Advisory Committee on Heritable Disorders in Newborns and Children

Meeting Summary
February 11-12, 2021

The Advisory Committee on Heritable Disorders in Newborns and Children (Advisory Committee) meeting was convened on February 11, 2021 and adjourned on February 12, 2021. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

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Advisory Committee Members

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Mia Morrison, MPH
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I. Administrative Business – February 11, 2021

Cynthia M. Powell, MD, 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

Mia Morrison, MPH
Designated Federal Official
Health Resources and Services Administration (HRSA)

A. Welcome and Roll Call

The Advisory Committee members in attendance were:

- Dr. Mei Baker
- Dr. Jeffrey Brosco
- Dr. Kyle Brothers
- Dr. Carla Cuthbert (Centers for Disease Control & Prevention)
- Dr. Jane DeLuca
- Dr. Kellie Kelm (Food & Drug Administration)
- Dr. Shawn McCandless
- Dr. Kamila Mistry (Agency for Healthcare Research & Quality)
- Dr. Melissa Parisi (National Institutes of Health)
- Dr. Cynthia Powell
- Ms. Annamarie Saarinen
- Dr. Scott Shone
- Dr. Michael Warren (Health Resources & Services Administration)

Organizational representatives in attendance were:

- American Academy of Family Physicians, Dr. Robert Ostrander
- American Academy of Pediatrics, Dr. Debra Freedenberg
- American College of Medical Genetics and Genomics, Dr. Max Muenke
- Association of Maternal and Child Health Programs, Dr. Jed Miller
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health Officials, Dr. Christopher Kus
- Association of Women's Health, Obstetric & Neonatal Nurses, Dr. Shakira Henderson
- Department of Defense, Dr. Jacob Hogue
- Genetic Alliance, Ms. Natasha Bonhomme
- March of Dimes, Dr. Siobhan Nolan
- National Society of Genetic Counselors, Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders, Dr. Georgianne Arnold

B. Committee Business

MPS II Nomination
HRSA received the resubmission of the nomination package for MPS II, Hunter Syndrome in December 2020. HRSA has completed its initial review for completeness, and the Nomination and Prioritization Workgroup currently is reviewing the information submitted in the package.

Final Report to the Secretary: Review of Newborn Screening Implementation for Spinal Muscular Atrophy (SMA)

Dr. Powell noted that, at its December 2020 meeting, the Advisory Committee approved the Review of Newborn Screening (NBS) Implementation for Spinal Muscular Atrophy (SMA) final report to the Secretary. After SMA was added to the Recommended Uniform Screening Panel (RUSP) in 2018, the Advisory Committee developed the report in response to the former Secretary's request for a report "describing the status of implementing newborn screening for SMA and clinical outcomes of early treatment, including any potential harms for infants diagnosed with SMA". Dr. Powell submitted the report to Secretary Azar after the December meeting, and she will inform the Advisory Committee of any response from the Department of Health & Human Services (HHS). The report is available on the ACHDNC's website.

Review of the ACHDNC's Evidence Review Process

The Advisory Committee has undertaken a review of its evidence review and decision-making processes. In February 2019, the Advisory Committee convened an Expert Advisory Panel (EAP) to consider the key components of the review. In 2020, the Advisory Committee continued to gather feedback from the Committee on ways to strengthen the evidence review process, including an examination of its newborn screening (NBS) decision-making criteria and decision matrix. Dr. Powell explained that the Advisory Committee would address two additional components during this meeting: the nomination process and a review of conditions currently included on the RUSP. Within the coming weeks, Dr. Powell will form a small working group to analyze the information gathered to date.

Any conditions nominated in calendar year 2021 will be subject to the current condition nomination and evidence review processes; the Advisory Committee aims to implement the updated condition nomination form in early 2022, along with any updated methodologies used to review nomination packages. The Advisory Committee will be kept apprised of the timeline, including any adjustments made to it.

As part of this review, the Advisory Committee will develop a manual of procedures, as well as consumer-friendly guidance materials for educating NBS stakeholders on Advisory Committee processes.

Once changes to the nomination and evidence review processes are finalized, the ACHDNC website will be updated with guidance materials and a summary of the revised processes.

C. Vote on December 2020 Meeting Minutes

The Advisory Committee voted unanimously to approve the December 2020 minutes.

II. Review of the Evidence Review Process: Evaluating Conditions on the Recommended Uniform Screening Panel (RUSP)

Alex R. Kemper, MD, MPH, MS
Lead, Evidence-based Reviews

The Advisory Committee currently is exploring ways to strengthen its NBS decision-making processes. Dr. Kemper shared considerations and approaches for systematically reviewing conditions on the RUSP for the purposes of gaining additional information about the condition, including lessons learned on adoption and implementation at the state and national levels.

Reviewing the conditions on the RUSP would allow the Advisory Committee to examine updates in the evidence for screening and treatment that have emerged since the condition was first added to the RUSP; these include new treatments, clinical recommendations, and clinical management issues, along with a better understanding of conditions during infancy and of the exact target of the screening. It would also give the Advisory Committee the ability to analyze longer-term follow-up outcomes; the impact of screening on public health, linkages to clinical services, and individuals and families; and explore any unresolved issue from a previous review. It is not the goal of this work to remove any condition from the RUSP.

Part of the Advisory Committee's work is to define the process for evaluating conditions included on the RUSP; this includes frequency—e.g., 3-, 5-, or 10-year reviews—or *ad hoc* reviews informed by changes related to the science or to the implementation of screening or treatment and guided by a formalized method for nomination for review. Dr. Kemper suggested that the Advisory Committee is likely to prefer a hybrid approach with regular and *ad hoc* reviews based on new information. The Committee should also consider the review criteria; Dr. Kemper asserted that these should remain essentially the same for new evaluations and reevaluations.

Dr. Kemper provided the following discussion questions:

I. What information would be most important for you to learn about from a review? What kind of findings would be helpful in general?
II. In what ways could a review help guide improvements in the process of NBS and follow-up?
III. How should conditions be selected for review (e.g., routine periodic review vs. *ad hoc* review)?

Discussion

- An Advisory Committee member suggested that the Committee review the entire panel on a regular basis to identify anything of concern or interest, and that such reviews include an assessment to determine whether a condition should be reevaluated based on specified indicators (e.g., diagnostic and/or therapeutic advancements).
- A Committee member asserted the need for the Advisory Committee to be careful when addressing the targeted conditions because screening biomarkers can potentially also pick up unintended conditions, and not everything is a disease state.
- A Committee member questioned what implications exist for states as they add conditions to their screening panels incrementally, such as funding decisions, impact on both laboratory and short-term follow-up resources, and gaps in follow-up and access to care. Another question is around equity: What does screening look like across populations? Is it being performed in an equitable manner (e.g., by race, ethnicity, rurality)? Is there capacity to ensure proper confirmatory testing, diagnosis, and continued care available for all populations?
- A Committee member mentioned that review should help identify gaps and obstacles to fulfilling the "promise of NBS". It should be a rigorous process and could help determine whether a secondary condition should be upgraded to a core condition for screening. She noted existing challenges around sustainability of funding, as well as the importance of exploring state-level challenges and successes. For challenges, it is important to identify risks as well as ways to strengthen testing, algorithms, and interpretations. Information about outcomes can feed back into testing algorithms and inform how testing is conducted. A checklist that mirrors the initial nomination package can ensure the Advisory Committee performs a solid comparison.
- A Committee member reminded the meeting attendees that these types of questions would be addressed in the Follow-up and Treatment Workgroup session later in the day

and in the "Innovations in Long-term Follow-up" panel discussion the following day. He noted the necessity of determining the Committee's role, as well as the roles of states, professional organizations, research teams, or treatment groups.

- An Advisory Committee member asserted that the purposes of review should be to document the goals of adding a particular condition to the NBS panel and to confirm that public health is meeting those goals. State-level evidence of benefits, harms, and value of NBS programs should be collected; this would include data on sensitivity and specificity of disorders, false positive rates, costs, and other aspects related to outcomes, as well as new information on natural disease history, altered disease history after initiation of therapy, new therapies, unexpected consequences of therapies, and long-term outcomes. He suggested that monitoring for sentinel events related to the NBS process would help the Advisory Committee assess the process for screening for a particular condition. If a question arises during the review process, a matrix-based review to determine possible removal of the condition should follow. Review intervals may vary by condition, and he advocated for flexibility in setting the review schedule.
- An organizational representative highlighted the existence of unintended consequences of public health measures initially based on small studies and pilot studies, asserting that one of the main purposes of reviews is to identify these consequences or harms compared with the proportion to benefits. He suggested that any new concerns around potential harms of a RUSP condition should prompt an *ad hoc* review.
- A Committee member suggested gathering information on a set of core elements across conditions.
- An organizational representative commented that identifying existing systemic barriers to follow-up could provide an opportunity to provide more information around equity and provided the example of sickle cell disease. Others agreed with the need to focus on equity issues.
- An organizational representative noted that there have been considerable advances in technology and therapies since many of the legacy conditions were added to the RUSP. It would be important for the Committee to explore issues around access within the context of health equity.
- A Committee member noted that it is important to think about how states will track and share data on follow-up (particularly longer term), as well as funding for such efforts.

III. Reviewing the ACHDNC Evidence-Review Process: RUSP Nomination

Alex R. Kemper, MD, MPH, MS
Lead, Evidence-Based Reviews

Dr. Kemper explored potential updates to the ACHDNC condition nomination form, some of which have been suggested to the Advisory Committee within the past few years. The goal is to strengthen the overall nomination and evidence review process. The current process is as follows:

1. External nominators prepare and submit the nomination package to HRSA.
2. HRSA reviews the package for completeness and works with the nominators to ensure all the required information has been submitted.
3. Once the package is complete, it goes to the Advisory Committee's Nomination and Prioritization (N&P) Workgroup, which reviews the nomination for six key questions.

4. The N&P Workgroup assesses whether the information meets all requirements and that there is sufficient evidence for presenting to the full Committee.
5. The Committee then votes on whether or not to refer the package to full evidence review which must be completed within nine months.

In thinking about potential revisions to the nomination form, it is important to consider what information would streamline and facilitate the evidence review process. Dr. Kemper reviewed suggested updates to the nomination form and pointed to issues that need to be addressed. For example, requesting contact information for experts in the field could support the Advisory Committee assemble its Technical Expert Panel. The Committee plans to ensure that any changes to the nomination and review process are announced and instituted with appropriate lead time, and that they are clearly messaged to potential nominators and to the public.

Dr. Kemper shared screenshots of the nomination form and the following potential areas of expansion:

Current Nomination Form	**Selected Areas of Potential Expansion**
Nominator contact information	• Other experts in screening or treatment of the condition
Condition information and treatment	• Specific case definition, screening target
Evidence-based information – screening • Validity of laboratory screening test • Availability of accurate confirmatory and diagnostic testing • Prospective population-based pilot study	• Pilot study contacts • Screening algorithm piloted and results • Confirmatory, STFU, and LTFU • Specialists • Available long-term follow-up and plans • for collecting long-term outcomes
Key references from scientific publications	• Available registries • Availability of unpublished data

Dr. Kemper noted that receiving all of the information listed in the "Potential Expansion" column would facilitate the review process.

Dr. Kemper posed the following questions for discussion:

- Do the elements on the nomination form align with what will be needed to recommend evidence review?
- If not, what should be added and how would it be used?
- What opportunities are available to facilitate the nomination process?

Discussion

- A Committee member suggested that the nomination form request information on any specific markers used in testing in order to develop case definitions.
- An organizational representative noted that the nomination form should include information on longitudinal follow-up. It would be helpful to have a vision of long-term follow-up needs and key outcomes.
- An organizational representative highlighted the potential value of including some form of funding disclosure (total operating budget of an organization, and if any money has been specifically allocated

for this nomination process), suggesting it could provide better context for the nomination and could be used to level the playing field. He added that such information could be redacted for review to ensure that decisions are based purely on the merits of the package.

- A Committee member suggested including a question asking whether the nominator foresees later modification to a condition's case definition, noting that both expansion and refinement of case definitions are possibilities.
- An organizational representative highlighted the value of requesting the nominators to define the goals for adding the condition to the RUSP. It would provide an avenue for gathering parents' perspectives.
- Ms. Morrison reminded the group that HRSA is available to provide technical assistance (TA) to groups nominating conditions, and it provided TA to nominating groups earlier this year.

IV. Consumer-Friendly Guidance Materials

Cynthia M. Powell, MD, FACMG, FAAP
Committee Chair

Dr. Powell explained that the ACHDNC plans to develop educational resources directed to NBS stakeholders on the nomination and evidence review processes, with the goal of demystifying the complex nomination and evidence review processes. She noted that HRSA reviews nomination packages very carefully and alerts nominators to what information is missing.

The Advisory Committee and HRSA plan to incorporate changes from review of the evidence review process and hope to post a Condition Nomination FAQ and other content (text and graphics) to the ACHDNC website.

Discussion

- An organizational representative highlighted the importance of ensuring that consumers and those going through this process have access to these types of resources. She plans to share draft materials (text and diagrams) to members of this group that were developed to explain the nomination process.

V. Public Comments

The Advisory Committee received one written comment, focusing on WHIM Syndrome. Seven people provided oral public comment:

A. Brittany Hernandez, Muscular Dystrophy Association

Ms. Hernandez is the Senior Director of Policy and Advocacy for the Muscular Dystrophy Association (MDA). She provided an update on the reauthorization status of the Newborn Screening Saves Lives Act. Rep. Lucille Roybal-Allard of New York has introduced the reauthorization bill in the House of Representatives, and quick introduction is expected in the Senate by Sen. Maggie Hassan.

B. Mike Hu, Parent

Mr. Hu is a former molecular diagnostic test developer and the parent of three boys, the older two of whom were diagnosed with MPS II. He highlighted the exponential growth in technology and therapeutic innovations, and he pressed for making systemic changes that can help accommodate disruptive technology advancements and maximize the therapeutic benefits of those innovations.

C. Dr. Don Bailey, RTI International

Dr. Bailey is a Distinguished Fellow at RTI International, an independent, non-profit institute that provides research, development, and technical services to government and commercial clients worldwide. He informed the Committee that RTI International and the EveryLife Foundation has launched an independent effort to evaluate the capacity of NBS in the United States to provide timely diagnosis of all newborns who may benefit from new treatment if and when such treatments are approved for use in the U.S. Dr. Bailey's team will complete the first phase of the project, a study of the strengths and limitations of the current system.. Dr. Bailey expressed the hope that the findings of this modernization assessment will inform and support the ADHDNC's efforts, and he would be pleased to present a full report of findings and recommendations at a future Committee meeting.

D. Dylan Simon, EveryLife Foundation

Mr. Simon is the Newborn Screening Policy Manager at the EveryLife Foundation, a non-profit, nonpartisan organization dedicated to empower the rare disease patient community to advocate for impactful science legislation and policy that advances the equitable development of lifesaving diagnosis, treatment, and cures. He gave an update on EveryLife's recent NBS initiatives, including leading rare disease community coalition efforts dedicated to the passage of the Newborn Screening Saves Lives Reauthorization Act; EveryLife remains focused on shortening the timeline between when a condition is added to the RUSP and what is screened for at the state level.

In December 2020, EveryLife convened a panel to review the impact of COVID-19 on NBS programs. One central theme throughout the discussion was the importance of considering NBS as an essential service to ensure the existence of a plan in support of the programming in times of public health emergency that encompasses a full range of services rather than only focused on emergency planning for laboratory services

E. Elisa Seeger, ALD Alliance and EveryLife Foundation

Ms. Seeger, Founder of the ALD Alliance offered comments on behalf of the EveryLife Foundation to inform the ACHDNC's ongoing conversations about the review process for new RUSP nomination packages.

Over the next decade, EveryLife anticipates an increase in the number of RUSP nomination submissions. Since the creation of the RUSP, patient organizations have led the nomination effort for multiple conditions, often spending years generating the evidence needed to submit a successful nomination. Ms. Seeger asserted that the current requirements make it impossible to bring forth RUSP approvals fast enough to keep pace with the opportunities innovation is bringing to the rare disease community, and she urged the Advisory Committee to consider significant challenges, including the non-feasibility for many patient organizations to run required prospective population-based pilots.

Recognizing the significant workload of the Advisory Committee and the pipeline of conditions that may be nominated, Ms. Seeger urged the Committee to consider accepting a degree of uncertainty regarding the amount of data available following the approval of a treatment or intervention and include other sources such as patient and community insights in order to accelerate the review of new disorders to the RUSP.

F. Niki Armstrong, Parent Project Muscular Dystrophy

Ms. Armstrong is the Director of Community Research and Genetic Services and Newborn Screening Program Manager at Parent Project Muscular Dystrophy (PPMD), which has, for the last seven years, been leading a national effort to build an NBS infrastructure for Duchenne Muscular

Dystrophy in the U.S. aimed at developing the evidence to support Duchenne NBS. This initiative and associated collaborations have resulted in multiple publications, diagnostic tools, and resources for primary care providers and families. PPMD's Duchenne NBS program incorporates expertise from leaders within the National Institutes of Health (NIH), HRSA, SCA, Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics (AAP), the American College of Medical Genetics and Genomics, past Congenital Muscular Dystrophy (CMD) pilots, the broader NBS community, and the Duchenne community. She presented information about the NBS Duchenne pilot in New York State, which PPMD initiated in October 2019.

More than 20,000 babies have been screened in the State of New York as of the end of 2020; three newborn boys with Duchenne or Becker and one female carrier have been identified.

G. Heidi Wallace, Association for Creatine Deficiencies

Ms. Wallace is the parent of two children with GAMT deficiency, including a girl age 17 who was diagnosed at age 5 and who suffers from intellectual disability and is not independent. Her 9-year-old son was diagnosed at birth and is in every way a typical 9-year-old. She also is the president of the Association for Creatine Deficiencies and works in the Utah Public Health Lab in the Newborn Screening Informatics Program.

Ms. Wallace explained that GAMT is detected by elevated guanidinoacetate, which can be multiplexed with existing amino acid and acylcarnitine screening. The treatment for GAMT is over-the-counter supplements that cost less than $100 for the first year of life

Ms. Wallace shared the difficulty that the one true positive criteria places on very rare disease groups like hers that have small communities and therefore not a lot of funding. This criterion has been very difficult, and she encouraged deep thought about the one true positive criterion.

The Association for Creatine Deficiencies is hopeful that the one true positive criterion is reconsidered so that the Advisory Committee's hands are not tied and best decisions can be made for other disorders in the future.

VI. Panel: Continuity of Operations Planning (COOP) and COVID-19

A. The National Landscape: COOP, COVID-19, and NBS

Susan Tanksley, PhD
Texas Department of State Health Services

On behalf of the Association of Public Health Laboratories (APHL), Dr. Tanksley shared information on the impact of COVID-19 on NBS, as well as Continuity of Operations Planning (COOP) resources that have been developed for NBS programs. According to the Newborn Screening Contingency Plan Version 2, the COOP for an NBS program and its public health laboratories should provide:

- *A comprehensive, pre-identified list* of all core testing, support activities (including reporting), and supplies that must be maintained if the laboratory or birthing facility experiences a partial or complete operational disruption; and
- *A prearranged plan of action* to ensure that all core activities are continued without delay.

An “emergency” in the context of NBS includes more than merely disaster conditions—it is anything that prevents timely identification of and/or adequate interventions for babies born with any of the disorders included in the NBS panel.

Emergency Measures After Hurricane Katrina

Dr. Tanksley reviewed the Louisiana Public Health Lab's actions in the wake of 2005's Hurricane Katrina, in which the lab utilized the Emergency Management Assistance Compact (EMAC) and received help from Iowa within one week. She noted that an immense amount of work occurred during that week, as Louisiana and Iowa did not have a Continuity of Operations agreement at that time; the states needed to work out all logistics, including specimen transport to Iowa, from which facilities Iowa would receive the specimens, differences in mandated disorders and in testing methodology, policies impacting test results, what Iowa would do about missing information or rejected specimens, and how results would be reported. Iowa also needed to figure out how to rapidly increase its throughput. The most important issues that EMAC resolves is liability and reimbursement.

Hurricane Sandy: Building on the Katrina Experience

New Jersey learned a lot from Louisiana's Hurricane Katrina experience. In 2013, New Jersey had not developed a formal COOP, but it was under discussion. The state had started to meet with EMAC about its potential use in the case of an emergency. The public health lab had organizationally been placed within emergency preparedness and had recently moved onto the campus of the New Jersey State Police, which also housed the Regional Operations Emergency Center, and discussions were underway with UPS. When it appeared that Hurricane Sandy could severely impact the state, discussions were held with key partners around things such as messaging on the essential nature of NBS and transporting of samples if the infrastructure was shut down. Once it became clear that the storm would be a direct hit, the state coordinated with UPS (which had otherwise shut down) and then with the police to ensure lab deliveries would be made. Communication was sent out through the New Jersey Hospital Association that hospitals were to transport specimens to the Regional Medical Coordinating Centers; the New Jersey State Police transported the specimens to the lab, where a skeleton crew worked tirelessly to process as many specimens as possible. After the storm, the lab had to be relocated, additional staff reported for duty, and UPS resumed some deliveries. Couriers were used for hospitals that UPS was unable to service.

Lessons Learned

After an emergency situation is over, it is important to identify lessons learned. The State of Iowa put together initial lessons learned from Katrina:

- *Interstate cooperation during emergencies is possible, and capacity exists within the NBS community.* Even without an agreement in place, Iowa and Louisiana were able to work together and rapidly develop and implement a plan of action.
- *EMAC provides an essential structure for rapid state-to-state emergency agreements for NBS*. This is not only for major catastrophes.
- *The states had great partners,* in particular benefiting from support by PerkinElmer.
- *It is essential to have a clear understanding of purpose and objectives.*

Emergency Planning

- The partnership between Iowa and Louisiana, while successful, highlighted the urgent need for states to develop COOP plans. It is important to remember that each emergency will have its own fingerprint and will require some degree of adaptive creativity in implementing any plan. Although it was compressed to just a few days, the planning between Iowa and Louisiana was essential. The opportunity now exists to establish planned procedures for reliable execution for future emergencies. Dr. Tanksley noted that NBS is a system with multiple partners, all of whom need to be involved in COOP planning and cross-collaboration.

COVID-19 COOP Planning: Surveying State NBS Programs

APHL administered a survey in November 2020 to gather information on the impacts of the pandemic on NBS processes. The survey was sent to all state NBS programs as well as DC, Puerto Rico, and Guam (53 programs total) with the goal of capturing laboratory, follow-up, and other perspectives. A total of 34 programs responded, with 11 of those submitting responses from laboratory and follow-up staff.

Challenges During COVID-19

Challenges reported by the state NBS programs include the following:

- *Transport issues included postal service or private courier delays, or changes with pickup and delivery schedules or locations.* Other transport issues involved changes in hospital or birthing facility processes that caused delay or loss due to specimens being misplaced or to changes in courier personnel.
- *All but one state program that responded has faced some sort of staffing challenge throughout the pandemic.* Many states noted that some of their staff that were reassigned to focus on COVID efforts. States have experienced staff who retired early or changed jobs; because of the vast demand for laboratory staff, labs have lost experienced staff to companies offering higher salaries to perform COVID testing. Some staff had problems with homeschooling and childcare due to shutdowns, many of which are ongoing. Hiring freezes and furloughs have served to make the problem worse. Low staff morale and first-time teleworking and the associated changes (e.g., going from paper to paperless processes) have presented challenges. Staff or their family members have tested positive, which has caused the inability to work. Staff have also dealt with transportation systems being shut down and home technology issues.
- *Supply shortages have been created by the pandemic, most notably in this context a worldwide shortage of plastics.* Pipette tips in particular have been an extreme concern for NBS programs. Even the ability to service instruments has been limited or delayed due to the incredible demand created by COVID testing.
- *Even when NBS is considered an essential service, different parts of the program may be prioritized differently.* In one example, long-term follow-up was not considered a priority program within NBS; most follow-up staff were reassigned to COVID duties.

Survey respondents believe that multiple methods are needed to ensure that NBS becomes a priority, including communicating with leadership, developing COOP, engaging external stakeholders, and establishing NBS as an essential service within the health department. Since the survey was fielded, state programs have expressed concerns about individuals who need to work onsite, such as in the lab, being considered essential for the purpose of vaccine distribution.

B. National Newborn Screening Contingency Plan (CONPLAN Version 2)

Scott Shone, PhD, HCLD(ABB)

Director, North Carolina State Laboratory of Public Health

CONPLAN Development

CONPLAN Background

Dr. Shone provided background on the National Newborn Screening Contingency Plan (CONPLAN), noting that the Newborn Screening Saves Lives Act of 2007 directs CDC, with HRSA and state agencies, to develop a national NBS CONPLAN for use by a state, region, or consortium of states in the event of a public health emergency. In 2008, federal partners, state public health programs (including NBS programs, state labs, and maternal child health programs), state emergency preparedness programs, and clinicians developed the initial CONPLAN Version 1 the plan was subsequently published in 2010.

In 2015, the Association of Maternal & Child Health Programs (AMCHP) partnered with CDC, HRSA, APHL, and expert stakeholders from the NBS system to develop CONPLAN Version 2. It included wide representation from NBS programs, public health labs, regional collaboratives, family voices, newborn screening Health Information Technology (HIT), metabolic specialists, Title V, and numerous professional organizations. CONPLAN Version 2 included four main areas of updates—Strategic Objectives (revised and reordered by NBS system chronology), Point-of-Care Resources (not included in CONPLAN V1), Responsibility Matrix (goal: ensuring that people understand their roles), and Appendices (including new resources).

Strategic Objectives of CONPLAN 2

CONPLAN 2's strategic objectives encompass the entire NBS process, including a cascade of communication to families, providers, birth facilities, and agency staff; education for families; assuring that the existence of a framework for blood spot, hearing, and CCHD specimen collection and transport; diagnostic testing; results reporting; diagnostic follow-up; treatment management; and other activities. Dr. Shone noted that only two of these elements—specimen processing and testing, and reporting and follow- up rely solely on the state NBS programs; all others involve the entire system. The most effective continuity plans will include more than NBS programs.

North Carolina's NBS Program COVID Experience

Challenges

Before masking, plexiglass, and lab reorganization, staff were split into two groups that worked onsite on different days; this helped avoid exposure but obviously presented challenges to the work. There was a noticeable reallocation of resources to COVID by vendors, which affected the NBS program's supply chain. The lab experienced delays in transport as courier services were impacted by COVID.

The NBS program's IT team was working out how to configure multiple COVID tests ; the facilities team was working to ensure new instruments for COVID were added; and the NBS team was in the process of a massive expansion of disorders. Another issue was decision-making by leadership, whose focus was, understandably, on COVID for a long period of time.

Dr. Shone pointed out that, even with an overwhelming amount to tackle, NBS programs keep things moving, addressing timeliness and unsatisfactory samples, adding disorders, and conducting follow-up.

Next Steps 2020

Dr. Shone shared what he sees as necessary for moving forward on COOP development:

- *Assure NBS is part of public health (lessons learned from COVID-19 response.)*
- *Continuous process improvement prepares systems.*
    - Contingency planning does not equal preparedness. To be prepared, systems need to learn lessons and use time between these events for ongoing quality improvements to processes.
- *Identify "cranes".*
    - Find resources and supports that allow for efficient, effective expansion of effort.
- *Use a whole system approach.*
    - Every program has to work together to make this happen.

C. COVID-19 Impacts on the North Dakota Newborn Screening and Follow-up Program

Joyal Meyer, RN, MSN
Program Director, North Dakota Newborn Screening Program
North Dakota Health Department

Public Health System
North Dakota has 28 independent local public health agencies, some of which are combined. Seventy-five percent of the local public health systems and units serve as a single city or combined city and county jurisdiction, and 25% serve multicounty jurisdictions; the majority of those multicounty public health units—which are required to meet standards and follow state laws and regulations, but are allowed to exercise powers and have administrative authorities to make decisions that meet their local needs—are in the western portion of the state.

NBS Challenges
Because tribal governments function independently from federal and state governments, the state has no authority to track down children and families on the reservations. At times, this has posed challenges in locating babies with abnormal screens. Also, in 2019, there was a significant rise in the state of confirmed traits and disorders, which included hemoglobin and cystic fibrosis traits, as well as babies diagnosed with cystic fibrosis.

NBS History and Processes
The University of Iowa State Hygienic Library (SHL) began screening newborns in North Dakota in 1992. In 2007, nurses at University of Iowa hospitals and clinics began doing short-term follow-up services for North Dakota. North Dakota and Iowa currently have an MOU for laboratory screening and follow-up services. North Dakota began outsourcing NBS in the 1990s because of the increasing fees of equipment and laboratory costs; it also was more feasible for North Dakota to partner with Iowa on screening for metabolic disorders since Iowa had the expertise and infrastructure in this area.

The SHL also provides screening and follow-up services to South Dakota and Alaska, and Iowa processes the billing for North Dakota newborn screens and invoices North Dakota facilities who, in turn, bill the patient's insurance. The current NBS fee in North Dakota of $96.00 includes lab processing; short-term follow-up services (provided by Iowa); courier service; and medical consultation by Iowa physicians as a backup for North Dakota specialists on evenings, weekends, and holidays.

Courier Transportation
Meadowlark Logistics has transported specimens from all 12 North Dakota birthing facilities to Iowa seven days per week, 365 days per year since July 2019. Prior to that, there was no transport on Sundays and limited transport on Saturdays. North Dakota has weekday and weekend transport processes with shared Meadowlark customers in surrounding states.

NBS Reporting Results
Since 2016, more than 95% of our specimens collected with time-critical results were reported out by five days of life. This high percentage is a result of continuous education of the 12 birthing facilities, outstanding courier service, and the work of partners in the Iowa lab and short-term follow-up programs.

NBS Education
The Newborn Screening Century Code for North Dakota mandates that the program provide education to licensed clinicians, hospital staff, public health nurses, and citizens of the state.

North Dakota has an NBS advisory committee, with representation from all 12 birthing facilities as well as from partners including parents, and family support groups.

Education modules provide an overview of the NBS program and disorders that are included in the state panel. The program has hosted hot topic lunch and learn sessions for partners, and it held two well attended conferences. Throughout the pandemic, the NBS program has continued to provide virtual education to hospitals and clinic staff on a routine or as-needed basis.

This education has led to a significant decrease in the percentage of our poor-quality specimens. North Dakota had been fairly stable with poor-quality specimen (below 1%) until the beginning of COVID in spring 2020, when it experienced an increase of poor-quality samples similar to other state NBS programs. The poor-quality rate has since declined.

Reaching Underserved Populations
North Dakota is one of eight member states in the Heartland Regional Genetics Collaborative. The goal of this network is to increase genetic services, particularly for medically underserved populations. This is accomplished by helping to increase accessibility to care through high-quality telehealth and telegenetic services offered to parents or patients and their families.

The only metabolic geneticist in North Dakota is located in Fargo, in the eastern part of the state. Telehealth has really been a great opportunity to connect with families in the western part of the state, especially through COVID and during the winter months.

Contingency Planning
Although the North Dakota Newborn Screening Program currently does not have a formal contingency plan, it is planning to partner with the other states who use Iowa as their screening laboratory. The North Dakota Public Health Laboratory and the NBS program use the same courier service, the state lab will be included in developing the COOP to help streamline processes.

COVID Impacts on the NBS Program
The North Dakota Public Health Lab is a member of the Northern Plain Consortium, which includes North Dakota, South Dakota, Idaho, Montana, and Wyoming. Prior to COVID, the Consortium had 18 employees, included laboratory and support staff; after COVID, that staff number increased to 140 full-time and part-time employees, with all 140 working full time at the peak of testing. With COVID, the state lab went from operating hours of 8 a.m. to 5 p.m. weekdays only (no holidays) to 24 hours a day currently seven days a week, including holidays. The courier transportation ramped up from five to seven days a week.

The NBS program has two FTEs at the state level, and both have been a part of the COVID response since March 2020. Ms. Meyer was relieved of her COVID response duties just earlier in the week, and her coworker still is assisting with the COVID response for the time being. If there is another surge in cases, they will need to assist with the response.

D. The Impact of COVID-19 on Newborn Screening in New York State

Michele Caggana, ScD, FACMG
Director, Newborn Screening, Wadsworth Center
New York State Department of Health

The Early Days of COVID

In early March 2020, the New York State Newborn Screening Program became aware of several potential changes in New York City, early discharges from hospitals (between 12-24 hours – this ultimately did not happen on a large scale) and of changing availability of specialists and providers, as some were deployed to emergency departments or told to close their offices and move to telehealth. The NBS program began to receive reports from downstate New York of parental hesitancy in bringing their babies on public transport or to the hospital/pediatrician. Many provider outpatient clinics and offices were closing or not allowing families to return to the nursery for specimen collections, and some hospitals reported that couriers were not allowed to enter the hospital, let alone go to through the building to pick up specimens. The program staff were also concerned about the impact of potential reductions in staff. By March 15, the state reduced staffing to only essential staff; on March 28, it went into full NY PAUSE, with businesses closed.

Rapid Response

The NBS program developed a protocol for handling of forms from babies of COVID-positive moms, batching them separately; this prevented data entry staff from having to handle them, and it would allow for potential study access. On March 26, the program sent an email blast to almost 10,000 health care providers, informing them of the various changes; education about specimen collection and information on how to order NBS collection forms (collecting repeats was something they were not necessarily accustomed to doing) as well as fact sheets on the various NBS conditions in case a provider had to work on a referral for a metabolic condition on their own. Requests for collection forms rose following that communication.

The NBS program also initiated Saturday testing in order to allow for time to find babies with critical screening results, knowing that parents were hesitant to answer phones and bring babies into facilities. This also helped staff to manage its daily workflow, as they anticipated a decrease in the number of people performing the lab work.

Staffing and Process Adjustments

Data entry, follow-up, laboratory, IT, and other staff continually adjusted to new protocols as the NBS program reworked processes and improved efficiencies in response to COVID requirements, expanded laboratory use, and staffing realities. NBS essentially condensed to allow for potential expansion of COVID testing. It set up remote IT access for staff; implemented an all-hands-on-deck, offsite-friendly data entry and analysis model; cross-trained some NBS staff and pulled in some nonessential staff from the environmental mass-specimen lab as back-up; communicated consistently with supply and equipment vendors; created more thorough, detailed, descriptive educational materials; and gathered and updated provider contact information. The NBS program also helped with COVID sero-prevalent studies, which were offered to the public, health care workers, and other essential workers.

While early discharge after delivery did not happen on a large scale, the NBS program continues to receive specimens collected very close to the 24-hour mark. Also, there was not a rise in time to collect repeat specimens, thanks to providers who found a way to collect repeats in a timely fashion.

Lessons for COOP

While a program can plan for disruptions such as an instrument outage, changes in test reagent availability, or a localized weather challenge, it is difficult to plan for an event that takes out half/the entire state. Throughout the pandemic, teamwork was critical. The New York State NBS Program relied on providers, clinics, hospitals, labor and delivery departments, couriers, care coordinators, specialists, its own staff, parents, and others to ensure that no babies fell through the cracks.

Current Realities
Supply chain shortages remain for pipette tips, plastics, and gloves. This has led the program to reformat some of its testing, specifically with tip usage, to ensure a constant supply of reagents. NBS programs are dealing with increases in staff departures, due to early retirements, normal job changes and hiring freezes. Also, budget shortfalls and other issues exist while the program works to maintain operations. While the focus has changed, COVID-related COOP is still evolving.

VII. Workgroup Meetings (Breakout Session)

Prior to the three ACHDNC workgroups—Education and Training, Follow-up and Treatment, and Laboratory Standards and Procedures—breaking for their individual sessions, Dr. Powell provided them with the following discussion questions:

Education and Training Workgroup

- What range of issues related to education should the Advisory Committee consider when a condition is added to the RUSP?
- What types of information and educational resources would be most helpful when a condition is added to the RUSP?

Follow-up and Treatment Workgroup

- What type of long-term follow-up information should be considered when a condition is added to the RUSP?
- What type of information should be considered in a systematic review of conditions on the RUSP?
- Should the cost of treatment be a factor in both the nomination process and the review of conditions on the RUSP?

Laboratory Standards and Procedures Workgroup

- What information would be most helpful from newborn screening labs related to the review of conditions on the RUSP? How can we prepare newborn screening labs to collect and report this data?
- Should there be more in-depth information regarding cost to labs for adding a new condition to the panel, or is there already enough information provided?

All Workgroups

- Are there any other considerations for enhancing either the nomination process or review of conditions on the RUSP?

VIII. Administrative Business – February 12, 2021

A. Welcome and Roll Call

Dr. Powell welcomed participants to Day 2 of the February 2021 meeting of the Advisory Committee on Heritable Disorders in Newborns and Children.

The Committee members in attendance were:

- Dr. Mei Baker
- Dr. Jeffrey Brosco
- Dr. Kyle Brothers
- Dr. Carla Cuthbert (Centers for Disease Control & Prevention)

- Dr. Jane DeLuca
- Dr. Kellie Kelm (Food & Drug Administration)
- Dr. Kamila Mistry (Agency for Healthcare Research & Quality)
- Dr. Melissa Parisi (National Institutes of Health)
- Dr. Cynthia Powell
- Ms. Annamarie Saarinen
- Dr. Scott Shone
- Dr. Michael Warren (Health Resources & Services Administration)
- Ms. Mia Morrison (Designated Federal Official)

Organizational representatives in attendance were:

- American Academy of Family Physicians, Dr. Robert Ostrander
- American Academy of Pediatrics, Dr. Debra Freedenberg
- Association of Maternal and Child Health Programs, Dr. Jed Miller
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health Officials, Dr. Christopher Kus
- Association of Women's Health, Obstetric & Neonatal Nurses, Ms. Shakira Henderson
- Child Neurology Society, Dr. Jennifer Kwon
- Department of Defense, Dr. Jacob Hogue
- Genetic Alliance, Ms. Natasha Bonhomme
- March of Dimes, Dr. Siobhan Nolan
- National Society of Genetic Counselors, Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders, Dr. Georgianne Arnold

IX. Workgroup Updates

A. Education and Training Workgroup Update

Jane DeLuca, PhD, RN, CPNP
Workgroup Chair

Discussion Questions

- What range of issues related to education should the Advisory Committee consider when a condition is added to the RUSP?
- What types of information and educational resources would be most helpful when a conditions is added to the RUSP?

The workgroup concentrated mostly on the first question for its discussion, beginning by considering what we are trying to achieve or improve through informational efforts. Questions that arose were: What do we mean when we say education? Is this awareness, is it training? Should it be directed towards parents, providers, or other stakeholders? Are there increased risks in screening for certain populations? What does the diagnostic and treatment process look like? Do we have a roadmap? How do parents and providers navigate this? What are some of the aspects of providing support to parents upon notification of an abnormal newborn screen? What types of tools are needed, and in what languages, so we can appropriately educate various stakeholders?

The workgroup discussed the following issues related to education:

- Many types of learners exist in NBS.

    - The Advisory Committee has an Education Planning Guide (the "grid") on its website; it includes 31 stakeholder groups and matches them with 28 categories of knowledge.
- Where does education fit in the nomination process?
    - The workgroup felt that education during the decision-making process has not been considered to any large extent. Perhaps the APHL survey of the state programs has data on this.
- Consider education early in the nomination process.
    - This can be a bidirectional dialogue to increase awareness across various stakeholders.
    - Early dialogue between stakeholders from the nomination point to implementation can aid in messaging expectations.
    - Identifying educational needs early in the nomination phase rather than waiting until a disorder is implemented could be useful.
- There is a wide variety of state screening systems.
    - Some states take the federal recommendations as is, while others have their own RUSP processes or decision-making mechanisms.
    - It could be important to educate the public of differences in approaches to screening and available resources among states.
    - Especially important now are limited resources in states for screening, which has been exacerbated as COVID has seized health departments. New disorders may not be added by a state.
- Develop education for stakeholders with varying levels of NBS knowledge.
    - NBS staff, policy-makers, health care providers may require targeted education.
- No agreement exists among stakeholders as to what constitutes benefits and harms of screening.
    - How can we define physical versus psychosocial harms and benefits and the magnitude of each?
    - How do we educate about potential harms? Is there a way to communicate this within the nomination process? Should it be requested of a nominating group, for example, that they consider benefits and also harms of screening from their perspectives?
    - Education could help mitigate some of the harm and support families through the process.
- What role can the Advisory Committee play within its framework and limited resources? What is the Advisory Committee set up to do?
    - After a condition is added to the RUSP, the Advisory Committee could produce a one-page description of why the disorder was added and what happens next.

B. Follow-up and Treatment Workgroup Update

Jeffrey Brosco, MD, PhD
Workgroup Co-Chair

Discussion Questions

- What type of long-term follow-up information should be considered when a condition is added to the RUSP?
- What type of information should be considered in a systematic review of conditions on the RUSP?
- Should the cost of treatment be a factor in both the nomination process and the review of conditions on the RUSP?

What type of long-term follow-up information should be considered when a condition is added to the RUSP?

The workgroup reviewed ideas initially suggested in 2019 and made only minor changes:

- Longitudinal follow-up should be considered from the beginning.
- The nomination process could include a "blueprint" for longitudinal follow-up. Questions to be answered include:
    - Will identified infants have access to treatment?
        - Equity issues need to be addressed.
    - What are the best outcome measures (e.g., death, quality of life, ability to walk, need for a ventilator) for the particular condition?
        - The nominating group should communicate what researchers, clinicians, family members, youth and adults with the condition feel are important outcomes.
    - What will be the (potential) process for obtaining population-level data? (e.g., a patient registry)
- The process should take into account that different conditions have varying levels of resources.
    - The workgroup was clear that these suggestions should not be scored but that the Advisory Committee should at least begin thinking about longitudinal follow-up from the beginning of the nomination/review process.

What type of information should be considered in a systematic review of conditions on the RUSP?

- Can the Evidence Review Group develop models of potential benefit-harm ratios as a way of organizing later systematic review?
- How accurate was the prediction of benefits and harms (lessons learned)?
    - The modeling noted above could be used to gather lessons learned (comparing modeling with outcomes).
- Should harms be used as a way to prioritize?
    - Identify red flags and review a condition if the ratio of benefit to harm shift
- Did everyone benefit from NBS? (equity, population health)
    - Are there disparities that need to be addressed?
- Natural history of the condition?
    - This includes the range of diseases, secondary targets, late onset, true prevalence, etc. These will be important for informing future decisions.
- What barriers exist and are they condition specific?
    - Systemic data collection in common categories would allow states to learn from each other over time.

- When/what conditions to review?
    - One idea is to develop a two-step process to set priorities, perhaps briefly reviewing 10 conditions each year (published data say, a quick survey), and identifying any condition for which the ratio of benefit to harm has changed significantly and therefore requires closer examination.

Should the cost of treatment be a factor in both the nomination process and the review of conditions on the RUSP?

All workgroup members agreed that this an area that needs more focus. The overwhelming sense was that cost probably should not influence whether or not a condition is added to the RUSP. Instead of cost, we should probably be thinking about access.

C. Laboratory Standards and Procedures Workgroup Update

Kellie Kelm, PhD
Workgroup Chair

Discussion Questions

- What information would be most helpful from newborn screening labs related to the review of conditions on the RUSP? How can we prepare newborn screening labs to collect and report this data?
- Should there be more in-depth information regarding cost to labs for adding a new condition to the panel, or is there already enough information provided?

What information would be most helpful from newborn screening labs related to the review of conditions on the RUSP? How can we prepare newborn screening labs to collect and report this data?

The workgroup's discussion produced the following ideas:

- It would be beneficial to develop and implement objective performance metrics in screening for conditions.
    - The Advisory Committee could provide expected positive predictive value (PPV) and negative predictive value (NPV), for every condition.
    - States could then look at their own systems and determine whether or not they are meeting the NPV and PPV for each condition.
    - We should also be looking at evaluating and reporting the false positive rate (FPR) and false negative rate (FNR). Many of the conditions on the RUSP already include a second-tier test, but it may also be useful to examine some of them.
- It is necessary to begin with a clear case definition.
    - We need to examine which conditions states screen for and what else they are finding.
    - Note that the case definition could change over time.
- NewSTEPs could be used to collect the data.

Should there be more in-depth information regarding cost to labs for adding a new condition to the panel, or is there already enough information provided?

The workgroup suggested that the following would be helpful in addition to what is gathered through the Public Health Impact Assessment:

- *Have states provided the cost* of adding a specific condition to the overall system, not just the lab costs such as reagents, employees, instruments, second-tier testing, LIMS, etc.
- *Use a bucket approach* (small, medium, large); breaking costs down by states, that start at differing levels of readiness to bring on a new condition.
    - One example is when SCID was added to the RUSP: Some states were much more ready than others to add molecular testing.

Are there any other considerations for enhancing either the nomination process or review of conditions on the RUSP?

Although the workgroup did not have much time to discuss this, it did note the following:

- It is helpful for NBS programs to have clear case definitions.
- There is confusion about what the RUSP is and whether it is for both the primary and secondary targets on the list.
    - Suggestions: 1) educate stakeholders (states and clinicians); 2) clarify the RUSP on the ACHDNC website.

D. Discussion: Workgroup Ideas

- A Committee member addressed the difficulty in gathering cost information, suggesting that it could be helpful to separate information the Advisory Committee gathers from the evidence review and information gathered after a condition is added to the RUSP. He noted the benefit of collecting information beyond projected financial costs, such as human capital (e.g., how many neurologists a state has), access to resources, and level of effort for getting up to speed on testing for a particular condition. Finally, he asserted that such information could help states as they work to implement a new screening.
- A Committee member highlighted the importance of educating stakeholder on the purpose of nominating a condition and the goals of NBS.
- While state NBS programs vary widely, there are buckets of states that have developed similar solutions for implementing new conditions. Perhaps the Advisory Committee could find a way to work with HRSA to categorize the state programs for use in assessing impacts.
- A Committee member noted that the spectrum of disease defined as “mild” can have a significant impact on a child’s medical care and morbidity. Examples include MPS1, CAH, and X-ALD. She also agreed with the importance of envisioning a system-wide approach for long-term follow-up.
- A Committee member used critical congenital heart disease (CCHD) as an example of a condition that varies widely in newborns and requires monitoring over time. She expressed concern around the lack of clarity about how secondary conditions fit into the Advisory Committee’s framework for data collection and tracking.
- An organizational representative noted that the Advisory Committee generally has a good understanding of implementation/short-term follow-up for a new condition. However, often times more information is needed on long-term follow-up needs (e.g., two years, five years). He would like to see the nominations indicate a vision for that care.

- An organizational representative believes that the Committee should investigate harms when RUSP conditions are brought up for review, and recommended getting input from the United States Preventive Services Task Force (USPSTF) as it has a system in place for periodically reviewing its public health recommendations and making revisions. Much of that has to do with harm/benefit reviews and evaluating the benefits to harms by assigning harms to categories (e.g., economic, psychosocial, medical).
- An organizational representative would appreciate the Advisory Committee coming to consensus on its scope of responsibility. As it reviews the existing RUSP conditions, she suggests that the Committee keep in mind the complexity of surveillance and long-term treatment.

X. Panel: Innovations in Long-term Follow-up

A. Long-term Follow-up for Infants and Children Identified Through Newborn Screening

Jeffrey Brosco, MD, PhD
Professor of Clinical Pediatrics, University of Miami School of Medicine Department of Pediatrics
Deputy Secretary, Children's Medical Services, Florida State Department of Health

2019 FUTR Workgroup Proposal: A 'Federated System'

The FUTR Workgroup proposes a "federated system" that assures every child identified with an NBS condition receives high-quality, evidence-based, family-centered care. Dr. Brosco emphasized the varied nature of U.S. health care systems; fortunately, the NBS system is one of the very few systems that tries to establish national standards that states then implement. The goal is for different stakeholders to work together to create an interconnected NBS system; one way to do this is to leverage the electronic health record (EHR) and artificial intelligence (AI) for more efficient data collection. A major gap exists in financial resources to address loss to follow-up, and identifying potential barriers to equity is essential to planning and implementing post-diagnosis care.

<u>Why a Federal System? Varied Goals</u>

The three main categories of longitudinal follow-up* are:

- *Research*
    - What is the outcome of NBS (e.g., early treatment) for this condition? Would clinically diagnosing conditions have produced a similar outcome?
    - What else can we learn from changing the natural history of a condition by performing NBS?
- *Quality improvement/assurance/return on investment (ROI)*
    - Did the child identified by an NBS program receive treatment? What was the outcome of that treatment? Data points could include simple things such as the child being alive at age 5 and not needing special education at age 10.
    - What is the impact of the NBS program on a condition broadly? Is there a decrease in the number of children who experience long-term effects of the condition?

- *Clinical care*
    - How is a particular child doing? Is s/he receiving all necessary treatment? What is the outcome/prognosis?

Why a Federal System? Varied Groups with Interest in NBS Population

Children with NBS conditions are a subset of children with greater-than-usual need for medical, social, and/or educational intervention (children with special health care needs ([CSHCN]) and make up 1% or 2% of children overall, depending on what is included in NBS.

Specific interest groups may be interested in different groups of children.

- *Maternal and child health bureaus, Medicaid, and state departments of* health are concerned with all children and making sure that every child gets the care they need (assurance and equity for all children).
- *State Title V CSHCN programs* are particularly interested in assurance and equity (reduced disparities) for CSHCN children, who are 15% to 20% of the general child population.
- *State NBS programs* are interested in assurance and equity for children who are diagnosed through NBS.
- *Clinicians, researchers, and family members* tend to be focused on an individual child with an NBS condition; however, many feel a greater responsibility to the larger population of "NBS children".

State NBS: Equity in Diagnosis and Treatment

The FUTR Workgroup has developed ideas for working toward equity in state NBS programs.

Diagnosis

Dr. Brosco noted that NBS program diagnoses create equality, giving the example of how SCID NBS led to racial/ethnic heterogeneity of treatment in California. Article on NBS program here.

Treatment

Equity is lacking in treatment. Examples of disparities include a lack of access to antibiotics for Sickle Cell Disease (SCD), to treatments for congenital hypothyroidism, and to specialists and medical foods necessary to protect cognitive development for Phenylketonuria (PKU) patients.

Equity: Redefine Cost of Treatment as Access to Care

Dr. Brosco suggested that the Advisory Committee use the World Health Organization (WHO) definition of access, which is the interaction of availability, affordability, accessibility, appropriateness, acceptability, and quality:

Sometimes, a system cannot have everything in place to start treating some patients. Of course, children should have access to treatment for identified conditions. Equity needs to be the goal, but completely leveling the playing field cannot be used as an excuse to delay implementation. In fact, sometimes simply starting implementation can spur equity.

Explicit bias and implicit bias are rife in the U.S. health care system, and disparities sadly are the norm. State NBS programs, researchers, clinicians, family advocacy cannot be expected to solve our health care system or issues of racism and economic inequality. However, NBS is a public health program, so it has a greater obligation to meet the treatment needs of infants and children. Equity has some impact on the Advisory Committee as it thinks about how to expand NBS to new conditions if treatment is not available to every child.

B. NewSTEPs Long-term Follow-up Taskforce

Carol Johnson
Follow-up Coordinator, Iowa Newborn Screening Program
Co-Chair, APHL Short-term Follow-up Workgroup
Co-Chair, APHL Workforce Workgroup

In May 2018, APHL hosted the NewSTEPs Short-term Follow-up National Meeting to present a forum for follow-up staff to discuss solutions to common issues. From that meeting, five taskforces were created to address LTFU needs within the NBS community; one of those is the LTFU Taskforce.

LTFU Taskforce Deliverables
The taskforce developed *a working definition of LTFU* and used it to guide development of questions and data elements for a survey it sent to NBS follow-up programs.

LTFU Landscape Survey
The 20-question *LTFU Landscape Survey* assessed LTFU activities, program needs, and barriers across NBS programs in 54 states. It was distributed to 76 distinct contacts (NBS staff from hearing, CCHD, and dried blood spot screening programs), and the taskforce welcomed responses from multiple entities per state. Ultimately, 42 responses (a 55% completion rate) were received. Of these, 32 were complete responses; only these were included in the data analysis.

Survey Results
Ms. Johnson highlighted selected data from the survey responses. Approximately half of programs do at least some LTFU activities, but 41% responded that they have no plans to implement a LTFU program at this time. Several programs are funding their LTFU activities by using their NBS fee, some are using grant funding, and some are using state funding; more than half of those using their NBS fee reported it as the sole funding source for LTFU activities. NBS programs are performing a range of LTFU activities (top activities include data collection from clinical providers, clinical care follow-up, connecting individual families to services and supports, and data collection from the state health department NBS program); 42% of respondents stated that they actually do more than four distinct LTFU activities.

Programs shared the percentage of conditions on their NBS panel that receive services or activities, with responses ranging from low to high percentages. Several programs are using data they collect to track babies lost to follow-up, track clinical outcomes, assess the needs of individuals and families for services, evaluate provider performance, and conduct cost-benefit analysis of testing.

Programs conduct LTFU for a wide range of time periods, with a general decrease over time. Just 25% of state programs that responded to the survey currently conduct LTFU for the lifetime of the individual.

Finally, respondents were asked to comment on what NewSTEPs could do to help states maintain an LTFU program. Many states expressed frustration with lack of support from program leadership for implementing or expanding their LTFU; program leadership does not consider it a priority, even though the Advisory Committee has stated that "all NBS conditions are chronic and therefore require medical care and intervention throughout the affected individual's lifetime." (ACHDNC, 2008)

APHL's Role in LTFU
LTFU is a critical component of the NBS system, and the APHL LTFU Taskforce plans to develop and submit a *manuscript* for publication on the status of LTFU to *The International Journal of Neonatal Screening* for its special follow-up edition. It also hopes to develop a *position paper*

identifying a role for APHL and LTFU, to develop a definition for LTFU, and/or to identify those key components of an LTFU program. The taskforce is considering developing an *LTFU fact sheet* for programs to demonstrate the importance of LTFU to their leadership, and to offer technical assistance to programs that want to develop and implement an LTFU system as well as those who need and want to maintain and enhance their current program.

ACHDNC's Role in LTFU
The taskforce would value any input from the Advisory Committee in this area.

C. Spinal Muscular Atrophy (SMA) Newborn Screening Long-term Follow-up

Mary Schroth, MD, FAAP, FCCP
Chief Medical Officer, Cure SMA

About Cure SMA
Dr. Schroth explained that Cure SMA is a nonprofit patient advocacy organization that funds and directs comprehensive research that drives breakthroughs in treatment and care. Its focus is patients and families living with Spinal Muscular Atrophy (SMA). Cure SMA has 36 volunteer-led chapters totaling 120,000 families and supporters throughout the U.S.

SMA Screening
Thirty-three states screen for SMA, including those that are permanently implemented and those that are conducting pilots. Based on some of Cure SMA's modeling, that represents a little over 68% of all infants in the U.S. currently being screened.

SMA was added to the RUSP in 2018.Twenty-five states have screened approximately 2.5 million infants since January 2018. Among those screened, 173 infants were identified through NBS. About 180 families have contacted Cure SMA after diagnosis.

SMA Data
Data Collection
It is critically important to gather data about SMA populations. Cure SMA is committed to gathering real-world data and currently has three pathways to collect data:

- The *SMA Newborn Screening Registry* is available to families through the Cure SMA website. Families provide consent and answer NBS Registry Survey questions about their child including the date of the child's confirmatory diagnosis, treatment start date and type, and symptoms at time of treatment. Families are invited back every year to answer additional questions for this longitudinal registry. The survey is supported by the Cure SMA Newborn Screening Coalition, comprised of Cure SMA, Novartis, and Genentech.
- The *Cure SMA Membership Database* houses information families provide when they contact the organization and through an annual survey for patients, families, and caregivers. This database is also used to recruit for clinical trials and surveys, to better understand the experience of SMA over time, to share information with regulatory officials, and to advance care and opportunities for the SMA community.
- The *Cure SMA Clinical Data Registry (CDR)* is approximately three years old and is fed by the growing SMA Care Center Network. Nineteen centers affiliated with the network for SMA consent patients and clinically collect information within their EHR that is electronically transferred to the registry. A goal is to understand and maximize moving data from EHRs to the registry for analyzing and mining that data.

Data Points

Dr. Schroth highlighted some patient-provided data:

- New contacts diagnosed via NBS have gradually increased, an expected outcome of the growth in the number of states implementing NBS for SMA.
- During the early months of COVID, fewer infants were diagnosed clinically and through NBS, reflecting decreased in-person visits and evaluations of infants under two years old. This could mean delayed diagnoses for infants with clinical symptoms of SMA.
- SMN2 copy number results:
    - Membership Database: Approximately 50% of children have two copies. A small percentage has one copy, 32% have three copies, and 17% have four of more.
    - SMA Newborn Screening Registry Survey: Ten percent of children have one copy, 42% have two copies, 31% have three copies, and 17% have four or more.
        - Treatment status by copy number: The majority of the infants receive treatment. Some families decline treatment for their infants.
        - Median age at diagnosis and treatment: Range diagnosis age is 0-22 days with a median of 6. Age of treatment ranges vary by copy number, with the greatest spread at four or more copies.

Future Plans

NBS is dramatically changing processes and disease outcomes, and Cure SMA continues to collect data with the goal of understanding processes time of symptom onset until diagnosis by copy number.

Plans are to evaluate the SMA NBS outcomes across the real world evidence data searches with an eye toward improving time to diagnosis. This involves reviewing clinical care delivery, referral processes, time to treatment, symptom spectrum, and SMA phenotype.

Discussing SMA by types is transitioning to SMN2 copy number and maximum motor function achieved, as many children being treated pre-symptomatically cannot be defined accurately by type. Cure SMA has added an "unspecified" category for clinician discussions because pre-treatment teens and adolescents groups identify an SMA type, but infants being treated pre-symptomatically are being thought of in a different way.

D. Data Tools and Resources from the Newborn Screening Translational Research Network (NBSTRN)

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NBSTRN Background

Funded by a contract from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the NBSTRN has matured into a dynamic and committed network comprised of researchers, health care professionals, state NBS programs, families, and advocacy groups. The NBSTRN team at the American College of Medical Genetics and Genomics (ACMG) is beginning its 13th year with a renewed mission to facilitate the discovery and validation of novel technologies to screen and diagnose disease; pilot new technologies and treatments; describe the ethical, legal, and social implications of NBS research; and collect longitudinal health and genomic data.

NBS in the U.S. is a multicomponent, multi-stakeholder system of prenatal education; hospital and state-based public health laboratory screening; clinician, and state-based laboratory confirmation and diagnosis; clinical treatment and management; and health outcome analysis. NBSTRN data tools, resources, and expertise are designed to facilitate the efforts of all stakeholders and leverages each component of the NBS system to advance research.

NBSTRN Data Collection

Data Tool

NBSTRN developed the Longitudinal Pediatric Data Resource (LPDR) to provide a secure environment for researchers to collect, aggregate, analyze, and share phenotypic and genomic data in question-and-answer sets (commonly called common data elements) developed by subject matter experts. Since its launch in 2013, the cloud-based, stakeholder-accessible LPDR has been utilized by several research teams and state NBS programs conducting longitudinal data collection of both RUSP and candidate conditions, efforts that explore the use of genomic sequencing in the newborn period, and groups conducting pilots of candidate conditions.

Key objectives of the LPDR are the sharing of findings and secondary use of data. The LPDR facilitates this data sharing and data standardization with third-party databases including the NIH's National Center for Biotechnology Information (NCBI), the Database of Genotypes and Phenotypes (dbGaP), and the National Library of Medicine's NIH COVID Repository. The LPDR also provides access to data dictionaries from studies that can be used to create electronic data entry forms and also features case-level datasets that are deidentified and available for data mining.

Secondarily, the accrued LPDR data may help to establish the efficacy of new treatments and management approaches, inform the community about the value of early identification and treatment for NBS, and identify areas for improvement in disease management throughout the lifespan.

More than 100 researchers, NBS state programs, and advocacy groups throughout the nation have used the LPDR in over 30 basic translational public health and clinical research projects. The LPDR is designed to share these teams' new findings and foster the secondary use of these original datasets. The newly launched NBSTRN website enables investigators to explore unique datasets, collaborate with leading investigators, and design studies using validated common data elements.

The LPDR has been utilized in a variety of efforts, including the 10-year collection, analysis, and dissemination of health information on individuals with one of 42 different NBS conditions collected in 30 clinical sites located in 22 states. It also has been used in multi-state pilots of four conditions that collectively screened over 1.2 million births. The LPDR has been used in genomic sequencing of four cohorts of newborns, including infants in a neonatal intensive care unit, and was used in studies that are beginning to expand the diagnostic window of NBS both beyond and before the neonatal period.

Additionally, the LPDR has been used recently by patient registries, and NBSTRN is helping groups and advocacy organizations with patient registries to consolidate them into a single data dictionary that will support future expansions of the NBS panel.

Common Dataset Development and Use

In NBS, the use and development of common data elements (CDE) is focused on facilitating data collection, sharing, aggregation, analysis, and dissemination. The ability to combine datasets is especially important in NBS because the majority of conditions are rare, and accumulating enough subjects to have statistical power often is a barrier to understanding health outcomes and the benefits of early identification and treatment.

The NBSTRN Clinical Integration Group, made up of subject matter experts (mostly clinicians), has generated CDE sets containing more than 24,000 data elements across 75 conditions; these sets have been used to develop electronic case review report forms and have been utilized in a variety of research projects, resulting in case-level data for more than 8,000 subjects with an average of four data collection time points per subject. As the data accumulate, they become more useful.

The NBSTRN team has worked with the National Library of Medicine (NLM), which is creating a repository of CDEs to facilitate data sharing. The NIH CDE Repository, designed to allow researchers to build data collection instruments from shared CDEs and also to contribute generated data elements, currently catalogs

more than 26,000 elements across 16 classifications with multiple NIH institutes and efforts represented; the NBSTRN work is represented within the NICHD module and includes question-and-answer sets for use by the research community.

Additional Resources

NBSTRN collaborated with the National Coordinating Center for the Regional Genetic Network, which worked with state NBS programs and public health departments to develop a consensus minimum data set of four questions for NBS LTFU data collection.

It also recently launched a new website that fosters collaboration among NBS stakeholders and facilitates research. Included in the site are two new tools: the interactive, centralized Newborn Screening Conditions Resource, a collection of facts and statistics on both screened and candidate conditions; and the NBS Virtual Repository of States, Subjects, and Samples (NBS-VR), which provides national and state-level views of policies and procedures of interest to researchers, clinicians, families, and advocacy groups. The NBS-VR gives users insight into the number of conditions screened in each state or territory, the number of expected cases, and the incidence rate of conditions currently part of nationwide screening or of conditions that are candidates for pilots.

E. Discussion

- Moving ahead with NBS before all equity issues are solved provides access to treatment where it can exist while developing evidence that can drive advocates and policy-makers to make the required improvements that then lead to wider access. A Committee member asserted that the NBS community has an obligation to evaluate existing efforts and data to help push the needle on equity.
- Cure SMA cross-matches the data collected through its three pathways to ensure accurate reporting.
- An organizational representative wondered whether the LPDR and other tools can help answer questions around improved outcomes and around existing disparities and efforts to address them. A presenter explained that, while the data become more useful as they accumulate, not everyone is being captured. A first good step is that states are conducting annual check-ins, but there is much work to be done. For example, evaluating through an equity lens how question are asked and adjusting questions based on that information.
- An organizational representative was curious if LTFU work is being done from a whole public health systems perspective. A presenter noted that it encompasses currently possible efforts and a view to future system-level work.
- An organizational representative asked whether LPDR respondents volunteered information about efforts to find patients lost to follow-up to discern if they were truly lost (vs. only administratively, such as through a state-to-state move or by changing providers). A presenter explained that some programs have robust tracking systems; the level of effort varies widely by program, with some expending great deal of effort into finding children lost to follow-up.
- An organizational representative wanted to know whether progress has been made regarding NBS follow-up over the past 5-10 years, as well as what needs to be done to make progress. A presenter pointed out NBS programs want to do the right thing, and they are looking for guidance and assistance, but barriers exist and can become insurmountable. Also, LTFU programs vary by state program. Standards are needed, and decision-makers need to be convinced that LTFU is an essential component of NBS. Not having a national system creates a missed opportunity in following children. Another presenter added the need to appropriately staff and fund follow-up activities.
- An organizational representative mentioned that, from a research perspective, in the best of all possible worlds, every child identified with an NBS condition would automatically be enrolled in an LTFU research program in which researchers would track and acquire the information needed to understand the natural history of these conditions. To the extent that some systems can be put into

place through APHL NewSTEPs or the NBSTRN to allow for the accumulation of data in a deidentified manner, this would be win-win and help create opportunities for true equity.

- An organizational representative suggested that a good place to start to develop a federated system is to drive data collection by specialty centers for conditions, which make up a nationwide network by default. Dr. Powell shared that specialty centers are spread very thin financially, which limits the ability to hire additional data entry workers. Thinking outside the box on funding the work at the lab and clinical levels is key.
- An organizational representative asserted that incredible progress has been made in treatment of children with rare disorders and that the Advisory Committee has done great work on this.
- A Committee member noted that models exist of action plans for implementing a new condition on the panel, pointing to the 2010 then-Secretary's letter with clear CCHD implementation guidance (required actions and responsible parties) for the ACHDNC. Reauthorization of the Newborn Screening Saves Lives Act could present an opportunity to embed requirements at the policy level to ensure that the fiscal and human burden does not fall on currently underfunded and understaffed programs.
- A Committee member suggested that the ACHDNC consider making program evaluation obligatory.

XI. New Business

The next meeting of the Advisory Committee will be held May 13-14, 2021.

XII. Adjourn

Dr. Powell adjourned the meeting at 1:01 p.m.