up by stating that the decision ultimately is whether or not conditions are added to state newborn screening programs, and not at the individual level, which is why it is important to assess values and preferences and incorporate it into the process.
- A Committee member asked what it would mean to bring all values and preferences as a part of a report versus the Committee being in a position to make a decision and consider stakeholders directly speaking with us. The presenter's response was that the notion of assessing values was to be able to reach beyond a group of individuals to make sure there is a holistic assessment of values and preferences. A different Committee member responded that adding values and preferences would move from individual experiences to a group perspective. There was a discussion on if there is a way to systematize and better reflect that group perspective for the Committee.
- A Committee member mentioned the possibility of doing a citizens' jury in one state while looking at different methods in other states. The Committee member also mentioned the option of focus groups for assessing how different audiences will respond. The perspectives among families who are impacted by conditions is important. Trying a to equalize this perspective that of the general population may impact the utility of the information. A Committee member noted that the intention is to make sure there is a more complete representation of the perspective of patient and families integrated into the assessment process.
- A Committee member mentioned a quick note about the amount of time and energy that Baby's First Test and other resources have put into providing an understanding of newborn screening to the general public and that there is still relevant data that is not condition specific that we can draw from.
- An organizational representative posed that if there is early detection, it does not necessarily change the outcome but on the other hand, if you diagnose somebody in the pre-clinical phase, the harms of early detection are very real, as simple as losing good quality of life years worrying. So how do we create understanding for individuals within the citizens' jury on the harms of early detection and include that in our value matrix when it comes to these situations where there is a question about the value of early detection. A Committee member stated she has facilitated a citizens' jury where it was done very carefully through a series of lectures, as well as question and answer sessions, which touched on all of the issues. A different Committee member noted that the advantage of having a citizens' jury in this context would be the ability to educate over time as opposed to a one-time focus group. A third Committee member stated that if done well, some of these complex issues can be communicated in a way the public can understand.

- A Committee member wanted to remind the Committee that when we say public at this meeting, many of us think of advocacy groups and when we say public in a citizens' jury we mean the general public.
- An organizational representative wanted to follow up on the comment based on their experience running some like a citizens' jury, that approval often goes down as individuals learn more.
- An organizational representative asked if there is a potential role for information that, when using one of these approaches, we could find out where the pinpoints are or what are the criteria by which individuals judge things as opposed to every nuance of every condition that may come up. The response from a Committee member was that the disorders were aggregated as best as they could be and the types of disorders we knew of and could imagine as well as the treatment and everything into various attributes.
- A Committee member asked at what extent do we let public view affect a decision in terms of what weight does it carry and how do we decide that weight? There is evidence that hypothetical situations can be very different in comparison to real situations and the responses we get are neutral responses. Another Committee member answered that she does not know that it is really a qualitative study because it is not hypothesis generating.

# V. Administrative Business — August 2, 2019

## A. Welcome and Roll Call

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

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

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

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

- Dr. Mei Baker
- Dr. Susan Berry
- Dr. Kyle Brothers
- Dr. Jane DeLuca
- Dr. Carla Cuthbert (Centers for Disease Control and Prevention)
- Dr. Kellie Kelm (Food and Drug Administration)
- Dr. Michael Warren (Health Resources and Services Administration)
- Dr. Cynthia Powell
- Dr. Melissa Parisi (National Institutes of Health)

- Ms. Annamarie Saarinen (webcast)
- Dr. Scott Shone (webcast)
- 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 (webcast)
- American College of Medical Genetics & Genomics, Dr. Michael Watson
- Association of Maternal & Child Health Programs, Dr. Jed Miller
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health Officials, Dr. Christopher Kus (webcast)
- Child Neurology Society, Dr. Jennifer Kwon
- Department of Defense, Ms. Theresa Hart
- Genetic Alliance, Ms. Natasha Bonhomme
- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Ms. Amy Gaviglio
- Society for Inherited Metabolic Disorders, Dr. Georgianne Arnold

# VI. International Rare Disease Consortium (IRDiRC)

***Anne R. Pariser, M.D.***
Director, Office of Rare Diseases Research
National Center for Advancing Translational Sciences
National Institutes of Health

The purpose of IRDiRC was to promote international collaboration and advanced rare diseases research worldwide. IRDiRC was international from the beginning because the very first meeting included members from Europe, North America, Asia, Australia, and the Middle East. The initial focus was on developing common scientific and policy frameworks that could be recognized and disseminated to the individual members to try to promote collaborative and efficient approaches. IRDiRC's vision is to enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention. The overarching goal was very ambitious, so it was divided into three goals. The first goal is that patients receive a diagnosis within 1 year if the disorder is known. If it is not known, undiagnosed individuals are entered into a globally coordinated diagnostic pipeline. The second goal is to develop 1,000 new therapies for rare diseases, and the third goal is to develop methodologies to assess the impacts of the diagnosis and the therapy.

To achieve these goals, IRDiRC developed a roadmap to break it down into individual pieces, stand up committees, and at times taskforces. They identified the top priorities and consolidating them into an organized plan and then distributed that plan internationally. IRDiRC does not have regulatory power in any particular area of the world, however what they do provide is guidance and recommendations that can then be adopted by the individual member organizations for their own research programs or priorities. Member organizations are responsible for enacting this using their own funding. For rare diseases the key priority areas that they focus on are things like ontologies, diagnostics, biomarkers, registries, and natural history studies.

There are three constituent committees including the funders, patient advocates, and companies. Their job is to: identify roadblocks or priorities; implement task forces and activities to address priorities; establish and promulgate best practices, operating procedures, quality standards, and the roadmap to address priorities; inform other committees of scientific and programmatic states, needs, opportunities, and emerging issues. Task forces are used to tackle specific topics of importance. For example, the diagnostics scientific committee worked on "solving the unsolved", clinical data sharing, carrier screening, and underrepresented populations.

IRDiRC developed a website of IRDiRC-recognized resources to look for the best practices and models that are of good quality and has the potential utility to a lot of members. These resources are posted on the website in an effort to try to disseminate what has already been developed so that people can leverage and use these resources. There are currently 22 IRDiRC recognized resources and a broad range of categories, like guidelines, databases, and tools. What they are trying to do is not just introduce efficiency into the process and improve a little bit on what we are doing now, but to truly transform the research environment for rare diseases. The goal is reaching this very ambitious vision by 2027, but also to improve the research and the lives of patients with rare diseases.

## A. Discussion

Dr. Powell moderated the discussion:

- A Committee member asked about therapeutics and how things that are not medications fit into the effort, if at all. The presenter's response was that IRDiRC mainly focuses on therapeutics, drugs, biologics, or devices and not as much on patient care, physical therapy, dietary modifications, or educational interventions. Most of the efforts focus on the cross-border collaborations but the topic would fall under the patient constituent committee.
- A Committee member asked if there are opportunities to partner in the newborn screening space that we have not considered. The presenter responded that the diagnostic committee has been looking at cross-border study, early diagnosis, and registries. The presenter urged the Committee member to contact Gareth, who is interested in the topic.
- A Committee member asked if the presenter could comment on how they collect data and the terms for the duration and unified ID. The presenter responded that IRDiRC itself is not collecting any of the data. Data collection falls to the members and regional authorities. It is more about trying to come up with best practices or even awareness that these tools and repositories exist and then encourage collaboration to increase interaction and access to data that may already be there.
- A Committee member asked in terms of your goal of individuals receiving a diagnosis in a year if the disorder is known, could you talk a little bit about how you are approaching that, both in the US, as well as what is being done internationally? The presenter responded by saying they are seeing just a lot of new drugs and breakthroughs and targets to aim at in understanding the molecular underpinning. Diagnosis has been a challenge and we have not really seen as much movement in that area. It is a goal, but we are not there yet.
- A Committee member asked if doing something like journey mapping with patients and patient groups was considered? The presenter responded that they are looking into a number of ways to gather this information. It is becoming more accessible to do journey mapping, but trying to get a good look at one patient's journey is difficult. This is a real growth area. We do not have the magic formula yet, but we are working on it.

- A Committee member mentioned that genomic sequencing is certainly a way to determine a diagnosis in some cases, but many insurance companies are not covering genomic sequencing. Ae there any efforts under way to promote coverage? The presenter responded saying it is getting easier now to make a case to an insurance company to go to a quicker genomic analysis, but it is not perfect. There are some academic centers that have looked at this in high-risk populations.
- A Committee member wondered what the growth is like of recruiting additional rare disease organizations; the barriers to getting genomic diagnostic testing are quite substantial. One way to even the playing field might be to shine a light on how easy or difficult it may be in different systems to get this testing done. The presenter responded if anybody is interested in joining and devoting their time, we are usually very glad to have you. It is hard to find the patients because they are often silent and these databases are hard to find.
- A Committee member asked is there any real effort to correlate or to collect some of this information that those of us just in the trenches, just getting all of the information that we end up finding and we are the ones who have the phenotypes, not anybody else. The presenter responded with there are disease specific registries and natural history studies that almost always collect genomic information in this day and age.

# VII. Implementation of RUSP Conditions Report

***Alex R. Kemper, M.D., M.P.H., M.S.***
Lead, Evidence-based Reviews
Division Chief, Ambulatory Pediatrics, Nationwide Children's Hospital
Professor of Pediatrics, Ohio State University College of Medicine

This presentation focuses on a review of the implementation conditions that were added to the RUSP between 2010-2017, and the development of methods to evaluate screening implementation and outcomes after addition to RUSP. Dr. Kemper and his team are looking at SCIDs, CCHD, Pompe disease, MPS1, and X-linked adrenoleukodystrophy to review what has happened since they were added to the RUSP. They are focusing on state implementation, public health implications, and clinical outcomes and impacts. Their guiding issues include condition specific factors and the newborn screening program.

Severe Combined Immune Deficiency (SCID), which was initially evaluated in September of 2007, was added to the RUSP in May 2010. The challenges with implementing SCID was that it was the first use of molecular testing for first-tier screening, there were variations in targets of screening, preterm infants had a high retest rate compared to full-term infants, and there was variation in incidence by race/ethnicity. However, there were many facilitators to implementing SCID screening including: collaborations and partnerships established among federal, state, nonprofit organizations, national technical assistance activities, SCID newborn screening pilots, and commercially available kits that were relatively straightforward to use and ensured uniformity. They were able to implement SCID within less than a year.

Originally nominated in 2010, CCHD was added to the RUSP in September 2011. The average time to implement CCHD newborn screening after it was added to the RUSP was 2.6 years. Some of the challenges of implementing CCHD screening included: point-of-care test, variability in approach to requiring the screening, decentralization in hospitals, birthing centers, homes, variable reporting requirements, and in screening algorithms, as well as special settings like high altitudes and NICU's.

However, some facilitators of implementing CCHD screening include the development of educational material, use of birth defect registries, and telemedicine.

Pompe disease was initially nominated in 2006 and nominated again in 2012. It was added to the RUSP in March of 2015. The average time to implement Pompe screening was a little over two years in states that have begun screening. MPS1 was nominated in May of 2012 and added to the RUSP in February 2016. The average time for implementation has been about 1.6 years in states that have begun screening. The challenges of implementing Pompe disease and MPSI screening include: commercial testing kits are labor and time intensive, reference testing samples are challenging to obtain, pseudodeficiency occurs, diagnostic uncertainty occurs, and identification of late-onset forms causes problems. Facilitators to implementing Pompe and MPS1 screening includes the ability of LSD's to be multiplexed, second-tier biochemical tests and post-analytical tools can reduce false positives, pilot studies to determine cut-offs, and registry databases with mutations and expected clinical characters.

X-linked adrenoleukodystrophy (X-ALD) was nominated in 2012 and added to the RUSP in February 2016. The challenge of implementing X-ALD screening includes: delays in FDA approval for commercially available reagents and discontinuation of LC-MS/MS columns impeded screening optimization and implementation, diagnostic challenges, long-term follow-up, cascade testing, and higher incidence than expected. Facilitators to implementing X-ALD screening include: adjustments to follow-up algorithm to expedite confirmatory testing by immediately referring screen positives to genetic counselors and specialists, potential for multiplexing with Pompe disease and MPSI, and registry databases.

Common challenges to new disorder implementation are hiring and training new personnel, delays in procurement and installation of equipment, updating laboratory information management systems, lack of shared genomic variant databases, and developing follow-up programs and clinical management plans for infants with late-onset or unknown disease risk. Common facilitators are peer research networks, pilot and/or implementation funding, working group for newborn screening and clinical follow-up and management, especially for disorders with later-onset forms, next-generation sequencing for second-tier testing, and common legislative approaches.

Next step in the review process is interviewing newborn screening programs at the state level regarding issues of implementation, and specifically looking at early adopters and late adopters to understand how things came about.

## A. Discussion

Dr. Powell moderated the discussion:

- A Committee member mentioned the studies seemed to be pilots and health systems, small groups as you alluded to, biased populations. Is that your sense when you look at this data? The presenter responded with yes there are variables, more state level data in terms of reporting out the number of positives and the diagnostic workup.
- A Committee member asked is there a way to leverage the infrastructure we have with APHL to help the programs. The presenter responded that a great deal of thought has gone into what the expectation should be from the program when they accept funding in terms of sharing their experience, but asked Mr. Ojodu to talk about what NewSTEPs can access. Mr. Ojodu said when funds are provided to states for implementation of any one of the new conditions; one of the things they try to stipulate is that data are provided back to them.

- A Committee member asked if there could be a mechanism for this Committee to review that data as a peer review first step. Mr. Ojodu said he does not think so because the data are still being accumulated.
- A Committee member asked what can be done to support states, and is there a sense of weighting the challenges? The presenter responded by saying that is something that they hope to get to with the newborn screening program interviews.
- The same Committee member had a follow up question regarding funds; are general state funds being used? Are they putting it into the payer's hands? The presenter thought this was good idea, and said it could be set up, but it is not something he had previously considered.
- A Committee member inquired what metrics may be useful for assessing the actual value, and efficiency of screening attempts. The presenter mentioned that one of the problems when you look at the results of the screening studies is that people use language a little bit differently, so when you look at the data it becomes very difficult to understand what the overall impact was.
- A Committee member asked the presenter to explain a little bit more about the challenges with ELISA 199 screening, when you have less variation by race. The presenter responded that they were alluding to the fact that there are variation by subpopulation.
- A Committee member asked if the presenter had any thoughts about the requirement that the state actually implement the screening within a prescribed timeframe and whether that is a barrier to participation. The presenter said that newborn screening programs continue to refine their processes. That is actually why it is so hard to talk about outcomes in screening programs. In terms of the funding requirements for when to begin screening, that is a question for the funders.
- An organizational representative asked if there will be work done to ask about the impact on not only the medical system of having all these pseudo deficiencies and all these carriers, but also on the public health programs and the time it takes to call that out? The presenter responded with 100% yes.

# VIII. Linking Data Resources: Interoperability for Newborn Screening Programs

***Ashleigh Ragsdale, M.P.H.***
Newborn Screening Epidemiologist
Office of Newborn Screening
Washington State Department of Health

Ms. Ragsdale defined the terms being used, interoperability and interfacing, and offered a comparison between the terms. In some ways, interoperability is already incorporated within newborn screening programs in terms of Laboratory Management System (LIMS) interfacing with Case Management Systems (CMS). However, this can be expanded due to the number of stakeholders involved in newborn screening programs as well as the public health system.

Some of areas that could benefit from the use of interoperability through databases include: specimen tracking, electronic order and reporting (ETOR), hearing and CCHD screenings, record and birth defect registries, long-term follow-up (LTFU), pediatric specialists, as well as immunizations. These databases can then be provided to the professionals involved like doctors, laboratorians, and other providers in order to reach the best outcomes for patients.

One of the goals of newborn screening is to make sure every baby gets screened which is difficult for states to track. By linking vital records and birth records you could identify babies that have been missed and provide them with the screening. This will also provide a more accurate denominator of the babies born within program statistics and analysis for quality improvement and to better understand how the programs are functioning which can provide the ability to see what is being done state-wide.

Having interoperability within birth defect registries can lead to quicker data on outcomes, identify CCHD cases that were missed by pulse ox screening, as well as analyze the CCHD cases that were unreported. Electronic Test Ordering and Reporting (ETOR) is the electronic process of receiving information from the hospital, sending it to the laboratory, and then sending the results back to the hospital.

Dr. Ragsdale then gave an example of an ideal state, or "Xanadu". There would be a simplified electronic HL7 message system using an Admission, Discharge, and Transfer (ADT) message. The ADT message could be utilized to track birth notifications, specimen tracking, real-time quality monitoring, and real-time patient follow-up info. It can also provide an audit of the newborn screening system to assess if it is being done correctly and efficiently. Hospitals would then only need to make one connection to an agency who then is able to distribute that data to all the programs that need it instead of each program connecting to the other programs. It would provide connections between the hospitals and state or federal partners as well as between the hospitals or the partners and a possible health information hub. All facets would be able to connect to one place. Of course, there are some barriers to interoperability, which include agency policy, the informatics infrastructure within the agencies, program prioritization and opportunity cost, having the right partners, the sources of funding, as well as a lack of trained professionals in public health informatics.

Expanded interoperability allows newborn screening to gain efficiency, redirect FTEs, increase testing accuracy, and improve patient outcomes. This can be done through encouragement of the agencies to develop interoperability priorities, developing lab level interoperability plans by working with other lab programs, pursuit of funding opportunities, and the expansion of informatics workforce through training programs or internships.

## A. Discussion

Dr. Powell moderated the discussion:

- A Committee member mentioned that if we are so busy doing and less busy focusing on the infrastructure of our house and how well we are doing, we are in some ways doing a disservice to the system and to the families. They asked the presenter to speak to their experience when they have had to navigate this issue. The presenter responded that when budgets get tight, you drop the things that you cannot afford to do anymore and focus on the ones that you can. So definitely adding new conditions has taken time away from working on other projects like data interoperability
- A Committee member asked if there has been work or are there tools available for programs to say "here's where my gaps are", and then to kind of choose their own adventure on which path of interoperability they should go to get the most return? The presenter responded saying it is an interesting concept to think about, not just in moving towards full interoperability, but also what can really provide the most benefit at this time. That could definitely be integrated in that roadmap that we have been talking about.

- A Committee member asked if anybody has made a business case about revenue loss, FTE time loss, doing these things manually as opposed to electronically. The presenter responded by saying Minnesota has been working on a return on investment for the electronic test ordering and reporting. Another Committee member commented saying at one organization, we mapped out the process of newborn screening blood spots. We wound up with about 50 different discrete steps. By implementing this sort of system, we were able to cut that by more than half. The problem is that when you compare this to diabetes and heart disease, this is the appendix of a mosquito.
- A Committee member asked how many of the states have actually dedicated resources within newborn screening programs, at the public health lab level. Does the diminishing return, does it go up and is it unrelated? The presenter responded saying that there is a lot of work being done with ASTHO and some of the broader public health agency groups on informatics. There is even a public health informatics group at APHL to help with that.
- A Committee member commented that bearing in mind you just distinguished between the need for bioinformaticists because they do a separate task, and IT specialists, would you consider there to be a separate need for a dedicated newborn screening IT specialist, or would you suggest that the response or the solution is more agency wide? The presenter responded saying, you need to have some combination of expertise at the programmatic level or at the laboratory level, and then the expertise that comes from the training that you get when you are in an informatics program. There needs to be that combination. As far as whether it is short term or long term, there is definitely a need for a short term.
- A Committee member asked, what are the specific asks that you have of your database or your linkages. The presenter responded for her program, she is looking at electronic test ordering or reporting as priority number one, birth notification as priority number two, and the moving on to that follow-up feedback loop as the next steps priority.
- A Committee member noted that research-based tools ought to be included because there may be some opportunities for things to be mutually beneficial. For example, tools like the Longitudinal Pediatric Data Resource, NBSTRN, and Global Unique Identifiers (GUIDS).
- A Committee member noted that, we cannot automatically think every entity is the same (e.g. hospitals and midwives).We need to think about alternatives and the most efficient way to do things. The presenter responded saying, there are some challenges with electronic test ordering and reporting that we are just now beginning to figure out. However, the idea is that if we could get closer and closer to that ideal state, those challenges could be solved by some work that is done with our partners.
- A Committee member asked, what is known about cooperation from electronic health vendors regarding interoperability? The presenter responded saying, if we can all agree on common data elements and hospitals can agree on a common process, and their EMR can say that if you give me this common data model, then I can do this in every single one of my hospitals, that is a more efficient way of implementing data exchange. We are trying to take a systematic approach as we move forward, which would then translate into that long-term follow-up piece as well.

# IX. Public Comments

## A. Brittany Hernandez, Policy and Advocacy for Muscular Dystrophy Association

Ms. Hernandez is the Senior Director of Policy and Advocacy for the Muscular Dystrophy Association (MDA). She provided an overview of what is being worked on in relation to advancing newborn screening for neuromuscular conditions: the launch of a new patient registry called MOVR; state implementation of conditions on the RUSP (SMA and Pompe); working towards the nomination of Duchenne; education via outreach; and external education via a published JAMA neurology article.

## B. Rebecca Abbott, March of Dimes

Ms. Abbott is the Deputy Director of Federal Affairs at the March of Dimes and leads a coalition of public health providers and patient organizations dedicated to advancing the newborn screening system at the federal level. This coalition has developed a set of principles to guide the Newborn Screening Saves Lives Reauthorization Act (H.R. 2507). The bill was introduced in the House on May 2 to renew newborn screening programs at CDC, HRSA, and NIH for five years, improve the governing statutory text of those programs, increase funding authorized for newborn screening activities at CDC and HRSA, and to extend the authorization for this Committee and its work for an additional five years. It was approved by the House on July 24 by a voice vote and the Senate version (S.2158) was introduced on July 18. It is expected to be voted on in September. Once both bills are passed and reconciled, they are confident that Congress will pass it.

# X. Ad-Hoc Workgroup – Interpreting NBS Results

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

Dr. Baker reported that the workgroup plans to submit a report to the Committee, which could also be developed into a publication. The report will be structured into three parts: 1) an introduction that will include the rationale, 2) a discussion of newborn screening and risk assessment, with an emphasis on populations screening, how the individuals may not be exactly the same as the populations, and that further testing would need to be done, and 3) a discussion and conclusion section. Additionally, the timeline was discussed as the group is trying to complete the first draft that will be discussed at the end of the month which will be circulated amongst the group for review. The draft will be ready by mid-October so it can be included in November meeting materials and presented to the Committee for feedback. The goal is to have a final draft of the report by February 2020.

### A. Discussion

Dr. Powell moderated the discussion:

- A Committee member mentioned that it is a screening test and not a diagnostic test. Negative does not mean it should not be in your differential if people have symptoms. Positive does not mean that the person has the condition. Urgent-to-treat will need to be in explained as will what needs to be done while waiting for the confirmatory test results. The presenter indicated that as a laboratory, when they issue a report they have to follow CLIA and CAP.
- A Committee member mentioned how the receiving physician is responsible for the results, not the delivering laboratory.
- A Committee member noted that the messaging about the difference between a screening and a diagnostic test has to have that nuance that sometimes you act on screening tests if it is a time-critical condition while you are waiting. And making sure the messaging is clear. The presenter and another Committee member agreed.

## XI. Follow-Up and Treatment Workgroup Update

***Christopher Kus, M.D., M.P.H.***
Co-Chair, Follow-Up and Treatment Workgroup
Associate Medical Director
Division of Family Health, New York State Department of Health

The workgroup discussed what needs to be continued for long-term follow-up once a new condition is introduced, as it should be something that is incorporated within care. The major concern is how the data is collected which is through a standardized method with the possibility of developing core outcomes as the base of that data. It is also noted that there should be thought put into financial resources needed for long-term follow-up including access to care after diagnosis. Dr. Kus also pointed out that not all heritable disorders are newborn screening related and a discussion needs to be had about children who are identified with a condition outside of newborn screening and the long-term follow up for them.

With regard to the components of the RUSP condition nomination and evidence review processes, the workgroup recommends that a blueprint for long-term follow-up that includes both patient follow-up and health outcome measures. There is a process to discern the merit of the information, taking into consideration the resources that are available about the condition in the nomination process (realizing that some conditions may have more resources than others).

# XII. 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 reported on the activities of workgroup members. Natasha Bonhomme is reviewing questions from parents about newborn screening that were submitted to their website, in order to determine trends. Sylvia Mann is involved in a HRSA family education needs assessment looking at how people prefer to have their information delivered.

Ideas for new projects were discussed, such as: a newborn screening state education program; multilingual animated videos about newborn screening; linking newborn screening education materials within electronic medical record portals; and finding a way to bridge the information gap between obstetricians and pediatricians about newborn screening.

The workgroup also discussed the RUSP evidence review process, specifically the idea of a citizen's jury. A concern was raised about whether those who would have the time to sit on a jury would be accustomed to public speaking. Also, they feel that both the public health perspective and the individual perspective need to be taken in context. Finally, they discussed underutilized data, how to evaluate effectiveness of a screening test and what to do if disorder for screening is not performing as anticipated.

# XIII. 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
Food and Drug Administration

The workgroup is working on its existing projects, the most recent of which is assessing the impact of broad phenotypes on laboratories. A presentation was provided to the workgroup by Dr. Michele Caggana on next generation sequencing (NGS) in newborn screening. In New York, prior to next generation sequencing, 94% of referred Cystic Fibrosis (CF) screenings were false positives. Initially, the genotype panel included 39 CF mutations. A two-tiered test was then implemented which sent babies in the upper 5% of IRT levels to genotyping and babies with one or two variants or a very high IRT for diagnostic testing. Now the NGS for CF uses a 338-variant panel and only babies with 2 variants move on to diagnostic testing, which has reduced the number of false positives from 900 to 100. Since 2018, New York has reduced its referrals by 83% and increased positive predictive value from 3.8% to 25.2%. Infants with CF are now promptly referred and diagnosed. NY is introducing NGS within the context of SCID screening. Initially two platforms for 39-gene NGS immunodeficiency panels were validated and currently a 55-gene panel is being used.

Following the presentation provided to the group, there was a discussion of the various topics and information gaps. The top priorities and concerns that emerged were the need to have clear case

definitions, the possibility of predetermined performance goals for screening, making newborn screening conditions reportable similar to how infectious diseases are reported to CDC, additional work on second-tier tests, and learning courses for newborn screening community such as CDC Train.

The workgroup provided feedback on components of the RUSP Condition Nomination and Evidence Review Process. There is a need for clear case definitions. It was noted that the information gathered for the Committee would also be beneficial to the states. It was suggested the Committee revisit the criterion of having one prospectively identified case through newborn screening.

Additionally, the group discussed the public health system impact assessment and feel this assessment does not capture the state of state public health labs for adding screening. This raised the question of how to get information from other stakeholders through the utilization of the organizations that provide expertise to the ACHDNC, gathering information from insurance companies, and the possibility of getting supplementary information outside of the survey process.

# XIV. Discussion: Workgroup Ideas

Dr. Powell moderated the discussion:

- An organizational representative wanted to expand the notion of having a blueprint to follow regarding long-term follow-up and treatment, should be a condition that needs to be met before a condition should be added to the RUSP. This blueprint would describe how children with that condition would receive care and what their first few years of life would look like. They also stated that during the evidence review process disparities between the conditions (in terms of the amount of resources and data) should be considered. Dr. Powell followed up by asking if that blueprint would be supplied or something the evidence review group should get. The organizational representative clarified that it should be included as conditions are nominated.

# XV. New Business

Dr. Powell opened up the floor to Committee members to discuss new business:

- Ms. Saarinen asked who the Committee staff will be to look at collating the cross-cutting portions of the three different groups, or is there somebody or a separate smaller sub-group that will work on aligning the areas that can be in order to report back on it? Dr. Powell noted that plans have not been made yet and asked Committee members to reach out if interested. Ms. Saarinen stated that she was interested.
- Dr. Brothers asked what the plan is regarding the topics discussed with Dr. Kemper on day 1 of the meeting? Dr. Powell stated that Dr. Kemper will provide additional presentations at future meetings as that is a critical question.
- Dr. Powell went on to mention that there is a number of areas that people feel to be extremely important to address that we do not seem to receive information on with current system of Evidence-Based Review and its metric. In the next meeting we will be discussing the actual metric and see what changes can be made.

- Dr. Tanksley stated that it would be helpful to hear more from the states and what they are doing so the Committee can see how it can assist.
- Dr. Parisi wondered if there might be consideration in the future of a workgroup to address issues related to interoperability and IT as there is significant challenges and opportunities regarding them.
- Dr. Parisi had a comment regarding concerns of availability of treatments for some of the conditions currently on the RUSP. She mentioned it might be a good opportunity to get the current status with regard to SMA screening and access to treatments. Ms. Scott replied with a reminder that there was a request to get a report on it once approved by the Secretary, and that is part of what the Evidence Review Group is compiling about implementation.

# XVI. Adjourn

Dr. Powell adjourned the meeting at 1:45 p.m.