Advisory Committee on Heritable Disorders in Newborns and Children

Meeting Summary
May 9-10, 2018

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) meeting was convened on May 9-10, 2018 and adjourned on May 10. 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
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Co-Director, Newborn Screening Laboratory
Wisconsin State Laboratory of Hygiene

Susan A. Berry, M.D.
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Department of Pediatrics and Genetics
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Professor and Chairman
Department of Pediatrics
Louisiana State University

Jeffrey P. Brosco, M.D., Ph.D.
Professor of Clinical Pediatrics
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Department of Pediatrics
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Annamarie Saarinen
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Scott M. Shone, Ph.D.
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Beth Tarini, M.D., M.S., FAAP
Associate Professor and Division Director
General Pediatrics & Adolescent Medicine
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Catherine A. L. Wicklund, M.S., C.G.C.
Northwestern University Feinberg School of Medicine Center for Genetic Medicine

Ex-Officio Members

Agency for Healthcare Research & Quality
Kamila B. Mistry, Ph.D., M.P.H.
Senior Advisor
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Centers for Disease Control & Prevention
Carla Cuthbert, Ph.D.
Chief, Newborn Screening and Molecular Biology Branch
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Food and Drug Administration
Kellie B. Kelm, Ph.D.
Chief, Cardio-Renal Diagnostic Devices Branch,
Office of In Vitro Diagnostic Devices Evaluation & Safety

Health Resources & Services Administration
Laura Kavanagh, MPP
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National Institutes of Health
Diana W. Bianchi, M.D.
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Designated Federal Official

Catharine Riley, Ph.D., M.P.H.
Health Resources and Services Administration
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Organizational Representatives

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

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

American College of Medical Genetics
Michael S. Watson, Ph.D., FACMG
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American College of Obstetricians & Gynecologists
Britton Rink, M.D., M.S.
Mount Carmel Health Systems

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

Association of Public Health Laboratories
Susan M. Tanksley, Ph.D.
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Christopher Kus, M.D., M.P.H.
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Department of Defense
COL Adam Kanis, M.D.
Lieutenant Colonel, Medical Corps, U.S. Army
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Department of Pediatrics, MCHK-PE Tripler

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

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

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

I. Administrative Business — May 9, 2018

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

A. Welcome and Roll Call

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

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

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

Organizational representatives in attendance were:

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

*Dr. Bocchini introduced Dr. Miller as the new organizational representative for the Association of Maternal and Child Health Programs, succeeding Kate Tullis, whom he thanked for the work she had done representing the association. Dr. Miller is on the Maryland Department of Health Maternal and

Child Health Bureau, serving as director of the Office for Genetics and People with Special Health Care Needs. Previously, he was a general pediatrician in private practice and then an environmental health advisor at the Maryland Department of the Environment.

Dr. Bocchini also mentioned that, beginning with the next ACHDNC meeting, Dr. Shawn McCandless will serve as the new organizational representative for the Society of Inherited Metabolic Disorders, succeeding Dr. Carol Greene. He thanked Dr. Greene for her many years of service on behalf of the society and the many roles she had played as an organizational representative, including her membership on the Follow-up and Treatment Workgroup and the recent report on medical foods.

B. Committee Correspondence

Dr. Bocchini reported that he sent a letter to the Secretary of HHS on behalf of the Committee to convey its recommendation that spinal muscular atrophy (SMA) be added to the Recommended Uniform Screening Panel (RUSP) due to the homozygous deletion of exon 7 in SMN1. The Department of Health and Human Services (HHS) returned an interim response indicating receipt of the letter and saying that the agency would respond within 120 days as required by the Newborn Screening Saves Lives Reauthorization Act of 2014. Both letters and the full SMA evidence review report have been posted on the Committee's website.

C. Call for Organizational Representatives

Dr. Bocchini also said that HRSA will be issuing a call for organizations to express interest in sending representatives to attend Committee meetings. He thanked those that have already submitted applications, which are under review.

D. Evidence Review Process

Dr. Bocchini announced that the Committee will establish a steering committee to revisit the evidence review process to ensure that it acknowledges and reflects the extent to which evidence review standards have evolved over time and collect lessons learned. The steering committee will consist of Committee members, HRSA staff, members of the current Evidence Review Group and experts from the evidence-based medicine field and public health. This group will explore potential changes in the evidence review process, how well the decision matrix is working and whether it needs revision, and a potential process for nominating conditions for removal from the RUSP.

- A Committee member asked whether the steering committee would consider a process whereby a condition could be upgraded from a secondary to a primary target or a primary target downgraded to a secondary one. Dr. Bocchini welcomed the suggestion and said it would be included in the steering committee's work.
- A Committee member asked whether relevant ethical and economic issues will be addressed, such as treatment availability. Dr. Bocchini said that these issues would be addressed.

E. Implementation of New Conditions to the RUSP

Dr. Bocchini announced the Committee will be looking into ways to examine the implementation of conditions that have been recently added to the RUSP, in terms of estimated time frames and what challenges or barriers were encountered that had not been anticipated by the Committee or through evidence review. He anticipates this effort will begin in late summer.

F. Vote on November 2017 Meeting Minutes

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

G. Vote on February 2018 Meeting Minutes

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

II. Newborn Screening Education and Training Tools: a Communication Aid and an Educational Planning Guide

Catherine Wicklund, M.S., GCP
Feinberg School of Medicine
Center for Genetic Medicine
Northwestern University

Beth Tarini M.D., M.S., FAAP
Associate Professor and Division Director
General Pediatrics & Adolescent Medicine
University of Iowa Hospitals & Clinics

Ms. Wicklund presented. Dr. Tarini planned to deliver this presentation but was unable to join the meeting by webcast until part way through the presentation. Dr. Bocchini reminded the Committee that in 2016 their direction to the Workgroup was to pursue two projects. The first was the development of a communications tool with guidance and tips physicians could use to discuss out-of-range newborn screening results with parents. The second project would map available educational materials and identify appropriate audiences for them.

Dr. Wicklund indicated these projects are in keeping in line with the Education and Training Workgroup's charge to review educational materials for a broad range of stakeholders to identify gaps and recommend approaches to fill them.

The educational planning guide is a matrix that lists newborn screening content areas and educational components and matches those with which stakeholders may need this information. Then newborn screening educational materials can be created and tailored to needs of different stakeholders. The tool could, for example be used to help newborn screening educators who were developing a brochure, video or other educational product determine what type of content that information vehicle should contain, while taking into account its intended audience. The Committee and various stakeholder groups have reviewed the matrix and provided feedback, which the Workgroup has used to refine the planning guide. Ideas for dissemination of the planning guide include: posting it on the Committee's website, linking to it from the Newborn Screening Clearinghouse , inviting other professional organizations to link to it, submitting it to the American College of Medical Genetics (ACMG) for consideration to accompany the ACT sheets, submitting a manuscript focused on the creation and applicability of the planning guide, offering a webinar through the Association of Public Health Laboratories (APHL), and/or announcing it on the NewSTEPs listserv.

Dr. Wicklund explained that the communication aid, which is now being called a communication guide, is designed to be used by health care providers to discuss—in broad, not condition-specific terms—out of range newborn screening results with parents. This guide, which is being developed in part to address the dissatisfaction parents expressed over initial notification discussions, is designed to help clinicians discuss results and relevant medical information and verify the family's comprehension level. It is also intended to help them provide support to families and help them develop a follow up plan. The guide could be sent directly to anyone who provides newborn screening results, be it a physician or state newborn programs that notify families of results. For example, the ACT sheets could contain a link to the guide or a copy of the guide could accompany the ACT sheets.

Dr. Bocchini asked the Committee whether there was consensus, and, hearing no objections, said efforts could proceed to disseminate both tools.

A. Discussion

- A Committee member called on the Committee to revisit the progress of both guides to verify the extent to which they are being used and to evaluate their effectiveness. Other Committee members and organizational representative agreed. Another Committee member indicated that such steps should be taken with every project—all of which have an educational component to them—that Workgroups undertake.
- Dr. Aaron Goldenberg, Case Western Reserve University, offered a comment from the audience that one of his genetic counseling students is working to validate the matrix by doing an analysis across all 50 states as well as Puerto Rico and Washington D.C. to assess states' brochures for readability, literacy and user friendliness. She is using the stakeholder categories identified by the Workgroup and presented at a previous Committee meeting.
- Other potential methods of dissemination offered by Committee members and Organizational Representatives include:
    - Introducing the communication guide through a board specialty Maintenance of Certification learning module that covers delivery of newborn screening results.
    - Adding it as a resource on the National Human Genome Research Institute's Genetic/Genomic Competency Center site.
    - Making the communication guide available through resources physicians refer to regularly for new information. This could include UpToDate, eMedicine and Medscape.
    - Asking the Organizational Representatives to make both guides available to their organizations.

CDC Quality Assurance and Harmonization Activities

Kostas Petritis, Ph.D.
Laboratory Chief
Biochemical Mass Spectrometry Laboratory
Newborn Screening and Molecular Biology Branch
Centers for Disease Control and Prevention

In introducing Dr. Petritis, Dr. Bocchini explained that the Biochemical Mass Spectrometry Laboratory (BMSL) at the CDC helps newborn screening laboratories by developing first- and second-tier screening

assays in-house, conducting hands-on mass spectrometry training, developing and characterizing quality assurance materials and providing technical assistance.

Dr. Petritis's presentation focused on normalization of tandem mass spectrometry results and cutoffs using CDC's newborn screening quality control materials and the BMSL's development of a new generation of proficiency testing materials. He explained that CDC's newborn screening quality assurance program is the only one of its kind that uses dried blood spots. They offer 16 proficiency testing programs and 13 quality control programs. CDC's program serves 660 participants from 84 countries, covering about 64 biochemical analytes.

Dr. Petritis explained that tandem mass spectrometry can detect more than 70% of disorders on the RUSP that utilize dried blood spots; however, the biomarker measurements and cutoffs can vary significantly among newborn screening laboratories due to different extraction methods. Some, but not all labs, derivatize their analytes and may or may not take analyte recovery into account. Other variables include using different analytes in connection with a disorder and use—or not—of second-tier testing. Other factors include population-tested instrumentation and varying standards for calibration techniques. CDC's quality control materials for mass spectrometry contain 29 amino acid and acylcarnitine markers enriched at four concentration levels. Participant labs are asked to run five duplicate tandem mass spectrometry interday runs of each level and report the results to CDC; CDC runs the same specimens the same way. The participating labs also use CDC's quality control materials to determine each instrument's results variability within a given day, over several days and to gauge how similar the results are among multiple instruments.

During the analysis, regression curves can be generated using measurements of identical quality control material submitted by participant labs and CDC. The equations can be used to normalize cutoffs and proficiency testing results. CDC can provide labs with de-identified data to allow programs to compare their cutoffs to those of other labs.

In addressing the creation of a new generation of proficiency testing materials, the CDC has recently developed a new method to enrich multiple analytes simultaneously with a high degree of accuracy, leading to enrichments within 5% of the desired concentration for multiple analytes. CDC can use this breakthrough, along with tandem mass spectrometry data from confirmed cases, to develop proficiency testing materials and other quality assurance materials that are biochemical copies of newborns who were diagnosed with a disorder.

CDC can now perform high-accuracy, multi-analyte blood spot enrichment and plans to create borderline materials for education purposes. The lab also plans to develop tandem mass spectrometry kits to provide states with new generation of quality assurance materials they can use to verify or validate methods or use to assess performance when there is a change in instruments or of kit lots.

A. Discussion

- A Committee member suggested that the Committee explore the potential to harmonize the way that abnormal results are reported and work to ensure that there is more uniformity in this area nationwide so that physicians who train in one state will not have to adapt to different information provided by another state.
- Other Committee members stressed the importance of determining case definitions, which are necessary if one plans to transition from normalizing or harmonizing a biomarker to confirming

the presence of a condition, which could require a series of second-tier tests to determine what the disorder is although ACT sheets could be useful in this regard.

- Another Committee member and an organizational representative cautioned that reports that are issued need to be comprehensible, not only to those in the lab but to physicians. Referring to a result as out-of-range may not be specific enough; a graded or graduated response should be considered; one that, differentiates, for example, between a borderline case and one with a result hundreds of times higher than an upper-limit cutoff.
- A Committee member cautioned not to confuse proficiency testing with quality control because proficiency testing is conducted quarterly whereas quality control is performed more frequently. Dr. Petritis explained that his lab distributes quality control materials every six months and proficiency testing materials three times per year.
- Dr. Cuthbert said that the CDC is examining ways to create quality assurance materials that reflect the levels of enzyme activity in blood spots similar to those seen in newborns.

III. Review and Committee Discussion: Cutoffs and Risk Assessment in Newborn Screening

Joseph Bocchini, M.D.
Committee Chair

Dr. Bocchini introduced the discussion by explaining that it was triggered partly in response to concerns expressed by stakeholders about missed cases and how borderline results are handled and communicated to affected families. He also hoped to address the potential lack of uniformity in laboratory methods or condition screening and how reporting out-of-range results and conducting proficiency testing may help in reducing false positive and false negative results.

He noted that presentations that were delivered to the Committee identified challenges, such as differences in algorithms and cutoffs among labs that make it difficult and in some cases not possible to compare results. He also noted the lack of a uniform definitions of borderline results or uniformity in processing such results. There is also a lack of data on false negatives, as not all missed cases are reported back to the states, and limited resources to implement quality assurance and quality control activities.

APHL is drafting a document on risk assessment in newborn screening for use by state programs that the Laboratory Standards and Procedures Workgroup and the Committee have provided their feedback on. APHL anticipates this will be published in June. In addition, CDC's harmonization activities will be available as a resource, as will the Newborn Screening Technical Assistance Center and Data Repository with the NewSTEPs program.

Dr. Bocchini asked the Committee to consider possible ways they can help, offering the following two ideas as possible ideas: provide support or guidance on how to using a systematic approach to evaluating cutoffs and screening algorithms; or support efforts to improve laboratorians', epidemiologists' and biostatisticians' access to state-level data for analysis or provide a rationale for states' development of such resources.

A. Discussion

- A Committee member suggested that the Education and Training Workgroup become involved in efforts to explain state lab activities and results, both to health care providers and to parents, including what results indicate and the potential for false positive and false negative results. Dr. Bocchini said that this Workgroup had focused on health care provider education and concurred that expanding the focus to parent education would be useful as well.
- A Committee member said that states should be encouraged to provide data to the CLIR database, which can be compared in de-identified ways and used to track false negatives when that information is available; this tool can contribute to harmonization. He questioned whether additional initiatives conducted by states are necessary or cost effective, given the existence of this resource.
- A Committee member pointed out that lack of state funding hampers many newborn screening programs' improvement efforts and that the Committee might help to address this by identifying best practices to which all state programs should adhere. Programs could point to these in asking legislators for increased funding.
- Another Committee member pointed out that improved practices can reduce a state program's false positive results, which decreases the amount of follow-up testing that is needed, thus saving the state money.
- Dr. Cuthbert mentioned that CDC will be offering a funding opportunity in the next year or two for state programs that calls on applicants to consider ways they can collaborate with the agency to harmonize their work. She hopes to be able to report any processes or projects that result from this to the Committee or the Laboratory Standards and Procedures Workgroup.
- An organizational representative pointed out that variations in setting cutoffs among states, due to different methods of establishing them, can make it difficult to explain cutoffs to the public. It may not make sense why a level of 2.3 may be declared normal in one state but abnormal in another. She suggested that the Committee could play a role in educating the public.
- An organizational representative called on the Committee to support efforts to record all false negative results (missed cases). Without this information, a lab cannot review the case to determine what went wrong. Ensuring that there are clear definitions of what states are screening for is important as well, in part because state program can be criticized for not detecting risk for a condition that it may not be screening for (e.g. congenital adrenal hyperplasia screening - one state may identify both simple virilizers and salt wasters, whereas, another may not). Perhaps the Committee should review existing definitions and/or relate them to those set by NewSTEPs.
- A Committee member noted that no mechanism is in place to find or collect data on late onset cases, which were not targeted when screening efforts began. Should screening programs be responsible for these types of conditions? It isn't clear. Establishing precise screening targets is important. Another Committee member said that the conditions a program screens for should be published on its website as well as any new information that is published about them.
- An organizational representative said that many states are reluctant to report false negatives, because the public could react negatively to this information. It would be helpful if the Committee could find a way to address this.

Dr. Bocchini called on the Laboratory Standards and Procedures Workgroup to continue discussing with APHL the risk assessment document it is working on and interacting with the NewSTEPs program and CDC to see whether opportunities arise to for the Committee to address some of the issues that were discussed. The Education and Training Workgroup can focus on some of these issues as well.

IV. Working on Timeliness in Newborn Screening: Lessons Learned from States

Tonya McCallister
Supervisor
Newborn Screening Lab
Public Health Laboratory
Oklahoma State Department of Health

Sondi Aponte
Education & Outreach Manager
Arizona State Laboratory — Office of Newborn Screening

Stanton L. Berberich, Ph.D.
Program Manager, Medical Screening
State Hygienic Laboratory at The University of Iowa

Dr. Bocchini introduced three presenters who would discuss how the state programs they represented approached timeliness issues and share lessons learned.

Tonya McCallister

Tonya McCallister has worked in the Oklahoma State Department of Public Health Laboratory's newborn screening lab since 2001. She supervises staff and newborn screening specimen accessioning and testing, oversees quality assurance and quality improvement processes and manages newborn screening laboratory information management system activities.

Ms. McCallister described the Every Baby Counts program, created by the Oklahoma Newborn Screening Program and the Oklahoma Hospital Association, to improve transit time efficiencies by collaborating with the state-contracted courier service and birthing hospitals. Although the Committee recommends that, ideally, 95% of specimens collected should reach the state health department's lab within 24 hours of collection, the program's goal was to comply with Oklahoma law which calls for specimen receipt within 48 hours of collection. The Oklahoma Newborn Screening Program received grant funding from NewSTEPs 360 in September 2015 to:

- Replace quarterly transit time reports with more user-friendly monthly reports;
- Expand courier service; by March 2017, 40 hospitals had instituted 7-day courier service, accounting for 94% of initial specimens;
- Produce a newborn screening resource guide;
- Create a train-the-trainer resource;
- Conduct site visits involving walkthroughs of all relevant hospital departments; and
- Institute newborn screening lab process changes.

Ms. McCallister concluded that, when the Every Baby Counts program started, transit time compliance with the Committee's newborn screening recommendation was at 35.87%. In March 2018, the state had achieved 86.53% compliance. During that month, for the first time, less than 2% of specimens—1.97%—were deemed unsatisfactory.

Sondi Aponte

Sondi Aponte is the education and outreach manager in the Office of Newborn Screening at the Arizona Department of Public Health. She began by pointing out that Arizona is the nation's sixth-largest state with a widely dispersed, rural population. A newspaper article reported in 2012 that 17% of all newborn screening samples arrived at the state lab five or more days after collection and the fact that Arizona ranked near the bottom among states who reported transit data; this information was viewed as a call to action.

In 2014, the state department of health's director set transit time improvement as a priority, conducted outreach to identify challenges and announced a statewide goal of delivering 95% of initial samples to the state lab within three days. In addition, an executive-sponsored task force was formed and the following problems identified:

- Hospitals were frequently batching specimens;
- Staff lacked awareness of the urgency of delivering specimens to the state laboratory in a timely manner;
- Hospitals used five-day courier service and labs functioned on a similar schedule with no holiday hours;
- High staff turnover and inconsistent or deficient staff training; and
- Inadequate quality assurance/quality improvement systems and failure to provide routine performance reports.

The task force applied continuous quality improvement methods (identify need/issue, define current situation, analyze problem, develop action plan and make predictions). With the courier service now delivering specimens to the state lab six days per week, they reached their statewide goal in five months, leading to Arizona winning the first-ever Newborn Screening Award for timeliness.

In 2016, the state began a grant-funded project with APHL, NewSTEPs 360 and the Colorado School of Public Health to modify internal workflows. Thanks to workflow changes, revisions to forms and structures and retraining, turnaround time for hemoglobin testing has improved from a baseline of 12% of samples processed within 48 hours to 91%.

This year, the state is confronting one of its biggest challenges, demographic data entry delays which were a large contributor to only getting 60% of normal and out-of-range results reported within seven days. Two full-time-equivalent employees were hired and changes in the methods and verification times were made. From the fourth quarter of 2017 to the first quarter of 2018, the state achieved 70% of time-critical results reported out within five days of birth and 90% within two days of specimen receipt.

Stanton Berberich

Stanton Berberich has been the newborn screening program manager for the State Hygienic Laboratory at the University of Iowa for 18 years.

He began his presentation by noting that disparities in timeliness are linked to the day a baby is born. Half as many births occur on weekends as on week days because scheduled births typically occur Monday through Friday. The days with the fewest births have the shortest times between birth and reporting of newborn screening results. With this in mind, specimens are collected from across Iowa daily. They are picked up and delivered to the newborn screening laboratory on the same day. Testing,

including data entry, is conducted daily, as are the reporting of results to short-term follow-up staff and their reporting of results to health care providers with recommendations to permit appropriate interventions when necessary. The state's courier service collects and delivers specimens 365 days per year and the screening laboratory operates 20 hours per day, 360 days per year. The majority of results are available within three days of life and more than 90% are available before the baby is four days old.

Dr. Berberich stressed that all newborn screening system staff must understand why and how their roles are critical to protecting newborns and what resources they can access.

He noted in closing that only two states, Iowa and North Dakota, consistently meet the Committee's 95% recommendation for time-critical conditions and Iowa provides laboratory and short-term follow up support for North Dakota. Thus, both states benefit from Iowa's 365- day-per-year specimen collection, delivery, testing and reporting system.

A. Discussion

- A Committee member asked whether any of the presenters encountered challenges in dealing with birthing centers to improve timeliness and whether they incurred additional costs in pursuing this goal. Dr. Berberich said that, once those involved understood why timeliness is key to positive outcomes, a significant number moved from being reluctant to complying to pressing the state to improve its systems. He also said that his program was allowed to increase its fee by $15 to cover the added costs associated with improving timeliness. Ms. Aponte said that, despite doing targeted interventions over three to five years with licensed midwives who deliver 1% of the state's babies, they only saw 50% documented blood spot, hearing or critical congenital heart disease screening results among this subpopulation. In terms of expense, she said that contracting with a local courier that provides customized service, rather than relying on a national firm that provided next-day-at-10:30 a.m. service, costs $150,000 per year. However, the service provides six-day per week courier service, same-day pick-up and delivery for 80% of hospitals, and five drop-offs per day at the lab, all of which improve and streamline the processes.
- An ex-officio member asked how often staff need to be re-educated or reminded, or taught for the first time due to staff turnover, of the importance of timeliness measures. Dr. Berberich said that, in the past, when the processes were simpler and less time-constrained, only occasional reminders were needed about a given step. Now, ongoing interaction with hospitals, including the provision of feedback for assessment and comparison with other hospitals, is necessary with an emphasis on the "why." Ms. Aponte said that her team does walk-throughs and demonstrations at hospitals and inevitably finds process problems that need to be addressed. This outreach is done routinely.
- A Committee member asked Dr. Berberich how long it took his state to transition from a five-day to a seven-day collection-and-delivery operation. The damage caused by Hurricane Katrina delayed progress for up to several years in some areas after the state program got approval to improve its system. He noted, however, that it took several months to recruit, hire and train people to work the new night shift.
- A Committee member asked whether the three presenters felt it was necessary to have a champion educator or a specific person who would focus on quality assurance to implement steps to improve timeliness. All three presenters said that such an effort takes leadership to press for the provision of time, resources and financial support as well as finding or developing champions on the hospital end.

- Another Committee member asked how much FTE time a program should expect to need to adequately address timeliness challenges. Ms. McAllister said that her program has two to three people who spend a week out of each month on follow up, reporting and phone calls but would like to devote more resources to these tasks. Dr. Berberich said about a third of one person's time is devoted to it and other people in the laboratory, on the short-term follow up team and at the state level who help to educate and equip the hospitals. Ms. Aponte said that although her state program's Transit Time Task Force has been disbanded, staff continue to monitor timeliness performance, especially transit time. She felt it would be reasonable to assign a full-time equivalent staffer to manage timeliness.

Dr. Bocchini said that the ACHDNC's recommendations regarding timeliness in collecting and delivering specimens to the newborn screening labs and reporting results are listed on the Committee's website and it recommends that they be achieved by all states. He also stressed that states should report the results of their activities so that the public will know the extent and value of the newborn screening services their children are receiving and the extent to which states are meeting Committee-set standards.

V. Overview: Assessing the Public Health System Impact of Adding Conditions to the RUSP

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

Dr. Bocchini reminded attendees who were preparing to participate in Workgroup meetings that each Workgroup was asked to spend a portion of their time this afternoon discussing the public health system pact surveys that will be used to evaluate how adding conditions to the RUSP could affect newborn screening programs. The goal of the evaluation is to assess the state's ability to implement a population-based screening for a newly added condition, including the resources needed and the cost implications. He explained that the latest iteration of the Newborn Screening Saves Lives Act calls for an evaluation of the impact on the public health system, which will be included in the evidence-based review of each RUSP-nominated condition. The Evidence Review Group crafted a survey to be distributed to each state that asks:

- The entity or organization that houses the states' newborn screening program;
- The type of authorization that is needed to screen for a new condition;
- The screening methods that would be employed;
- The new screening's impact on the laboratory;
- Short- and long-term follow-up implications;
- Types of resources that would be needed to implement the screen; and
- The projected timeline for adoption.

He pointed out that the survey has already been administered in connection with four conditions that were considered for addition to the RUSP, three of which were added.

Two survey tools were developed: the first is administered to all state and territory newborn screening programs; the second is a follow-up survey, which is sent to a smaller number of programs to supplement information provided through the first survey. Both were approved by the Office of Management and Budget (OMB). The current approval expires this year. HRSA will be submitting a request to continue approval of the surveys. This is a good time to evaluate the surveys to assess whether more or different information should be requested. Dr. Bocchini asked the Workgroups to examine any high-level revisions that should be made to the survey, including the addition, removal or modification of questions. He also pointed out that a *Federal Register* notice will be published inviting public comment on the survey, which will be considered before submitting a potentially updated survey and the continuation application to OMB.

Workgroup meetings were held for the rest of the day.

VI. Administrative Business — May 10, 2018

A. Welcome and Roll Call

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

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

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

- Dr. Mei Baker
- Dr. Susan Berry
- Dr. Bocchini
- Dr. Jeffrey Brosco
- Dr. Carla Cuthbert (Centers for Disease Control and Prevention)
- Dr. Kellie Kelm (Food and Drug Administration)
- Dr. Dietrich Matern
- 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 and Services Administration)
- Dr. Scott Shone
- Ms. Catherine Wicklund
- Dr. Catharine Riley (Designated Federal Official)

Organizational representatives in attendance were:

- American Academy of Pediatrics, Dr. Debra Freedenberg
- American College of Medical Genetics, Dr. Michael Watson

- Association of Maternal and Child Health Programs, Dr. Jed Miller
- American College of Obstetricians & Gynecologists, Dr. Britton Rink
- Genetic Alliance, Ms. Jaclyn Seisman, M.P.H.
- March of Dimes, Dr. Siobhan Dolan
- National Society of Genetic Counselors, Ms. Cate Walsh-Vockley
- Society for Inherited Metabolic Disorders, Dr. Carol Greene
- American Academy of Family Physicians, Dr. Robert Ostrander
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health Officials, Dr. Chris Kus

B. Opening Remarks

Dr. Bocchini said that the Committee members have submitted edits to its annual report to Congress, which was then finalized and would be submitted today.

He highlighted two members for whom this is their last meeting because they are rotating off the Committee: Catharine Wicklund and Dietrich Matern.

He thanked Ms. Wicklund for her focus on patients and families and strong organizational skills, for participating in many key issues the Committee has undertaken and for chairing the Education and Training Workgroup.

Ms. Wicklund said that ACHDNC was the hardest committee she had ever sat on because the decisions it makes take a great deal of time, energy and attention and she commended all of its members for their contributions to the important and challenging work it does.

Dr. Bocchini thanked Dr. Matern for contributing his skills as a physician, laboratorian, newborn screening advocate and a researcher to the Committee. He served on the Laboratory Standards and Procedures Workgroup, was the senior author of the Committee's report on succinylacetone as a key marker for Tyrosinemia type 1 and has made important contributions during discussions of many key issues that came before the Committee.

Dr. Matern said that it had been an honor to serve on the Committee, which is dedicated to babies with heritable conditions with a focus on the public health system, and as such, must consider the impact of the decisions it makes both those who have these conditions but also those who do not. He thanked the Committee for the opportunity to serve and said he will look for ways to assist it in the future.

VII. Update on Newborn Screening for Guanidinoacetate Methyltransferase (GAMT) Deficiency

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

Dr. Bocchini explained that GAMT deficiency had been nominated for addition to the RUSP by Dr. Nicola Longo and Dr. Marzia Pasquali, both from the University of Utah, and the Association for Creatine

Deficiencies advocated for its inclusion. However, the Committee voted not to move it forward for full evidence review due to lack of available pilot study data. Dr. Cuthbert has been asked to follow up on pilot studies and other efforts in the field.

Dr. Cuthbert defined GAMT deficiency, its effects on the human body, screening, detection and treatment methods and why the Committee opted not to move it forward to evidence review.

In reviewing this condition for potential addition to the RUSP, the Committee found that, in its favor, the condition's natural history is widely understood and treatment is similar in principle to other inborn errors of metabolism. As noted above, the newborn screening assay can be multiplexed with existing tests as a laboratory-developed test and has been found to have high sensitivity and a low false positive rate. However, there were a number of negative factors:

- The natural history was based on only 110 patients worldwide;
- There was no firmly agreed-upon strategy for treatment;
- Metabolic control must be strict;
- There is no FDA-approved newborn screening kit or test for newborn screening or a diagnostic assay; and
- No patients had been identified through newborn screening.

The Committee recommended that the proponents work toward formalizing treatment guidelines and suggested that newborn screening programs in Australia, British Columbia, and the state of Utah be encouraged to maintain their established screening for GAMT deficiency and report any confirmed cases identified through such screening. Dr. Cuthbert asked the programs for updates. Approximately 1.4 million newborns have been screened for GAMT deficiency collectively in Australia, British Columbia and Utah. To date, no newborn has been diagnosed with GAMT deficiencies through newborn screening. Some false positive results have been reported.

Dr. Cuthbert said that the state of Michigan has received approval to begin screening for GAMT deficiency and expects to do so later this year and Georgia has expressed interest in doing so as well.

A. Discussion

- A Committee member said that a case of GAMT deficiency was identified through newborn screening in a pilot study. The patient was not followed up because the result was ruled a false positive but later developed symptoms. This seems to be an indication that the screen can identify cases.
- A Committee member recommended that CDC add creatinine to its panel, which can serve, in a newborn screening program, as a second-tier test for Pompe disease.
- Another Committee member asked how much money should be invested in mandating a screen for which the overwhelming majority of children may not be at risk of developing it? Another Committee member said the only cost would be for reagents and the low rate of false positives would limit the amount of follow up required and would save money. However, Dr. Cuthbert said that Dr. Pasquali reported a higher number of false positives in the NICU population and both she and a representative from the newborn screening program in British Columbia said that a second-tier test is helpful in reducing these results. On the other hand, including the covariates of birth weight and other screening card information may eliminate the need for a second-tier test, a Committee member observed.

- An organizational representative who has treated two children with GAMT deficiency noted that the treatment cost is also minor compared to those for other conditions on the RUSP.

VIII. Public Comment

A. Dean Suhr, President, MLD Foundation

Dr. Bocchini explained that Mr. Suhr would report on the most recent (the fifth) roundtable discussion among stakeholders about the RUSP. Mr. Suhr said that these discussions extend beyond the RUSP; they are intended to share perspectives and insights from newborn screening experts, expand the knowledge base and provide opportunities for coalition building and collaboration to make newborn screening more equitable and robust. Representatives from advocacy, state, federal, public health, pharmaceutical, technology and service organizations and a payer attended the most recent meeting. Among the topics discussed were the definitions and applications of benefit, what the terms "therapy," "cure" and "clinical care" mean, the Wilson-Younger criteria, international newborn screening, molecular screening and diagnostics and the state and federal RUSP disconnect.

Mr. Suhr also mentioned an initiative he started called Rare Army, which includes a focus on policy and is intended to disseminate sound policy that is being formulated around newborn screening. The initiative is intended to foster public education, engagement and involvement to influence legislation and regulations on behalf of newborn screening.

B. Ms. Heidi Wallace, Vice President, Association of Creatine Deficiencies

Ms. Wallace said that, in addition to her position with the association, she has two children with GAMT deficiency. Samantha was diagnosed at the age of five and exhibited developmental delays for years, which were incorrectly diagnosed as autism. Spectroscopy showed a creatine peak. After nine years of treatment, although she has improved, she is permanently intellectually disabled, continues to have seizures and requires lifelong care. Her six-year-old son was diagnosed with GAMT deficiency a few days after birth and began treatment. He has a relaxed diet, takes over the counter creatine, ornithine and sodium benzoate three times a day by mouth and the cost of each dose is 30 cents per day. He is meeting his milestones, is not receiving any other therapy and has attended and will soon graduate from a high-level kindergarten class.

Alluding to the earlier discussion of the cost of screening, Ms. Wallace said that Dr. Pasquali had quoted a cost of about 50 cents per child for reagents and less than a dollar when as-needed secondary testing is done. Neither of Ms. Wallace's children take metabolic formulas; when diet was controlled it was on a moderate basis and currently, only the creatine and GAA are monitored to ensure they receive a good supply of creatine and their GAA levels are kept low to prevent neurotoxicity.

C. Kim Tuminello, Co-Founder, Director of Advocacy for the Association of Creatine Deficiencies

Ms. Tuminello began advocating for the addition of GAMT to the RUSP in 2006 when her 10-month-old son Ty was diagnosed with GAMT. By then, he could not sit up or play like other babies and was severely underweight; he has since undergone years of physical, occupational, speech and other therapy. Her eight-year-old daughter, who was treated for the condition from birth, has developed normally without the need for treatment.

She reported that Quest Diagnostics began testing for elevated guanidinoacetate over the past year and over the last two months, detected three cases of GAMT deficiency. She called on the Committee to initiate the evidence review process for the condition, for which she believes there is an effective screen and a safe, affordable, effective treatment.

D. Dr. Marzia Pasquali, Professor of Pathology, Medical Director and Section Chief of Biochemical Genetics, Supplemental Screening, University of Utah School of Medicine

Dr. Pasquali explained that her team in Utah and the Association for Creatine Deficiencies nominated GAMT deficiency for addition to the RUSP. The testing method is robust, yielding a false positive rate of less than .002%; she said she knew of no false negative results in over three years of testing. The cost of the screen is low because it is integrated with routine screening, with the reagent as the only additional expense. She noted that the Committee's concerns about GAMT's candidacy for the RUSP centered on whether the new test would detect signs of GAMT deficiency in newborns and the reliability of confirmatory tests in symptomatic patients. Her team has screened more than 140,000 infants and no positive screens for GAMT deficiency have been detected. However, they also analyzed blood spots from two confirmed cases retrospectively and they would have been identified. With regard to the Committee's concern about the availability of reliable treatment, she explained that treatment methods and outcomes have been published widely and international experts on creatine deficiency syndromes have gotten together to draft a consensus document. With regard to treatment efficacy, Dr. Pasquali believes this has been proven by the positive development of children with GAMT deficiency who were identified and treated shortly after birth. Thus, she feels that the Committee's criteria for moving GAMT deficiency on to evidence review have been met and she urged the Committee to consider adding the condition to the RUSP.

Dr. Bocchini thanked those who provided public comments and noted that Dr. Nicola Longo, who had also nominated GAMT deficiency for addition to the RUSP, had hoped to deliver comments as well but was on travel and, therefore, unable to do so.

X. Education and Training Workgroup Update

Catherine Wicklund, M.S., CGC
Chair, Education and Training Workgroup

Ms. Wicklund began by discussing potential strategies for validating the education planning guide, which, she reiterated, is designed to help people who are developing educational materials to consider what type of content they should include. One member of the Workgroup mentors a graduate student is using the categories identified in a project to assess educational materials used by newborn screening programs. Per feedback the Workgroup is considering adding a legend or definition of the content areas. The Workgroup also decided that more feedback and validation is needed before the guide is disseminated widely. They will conduct a literature review and talk to education experts to address these steps. Members will also identify which organizations are likely to be receptive to and effective at disseminating this type of the document.

Ms. Wicklund went on to discuss the communication guide, which is designed to help health care providers to discuss out-of-range results and could potentially be used in conjunction with ACT sheets.

The Workgroup would like to improve its design and formatting. Dr. Riley said she would give some thought about how HRSA could assist with that. The Workgroup also discussed measuring the guide's usefulness. Another objective will be to consider how to convey basic screening and risk assessment concepts.

XI. Follow-Up and Treatment Workgroup Update

Jeffrey P. Brosco, M.D., Ph.D.
Chair, Follow-Up and Treatment Workgroup

Dr. Brosco said that the Workgroup's quality measures report has been completed and will be posted on the Committee's website in the near future; other dissemination plans are being considered, such as publishing an executive summary in a journal, possibly for an audience that would include pediatric neurologists. The Medical Foods for Inborn Errors in Metabolism report is undergoing final edits and work is already underway to prepare it for publication in an abbreviated form. The Workgroup discussed the environmental scan that Dr. K.K. Lam and Dr. Alex Kemper are working on and how this work can inform the Workgroup's efforts to improve long-term follow-up and treatment to ensure good outcomes across a broad range of measures. The Workgroup will focus on providing stakeholders with an effective road map toward achieving a federated system to do this. Although a lot of activities are underway, there are many gaps and no system in place to connect what is being done. The Workgroup hopes to collaborate with stakeholders to develop a report and consider interim steps by the end of the 2018 calendar year.

A. Discussion

- Dr. Brosco was asked what role larger scale organizations such as the National Organization for Rare Diseases might play in working with patients and patient registries and how to engage such groups in the process the Workgroup proposes. Dr. Brosco said that during their next meeting, the Workgroup will discuss who should participate in setting up the roadmap and envisions including patients, families and other consumers from the beginning.
- When asked by a Committee member to define the "federated system" the Workgroup had discussed, Dr. Brosco said that there was no definition per se; the term was meant to convey that different things are happening in different ways, in different places. This leads to the question of whether, in the context of newborn screening, a new system or relevant initiative should be set up; alternatively, efforts could be devoted to ensuring that each existing system has a newborn screening component.
- An organizational representative said that a federated system road map had been tied to a proposal to bring stakeholders together to explore what people's roles and responsibilities are and what stakeholders think they should be. The roadmap should focus, not only on collecting data and using it for quality improvement, but how to involve hospitals, insurance companies, health care providers and families to improve care.
- An organizational representative suggested that the system could be modeled on the NICU graduate type of programs and cancer registries that do annual patient follow ups, which could include questions for primary care physicians and specialty clinics, to determine the type and quality of outcomes in a variety of areas. Another organizational representative asked where

funding would come from to conduct such follow up and said that each NICU decides how it does follow up; there is no one model for doing so.

XII. Laboratory Standards and Procedures Workgroup Update

Kellie Kelm, Ph.D.
Chair, Laboratory Standards and Procedures Workgroup

Dr. Kelm began by discussing recommendations the Workgroup could make to the Committee in regard to assessing risk assessment and establishing cutoffs. The Workgroup suggested that states should have written processes for:

- Testing and validating systems to determine normal, low- and high-risk results;
- Revisiting cutoffs in algorithms that includes how often they will be reassessed;
- Reviewing missed cases that have been identified, followed by program assessment;
- Disclosing screening targets transparently; and
- Encouraging participation in data collection normalization to support downstream quality assurance/quality improvement efforts.

The Workgroup also plans to review the risk assessment guidance document that APHL will finalize by next month to see determine if there are any follow up activities or recommendations the Workgroup can offer the Committee. Dr. Bocchini endorsed the Workgroup's call for states to develop processes to assess and improve risk assessment and cutoff procedures in tandem with tracking and reviewing the APHL document.

A. Discussion

- A Committee member pointed out that the number of and types of conditions labs screen for differs widely from state to state; it would be helpful for the public to know what conditions each state can and do target.
- Another Committee member said it would also be useful for states to track false positive and false negative results to devise performance metrics that could also be targets. This could lead to a uniform screening panel that includes, not only conditions but also screening performance across the country.

XIII. Committee Discussion: Public Health System Impact Assessment — Survey Tools

Joseph Bocchini, M.D.
Committee Chair

Dr. Bocchini explained that the Committee is seeking high-level suggestions for revisions to the two *Survey Instruments for Assessing the Public Health System Impact* surveys. The first is administered to all state and territory newborn screening programs; the second is a follow-up survey, which is sent to a smaller number of programs to supplement information provided through the first survey. These surveys are used to evaluate state newborn screening programs' ability and readiness to implement and expand comprehensive screening. He asked Workgroups to identify gaps in the data that are being collected, which, if addressed, would enhance evaluation efforts. He also inquired if there are questions that should be added, deleted or modified. Some of the suggestions include:

- The Public Health Department might not be the best respondent to address some of the questions, such as the availability of specialists or impact on clinicians' practices. And sometimes the responses furnished by the newborn screening advisory committee conflict with those from specialists, which makes it difficult to know how to respond. To address this disconnect, perhaps create another survey that is geared to specialists or add wording to the existing one that is more geared to eliciting better responses from them.
- Question 6B and 7 are hypothetical and may be difficult to answer. Specifying the implementation phases more clearly. The follow-up survey might be more useful than the first one because it captures what is actually happening, not just potential or planned activities.
- Make it transparent to public health departments how the Committee weighs the survey data within the decision matrix it uses when considering adding conditions to the RUSP. If the results of these surveys do have weight—if they are significant to the evidence review process—that should be stated to encourage participation. It should also be stressed that public health programs can use the results to assess their newborn screening health systems, not just to focus on the public health impact of screening for a single condition. However, others thought that it is equally important to know what hurdles states face in adding a condition to their RUSPs because authority and funding challenges have to be justified and accepted by the state's legislature and executive branch.
- Although the survey results are intended to inform the Committee, they may help stakeholders to understand how hard it is or how long it may take to implement a new screen. Providing data about the steps that are typically involved can help stakeholders consider which ones might be most challenging.
- The survey should be more effective in capturing what challenges programs face in securing authorization and/or funding to introduce a new screen. NewSTEPs has been collecting this type of survey data for three conditions—X-ALD, Pompe and MPS I—from 45 states and is starting to collect it for SMA as well. Some of the questions it asks might be worth adding to these public health impact surveys. Would it be possible for APHL or NewSTEPs to pilot a new draft of the survey and elicit a sense from people whether it improves their ability to communicate their concerns, challenges and other perspectives?
- It would be useful to know, when exploring how hard it is to get screening authority, what process was followed: whether this was discussed by an advisory board, whether it was voted on, how many times and the vote results. It would also be worthwhile to know whether an adoption recommendation was made and whether it was accepted by the health commissioner or secretary. Also, is there a way to glean—perhaps through APHL or NEWSTEPs data—how long it took to get authority and funding and what changes in these areas occurred over time? It's also possible to get authority to add a condition to your state's RUSP but if it requires raising the cost of a newborn screening, the legislature may reject the request.

Dr. Bocchini said that this discussion had been fruitful and that the Committee will consider the feedback and craft an improved version of the surveys. Once revisions have been added, it will be published in the *Federal Regi*ster to disseminate and invite the public to comment on it. He also stressed that standardizing the process when possible, by gathering data from existing databases rather than eliciting it again through the surveys, would simplify the process for states. It would be helpful to determine the key stakeholders who should see the surveys, to expedite the data collection, which will help the Evidence Review Group complete its work within its the mandated nine-month time frame.

XIV. New Business

Joseph Bocchini, M.D.
Committee Chair

An organizational representative alluded to an earlier discussion of children who are being diagnosed with a condition at age 4 or older, for which there is a newborn screen, but were never evaluated by a neurologist or geneticist, perhaps because of the assumption that metabolic disorders do not need to be screened for because they are rare. It might be useful to develop a project, perhaps using GAMT deficiency as an example, to educate people, not necessarily about newborn screening but about how treatment for children with hereditary disease can be beneficial. The ACMG and other organizations are working on this but the Committee could also have a role.

XV. Adjourn

Dr. Bocchini thanked everyone for their participation, stressed again that the Committee invited comments about the surveys and the public health approach.

The next meeting will be held August 2, 2018 by webinar.