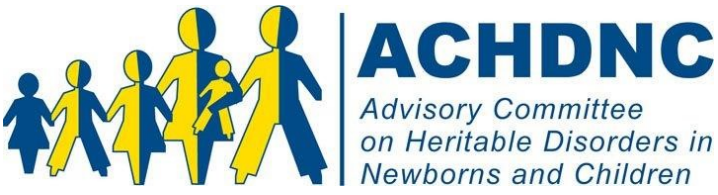
Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC)

Report to Congress (2021)



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EXECUTIVE SUMMARY

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC, or the Committee) was formed to advise and provide evidence-based recommendations to the Secretary of the U.S. Department of Health and Human Services regarding genetic conditions, newborn screening (NBS), and childhood screening. The Committee's advice and recommendations are intended for use by the Secretary to develop policies and priorities that enhance states' abilities to reduce morbidity and mortality in newborns and children who have or are at risk for heritable disorders. Such conditions can be present at birth and cause significant harm if left undetected, including disability or even death. Newborn and childhood screening saves lives and improves quality of life throughout the lifespan. The Health Resources and Services Administration provides coordination, management, and operational services to the Committee.

Selected highlights of the Committee's work from 2021 are as follows:

- The Committee reviewed nominations of two conditions to the Recommended Uniform Screening Panel (RUSP)—mucopolysaccharidosis type II (or Hunter syndrome) and guanidinoacetate methyltransferase deficiency—and approved both nominations for evidence review. The Committee also received nominations for Krabbe disease and congenital cytomegalovirus.
- The Committee strengthened its nomination, evidence-based review, and decision-making processes by updating the condition nomination form and methods to assess data and other evidence during the evidence-based review of conditions nominated to the RUSP and by developing written guidance for the use of the decision matrix.
- The Committee supported development of consumer-friendly guidance materials explaining the nomination, evidence-based review, and decision-making processes for nominations to the RUSP.
- The Committee discussed the impact of the COVID-19 pandemic on NBS systems across the United States, with particular attention to continuity of operations planning.
- The Committee explored challenges involved in building and sustaining the NBS workforce and heard presentations on workforce-related issues faced by laboratory and short- and long-term follow-up services.

The ACHDNC is committed to strengthening the NBS system to improve quality of life for all newborns and children.

KEY ABBREVIATIONS AND TERMS

Term	Definition
ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children. Also referred to as the Committee.
cCMV	Congenital cytomegalovirus: A type of herpes virus passed from the pregnant woman to the fetus during pregnancy that often has no effects but in some cases can cause health problems in infancy or later in childhood. Infection can cause damage to the brain, ears, and other organs, and the most common condition is hearing loss.
Heritable disorders and conditions	Disorders that result from alterations in genes or chromosomes.
GAMT deficiency	Guanidinoacetate methyltransferase deficiency: A genetic condition that prevents the body from making a substance called creatine. GAMT is an enzyme that helps make creatine from another substance called guanidinoacetate. Without enough creatine, the organs do not get enough energy. Left untreated, low levels of creatine and high levels of guanidinoacetate can damage the body's organs, especially those that need a lot of energy, such as the brain and muscles.
Krabbe disease	A genetic condition that prevents the body from recycling galactolipids. When not recycled, galactolipids build up and destroy the protective covering of nerve cells (myelin), which prevents nerve signals from traveling throughout the body. Krabbe disease can cause irritability, muscle weakness, stiffness and muscle spasms, feeding problems, fever, seizures, loss of motor milestones (developmental regression), and vision loss.
MPS I	Mucopolysaccharidosis type I: One of a group of genetic conditions that result in the body being unable to properly break down sugars known as glycosaminoglycans. These sugars build up in cells, blood, and connective tissue, leading to a variety of health problems. MPS I can result in physical malformations, developmental delays, hearing loss, and respiratory conditions.
MPS II	Mucopolysaccharidosis type II: Also known as Hunter syndrome, one of a group of genetic conditions that result in the body being unable to properly break down long-chain sugars known as glycosaminoglycans because it cannot manufacture enough of the enzyme iduronate 2-sulfatase. MPS II can result in permanent, progressive damage affecting appearance, mental development, organ function, and physical abilities.
NBS	Newborn screening: The process of checking babies to identify those who might have certain serious health conditions that can benefit from early treatment or intervention.
RUSP	Recommended Uniform Screening Panel: The list of conditions for which the U.S. Secretary of Health and Human Services recommends newborns receive screening.
SMA	Spinal muscular atrophy: An inherited condition of severe progressive muscle weakness and early death caused by abnormal function of the *SMN1* gene. While there are other genetic conditions often generically referred to as "spinal muscular atrophies," newborn screening only identifies those with homozygous deletion of exon 7 in the *SMN1* gene.

For more details on NBS and other heritable disorders, visit the HRSA Newborn Screening Condition Information page (https://newbornscreening.hrsa.gov/conditions).

REPORT

INTRODUCTION

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC, or the Committee) was formed to advise and provide evidence-based recommendations to the Secretary of the U.S. Department of Health and Human Services (HHS) regarding the best applications of newborn screening (NBS) tests, technologies, policies, guidelines, and standards. As part of its mission, the Committee provides the Secretary:

- Recommendations and advice regarding grants and projects funded, awarded, or authorized for the screening of heritable disorders in newborns and children
- Technical information required to develop policies and priorities for the Heritable Disorders Program meant to enhance the screening, counseling, and health care services provided at the state and local levels for newborns and children who either have or are at risk for heritable disorders
- Advice, recommendations, and information designed to enhance, expand, or improve the Secretary's ability to reduce mortality and morbidity from heritable disorders in newborns and children

The ACHDNC's authorizing legislation expired in 2019. The Committee's new discretionary charter was approved in November 2020. See the Appendix for the Committee membership in calendar year (CY) 2021. The Health Resources and Services Administration (HRSA) provides coordination, management, and operational services to the Committee.

This report summarizes ACHDNC activities for CY 2021, during which the Committee received four Recommended Uniform Screening Panel (RUSP) condition nominations, completed a multiyear assessment of the evidence-based review process for nominated conditions, developed consumer-friendly materials describing the evidence-based review process, explored challenges building and sustaining the NBS workforce, and considered the impact of the COVID-19 pandemic on NBS systems across the United States (with particular attention to continuity of operations planning [COOP]).

The report is subdivided into sections that correspond with the Committee's duties according to statute. For ease of reference, the specific legislation relating to each activity is presented alongside the activity descriptions.

ACHDNC ACTIVITIES

Section 1. Advice, Technical Information, and Systematic Evidence-Based and Peer-Reviewed Recommendations

> The Advisory Committee shall
>
> (1) provide advice and recommendations to the Secretary concerning grants and projects awarded or funded under section 300b-8 of this title
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> (2) provide technical information to the Secretary for the development of policies and priorities for the administration of grants under section 300b-8 of this title

(3) make systematic evidence-based and peer-reviewed recommendations that include the heritable disorders that have the potential to significantly impact public health for which all newborns should be screened, including secondary conditions that may be identified as a result of the laboratory methods used for screening

Section 1.1 Mucopolysaccharidosis Type II (MPS II)

The Committee reviewed the nomination of MPS II, also known as Hunter syndrome, to the RUSP and voted in favor of moving the condition forward to a full evidence-based review by the external Evidence-Based Review Group (ERG). MPS II is a genetic condition caused by inadequate quantities of the enzyme iduronate 2-sulfatase needed to break down long-chain sugars known as glycosaminoglycans. The buildup of glycosaminoglycans in the body results in permanent, progressive damage affecting appearance, organ function, physical abilities, and, in the severe form, cognitive development. Throughout the year, the Committee reviewed and discussed the interim findings of the evidence-based review of NBS for MPS II. The Committee reviewed data from two states (Illinois and Missouri) that screen for MPS II, results from the Hunter Outcome Survey that point to the effectiveness of enzyme replacement therapy, and a sibling case study demonstrating the effectiveness of early initiation of enzyme replacement therapy.

In CY 2022, the Committee will synthesize the information gathered throughout the evidence-based review, examining treatment impact related to earlier identification of MPS II; review the results of population-level modeling on screening outcomes; and complete the Public Health System Impact (PHSI) survey assessment and cost evaluation. The Committee plans to vote on whether to recommend to the Secretary of HHS that the condition be included on the RUSP at the February 2022 ACHDNC meeting.

Section 1.2 Guanidinoacetate Methyltransferase (GAMT) Deficiency

The Committee reviewed the nomination of GAMT deficiency and voted in favor of moving the condition forward to a full evidence-based review by the external ERG. GAMT deficiency prevents the body from making creatine from guanidinoacetate. Left untreated, low levels of creatine and high levels of guanidinoacetate can damage the body's organs, especially those that need a lot of energy, such as the brain and muscles.

The Committee reviewed findings from the first phase of the evidence-based review, including information gathered from technical experts, data from state NBS programs implementing screening for GAMT deficiency, and treatment protocols. In CY 2022, the Committee will continue to evaluate the information gathered throughout the evidence-based review, including data on outcomes of pre-symptomatic initiation of treatment, population-level modeling of screening outcomes based on the available evidence, and the PHSI survey assessment and cost evaluation.

Section 1.3 Krabbe Disease

The Committee's Nomination and Prioritization Workgroup was in the process of reviewing the nomination for Krabbe disease as of November 2021 (the last meeting of CY 2021). Krabbe disease destroys the protective covering of nerve cells and can cause loss of motor milestones (developmental regression), muscle weakness, stiffness and spasms, feeding problems, fever, seizures, irritability, and vision loss. In CY 2022, the Nomination and Prioritization Workgroup will

develop a recommendation as to whether Krabbe disease should move forward in the Committee's evidence-based review process.

Section 1.4 Evidence Review Process

The Committee strengthened the processes used to conduct evidence-based reviews of conditions nominated to the RUSP by adopting updates and clarifications to (1) the condition nomination form, (2) the methods used to assess and report data and information gathered during the evidence-based review of nominated conditions, and (3) the evidence review decision matrix guidance.

In February 2019, the Committee initiated a review of the nomination, evidence-based review, and decision-making processes. In its analysis, the Committee explored ways to strengthen processes used to make recommendations on conditions nominated to the RUSP. Throughout 2021, the Committee gathered stakeholder input, identified issues to address, and categorized proposed solutions according to actionability, ranging from those that could be acted on immediately to those that required change at the system or policy level. (See the August 2021 presentation to the Committee for details.) The Committee formed a workgroup to assess the proposed updates to the condition nomination form, evidence-based review process, and decision matrix. The Committee discussed the proposed updates and received public comment, which it took into account during its deliberations.

The Committee approved proposed updates to the condition nomination form, to be implemented in early 2022. The revised form solicits more information about the condition to strengthen the case definition, such as estimates of U.S. incidence, distribution, and prevalence of known phenotypes. Nominations should include current standards of care for treatment and the availability of follow-up treatment. The revised form expands on the methods of validation of the laboratory test for the condition, such as the timing of screening or specimen collection and the status of approval by the U.S. Food and Drug Administration (FDA) of second-tier tests. It also requests more details on confirmatory testing, including the sample specimen needed and the sensitivity and specificity of testing. The revised form encourages nominators to include more data that can assist with the evidence review, such as data from pilot studies, unpublished data sources, description and algorithms of screening methods, and long-term follow-up plans.

The Committee voted to approve the following updates to the evidence-based review process, effective immediately:

- Expand current procedures for assessing gray literature and incorporate standard procedures used in the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach for collecting expert-derived evidence to supplement unpublished evidence.
- Consider and review registry data and other unpublished sources of data.
- Report cost estimates obtained through the PHSI in ranges because the cost of implementation for new NBS conditions will vary based on pre-existing state-level resources that differ between states.

Although stakeholders seeking to nominate conditions to the RUSP will need to provide additional information in the nomination package, these updates to the condition nomination form will streamline and strengthen the evidence-review process by providing critically important information to the Committee. It will also benefit nominators by minimizing the need for revision and resubmission of nomination packages.

While no major changes to the decision matrix were proposed, additional guidance was drafted to facilitate use of the decision matrix, including detailed information about the net benefit and descriptions for each criterion (see Section 3).

Section 2. Technical Assistance and Nomination Review

> The Advisory Committee shall
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> (4) provide technical assistance, as appropriate, to individuals and organizations regarding the submission of nominations to the uniform screening panel, including prior to the submission of such nominations
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> (5) take appropriate steps, at its discretion, to prepare for the review of nominations prior to their submission, including for conditions for which a screening method has been validated but other nomination criteria are not yet met, in order to facilitate timely action by the Advisory Committee once such submission has been received by the Committee

As mentioned in Section 1, the Committee received nominations to consider MPS II, GAMT deficiency, and Krabbe disease for addition to the RUSP. In November 2021, a nomination to add congenital cytomegalovirus (cCMV) to the RUSP was submitted and was reviewed for completeness by HRSA officials. Technical assistance was provided to the nominators to facilitate submission of a complete nomination package.

Throughout the assessment of the evidence review process described in Section 1, the Committee identified a need to develop additional consumer-friendly guidance materials explaining the nomination, evidence-based review, and decision-making processes. These materials will be publicly available on the Committee's website in 2022.

The Committee identified a number of issues that require further discussion, additional research, or system-wide or policy changes, including the following:

- Development of a process for re-reviewing conditions on the RUSP
- Additional guidance for conditions assigned B ratings in the decision matrix
- Assessment of long-term follow-up of NBS, including evaluation of screening impact, identification of short- and long-term treatment and clinical outcomes, determination of the cost of implementation, assessment of the impact on the health care system and providers, and considerations for equity and long-term access
- Establishment of a priority list of ongoing research and development issues
- Formal methods for including stakeholder values and preferences in the Committee's decision-making process

The Committee identified other emerging issues related to the condition nomination and review processes that merit further examination, such as the Committee's capacity to review multiple conditions at once, the length of the review process, and the tradeoffs between detailed deliberation and expedited assessment. The Committee recognized the need to consider fairness

and equity, given that organizations with more resources or conditions supported by more funding may have an advantage in researching and collecting data that may confer an advantage in the nomination process. Other potential topics for discussion include the grouping of conditions together in a review and challenges around NBS workforce capacity once a condition is added to the RUSP.

Section 3. Decision Matrix

> The Advisory Committee shall
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> (6) develop a model decision-matrix for newborn screening expansion, including an evaluation of the potential public health impact, including the cost of such expansion, and periodically update the recommended uniform screening panel, as appropriate, based on such decision matrix

The Committee uses the decision matrix as a deliberation tool to evaluate the findings of the evidence-based review and make recommendations regarding the addition of conditions to the RUSP. The steps in this process include assessing the net benefit, the feasibility of implementing a comprehensive screening program for the condition, and the readiness of public health programs to implement expanded screening.

The Committee voted to approve decision matrix guidance that clarifies decision-making processes, specifically addressing the following:

- Purpose
- Use in deliberations
- Meaning of the criterion
- Process for consideration of each criterion individually
- Meaning of ratings
- Process for rating

The updated decision matrix guidance will be available to the public as part of the consumer-friendly guidance materials located on the Committee website (to be updated in CY 2022).

Section 4. State Capacity to Screen

> The Advisory Committee shall
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> (7) consider ways to ensure that all States attain the capacity to screen for the conditions described in paragraph (3), and include in such consideration the results of grant funding under section 300b-8 of this title

Committee discussions recognized the benefits of COOP for emergencies, including weather-related disasters and public health emergencies such as COVID-19. Within the context of challenges to developing COOPs at the state level, a number of presenters described the difficulties NBS programs face during an emergency, such as transporting specimens to laboratories and barriers to conducting short-term follow-up. The following sections provide additional details on the difficulties highlighted in the presentations to the Committee.

Section 4.1 Supply Chain Disruption

In New York, as of February 2021, supply chain shortages remained for pipette tips, plastics, and gloves, leading the NBS program to reformat some of its testing, specifically with tip usage, to

ensure a constant supply of reagents. The North Carolina NBS program experienced a noticeable reallocation of resources to COVID by vendors, which affected the NBS program's supply chain.

Section 4.2 Workforce Insufficiency and Attrition

The Association of Public Health Laboratories (APHL) conducted a survey in November 2020 that found that all but one state program responding faced some sort of staffing challenge during the pandemic. The challenges included staff reassigned to focus on COVID efforts, retiring early, changing jobs, or leaving for higher-paying jobs with companies that performed COVID testing; hiring freezes, furloughs, and low staff morale; and staff facing personal barriers to transportation, childcare, and home technology.

North Carolina's NBS laboratory split its workforce into two groups working on alternate days, which limited staff capacity. North Dakota's NBS program has two full-time employees at the state level, and both were part of the COVID response beginning in March 2020. As of February 2021, one was still assisting with the COVID response.

In New York, many specialists and other providers were deployed to the emergency department or closed their offices and switched to telehealth care only. Data entry, follow-up, laboratory, information technology, 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 strains and shortages. In New York, NBS programs were faced with increases in staff departures because of early retirements, job changes, and hiring freezes. Also, budget shortfalls and other issues persisted while the programs worked to maintain operations.

Section 4.3 Need for Continuous Updating

The New York NBS program found that, while a program can plan for localized disruptions, it is difficult to plan for an event affecting the entire state. Throughout the pandemic, teamwork was critical to ensure there were no missed cases. The focus of COVID-related COOP has changed in New York and is still evolving.

The National Newborn Screening Contingency Plan was updated in August 2017. Of the topics addressed by the plan, only two—specimen processing and testing, and reporting and follow-up—rely solely on the state NBS programs; all others involve the entire system. A presenter noted that the most effective continuity plans will include NBS programs and other key stakeholders.

Section 4.4 Need for Plan Integration Across States

During Hurricane Katrina (2005), the Louisiana Public Health Laboratory used an emergency management assistance compact to obtain help from Iowa within 1 week. The states did not have a COOP agreement and needed to work out all logistics, including specimen transport to Iowa, differences in testing mandates and methodology, different policies around test results, how to address missing information or rejected specimens, how to report results, and how to rapidly increase throughput.

A presenter noted that an emergency situation, such as a weather event, can impact multiple states, which can limit the number of nearby partners that are able to offer backup services. To this end, regionalization could help identify contingency measures if multiple states require assistance for NBS at the same time. Regionalization of COOP can result in more integrated systems, which should benefit NBS.

Section 4.5 Need for Cooperation Across Public Health Systems

The North Dakota Public Health Laboratory and the state NBS program use the same courier service, so the NBS program planned to include the state laboratory as it developed the NBS COOP to help streamline processes. A presenter observed that defining COOPs and integrating planning across facilities, including hospitals, providers' offices, and public health systems, can help ensure that supplies are shared when needed. In North Dakota and other states, these arrangements often rely on the good-faith efforts of each facility or agency.

Section 4.6 Transport Issues During an Emergency

The APHL survey identified problems with transport issues, including postal service or private courier delays and changes to pickup and delivery schedules or locations. In New York, some hospitals reported that couriers were not allowed to enter the hospital, let alone go to through the building to pick up specimens. North Carolina's NBS laboratory experienced delays in transport as courier services were also impacted by COVID.

Section 4.7 Tribal Health System Tracking Mechanisms

The North Dakota NBS program reported that because tribal governments function independently from federal and state governments, the state has no authority to track down children and families on reservations, which has at times posed challenges in locating babies with abnormal screening results.

Section 4.8 Positive Changes Affecting State Screening Capacity

During its deliberations, the Committee learned that the HHS prioritization letter to help public health laboratories get NBS supplies was helpful in addressing shortages caused by the pandemic. Presenters also noted that the use of telehealth and telegenetics, which has been integral to ensuring continued access to care during the COVID-19 public health emergency, has also been particularly effective in reaching underserved populations and people in remote areas (see Section 8).

Section 5. Recommendations, Advice, or Information (Morbidity and Mortality)

> The Advisory Committee shall
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> (8) provide such recommendations, advice or information as may be necessary to enhance, expand or improve the ability of the Secretary to reduce the mortality or morbidity from heritable disorders, which may include recommendations, advice, or information dealing with the following

The Committee provides the Secretary with recommendations, advice, and information on a broad range of topics relating to NBS to reduce newborn and child mortality or morbidity from heritable disorders. Sections 6 through 17 describe activities falling under this charge (A–L) that were undertaken or overseen by the ACHDNC in CY 2021.

Section 6. Follow-Up Activities

> (A) follow-up activities, including those necessary to achieve best practices in rapid diagnosis and appropriate treatment in the short-term, and those that ascertain long-term case management outcomes and appropriate access to related services

The Committee learned about existing and proposed strategies for improving long-term follow-up.

Section 6.1 APHL Newborn Screening Technical Assistance and Evaluation Program (NewSTEPs)

APHL established a task force to address long-term follow-up needs within NBS systems. The task force created a working definition of long-term follow-up that was used to develop a survey of NBS follow-up programs. The survey found that 41 percent of programs have no plans to implement a long-term follow-up program. Several are funding their long-term follow-up activities by using their state 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 long-term follow-up activities. The most common long-term follow-up activities include data collection from clinical providers, clinical care follow-up, connecting individual families to services and supports, and data collection. 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 analyses of testing. Only 25 percent of state programs that responded to the survey currently conduct long-term follow-up for the lifetime of the individual.

Many states indicated a lack of support from program leadership for implementing or expanding their long-term follow-up. The APHL task force plans to publish a paper on the status of long-term follow-up and to develop a position paper that identifies a role for APHL in long-term follow-up. The task force is considering developing a fact sheet to demonstrate the importance of long-term follow-up to program leadership and to offer technical assistance to programs that want to implement or enhance a long-term follow-up system.

Section 6.2 Cure SMA

Cure SMA, an organization that advocates for patients and families living with spinal muscular atrophy (SMA), hosts the SMA Newborn Screening Registry, the Cure SMA Membership Database, and the Cure SMA Clinical Data Registry. As a result of patient-provided data, Cure SMA determined that the number of new infants diagnosed via NBS has gradually increased, an expected outcome with more states implementing NBS for SMA. During the early months of COVID-19, fewer infants were diagnosed clinically and through NBS. This finding could be the result of decreased in-person visits and evaluations of infants less than 2 years old, leading to delayed diagnoses for infants with clinical symptoms of SMA. Data from the SMA Newborn Screening Registry and the Cure SMA Membership Database provide insights on *SMN2* gene copy numbers in children with SMA and the relationship of copy number to diagnosis and treatment. Cure SMA plans to evaluate the SMA NBS outcomes across the real-world evidence databases with an eye toward improving time to diagnosis.

Section 6.3 Newborn Screening Translational Research Network (NBSTRN)

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH) has provided funding to the American College of Medical Genetics and Genomics to support the NBSTRN. The network launched the Longitudinal Pediatric Data Resource (LPDR) to enable investigators to explore unique datasets, collaborate with leading investigators, and design studies using validated common data elements. The accrued LPDR data may help establish the efficacy of new treatments and management approaches; inform researchers, providers, families, and advocates about the value of early identification and treatment for current and future NBS conditions; and identify areas for improvement in disease management throughout the lifespan. The NBSTRN worked with the NIH National Library of Medicine to develop a set of common data elements for NBS reporting. The ability to combine datasets is especially important in NBS because most of the conditions are rare, and accumulating enough subjects to achieve statistical power often is a barrier to understanding health outcomes and the benefits of early identification and treatment. The NBSTRN is also working to facilitate data sharing.

Section 6.4 HRSA Newborn Screening Portfolio Evaluation

A HRSA evaluation of the NBS system identified a national long-term follow-up system as a current need. It proposed creating a long-term follow-up system and tracking health outcomes. The evaluation specifically recommended collaboration between federal agencies and patient advocacy groups, creation of a center of excellence to support the collection of long-term follow-up data, and financial investments to support (1) building staff skills to maintain and analyze data, (2) treatment for children who otherwise would have been lost to follow-up, and (3) more specialists to monitor children over time. For more information about this evaluation, see Section 12.2.

Section 7. Implementation, Monitoring, and Evaluation

> (B) implementation, monitoring, and evaluation of newborn screening activities, including diagnosis, screening, follow-up, and treatment activities

The Committee explored challenges involved in building and sustaining the NBS workforce and received presentations focused on workforce-related issues faced by laboratories and short- and long-term follow-up services. Presenters included the American Board of Medical Genetics and Genomics, APHL, and specialists in pediatric neurology, sickle cell disease, and endocrinology, among others. Some common challenges to building and sustaining the workforce were highlighted:

- Low compensation
- Excessive administrative burden, overwork, and low quality of life
- Lack of diversity
- Under-resourced public health programs
- Lack of training at all levels
- Aging workforce
- Lack of awareness of or interest in rare pediatric diseases
- Lack of access to relevant education

Presenters outlined potential solutions, such as increasing mentorship and fellowship programs and other training opportunities; expanding public health workforce incentives, such as loan forgiveness programs; improving recruitment and retention; and developing guidelines for minimal staffing of NBS programs. Some called for routine assessment of the NBS workforce and expertise and improved communication and coordination between laboratory and follow-up staff. Others asked for consistent funding for public health programs (particularly for state early hearing detection and intervention programs). HRSA's evaluation of its NBS portfolio echoed these ideas, especially the need for workforce education.

Section 8. Diagnostic and Other Technology

(C) diagnostic and other technology used in screening

The Committee's deliberations about COOP highlighted that telehealth and telegenetics services were initiated or expanded during the pandemic, providing families with access to genetic counseling and information from medical professionals when in-person visits were not possible. Retaining such services will improve access and reduce stress on patients and families. The increasing use of telehealth and telework is helping free up needed workspace in laboratories. It has also required laboratories to establish remote connections to equipment, which speeds up and streamlines reporting of critical results.

The Association of Maternal and Child Health Programs oversaw 21 awards to support telehealth activities, funded by the Coronavirus Aid, Relief, and Economic Security (CARES) Act. Awardees were located in 18 states, three territories, two tribal nations, and one freely associated state (Micronesia). For example, one of the awardees was the organization Expecting Health, which created a virtual, interactive triage platform to respond to families' questions about NBS and incorporated telehealth into its online educational module on COVID-19. In Puerto Rico, awardees established a program using telehealth for NBS follow-up to improve access to services and links to referrals. The Connecticut NBS program developed a telehealth system to expand access to health care, increase equity, and support families in the pre-diagnosis phase, which included creating a family advisory group to amplify families' voices.

The Committee discussed concerns that Medicaid and other insurers are reinstating interstate telehealth restrictions, which pose financial and administrative burdens and could reverse gains made with the use of telehealth. Some presenters indicated that telehealth and telegenetics approaches have been effective in reaching underserved populations and people in remote and tribal areas. It was observed that telehealth capabilities include adoption of new technology, such as Bluetooth-enabled blood pressure cuffs, and other innovative approaches that facilitate examination remotely and improve access to clinicians and specialists.

Section 9. Availability and Reporting of Testing

(D) the availability and reporting of testing for conditions for which there is no existing treatment, including information on cost and incidence

During CY 2021, the Committee did not undertake activities related to the availability or reporting of testing for conditions for which there is no existing treatment.

Section 10. Conditions Not Included in the RUSP

(E) conditions not included in the recommended uniform screening panel that are treatable with Food and Drug Administration-approved products or other safe and effective treatments, as determined by scientific evidence and peer review

The Committee heard presentations on NIH-funded pilot studies in two states that address conditions not included on the RUSP. ScreenPlus is a federally funded voluntary research study using a panel of 14 non-RUSP conditions being piloted in nine hospitals in New York. To be included, a disorder must be associated with a dried blood spot screening assay that can be multiplexed, is amenable to high-throughput assessment techniques, is reasonably priced, and has had positive baseline validation studies. The disorder should have significant morbidity and mortality if untreated and a pediatric phenotype. Finally, the disorder should also have an FDA-approved treatment or a promising treatment in the clinical trial stage. Parents who choose to participate are asked to complete a survey intended to improve understanding of how the NBS process meets family needs and the optimal ways to expand screening.

The Early Check research study is led by the Research Triangle Institute in North Carolina in collaboration with universities and the North Carolina Department of Health and Human Services with federal and private funding. Early Check offers voluntary NBS for up to three conditions—SMA, fragile X syndrome, and Duchenne muscular dystrophy—that are not on the North Carolina state NBS panel. The Early Check study's use of virtual technologies for recruitment, consent, counseling, assessment, and intervention allowed it to continue during the COVID-19 pandemic. While there are benefits to virtual recruitment, including cost savings, the researchers have found it is not as effective as in-person recruitment. Since the study was established in 2018, it has enrolled 18,000 individuals across North Carolina, with the highest recruitment rates in larger cities. Early Check aims to develop flexible systems for responding quickly to newly nominated conditions.

Findings from the ScreenPlus and Early Check studies will continue to inform the Committee about the feasibility and short-term outcomes of screening for conditions not on the RUSP.

Section 11. Minimum Standards and Related Policies and Procedures

(F) minimum standards and related policies and procedures used by State newborn screening programs, such as language and terminology used by State newborn screening programs to include standardization of case definitions and names of disorders for which newborn screening tests are performed

There were no updates from the Committee regarding minimum standards or related policies and procedures during CY 2021.

Section 12. Quality Assurance, Oversight, and Evaluation

(G) quality assurance, oversight, and evaluation of State newborn screening programs, including ensuring that tests and technologies used by each State meet established standards for detecting and reporting positive screening results

Two HRSA initiatives contributed to the Committee's understanding of quality assurance, oversight, and evaluation of state NBS programs: the National Survey of Children's Health and the evaluation of the NBS portfolio.

Section 12.1 Findings from HRSA's National Survey of Children's Health

The Committee learned of the following key findings from the National Survey of Children's Health:

- Genetic and inherited disorders ranked ninth of 12 (at 3.8 percent) among current or lifelong health conditions in children aged 0–17 years.
- Eighty percent of genetic conditions were identified in some manner other than NBS, whereas NBS identified two thirds of blood disorders.
- Children categorized as having "other" genetic conditions were more severely affected than those with blood disorders.
- Parents of children with cystic fibrosis reported dramatically high rates of unmet needs and frustration regarding obtaining services.

Section 12.2 Findings from HRSA's NBS Portfolio Evaluation

HRSA's evaluation of the NBS portfolio sought to assess the needs of the NBS system, its stakeholders, and the unique role of HRSA in addressing systems-level needs. The evaluation framework centered on the goals of the NBS system as outlined in the Newborn Screening Saves Lives Authorization Act of 2014.

For each goal, the evaluation assessed current unmet and future needs and described potential solutions to address gaps and needs, demonstrating the agency's attention to quality assurance and improvement for every aspect of the program. Policy and programmatic recommendations identified through the assessment included creating a strategic plan for NBS, conducting an evaluation of state NBS programs to identify areas of improvement, and identifying sources of increased funding to implement new conditions and reduce variability of the number of conditions for which states conduct screening. Practice recommendations included building on successful HRSA investments that provide technical assistance to states to implement new RUSP conditions and support to achieve NBS timeliness goals.

Section 13. Public and Provider Awareness and Education

(H) public and provider awareness and education

As noted in Sections 1 and 2, and in response to public input requesting more accessible information about the nomination and evidence review processes, the Committee developed additional consumer-friendly guidance materials explaining the nomination, evidence-based review, and decision-making processes. These materials will be added to the Committee website in 2022.

The HRSA evaluation of its NBS portfolio identified systems-level challenges and recommendations for improving training, education, and outreach to providers and consumers. For example, findings from the evaluation demonstrate a need for additional training and technical assistance for state laboratory and follow-up staff, especially in under-resourced states, and for health care providers to better understand new RUSP conditions and how to communicate with families. Some potential solutions included increasing the education and training provided to different stakeholders and revising training and technical assistance models, such as providing support for "early adopter" states to mentor others. The evaluation also concluded that HRSA could increase its focus on disseminating educational materials for parents

in the prenatal period, working with states on educational materials, and developing high-quality online educational materials—including materials tailored for specific consumer groups.

Section 14. Cost Effectiveness

> (I) the cost and effectiveness of newborn screening and medical evaluation systems and intervention programs conducted by State-based programs

As part of its assessment of the evidence-based review process, the Committee decided to report cost estimates in broad categories rather than point estimates to account for variability across states (see Section 1.4). The move addresses the concern that cost estimates gathered by the PHSI survey are not widely generalizable to all NBS programs.

Section 15. Causes, Public Health Impacts, and Risk Factors

> (J) identification of the causes of, public health impacts of, and risk factors for heritable disorders

There were no updates from the Committee regarding identification of the causes of, public health impacts of, and risk factors for heritable disorders during CY 2021.

Section 16. Coordination of Surveillance Activities

> (K) coordination of surveillance activities, including standardized data collection and reporting, harmonization of laboratory definitions for heritable disorders and testing results, and confirmatory testing and verification of positive results, in order to assess and enhance monitoring of newborn diseases

The Committee gathered information on long-term follow-up and noted that the development of patient registries is critical to understanding outcomes and improving care for individuals identified with rare heritable disorders. These surveillance mechanisms take planning, coordination across systems and stakeholders, and financial resources. The Committee learned that in 2018, HRSA's Sickle Cell Treatment Demonstration Project created a State Action Plan for California that named surveillance registries as a key priority alongside clinical care.

The Committee heard presentations on national registries for hemophilia and childhood cancer. Several key points emerged in relation to surveillance capacity and coordination. For example, Community Counts builds on previous surveillance systems developed by the Centers for Disease Control and Prevention for hemophilia and other bleeding disorders in patients at hemophilia treatment centers (HTCs). It identified the need to fully harmonize the original registry data forms with new electronic data infrastructure. The Community Counts Data Visualization Tool interactively displays de-identified patient data. HTC core teams include data managers and clinical research associates who implement and manage the registry. It was noted that a regional network model is critical to building a sustainable infrastructure and sharing expertise nationwide. It was also observed that insurance status limits patient access to HTCs, thereby skewing registries and data collection toward insured patients. Other data sources include the Hemostasis and Thrombosis Dataset, the U.S. HTC Network Patient Satisfaction Survey, and the Regional Comprehensive Care Data Set. These tools are primarily funded through reinvested income from the 340B drug pricing program.

NIH's National Childhood Cancer Registry (NCCR) links existing data sources, including the National Death Index, state vital records, and LexisNexis databases. NCCR also incorporates claims data and information on treatment and comorbidities. To protect patient privacy, NCCR

developed a tiered system for data sharing and in some instances requires institutional review board review as well as a data release system linked to the central authentication and authorization process at NIH.

The Committee also received an overview of long-term surveillance for individuals diagnosed with SMA, which was added to the RUSP in 2018. Cure SMA collects longitudinal data from families on a voluntary basis through its SMA Newborn Screening Registry. The Cure SMA Clinical Data Registry gathers information from electronic health records of patients at 19 SMA care centers. The Committee recognized that these registries and data sets are important for demonstrating the impact of early identification across the lifespan and for improving screening, follow-up services, and long-term health outcomes.

Section 17. Timeliness of Collection, Delivery, Receipt, and Screening

> (L) the timeliness of collection, delivery, receipt, and screening of specimens to be tested for heritable disorders in newborns in order to ensure rapid diagnosis and follow-up

The sustained strains placed on state NBS programs by the COVID-19 pandemic has underscored the importance of NBS COOP and the need to apply lessons learned to strengthen state programs' capacity to continue to provide uninterrupted services during acute and prolonged emergencies. In discussions about COOP in CY 2021, the Committee heard from various entities about efforts to address the timeliness of collection, delivery, receipt, and screening of specimens. For example, in the wake of Hurricane Katrina, Louisiana's Public Health Laboratory worked with the state of Iowa to ensure NBS program continuity, as described in Section 4.4. In preparation for Hurricane Sandy, New Jersey coordinated with United Parcel Service (UPS) and police departments to ensure laboratory deliveries were made despite the hurricane. In North Carolina, even as NBS program staff were assisting with COVID-19 testing, NBS programs continued to address timeliness and unsatisfactory samples, add disorders to the screening panel, and conduct follow-up.

North Dakota's NBS program relies on the University of Iowa State Hygienic Laboratory for screening and some follow-up services. Since July 2019, North Dakota has contracted with a logistics company that transports specimens from all 12 North Dakota birthing facilities to Iowa, 7 days per week, 365 days per year. Since 2016, more than 95 percent of North Dakota's specimens collected with time-critical results were reported out by 5 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 laboratory and short-term follow-up programs.

In light of the COVID-19 pandemic, New York's NBS program emailed almost 10,000 health care providers to provide education about specimen collection requirements. The NBS program also initiated Saturday testing to allow for time to locate babies with critical screening results, recognizing that parents were hesitant to answer phones and bring babies into facilities for repeat screening and other follow-up services. This approach also helped staff manage the daily workflow, as it was anticipated that fewer staff would be available to perform laboratory work. Early in the pandemic, concerns were raised about early discharge after delivery; although such discharges did not happen on a large scale, the NBS program continued to receive specimens collected very close to the 24-hour mark as of February 2021. The program did not see a rise in time to collect repeat specimens, thanks to providers who found ways to collect repeats in a

timely fashion. Teleworking required the New York public health laboratory to establish remote connections to equipment, which allowed for quicker and more streamlined reporting of critical results because, for example, results can now be checked after hours.

The Committee also identified that HRSA-funded technical assistance to support states in meeting NBS timeliness goals is a valuable, ongoing, and nationally available resource. HRSA's evaluation of its NBS portfolio, described in Section 12.2, found that timeliness initiatives were seen as a significant success for NBS programs, and HRSA programs contributed substantially to making significant improvements in timeliness. The evaluation recommended a continued focus on technical assistance, education, training, and support for achieving NBS timeliness goals across states.

FUTURE DIRECTIONS

In CY 2022, the Committee will continue to review conditions nominated to the RUSP and will complete the evidence-based reviews for MPS II and GAMT deficiency. The Committee will also continue to review the nomination package received for Krabbe disease. In addition, the Committee will review the nomination for cCMV that it received in November 2021.

The Committee will continue to explore topics that were identified during the review of its nomination, evidence-based review, and decision-making processes, including the following:

- The Committee's capacity to review multiple conditions at once
- Need for additional guidance for deliberations that result in a B rating on the decision matrix
- Routine review of conditions already on the RUSP
- Dissemination of consumer-friendly educational materials about Committee processes

The Committee will continue to assess the impact of COVID-19 on state NBS programs, equity in the NBS system, and challenges around workforce capacity.

CONCLUSION

This report was prepared to summarize the Committee's activities for CY 2021. The mission of the Committee is to reduce morbidity and mortality in newborns and children who have or are at risk for heritable disorders. The Committee accomplishes this mission by providing advice, recommendations, and technical information to the HHS Secretary and by helping to develop policies and priorities meant to enhance services at the state and local levels. In addition, the Committee invites public comments as an important way to identify issues and concerns relating to NBS.

In 2021, the Committee completed a multiyear review of the evidence-based review process for conditions nominated to the RUSP and voted to update the condition nomination form and methods of assessing published and unpublished evidence and develop guidance on the decision matrix. It reviewed three new conditions nominated to the RUSP and moved two conditions forward in the nomination process to full evidence-based review (MPS II and GAMT deficiency). Throughout the year, the Committee gathered stakeholder input on COOP and the

use of telehealth and telegenetics to expand access to NBS, follow-up, and treatment. Stakeholders also provided insights into the challenges affecting the NBS workforce and potential short- and long-term solutions.

The coordinated efforts of the Committee and stakeholders—including policymakers, state public health agencies, providers, and the public—will continue to ensure that newborns and children have universal access to high-quality screening, diagnosis, follow-up, disease management and treatment, evaluation, and education. Together, these efforts will support state NBS programs and continue to reduce or prevent the potentially devastating consequences of disabilities, life-threatening diseases, or death.

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