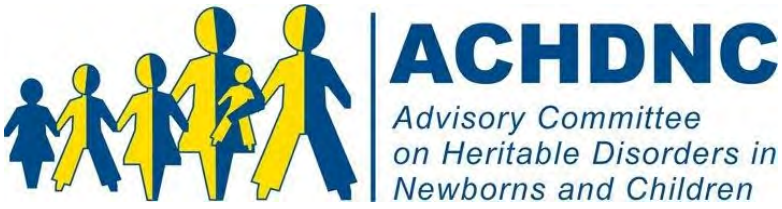
Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC)

Report to Congress (2020)



CONTENTS

EXECUTIVE SUMMARY

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC or Committee) was established to advise and provide evidence-based recommendations to the Secretary of the United States Department of Health and Human Services (HHS) 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 who are at risk for, genetic conditions. Such conditions can be present at birth and cause irreparable harm, including disability or even death, if left undetected. Newborn and childhood screening improves quality of life throughout the lifespan and saves lives. The Health Resources and Services Administration provides coordination, management and operational services to the Committee. The Secretary of HHS reauthorized the Committee's discretionary charter, shown in Appendix A, in November 2020.

Listed below are selected highlights of the Committee's work from 2020:

- The Committee completed a follow-up report on implementation of NBS for spinal muscular atrophy (SMA).
- The Committee reviewed a report on the implementation of NBS for five conditions added to the Recommended Universal Screening Panel (RUSP) since 2017: severe combined immunodeficiency (SCID), critical congenital heart disease (CCHD), Pompe disease, mucopolysaccharidosis type I (MPS I), X-linked adrenoleukodystrophy (XALD).
- The Committee completed a report on the timeliness of NBS results.
- The Committee reviewed the ACHDNC nomination and evidence review processes.
- The Committee assessed the impact of COVID-19 on NBS.

The ACHDNC is committed to identifying and helping to address challenges and strengthen the NBS system in order to improve the quality of life of all newborns and children.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children. Also referred to as the Committee.
CCHD	Critical congenital heart disease - a group of serious heart conditions present at birth. Children with these conditions usually need surgery or other intervention before one year of age.
Heritable disorders and conditions	A group of disorders that are the result of alterations in genes or chromosomes.
MPS	Mucopolysaccharidosis- a group of genetic conditions that result in the body being unable to properly breakdown mucopolysaccharides, which are long chains of sugar molecules found throughout the body. These sugars build up in cells, blood, and connective tissue, leading to a variety of health problems. Seven distinct forms and numerous subtypes of mucopolysaccharidosis have been identified.
MPS I	Mucopolysaccharidosis type I- a genetic condition that causes those who have it to be unable to manufacture alpha-L iduronidase, which is needed to break down sugars. These sugars build up in cells and cause damage throughout the body.
MPS II	Mucopolysaccharidosis type II- also known as Hunter Syndrome, a genetic condition that causes those who have it to be unable to manufacture adequate quantities of the enzyme iduronate 2-sulfatase, resulting 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 diagnosis and treatment.
Pompe disease	An autosomal recessive condition that leads to a deficiency of the enzyme acid α-glucosidase (GAA). Without treatment, classic infantile-onset disease is associated with cardiomyopathy and mortality within the first year of life. Non-classic infantile-onset disease without cardiomyopathy is associated with death later in childhood.
RUSP	Recommended Uniform Screening Panel - the list of conditions for which the United States Secretary of Health and Human Services recommends newborns receive screening.
SCID	Severe combined immunodeficiency - a group of conditions characterized by the absence of both humoral and cellular immunity.

Term	Definition
SMA	Spinal muscular atrophy- A group of inherited conditions that affect control of muscle movement. These conditions are caused by deterioration of the nerves in the spinal cord, which results in progressive motor weakness and can lead to death.
MS/MS	Tandem mass spectrometry - A method of newborn screening for errors of metabolism that uses two or more mass spectrometers to identify proteins in blood samples.
XALD	X-linked adrenoleukodystrophy- a peroxisomal condition that disrupts metabolism of very long chain fatty acids (VLCFAs). Accumulation of VLCFAs damages the myelin sheath, resulting in progressive neurological damage and also impairs adrenal cortex function.

REPORT

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC or the Committee) was formed to advise the Secretary of the United States (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 following to the Secretary:

- Recommendations and advice regarding grants and projects funded, awarded, or authorized for the screening of genetic conditions 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 genetic conditions;
- Advice, recommendations, and information designed to enhance, expand, or improve the Secretary's ability to reduce mortality and morbidity from genetic conditions in newborns and children.

The purpose of this report is to summarize the Committee's activities for the 2020 calendar year. The discussion of the Committee's activities in this report is subdivided into sections aligned with the Committee's duties.

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
>
> (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

The Committee received a package nominating mucopolysaccharidosis type II (MPS II) for addition to the Recommended Uniform Screening Panel (RUSP). The Committee will review this package during calendar year 2021.

Section 2. Technical Assistance and Nomination Review

> The Advisory Committee shall
>
> (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
>
> (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 a nomination to consider MPS II for addition to the RUSP.

Section 3. Decision Matrix

> The Advisory Committee shall
>
> (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

Appendix E presents the decision matrix used to determine whether to add a condition to the RUSP. The Committee developed the current decision matrix in 2014 to define steps and standards for assessing and rating net benefits of screening, certainty of evidence about those benefits, and feasibility of screening implementation. After a condition is nominated, the Committee reviews the evidence and assigns the condition a rating. Conditions with an "A" or "B" rating may be recommended to the Secretary of Health and Human Services for inclusion on the RUSP. In 2020, as part of the review of its internal processes (see Section 5.1,"RUSP Condition Nomination and Evidence Review Process"), the Committee considered ways to improve the decision matrix, such as providing written definitions of decision matrix rating categories and exploring the expansion of the "B" rating. The Committee plans to complete the review of its processes by the end of calendar year 2021.

The Committee also considered strategies for reviewing conditions currently on the RUSP, and discussed how often to conduct these reviews. Periodic reviews of current RUSP conditions should consider new information about the condition and impact of screening and could lead to better understanding of treatments, disease progression, long-term follow-up and the impact on public health systems, clinical services and families. Given the number of RUSP conditions, the Committee would need to implement a system to prioritize conditions for review.

Section 4. State Capacity to Screen

> The Advisory Committee shall
>
> (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

The Committee developed three reports that included sections about states' capacity for NBS. These reports were "Review of Newborn Screening Implementation for Spinal Muscular Atrophy: Final Report," "Review of NBS Implementation for Added RUSP Conditions: SCID, CCHD, Pompe, MPS I, XALD," and, "Review of Newborn Screening Timeliness."

Section 4.1 Key findings from "Review of Newborn Screening Implementation for Spinal Muscular Atrophy: Final Report"

In 2018, the Committee voted to recommend adding SMA to the RUSP. The U.S. Secretary of Health and Human Services accepted the Committee's recommendation and requested a follow-up report within two years, "describing the status of implementing newborn screening for SMA and clinical outcomes of early treatment, including any potential harms, for infants diagnosed with SMA." The Committee finalized the, "Review of Newborn Screening Implementation for Spinal Muscular Atrophy: Final Report," in 2020.

Between 2018 and 2020, the number of states offering universal SMA screening increased from two to 24, with ten more states planning to implement universal screening by the end of 2021. More than one million newborns have been screened, and 111 newborns have tested positive for

SMA since 2018. For most states, adopting screening for SMA has been facilitated by the ability to screen for SMA and SCID simultaneously in the same testing system and workflow.

Section 4.2 Key findings from "Review of NBS Implementation for Added RUSP Conditions: SCID, CCHD, Pompe, MPS I, XALD"

Between 2010 and 2017, the HHS Secretary accepted the Committee's recommendations to add five conditions to the RUSP. In 2020, the Committee reviewed the findings of a 2019 ACHDNC report titled, "Review of NBS Implementation for Added RUSP Conditions: SCID, CCHD, Pompe, MPS I, XALD," which describes the impact of adding these conditions on state NBS programs and population health (Lam et al., 2020). The table below summarizes when conditions were added to the RUSP and the number of states and territories conducting screening as of 2019.

Table 1. Number of states and territories screening added RUSP conditions as of 2019

Condition	Date added to RUSP	Number of states and territories screening
SCID	May 2010	50 states + District of Columbia (as of 2018)
CCHD	September 2011	50 states + District of Columbia (as of 2018)
Pompe disease	March 2015	19 states, + 1 state conducting a pilot
MPS I	February 2016	17 states + 2 states conducting pilots
XALD	February 2016	14 states + 2 states conducting pilots

The Committee found that facilitators to implementation of screening for new conditions include state mandates, funding, availability of tools to support accurate testing and interpretation, and registry databases to conduct long-term follow-up.

Examples of common barriers to implementing new RUSP conditions are obtaining legislative approval to increase funding to screen for new conditions, difficulty hiring and retaining necessary staff, and delays procuring necessary equipment. The report also identified solutions such as collaboration/learning from other NBS programs, encouraging workforce development in needed specialty areas, and ensuring laboratory information management system integration.

The Committee noted that long-term follow-up after NBS identifies infants as having a heritable condition helps ensure those infants get high quality care and, improves their health outcomes. Implementing screening for new conditions should include approaches to long-term follow-up tracking and care. The Committee noted that data collection on long-term outcomes varies widely across states and is often limited. Integrating screening, follow-up planning, and standardized data collection efforts would help coordination and efficiency. It also would facilitate the review of conditions that are added to the RUSP, and identify barriers to NBS implementation and technical assistance needs.

Section 4.3 Key findings from "Review of Newborn Screening Timeliness"

Section 17, "Timeliness of Collection, Delivery, Receipt, and Screening" describes findings of the Committee report, "Review of Newborn Screening Timeliness," which includes discussion of screening capacity.

Section 4.4 Impact of COVID-19 on state capacity to screen

The Committee assessed the impact of COVID-19 on state NBS programs. NBS has remained an essential public health service throughout the pandemic, and NBS programs continued to function despite unprecedented challenges. In some instances, the pandemic deferred state-level policymaking and budgeting, which are essential to NBS program implementation, and impact state capacity to screen.

The Committee invited the Association of Public Health Laboratories (APHL) and the National Center for Hearing Assessment and Management (NCHAM) to provide an overview of challenges and barriers to NBS during COVID-19, as well as solutions (Ojodu, 2020; White, 2020). Challenges to NBS included outpatient clinic closures, parents' hesitation to return to the hospital for repeat screening, neonatologists' being required to discharge infants within 24 hours while specimens should be collected after 24 hours (for accuracy), and delays to required equipment maintenance while staff worked remotely.

Newborn hearing screening also faced similar challenges, including the reassignment of staff who had knowledge of screening protocols or not allowing hearing screening staff into hospitals. Additionally, in some cases rushed hearing screens resulted in poor quality results. There were also delays in follow-up and fittings for hearing technology.

NBS programs implemented solutions to address challenges caused by the pandemic. Programs quickly instituted mandatory masks and temperature checks for patients and staff, and encouraged families to attend repeat screen appointments by disseminating information on the importance of NBS to pediatricians and other key stakeholders. NBS laboratories extended hours to ensure timeliness of screening results, and established remote connections to instruments for data collection and analysis. For hearing screening programs, hospitals allowed staff to return once they understood that newborn hearing screening services are essential. Hearing screening programs also leveraged telehealth to support delivery of early intervention services, such as speech therapy.

The Committee collected information from organizational representatives on their responses to the COVID-19 pandemic. For example, APHL (Tanksley, 2020) has leveraged their NewSTEPs program, which offers comprehensive NBS information and technical assistance, to disseminate information on conducting follow-up screens to state public health laboratories. The American Academy of Pediatrics (AAP) (Freedenberg, 2020) organizational representative cited data indicating that well child visits decreased during the pandemic. Organizations such as AAP and Genetic Alliance have responded with outreach and education campaigns to encourage families to bring infants to follow-up screening, reassure families that providers are implementing effective safety precautions and address other fears and barriers to accessing NBS and follow-up services (Bonhomme, 2020a; Freedenberg, 2020; Muenke & Keehn, 2020; Tanksley, 2020; Vockley, 2020). Organizations also responded by providing COVID-19 testing services (Muenke & Keehn, 2020), and participating in a study of genomic variants related to COVID-19 recovery (Muenke & Keehn, 2020).

NBS programs and other organizations utilized telehealth to support continued access to follow-up services. An American College of Medical Genetics and Genomics representative (Muenke & Keehn, 2020) described how the organization is supporting, enhancing, and expanding telehealth capacity, which improves access to genetic services for underserved populations. The Association of Maternal and Child Health Programs (Miller, 2020) reported that the organization supported the implementation of telehealth services to deliver virtual home visits and short-term

follow-up educational sessions with genetic counselors. The National Society of Genetic Counselors (Vockley, 2020) described the value of telemedicine for supporting genetic counseling services and NBS follow-up. The organization has developed a NBS toolkit that describes how to use telemedicine for these purposes.

States have never faced such a widespread and prolonged strain to their NBS systems. It is important to synthesize lessons that can be applied to strengthen continuity of operations planning (COOP) for future public health emergencies and natural disasters. The Committee will discuss strengthening NBS COOP within the context of COVID-19 throughout calendar year 2021.

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

> The Advisory Committee shall
>
> (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

Section 5.1. RUSP Condition Nomination and Evidence Review Process

In 2019, the Committee initiated a comprehensive review of its nomination and evidence review processes. The review considers: 1) the process for nominating conditions for inclusion on the RUSP, 2) the decision matrix used to determine whether to add a condition to the RUSP (discussed in Section 3), and 3) the decision-making process. When considering the nomination form and processes, the Committee discussed whether there are NBS outcomes that are relevant across all conditions, and whether to ask nominators to include information on condition-specific long-term follow-up. The Committee plans to complete its review by the end of calendar year 2021.

In 2020, the Committee also explored whether and to what extent the values and preferences of the NBS stakeholders should be taken into account as part of the evidence review process (Kemper, 20020a). The Committee noted that there is a wide range of stakeholders, including individuals with conditions and their families, those exposed to harm as a result of screening, pregnant women and their partners, clinicians, researchers, NBS program managers, public health officials, payers, and taxpayers. All of these stakeholders should have input in assessing values of screening for a specific condition. Values and preferences may differ between stakeholder groups. Preferences may vary depending on the condition under consideration. However, some values and preferences may be more general and may not require comprehensive assessment for each evidence review. Potential approaches include multi-criteria decision analysis, which weighs values and preferences along with scientific evidence, competing priorities, system capacity, and societal context. Any assessment of stakeholder values and preferences would need to occur within the nine-month timeframe allotted for the evidence review and decision-making process.

Section 5.2. Key findings from "Review of Newborn Screening Implementation for Spinal Muscular Atrophy"

As discussed in Section 4.1, in response to a request from the Secretary, the Committee released the report "Review of Newborn Screening Implementation for Spinal Muscular Atrophy." In addition to the information about state screening discussed in Section 4.1, the report also

provides recommendations, advice and information regarding morbidity specific to SMA, including discussion of evidence regarding testing to predict condition severity. The report explains that SMA is an inherited genetic condition that affects the body's ability to produce *SMN* protein and the nerve cells that carry messages from the brain to the muscles of the body. Identifying the *SMN2* (the "back-up" gene) copy number, is central to predicting the severity of the condition and planning treatment. One challenge to newborn screening programs is whether and how to include testing for *SMN2* copy number, which requires a separate assay. At least eight of the 24 states screening for SMA determine the *SMN2* copy number as part of NBS. Others defer this analysis as part of clinical follow-up care. Treatment guidelines published in 2020, recommend treating newborns with SMA who have between one and four *SMN2* copies. The process for determining the *SMN2* copy number is complex; research is ongoing to improve both the reliability and accuracy of results.

The Committee report presents data that indicate early detection of SMA through NBS followed by treatment is associated with improved motor functioning. The report presents the risks and benefits of current therapies, including nusinersen, risplidam, and gene therapy. Evidence to-date indicates that nusinersen is effective in improving survival rates without ventilator support as well as motor function, with low risk of adverse events. Nusinersen does require painful lumbar injections, which may be clinically inappropriate for patients with scoliosis. Risplidam, an oral medication that increases *SMN* protein production, was in clinical trials at the time the report was finalized and is now approved by the U.S. Food and Drug Administration (FDA). Studies conducted based on small samples suggest gene therapy is an effective SMA treatment.

The report identifies limited availability of clinical experts to treat individuals identified with SMA through NBS and lack of insurance coverage for treatment as challenges to equitable access to care.

Section 5.2 "Review of Newborn Screening Timeliness"

The Committee report, "Review of Newborn Screening Timeliness" addresses the impact of screening timeliness on mortality and morbidity. Key report findings are discussed in Section 17 of this report, "Timeliness of Collection, Delivery, Receipt, and Screening."

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

Section 4.4 of this report provides an overview of Committee information gathering on the impact of the COVID-19 pandemic on NBS systems, which includes discussions of challenges COVID-19 has posed or currently poses to NBS follow-up and corresponding solutions.

Section 7. Implementation, Monitoring, and Evaluation

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

In 2020 the Committee's work in the area of implementation, monitoring, and evaluation focused on states' progress toward meeting goals for timely NBS. Section 17, "Timeliness of Collection, Delivery, Receipt, and Screening" presents details.

Section 8. Diagnostic and Other Technology

(C) diagnostic and other technology used in screening

The Committee gathered information on the utilization of genomic sequencing and telehealth to optimize NBS.

Section 8.1 Genomic Sequencing

The Committee gathered information from the National Institutes of Health-funded Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) research program on the use of genomic medicine to improve health outcomes for infants and children at risk for heritable disorders and other genetic conditions. Researchers studied the potential to use genomic sequencing to screen for conditions not detectable with current NBS technology. These conditions include thyroid cancer predisposition, which begins in childhood and can be addressed with medical action, other childhood onset conditions for which medical actions are not yet available, and adult onset conditions that are medically actionable, such as breast and ovarian cancer predisposition. Study findings indicated that parental comfort with likely pathogenic results associated with adult onset disease varies and is lower when there is a higher risk of false positive or inactionable results (Berg, 2020). The research team recommended assessing use of genomic sequencing for well-understood, actionable conditions, and considered the implications of integrating this information into routine wellness visits for newborns and children.

The NSIGHT program also examined (Currier, 2020) the potential of exome sequencing to replace or augment tandem mass spectrometry (MS/MS). After analyzing 4.5 million dried blood spot results collected between 2006 and 2013 from the California Biobank, the researchers found that exome sequencing is less sensitive than standard MS/MS screening and would not be an appropriate substitute for MS/MS but may decrease the number of false positive newborn screens and contribute to accurate and timely case resolution.

NSIGHT also investigated the use of rapid and ultra-rapid whole genome sequencing in newborns in intensive care units with undiagnosed conditions (Kingsmore, 2020). In cases with and without findings of a genetic cause, investigators found that both physicians and parents found the procedure to be helpful for managing and treating symptoms. A substantial proportion of physicians reported that the procedure facilitated communication.

The final component of the NSIGHT program is research on use of genomic sequencing among healthy newborns and the potential for preventive genomics (Green, 2020). Results to-date indicate that risk of monogenic diseases in healthy newborns is more prevalent than expected. Sharing results about genetic disease risk did not affect parents' perceptions of their child's vulnerability or child-parent bonds. Future research will assess lifetime costs and benefits of preventive genomics.

Section 8.2 Telehealth

During discussions about the impact of COVID-19 on NBS and follow-up care, presenters and Committee members noted the value of telehealth in supporting the continuity of timely screening and access to follow-up care (Bonhomme, 2020a; Freedenberg, 2020; Miller, 2020; Muenke & Keehn, 2020; Tanksley, 2020; Vockley, 2020; White, 2020). Information gathered emphasized the value of telehealth in addressing the backlog of NBS services (e.g., follow-up, education) that accrued during the beginning of the pandemic. Telehealth also reduces barriers

for remote and underserved communities to access genetic services. Presenters emphasized the importance of expanding telehealth capacity, and of teaching providers, patients, and families to use telehealth resources.

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 the 2020 calendar year, 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"

During the 2020 calendar year, the Committee did not undertake activities relating to conditions not included in the RUSP that are treatable with FDA-approved products or other safe and effective treatments.

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"

Presentations about the impact of COVID-19 on NBS emphasized the importance of standardized protocols for ensuring timely and high-quality NBS services during public health emergencies (Bonhomme, 2020a, Bonhomme, 2020b; Ojodu, 2020).

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

Committee reports and presentations on SMA, conditions added to the RUSP, and timeliness of NBS describe barriers to optimal NBS implementation and strategies for addressing them. Section 4 and Section 17 of this report include summaries of Committee discussion, reports and presentations. The Committee noted that research is underway to improve reliability of the process for determining SMN2 copy number for SMA patients. In addition, greater workforce capacity of SMA clinical experts is needed to treat individuals diagnosed with the condition. The Committee agreed that increased consistency in laboratory cutoff methodology between states and long-term data collection are strategies that could improve reliability in true positive screens.

Section 13. Public and Provider Awareness and Education

> (H) public and provider awareness and education"

Discussion of COVID-19's impact emphasized the importance of clinicians' providing patients with information about NBS during the pandemic, as well as the need to offer clinicians the necessary information/education/training to educate their patients (Ojodu, 2020; Bonhomme, 2020; Tanksley, 2020). Presenters identified several resources for public education and shared specific examples. Details are available on the ACHDNC website.

Section 14. Cost Effectiveness

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

The Committee considered several potential strategies for improving cost assessment during their evidence-review process (Kemper, 2020e). Strategies included: 1) framing cost questions consistently across reviews of conditions nominated for the RUSP, 2) standardizing cost categories used in NBS pilot studies, 3) collecting retrospective data from programs that have implemented screening for new conditions, and 4) analyzing how birth rate, screens per infant, and annual number of screens predict cost variance. During discussion of this presentation, Committee members suggested that analysis should focus on cost ranges and thresholds.

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"

Committee work in this area included a report that discusses the clinical impact of adding SMA to the RUSP, discussed in Section 4.1, and a report that summarizes evidence regarding the public health benefits of adding other conditions to the RUSP, "Review of NBS Implementation for Added RUSP Conditions: SCID, CCHD, Pompe, MPS I, XALD" (Lam et al., 2020), discussed in Section 4.2.

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"

During the 2020 calendar year, the Committee did not undertake activities relating to the coordination of surveillance activities.

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

In 2020, the Committee finalized a report, "Review of Newborn Screening Timeliness," that examined state progress on achieving NBS timeliness goals (Kemper, Lam & Sullivan, 2020). Data collection methods included review of published and unpublished scientific literature, review of policies and other initiatives, convening an expert panel, and a review of APHL's NewSTEPs quality indicators. Results indicate that, since 2012, states have made progress toward meeting goals, but have not yet met all goals. According to the report, "The median percentage of specimens collected within 48 hours of birth across NBS programs has increased from 86.3% in 2012, to >95% in 2016-2018. Reported numbers of states with 95% of specimens collected within 48 hours has increased from 3 in 2012 to 14 states in 2018 (p.18)." The percentage of state NBS laboratories receiving specimens within 24 hours of collection increased from a median of 3.4 in 2012 to 41.8 in 2018. However, no state programs have met the goal of 95 percent of specimens being transported to laboratories within 24 hours of collection. Between 2012 and 2018, the median percentage of results reported within 5 days of collection increased from 22.7 to 63.5.

Examples of barriers to NBS timeliness include laboratory operating hours, high turnover rate of laboratory staff, limited availability of overnight and dependability of courier services, incomplete data collection, specimen batching from birthing hospitals, and lack of knowledge of NBS timeliness goals among NBS facility and hospital personnel. Strategies for overcoming these barriers include expanding courier services, extending laboratory hours, training laboratory personnel in a broader range of skills to address barriers resulting from staffing constraints and educating hospital staff.

The Committee affirmed the value of sharing guidance and lessons learned to support states in meeting NBS timeliness goals and continuing quality improvement practices for specimen transport, analysis and reporting to support quality screening and linkage to follow-up care (Kemper, 2020d).

FUTURE DIRECTIONS

During calendar year 2021, the Committee plans to conduct the following activities:

- Review the RUSP nomination for MPS II
- Complete the review of the evidence review process
- Develop consumer-friendly materials to align with updates identified through the Committee's review of the evidence review process
- Consider the impact of the COVID-19 pandemic on NBS systems across the U.S.
- Study approaches for assessing stakeholder values.

CONCLUSIONS

This report was prepared to summarize the Committee's activities for the 2020 calendar year. The mission of the Committee is to reduce morbidity and mortality in newborns and children who have, or who are at risk for, genetic conditions. ACHDNC accomplishes this mission by providing advice, recommendations, and technical information to the Secretary of the Department of Health and Human Services, and by helping to develop policies and priorities meant to enhance services at the state and local levels. In addition, ACHDNC invites public comments as an important way to identify issues and concerns relating to NBS.

In 2020, the Committee finalized a report on the status and impact of SMA screening, a report on other conditions added to the RUSP since 2017, and a report on state programs' efforts to meet goals for NBS timeliness. The Committee continued to review its evidence review processes including examining potential updates to the condition nomination form and decision matrix. The Committee also gathered information from experts on utilizing information obtained from genomic sequencing in NBS to support improved health outcomes, the impact of the pandemic on NBS, and the use of telehealth and other innovations to minimize disruptions to screening and follow-up.

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

REFERENCES

Berg, J.S. (2020). Newborn genomic sequencing in the NC NEXUS project. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children December 1 meeting. Convened virtually.

Bonhomme, N.F. (2020a). Genetic Alliance organizational updates regarding COVID-19. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children August 7 information sharing session. Convened virtually.

Bonhomme, N.F. (2020b). Parent perspectives: The reality of being a new and expectant parent during COVID-19. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children August 7 information sharing session. Convened virtually.

Currier, R. (2020). NSIGHT NBSeq: Evaluating the potential of exome sequencing for newborn sequencing. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children December 1 meeting. Convened virtually.

Freedenberg, D. (2020). American Academy of Pediatrics COVID-19 updates. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children August 7 information sharing session. Convened virtually.

Green, R.C. (2020). The BabySeq Project: Sequencing healthy newborns and the path to preventive genomics. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children December 1 meeting. Convened virtually.

Kemper, A.R. (2020a). Considerations for assessing values in newborn screening decision making. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children August 6 information sharing session. Convened virtually.

Kemper, A.R. (2020b). Newborn screening decision making criteria and matrix. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children December 1 meeting. Convened virtually.

Kemper, A.R. (2020c). Newborn screening implementation for spinal muscular atrophy-Committee feedback. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children August 7 information sharing session. Convened virtually.

Kemper, A.R. (2020d). Newborn screening timeliness. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children August 7 information sharing session. Convened virtually.

Kemper, A.R. (2020e). Overview of the ACHDNC's review process. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children August 6 information sharing session. Convened virtually.

Kemper, A.R. (2020f). Overview of the review of newborn screening implementation for spinal muscular atrophy report. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children December 1 meeting. Convened virtually.

Kemper, A.R. (2020g). Review of newborn sequencing implementation for added RUSP conditions: SCID, CCHD, Pompe, MPS I, XALD. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children December 1 meeting. Convened virtually.

Kemper, A.R.; Lam, K.K. & Sullivan, S. (2020). Review of newborn screening timeliness. Prepared for the US Department of Health and Human Services Health Resources and Services Administration Maternal and Child Health Bureau

Kemper, A.R.; Ream, M. & Lam, K.K. (2020). Review of newborn screening implementation for Spinal Muscular Atrophy: Final report. Prepared for the US Department of Health and Human Services Health Resources and Services Administration Maternal and Child Health Bureau.

Kinsgsmore, S.F. (2020). Rapid and ultra-rapid whole genome sequencing in newborns and children in intensive care units (ICUs) with undiagnosed diseases. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children December 1 meeting. Convened virtually.

Lam, K.K.; Lennox, A.; Kemper, A.R. & Reams, M. (2020.) Review of NBS implementation for added RUSP conditions: SCID, CCHD, Pompe, MPS I, XALD. Prepared for the US Department of Health and Human Services Health Resources and Services Administration Maternal and Child Health Bureau.

Miller, J. (2020). Association of Maternal and Child Health Programs COVID-19 response activities. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children August 7 information sharing session. Convened virtually.

Muenke, M. & Keehn, A. (2020). COVID-19: American College of Medical Genetics and Genomics members' response and national coordinating centers' and regional genetics networks' responses. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children August 7 information sharing session. Convened virtually.

Ojodu, J. (2020). Impact of COVID-19 on newborn screening systems in the United States. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children August 7 information sharing session. Convened virtually.

Tanksley, S.M. (2020). American Public Health Laboratories resources and strategies for NBS during COVID-19. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children August 7 information sharing session. Convened virtually.

Vockley, C.W. (2020). National Society of Genetic Counselors COVID resources. Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children August 7 information sharing session. Convened virtually.

White, K.R. (2020). Newborn hearing screening programs (early hearing detection programs-EHDI). Presentation at the Advisory Committee on Heritable Disorders in Newborns and Children August 7 information sharing session. Convened virtually.

APPENDIX A-ACHDNC Charter

Secretary of Health and Human Services
Washington, D.C. 20201

CHARTER

ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

1. Committee's Official Designation: The Committee shall be known as the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC).

2. Authority: ACHDNC was established under the Public Health Service (PHS) Act, 42 U.S.C. 217a: Advisory councils or committees, and Title XI § 1111 (42 U.S.C. § 300b-10 (g)). ACHDNC will fulfill the functions previously undertaken by the former Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, established under the PHS Act, Title XI § 1111 (42 U.S.C. § 300b-10). The ACHDNC is also governed by the provisions of the Federal Advisory Committee Act (FACA), as amended (5 U.S.C. App.), which sets forth standards for the formation and use of advisory committees.

3. Objective and Scope of Activities: The ACHDNC advises the Secretary of Health and Human Services (HHS) about aspects of newborn and childhood screening and technical information for the development of policies and priorities that will enhance the ability of the state and local health agencies to provide for newborn and child screening, counseling and health care services for newborns and children having, or at risk for, heritable disorders. The ACHDNC will review and report regularly on newborn and childhood screening practices, recommend improvements in the national newborn and childhood screening programs, as well as fulfill the list of requirements stated in the original authorizing legislation.

4. Description of Duties: The ACHDNC shall:

   (1) Provide advice and recommendations to the Secretary of HHS concerning grants and projects awarded or funded pursuant to 42 U.S.C. §§300b-8;

   (2) Provide technical information to the Secretary of HHS for the development of policies and priorities for the administration of grants pursuant to 42 U.S.C. §§300b-8;

   (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;

(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;

(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;

(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;

(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 pursuant to 42 U.S.C. §300b-8; and

(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.

As part of its general duties, the ACHDNC will approve by-laws.

5. Agency or Official to Whom the Committee Reports: The ACHDNC provides advice and recommendations to the Secretary.

6. Support: Management and support service are provided by the Maternal and Child Health Bureau, Health Resources and Services Administration (HRSA).

7. Estimated Annual Operating Costs and Staff Years: The estimated annual operating cost for the ACHDNC, including compensation and travel expenses for members but excluding staff support, is $142,081. The estimated annual person year(s) of staff support required is 1.8 FTE, at an annual cost of $283,343. The estimated annual costs for future fiscal years are subject to the availability of appropriations.

8. Designated Federal Official: A full-time or permanent part-time federal employee, appointed in accordance with Agency procedure, will serve as the Designated Federal Official (DFO) (or designee) and ensure that all procedures are within applicable statutory, regulatory, and HHS General Administration Manual directives. The DFO (or designee) approves and prepares all meeting agendas, calls all Advisory Committee or subcommittee meetings, attends all Advisory Committee and subcommittee meetings, adjourns any meeting when the DFO (or designee) determines adjournment to be in the public interest, and chairs meetings when directed to do so by the Secretary.

9. Estimated Number and Frequency of Meetings: The ACHDNC shall meet approximately four times per year as deemed necessary by the DFO (or designee), in consultation with the Committee Chair. Meetings shall be open to the public except as determined otherwise by the Secretary or designee in accordance with the Government in the Sunshine Act (5 U.S.C. 552b(c)) and the FACA, as amended (5 U.S.C. App.). Notice of all meetings shall be given to the public. Meetings shall be conducted, and records of the proceedings kept, as required by applicable laws and departmental regulations.

10. Duration: Continuing.

11. Termination: Unless renewed by appropriate action prior to its expiration, the ACHDNC will terminate two years from the date the charter is filed.

12. Membership and Designation: The ACHDNC consists of 15 members appointed by the Secretary for a term not to exceed 2 years and shall include:

    (1) Medical, technical, public health, or scientific professionals with special expertise in the field of heritable disorders or in providing screening, counseling, testing, or specialty services for newborns and children at risk for heritable disorders;
    (2) Experts in ethics and heritable disorders who have worked and published material in the area of newborn screening;
    (3) Members from the public sector having special expertise about or concern with heritable disorders; and
    (4) Representatives from such federal agencies, public health constituencies, and medical professional societies (as determined to be necessary by the Secretary of HHS) to fulfill the duties of the Committee.

In addition, the ACHDNC will have the following ex-officio members or their designees from these agencies:

    (1) Administrator of HRSA;
    (2) Director of the Centers for Disease Control and Prevention;
    (3) Director of the National Institutes of Health;
    (4) Director of the Agency for Healthcare Research and Quality; and
    (5) Commissioner of the Food and Drug Administration.

13. Subcommittees of the ACHDNC: Standing and ad hoc subcommittees, composed of members of the parent committee, may be established with the approval of the Secretary or designee to perform specific functions within the ACHDNC's jurisdiction. Subcommittees must report back to the parent Advisory Committee and do not provide advice or work products directly to the Department or HRSA. The Department's Committee Management Officer will be notified upon the establishment of each subcommittee and will be provided information on the subcommittee's name, membership, function, and estimated frequency of meetings.

14. Recordkeeping: Records of the Advisory Committee, formally and informally established subcommittees, or other subgroups of the Advisory Committee, shall be handled in accordance with General Records Schedule 6.2, or other approved agency records disposition schedule. These records shall be available for public inspection and copying, subject to the Freedom of Information Act, 5 U.S.C. 552.

15. Filing Date: MAR 2 0 2020

Approved:

MAR 1 1 2020

Date

/Alex M. Azar II/

APPENDIX B- Membership of ACHDNC

Committee Members

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

Jeffrey P. Brosco, M.D., Ph.D.
Professor of Clinical Pediatrics, University of Miami
Title V CYSHCN Director, Florida Department of Health
Associate Director, Mailman Center for Child Development
Director, Population Health Ethics, UM Institute for Bioethics and Health Policy

Kyle Brothers, M.D., Ph.D.
Endowed Chair of Pediatric Clinical and Translational Research
Associate Professor of Pediatrics
University of Louisville School of Medicine

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

Shawn McCandless, M.D.
Professor, Department of Pediatrics
Head, Section of Genetics and Metabolism
University of Colorado Anschutz Medical Campus
Children's Hospital Colorado

Cynthia M. Powell, M.D., FACMG, FAAP (Chairperson)
Professor of Pediatrics and Genetics
Director, Medical Genetics Residency Program
Pediatric Genetics and Metabolism
The University of North Carolina at Chapel Hill

Annamarie Saarinen
Co-founder, CEO
Newborn Foundation

Scott M. Shone, Ph.D., HCLD (ABB)
Director
North Carolina State Laboratory of Public Health

Ex-Officio Members

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

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

Food and Drug Administration
Kellie B. Kelm, Ph.D.
Deputy Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics and Radiological Health

Health Resources & Services Administration
Michael Warren, M.D., M.P.H., FAAP
Associate Administrator,
Maternal and Child Health Bureau

National Institutes of Health
Diana W. Bianchi, M.D.
Director
Eunice Kennedy Shriver National Institute

Designated Federal Official
Mia Morrison, M.P.H.
Health Resources and Services Administration
Genetic Services Branch
Maternal and Child Health Bureau

APPENDIX C- Summary of Committee Recommendations and Secretary Responses during 2020

The Committee did not make recommendations during 2020. It developed three reports to submit to the Secretary, listed in Appendix D.

APPENDIX D-List of Committee Publications during 2020

Kemper, A.R.; Lam, K.K. & Sullivan, S. (2020). Review of newborn screening timeliness. Prepared for the US Department of Health and Human Services Health Resources and Services Administration Maternal and Child Health Bureau

Kemper, A.R.; Ream, M. & Lam, K.K. (2020). Review of newborn screening implementation for Spinal Muscular Atrophy: Final report. Prepared for the US Department of Health and Human Services Health Resources and Services Administration Maternal and Child Health Bureau.

Lam, K.K.; Lennox, A.; Kemper, A.R. & Reams, M. (2020.) Review of NBS implementation for added RUSP conditions: SCID, CCHD, Pompe, MPS I, XALD. Prepared for the US Department of Health and Human Services Health Resources and Services Administration Maternal and Child Health Bureau.

APPENDIX E-Decision Matrix

ACHDNC
Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

NET BENEFIT/ CERTAINTY			READINESS			FEASIBILITY	
			Ready	Developmental	Unprepared		
SIGNIFICANT Benefit	Certainty	HIGH	**A1** Screening for the condition has a high certainty of significant net benefits, screening has high or moderate feasibility. Most public health departments are ready to screen.	**A2** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments have only developmental readiness.	**A3** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments are unprepared for screening.	Feasibility	HIGH or MODERATE
			A4 There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.				LOW
		MOD	**B 1-4** There is moderate certainty that screening would have a significant benefit.			----	
Small to ZERO Benefit	Certainty	MOD/HIGH	**C 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a small to zero net benefit.			----	
NEG Benefit			**D 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a negative net benefit.			----	
---		LOW	**L 1-4** There is low certainty regarding the potential net benefit from screening.			----	