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

The Advisory Committee on Heritable Disorders in Newborns and Children

Report to Congress
2013 – 2017

April 2018

Advisory Committee on Heritable Disorders in Newborns and Children

2017 Report to Congress

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Executive Summary

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) was established to advise and provide recommendations to the Secretary of the U.S. Department of Health and Human Services (HHS) regarding heritable disorders, newborn screening and childhood screening. The Committee's advice and recommendations are intended for use by the Secretary to develop policies and priorities that can enhance the states' ability to reduce morbidity and mortality in newborns and children either having, or at risk for, heritable disorders. These disorders, which can be present at birth, if left undetected can cause irreparable harm to newborn infants whether by causing disability or even death. Newborn and childhood screening improves quality of life and save lives.

Listed below are highlights of the Committee's work from 2013-2017:

- The Committee recommended to the Secretary that Pompe Disease, Mucopolysaccharidosis I, and Adrenoleukodystrophy be added to the Recommended Uniform Screening Panel (RUSP). The Secretary approved the three additions.
- A condition review matrix was refined. The matrix is a methodological tool for systematically evaluating the magnitude and certainty of the net benefit of screening, the capacity of state newborn screening programs to implement screening for nominated conditions, and the laboratory cost associated with adding a condition.
- The Committee supported activities related to improving state capacity to screen for conditions included in the RUSP.
- The Committee developed a policy regarding the minimum data required to move a nominated condition into the evidence review process.
- The Committee provided advice to the Secretary regarding standard terminologies and coding for test results and conditions identified by newborn screening be used to ensure reliable clinical communication, accurate statistical reporting, and quality assurance.
- The Committee provided advice to the Secretary regarding Section 12 of the Newborn Screening Saves Lives Reauthorization Act of 2014 (P.L. 113-240) that defines research on newborn dried blood spots as research carried out on human subjects.
- The Committee recommended that the Secretary facilitate a national dialogue on the necessity of measuring succinylacetone in dried blood spots for screening Tyrosenimia Type I in newborns.
- The Committee provided advice to the Secretary on several best practices in newborn screening including goals for achieving timely newborn screening.

The Committee has demonstrated through collaborative efforts that it is making a lasting impact on improving newborn screening. The Committee is committed towards identifying problems and gaps that need to be solved to improve the quality of life for all newborns and children.

Report

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) was formed with the purpose to advise the Secretary of the U.S. Department of Health and Human Services regarding the best applications of newborn screening tests, technologies, policies, guidelines, and standards (ACHDNC, 2018). As part of their mission, the Committee informs and updates the Secretary by providing:

- 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; and
- 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 intent of this report is to summarize the Committee's activities and outcomes for calendar years 2013 through 2017 to fulfill the legislative requirement for the submission of an annual report to Congress, the Secretary, the Interagency Coordinating Committee on Newborn and Child Screening, and State Health Departments. The discussion of these activities and outcomes relative to recommendations, advice, or information on mortality and morbidity will be subdivided into sections that are in alignment with the Committee's legislative duties.

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;

In this section, the following updates will be discussed: A) evidence-based reviews; B) considering the type of data needed for an evidence review and C) agreement with the U.S. Preventative Services Task Force (USPSTF) for the Committee to review newborn screening conditions referred to the USPSTF.

A. Evidence-based Reviews

The Committee reviews heritable conditions that have been nominated for inclusion on the Recommended Uniform Screening Panel (RUSP), a list of conditions recommended by the Secretary of HHS for inclusion on state newborn screening panels. Based on established criteria, the Committee assigns nominated conditions to an external, independent group known as the Committee's Evidence Review Group (ERG). The ERG is comprised of subject matter and evidence-review experts with representation from the Committee. The ERG conducts a systematic evaluation of published and unpublished data on the condition, treatment, analytic and clinical validity of screening and confirmatory testing, the potential net benefit of screening, public health impact of screening, and the laboratory cost of adding the condition.

Upon consideration and in-depth discussion of the evidence, the Committee votes to recommend, or not recommend, adding the nominated condition to the RUSP. Conditions recommended for addition are sent to the Secretary of HHS for final decision. Between 2013 and 2016, the Committee reviewed nominations for the following conditions and recommended the Secretary add them to the RUSP:

- Pompe Disease, a genetic condition that results in accumulation of glycogen in certain organs and tissues impairing muscle function, the infantile form of which can result in significant morbidity and death in early childhood;

- Mucopolysaccharidosis Type I (MPS I), a genetic condition caused by a deficiency of the enzyme alpha-L-iduronidase which prevents effective metabolic processing and leads to accumulation of materials in cells resulting in poor cell performance and progressive damage throughout the body; and

- X-linked Adrenoleukodystrophy (X-ALD), a genetic condition that affects the nervous system and adrenal glands, the most serious form of which is childhood cerebral X-ALD which presents between 2.5 and 10 years of age and is associated with rapid neurologic decline and death or disability within 3 years.

The Secretary approved the addition of all three conditions to the RUSP.

During the May 2017 meeting, the Committee reviewed an application for Spinal Muscular Atrophy (SMA). In May 2017, based on the information provided, the Committee voted to move SMA forward to Evidence Review (Tarini, 2017 May). This condition, which causes weakness and atrophy through the progressive degeneration of the anterior horn cells in the spinal cord and brain stem, ranges in degrees of severity with the most severe type having a median survival rate of 24 months. The subsequent nine-month review process is currently ongoing and will continue into 2018.

B. Pilot Studies

An effective evidence-based review relies on the availability of high quality, accurate data. The Committee established the Pilot Studies Workgroup in 2015 to determine the quantity and quality of data needed to move a condition to evidence review.

In August 2016, the Committee considered and accepted the following recommendations:

- Data should be available on the analytical validation of one or more screening modalities proposed for use in population-based screening in newborns.

- Data should be available on the net benefits of clinical interventions following early detection compared to late diagnosis.

- Data should be available from pilot studies involving population-based screening of identifiable newborns. The study should evaluate the newborn screening process from collection through diagnosis and identify at least one screen positive newborn with confirmation of presence of the condition under consideration. The population included in the pilot study, and the screening protocol used, should be similar to the US population and to state NBS programs with respect to known prevalence of the condition, and the timing and approach to screening. The screening modality used in the pilot study should be comparable to the method proposed in the application.

- Continued support should be provided for NIH initiatives relevant to pilot studies in newborn screening including NBSTRN, NSIGHT, Pilot Studies grants, Natural History grants, Innovative Therapies grants, and grants supported under the Parent Announcement.

- Continued support should be provided to CDC for its activities relevant to pilot studies that address technical training and quality materials for state laboratories, assistance to state and other programs in obtaining laboratory equipment, creation and distribution of "Validation Test Packages," population surveillance, and fostering of "Laboratories of Excellence."

- HHS should support the development of a research network comprised of state-based public health programs, laboratories, and academic or other research centers that would provide a stable, experienced, compliant, efficient, and quality infrastructure for the conduct of population-based pilot studies for newborn screening.

C. Newborn screening conditions referred by the U.S. Preventative Services Task Force

The U.S. Preventive Services Task Force (USPSTF) is an independent, volunteer panel of national experts who make evidence-based recommendations about clinical preventive services such as screenings, counseling services, and preventive medications. In 2015, the USPSTF decided to refer its newborn screening topics, including sickle cell disease, phenylketonuria (PKU), and congenital hypothyroidism to the ACHDNC as well as any future newborn screening topics. USPSTF recommendations are based on a rigorous review of existing peer-reviewed evidence so the decision to refer these newborn screening topics to the ACHDNC recognizes the rigor of the Committee's evidence-based review process.

In 2016, the Committee reviewed a nomination to add guanidinoacetate methyltransferase (GAMT) deficiency to the RUSP. GAMT is a disorder that affects the brain and muscles and can lead to intellectual disability, limited speech development, and epilepsy. While recognizing GAMT as a medically important disorder that deserves serious attention, the Committee voted to not send the nomination forward for evidence review based on the determination that no case had been prospectively identified through a newborn screening system. The Committee encourages a resubmission of the nomination following the prospective identification and diagnosis of a GAMT patient through newborn screening.

2. Decision Matrix for Newborn Screening Expansion

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

This section describes work of the Committee conducted between 2013 and 2014 to revise the decision matrix and take into consideration population-level benefits of adding a condition to the RUSP, the feasibility and readiness of states to incorporate screening into their NBS programs, and the cost to a laboratory to add a condition.

A. Public Health Impact Analysis

In 2013 the ACHDNC established an Expert Advisory Panel to make recommendations for the development of a public health system impact survey instrument to assess the feasibility and readiness of states to implement screening for a new condition. An OMB-approved tool is administered to states and assesses states' ability to screen for the condition, the availability of follow-up diagnostic and clinical referrals, and provides an estimate of how long it would take to implement testing once their state had made the decision to screen for the condition.

B. Cost Analysis

To assess the costs of newborn screening expansion, in Fiscal Year (FY) 2015 the ACHDNC convened a Cost Analysis Workgroup (CAW) charged with considering methods to assess the cost of newborn screening expansion, focusing on the cost incurred to the state to add newborn screening for a particular condition. Specifically, the workgroup considered:

- Which costs of newborn screening expansion should be included within a condition review;
- What critical data elements are needed to address the cost of newborn screening expansion;
- What is the availability and feasibility of collecting data;
- Where are the sources of data; and
- How this will impact the nomination and review process.

The CAW presented its findings to the ACHDNC in February 2016. The Committee agreed that the cost to the laboratory to add a condition to their screening panel was the most feasible cost to determine within the legislatively mandated time to complete an evidence review (nine months).

3. State Capacity to Screen

The Advisory Committee shall—

(5) 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 HRSA-funded Newborn Screening Technical Assistance and Evaluation Program (NewSTEPs) provided the Committee with information on quality improvement initiatives, their data repository, and technical resources made available to state NBS programs during the past four years. The repository supports data standardization to more accurately track and estimate the incidence of conditions. Data are used to inform efforts to help states and territories implement quality improvement activities, evaluate the impact of their NBS programs, and address gaps within the newborn screening system. NewSTEPs is also collaborating with state NBS programs to develop solutions for strengthening the NBS system capacity by focusing on data quality data, technical assistance, and the sharing of ideas and experiences. Refer to Section L for more information on the Newborn Screening Timeliness Collaborative Improvement and Innovation Network (CoIIN).

4. Recommendations, Advice, or Information on Mortality and Morbidity

As per the Public Health Service Act, Title XI, § 1109 42 U.S.C. 300b-10, the Advisory Committee shall—

(6) 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—

A. Follow-Up Activities

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

<u>Contingency Planning</u>

In February 2017, the Committee discussed updates to the Newborn Screening Contingency Plan (CONPLAN) (Taft, 2017 February). The plan was originally published in 2010, and designed for use by states and regions during a public health emergency or interruption in service and contributed towards preparedness and recovery from Hurricane Sandy in 2012.

The Association of Maternal and Child Health Programs (AMCHP), the Centers for Disease Control and Prevention (CDC), the Health Resources and Services Administration (HRSA), the Association of Public Health Laboratories (APHL) and expert stakeholders participated in updating the plan which focused on addressing gaps in laboratory, clinical and long-term follow-up, addressing point-of-care screenings and emphasizing family engagement. New communications and family education objectives were proposed as first steps in contingency

planning for newborn screening programs along with outlines for strategic objectives, supporting activities, and organizational responsibilities. Contingency planning checklists, resource lists, tools and templates have also been added that can be applied towards achieving uninterrupted newborn screening.

Medical Foods

In 2017, the Committee tasked a workgroup to develop a white paper summarizing issues related to coverage of medical foods for infants, children and adults with Inborn Errors of Metabolism (IEM), conditions detectable through newborn screening. Medical foods are the primary form of intervention for many IEMs, require supervision by medical providers, and are not available for conventional purchase. Since they are not considered medical drugs, insurance may not cover the costs. The intended outcomes of the white paper were to provide background information about medical foods, affirm the principles of the Committee that medical foods should be covered, and provide suggestions for policy analysis aimed at increasing food availability for those who require this intervention.

Quality Measures

In 2017, the Committee examined issues related to the use of quality measures to assess long-term outcomes for infants identified through newborn screening. A presentation was heard during the August 2017 meeting regarding the kinds of measures used as standardized and quantitative assessment tools that can be employed to assess health outcomes such as mortality, tracking processes, and quality improvement and assurance (Zuckerman, 2017 August). The Committee tasked the Follow-Up and Treatment Workgroup to examine the value and feasibility for using quality measures towards follow-up of newborn screening and to identify any barriers that would need to be overcome.

Timeliness

In 2017, the Committee heard a presentation with the preliminary results from NewSTEPS 360, the HRSA-funded newborn screening timeliness CoIIN. Please refer to Section L of this report for additional details.

B. Implementation, Monitoring, and Evaluation

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

During 2017, the Committee heard several presentations and participated in discussions related to the clinical and public health implications of critical congenital heart disease (CCHD) in newborn screening (Grosse, 2017 August; Oster, 2017 August), as well as, the clinical and public health impacts of SCID screening (Kobrynski, 2017 November; Manning, 2017 November; Singh, 2017 November). CCHD is identified as a specific set of heart defects associated with impaired oxygen circulation and is screened for using a pulse oximetry test. States can vary on their testing policies. Regarding SCID screening, a panel of presentations at the November 2017 meeting (Kobrynski, 2017 November; Manning, 2017 November; Singh, 2017 November) focused on an overview of the clinical and public health

impact of SCID screening along with the general landscape of where states are in relation to their screening efforts.

C. Diagnostic and Other Technology

(C) diagnostic and other technology used in screening;

In 2014, the National Committee on Vital and Health Statistics (NCVHS) presented to the Committee on the use of standard terminologies and coding for test results and conditions identified by newborn screening and how important they are for reliable clinical communication, accurate statistical reporting, quality assurance, and research. Based on the presentation, the Committee Chair sent a letter to the Secretary in support of the NCVHS recommendations and promoted a collaborative effort to adopt standardized public health information systems.

In 2014, the CDC presented to the Committee on the impact of electronic health record implementation on early hearing detection and intervention programs. The presentation showed how newborn screening information could be transferred from system to system from the time of birth, through the state health department to the primary care provider and, ultimately, to the audiologist in real time. This provides the ability to track events from both a public health and a clinical systems perspective and enables evaluation of the timeliness of the process.

D. Availability and Reporting of Testing

(D) the availability and reporting of testing for conditions for which there is no existing treatment;

There are no updates at this time regarding the availability and reporting of testing for conditions for which there is no existing treatment.

E. 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;

There are no updates at this time regarding 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.

F. 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;

In this section we discuss the Committee's work on research in newborn screening, developing case definitions for surveillance, and laboratory practices related to determining an out-of-range result.

1. Research using newborn screening bloodspots

In 2015, the ACHDNC discussed Section 12 of the Newborn Screening Saves Lives Reauthorization Act of 2014 (P.L. 113-240), which defines research on newborn dried blood spots as research carried out on human subjects. The Committee submitted the following recommendations to the Secretary:

- Adopt the Secretary's Advisory Committee on Human Research Protections "Recommendations Regarding Research Uses of Newborn Dried Bloodspots and the Newborn Screening Saves Lives Reauthorization Act of 2014."
- Partner with states to inform the development of guidance for Institutional Review Boards (IRBs) that distinguishes between the use of dried blood spots for research and non-research in the context of required, routine NBS program activities such as quality assurance, quality improvement, and method development for new tests for conditions currently recommended for screening and for conditions being evaluated for possible inclusion on the RUSP.
- Partner with states to inform the development of guidance for IRBs on models for broad informed consent for using residual dried blood spots to perform newborn screening research.
- Partner with states to inform the development of guidance for IRBs that identifies appropriate models for broad informed consent for states that choose to store residual dried blood spots for future research purposes.
- Create and distribute communication materials targeted to professional organizations associated with obstetricians, nurses, midwives, and other health care workers who care for pregnant women and to the public on the importance of newborn screening and options for parents to participate in newborn screening research.
- Consider mechanisms to fund states for translational research to:
    - Develop practice/evidence-based guidelines on informed consent for use of residual dried blood spots which include a cost effectiveness analysis.
    - Monitor research activities that require informed consent.

The Deputy Secretary, on behalf of the Secretary, accepted the Committee's fifth recommendation to create and distribute targeted materials on the importance of newborn screening and options for parents to participate in newborn screening research. The Secretary asked the Centers for Disease Control and Prevention to work with states, HRSA, the U.S. Food and Drug Administration, and the Assistant Secretary for Health's Office for Human Research Protections to develop guidance and educational materials on this issue.

2. Case definitions

In November 2016, NewSTEPS presented their efforts to develop standardized case definitions for public health surveillance of newborn screening. Surveillance case definitions establish uniform criteria for disease reporting. The case definitions will allow for monitoring of trends

for reported conditions, detection of unusual occurrence, and defining uniform populations to allow for evaluation of intervention and long-term follow-up for newborn screening. NewSTEPS is also assisting states to develop systems for implementing the definitions for their own use. The definitions have been incorporated into the national data repository maintained by NewSTEPS.

3. Establishing out-of-range newborn screening results.

Over the course of several meetings in 2017, the Committee heard presentations on the topic of newborn screening algorithms used to establish out-of-range laboratory results. (Caggana, 2017 February; Johnson, 2017 February; Thompson, 2017 February). Newborn screening clinical laboratories are subject to the Clinical Laboratory Improvement Amendments (CLIA) of 1988 which are regulatory standards applicable to all clinical laboratory testing in the United States. CLIA requires good laboratory practices to ensure the accuracy and reliability of clinical laboratory testing. Some state laboratories have more stringent quality standards and seek additional accreditation. Numerous variables will result in laboratories setting different reference ranges and cutoffs including, but not limited to, the testing methodology, kits, or equipment used, the environment of the laboratory, the biomarker being tested, and the population of the state.

Programs and tools are available to help states achieve quality improvement in this area. The CDC's Newborn Screening QA/QC Program works with state programs to ensure the usefulness and analytic validity of newborn screening tests and can provide quality control and test materials to assess the performance of new screening tools. These roles were authorized to the CDC as part of the Newborn Screening Saves Lives Act of 2014 with the Program's goal set to ensure early and accurate detection of newborn conditions through blood spot testing. The presentation given to the Committee in May 2017 provided a general overview of the Newborn Screening QA/QC Program and its functions and scope of initiatives. This information provided an understanding on how to help support those who may want to nominate a condition for addition to the RUSP, such as assuring methods and quality assurance materials are developed to cover that condition.

The Association of Public Health Laboratories presented quality indicator data from the NewSTEPs database, a HRSA-funded initiative, covering topics such as case definitions and the number of states screening for conditions added to the RUSP. In 2017 data on the public health impact of CCHD and SCID screening was presented, including lessons learned from the implementation of these newer RUSP conditions.

Other tools that could assist states with newborn screening algorithms include interactive web tools such as Region 4 Stork (R4S) and Collaborative Laboratory Integrated Reports (CLIR). R4S focuses on laboratory quality improvement of newborn screening by tandem mass spectrometry (MS/MS). R4S creates post-analytical interpretation support tools where results are combined into a likelihood score for each case being a true or false positive. CLIR, the successor of R4S, is a web based multivariate pattern recognition software applicable to a variety of test results including newborn screening results. CLIR can account for user selectable variables such as age at sample collection, birth weight, and gestational age. These multivariate reference and disease ranges are derived through retrospective

analysis of hundreds of thousands of data points contributed by a worldwide community of collaborators.

G. 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:

In September 2014, the ACHDNC reviewed a report on *Succinylacetone as Primary Marker to Detect Tyrosemia Type I in Newborns and its Measurement by Newborn Screening Programs* and submitted the following recommendation to the Secretary:

- The Secretary of HHS should facilitate a national dialogue among federal and state stakeholders on the benefits of measuring succinylacetone in dried blood spots to improve the specificity of newborn screening for Tyrosinemia type I, a condition on the RUSP.

The Deputy Secretary, on behalf of the Secretary, accepted the Committee's recommendation and asked the CDC to facilitate a national discussion to address technical and practice issues in measuring succinylacetone for screening newborns.

During 2017, the Committee heard several presentations and has had discussions on setting cutoffs for newborn screening. Please refer to Section F for more information.

H. Public and Provider Awareness

(H) public and provider awareness and education;

Baby's First Test is a HRSA-funded program serving as the central avenue for informing and empowering families and healthcare providers about the newborn screening experience in order to increase their awareness, knowledge, and understanding of newborn screening and genetic conditions. Between 2014 and 2015, traffic to the website increased nearly 150 percent, reaching 663,000 visitors in 2015. Mobile traffic has become the most popular method of accessing the site and web content is formatted appropriately for this platform. From the launch of Baby's First Test in September 2011 through January 30, 2017, the website has reached more than 1.7 million unique users and has been accessed more than 3.5 million times. Of users surveyed, 65 percent report that they learned something new from the website that they did not know before about newborn screening and state testing policies. Baby's First Test has been involved in several initiatives, including virtual "town halls" and bi-monthly informational webinars.

I. Cost and Effectiveness

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

See Section 2 – Decision Matrix for Newborn Screening Expansion, Part B – Cost Analysis, for details on the development of cost assessment methods for expanding newborn screening (Kemper, 2017 May).

J. Causes, Public Health Impacts, and Risk Factors

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

During the November 2017 meeting, the Committee heard a panel of presentations and engaged in discussion focused on the implications of detecting carriers through newborn screening. Newborn screening aims to identify those with disorders requiring treatment, however some testing methods have the capacity to identify carriers. There are different ethical considerations when carriers are detected and there may not be immediate clinical relevance. The initial presentation explored the types of carriers that could be detected in the context of newborn screening, as well as other disorders that could be identified due to patterns of inheritance (e.g. autosomal recessive/Cystic Fibrosis/Sickle Cell Anemia, X-linked/adrenal leukodystrophy, and Duchenne Muscular Dystrophy) (Watson, 2017 November). Ultimately, newborn screening programs must decide whether providing carrier status results in a clinical benefit to the individual. This will most likely vary based on the state and by condition.

K. 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.

In August 2015, NewSTEPs described their activities including the data repository which provides tools to state NBS systems to adequately evaluate, analyze, and benchmark the performance of their tests and the quality of their NBS programs. NewSTEPs data have been used to show the progression of states adopting screening for SCID, CCHD, Pompe disease, MPS 1 and X-ALD. As part of their data services, NewSTEPS provides a data repository where newborn screening programs can voluntarily add data once they have a fully ratified Memorandum of Understanding with the APHL. In this database repository, newborn screening data are collected to include state profile information, case data, and quality indicator data for quality improvement initiatives at the program level. In addition, over the course of 2017, the Committee heard several presentations and engaged in discussion focused on establishing and reevaluating newborn screening cutoffs. Specific topics falling under this subject included an overview of state experiences, tools that are available for use, and the possible next steps needed to advance these efforts. One specific presentation explained the use of the R4S and CLIR interactive web tools, which is discussed under Section F.

L. Timeliness of Data

(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.

Between 2014 and 2015, the ACHDNC reviewed policies and practices related to newborn screening timeliness in the United States. Specifically, the Laboratory Procedures and Standards Workgroup gathered information on newborn screening timeliness through focus groups, surveys, and stakeholder interviews to identify time-critical conditions that require urgent follow-up; existing gaps and barriers to screening and follow-up in the NBS systems; and strategies for improvement. The ACHDNC provided to the Secretary advice regarding best practices for timely newborn screening.

- To achieve the goals of timely diagnosis and treatment of screened conditions and to avoid associated disability, morbidity, and mortality, the following timelines should be achieved by NBS systems for the initial newborn screening specimen.
  - Presumptive positive results for time-critical conditions should be communicated immediately to the newborn's healthcare provider but no later than five days of life.
  - Presumptive positive results for all other conditions should be communicated to the newborn's healthcare provider as soon as possible but no later than seven days of life.
  - All newborn screening tests should be completed within seven days of life with results reported to the healthcare provider as soon as possible.
- In order to achieve the above goals, the following goals for specimen collection and processing were identified. The goal is that 95% of the specimens tested meet the following timelines:
  - Initial newborn screening specimens should be collected in the appropriate timeframe for the newborn's condition but no later than 48 hours after birth; and
  - Newborn screening specimens should be received at the laboratory as soon as possible; ideally within 24 hours of collection.

These timeframes are goals for the entire NBS system to achieve the best outcomes for infants identified through the newborn screening process with a potentially harmful or life-threatening condition. In addition, the Committee stated that state newborn screening programs should aim to have 95% of results reported within these timeframes. The Committee recommends state NBS programs monitor their progress in achieving the above timeframes and make the information readily available to the general public, hospitals, providers, and other stakeholders.

The HRSA-funded Newborn Screening Timeliness CoIIN, led by NewSTEPs 360, consists of at least 20 states working to achieve timely reporting of results in 95 percent of newborns who receive dried-blood spot newborn screening. States receive financial assistance, training, and coaching on continuous quality improvement techniques. States also share resources and are on monthly calls with the other stakeholders. In August 2016 and November 2017, the ACHDNC received an update on timeliness activities, including a presentation focused on the work conducted by the NewSTEPS 360 for Newborn Screening Timeliness. The project focused on three major steps of newborn screening process: the collection, the transport, and the processing of the specimen. Examples of successes include: 1) Montana made improvements through extending courier services to add a sixth day on

Sundays for their larger facilities and providing overnight service for the smaller ones. As a result, they are now reporting 95% of all results within the Committee's recommended seven-day window. 2) Other states have adjusted as well, ranging from altering staffing hours to ensure samples are processed when they are typically received (Texas), to flying samples via commercial air courier to nearby states with better testing capabilities (Alaska to Oregon). These types of changes are making huge differences in newborn screening programs achieving timeliness goals.

The Committee also heard a presentation on the preliminary findings of a Robert Wood Johnson Foundation (RWJ) project focused on improving the efficiency of newborn screening from collection to test results in the state of Michigan.

In 2017, the Committee heard a presentation on the Government Accountability Office's (GAO) report addressing newborn screening timeliness (Bocchini, 2017 February). The Newborn Screening Saves Lives Reauthorization Act of 2014 stipulates that the GAO review the timeliness of newborn screening. GAO reports that most states have not yet met their goal to screen 95 percent of blood samples within 7 days of birth by 2017, although some have improved screening time. The GAO identified three significant barriers for meeting the timeliness goals set by the Committee: (1) lack of awareness of the importance of timely screening for those who collect and submit specimens; (2) limited access to couriers for specimen transport; and (3) insufficient laboratory hours. The report also described current activities funded by HRSA to support states in achieving the Committee's timeliness goals.

5. Technical Assistance and Preparation for Nominations to the RUSP

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;

In November 2016, the Evidence Review Group reported that it is working to develop consumer-friendly guides to help consumers and advocacy groups understand how the screening guidelines are developed and updated. These guides include an outline of the condition and the evidence review conducted. With consumers and advocates in mind, this group worked on materials to help describe the stages of the nomination process, what is needed to complete the nomination forms, and the type of information considered during review.

Future Directions

The Committee has several ongoing projects that are expected to continue through or to be finalized in 2018. These projects include:

- Assessment of the applications of next-generation sequencing in newborn screening. This effort is expected to be ongoing in 2018.

- Development of a health care provider communication guide designed for use in discussing newborn screening results with parents. It would provide primary care providers with guidance and tips for discussing positive (i.e. out of range) newborn screening results with parents. This tool could be used alongside ACTion (or ACT) sheets, which support point of care education and clinical decision-making for all newborn screening conditions.
- Development of an educational planning guide that can be used by newborn screening programs to develop and improve their educational resources. The guide is designed to identify the educational needs of the various stakeholders with regard to access to appropriate, accurate, and informative educational resources. This effort is expected to be completed in 2018.
- The Committee has been working on understanding and improving risk assessment in newborn screening. These efforts will be ongoing in 2018.
- Reviewing the condition nomination and evidence review processes.

Conclusion

As stated previously, the mission of the Committee is to "reduce morbidity and mortality in newborns and children who have, or are at risk for, heritable disorders" (ACHDNC, 2018). To that end, the Committee continues to provide advice, recommendations, and technical information to the HHS Secretary to enhance, expand or improve their ability to reduce the mortality and morbidity of heritable disorders and towards developing policies and priorities meant to enhance screening, counseling, and health care services at the state and local levels. The Committee also continues, as part of their mission, to invite public comments as one of the important ways to identify issues and concerns.

The ACHDNC continued to make systematic, evidence-based, and peer-reviewed recommendations for conditions for which all newborns should be screened. The Committee reviewed and recommended adding Pompe disease, MPS I, and X-ALD. The ACHDNC also continues to seek to improve and inform the review process. The Committee developed recommendations on how to identify the minimum data required to move a condition to evidence review. In addition, the Committee developed an updated condition review decision matrix to include the public health impact of screening as well as an analysis of the state NBS program's capacity to implement screening for nominated conditions. Finally, the Committee convened a Cost Analysis Working group to consider methods to assess the cost to the state of adding newborn screening for a particular condition.

The Committee continues to serve in a leadership role in the field of newborn screening and heritable disorders. The Committee issued and supported efforts to improve data quality and quality assurance in newborn screening, establish standardized newborn screening case definitions for public health surveillance, and improve timeliness by identifying ways to assess and address barriers to screening and diagnosis. The coordinated efforts of the ACHDNC and policymakers, state public health agencies, providers, and the public—will continue to ensure that newborns and children have universal access to high-quality screening, follow-up, diagnosis,

disease management and treatment, evaluation, and education, which may prevent the potentially devastating consequences of disabilities, life-threatening disorders, or death.

This report was prepared to summarize the Committee's activities and outcomes for the 2013 - 2017 calendar years and to fulfill the legislative requirement for the submission of an annual report to Congress, the Secretary, the Interagency Coordinating Committee on Newborn and Child Screening, and State Health Departments.

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Appendix A: Recommended Uniform Screening Panel

(As of November 2016)

ACMG Code	Core Condition	Metabolic Disorder			Endocrine Disorder	Hemoglobin Disorder	Other Disorder
		Organic acid conditi	Fatty acid oxidatio	Amino acid disord			
PROP	Propionic Acidemia	X					
MUT	Methylmalonic Acidemia (methylmalonyl-CoA	X					
Cbl A,B	Methylmalonic Acidemia	X					
IVA	Isovaleric Acidemia						
3-MCC	3-Methylcrotonyl-CoA Carboxylase	X					
HMG	3-Hydroxy-3-Methyglutaric	X					
MCD	Holocarboxylase Synthase Deficiency	X					
ßKT	ß-Ketothiolase Deficiency	X					
GA1	Glutaric Acidemia Type I	X					
CUD	Carnitine Uptake Defect/Carnitine Transport		X				
MCAD	Medium-chain Acyl-CoA Dehydrogenase		X				
VLCAD	Very Long-chain Acyl-CoA Dehydrogenase		X				
LCHAD	Long-chain L-3 Hydroxyacyl-CoA Dehydrogenase		X				
TFP	Trifunctional Protein Deficiency		X				
ASA	Argininosuccinic Aciduria			X			
CIT	Citrullinemia, Type I			X			
MSUD	Maple Syrup Urine Disease			X			
HCY	Homocystinuria			X			
PKU	Classic Phenylketonuria			X			
TYR I	Tyrosinemia, Type I			X			
CH	Primary Congenital				X		
CAH	Congenital adrenal hyperplasia				X		
Hb SS	S,S Disease (Sickle Cell					X	
Hb S/ßTh	S, βeta-Thalassemia					X	
Hb S/C	S,C Disease					X	
BIOT	Biotinidase Deficiency						X
CCHD	Critical Congenital Heart						X
CF	Cystic Fibrosis						X
GALT	Classic Galactosemia						X
GSD II	Glycogen Storage Disease Type II (Pompe)						X
HEAR	Hearing Loss						X
SCID	Severe Combined						X
MPS I	Mucopolysaccharidosis Type 1						X
X-ALD	X-linked Adrenoleukodystrophy						X

Recommended Uniform Screening Panel[1] SECONDARY[2] CONDITIONS [3]

(As of November 2016)

ACMG Code	Secondary Condition	Metabolic Disorder			Hemoglobin Disorder	Other Disorder
		Organic acid conditio	Fatty acid oxidation	Amino acid disorder		
Cbl C,D	Methylmalonic acidemia with homocystinuria	X				
MAL	Malonic acidemia	X				
IBG	Isobutyrylglycinuria	X				
2MBG	2-Methylbutyrylglycinuria	X				
3MGA	3-Methylglutaconic aciduria	X				
2M3HBA	2-Methyl-3-hydroxybutyric aciduria	X				
SCAD	Short-chain acyl-CoA dehydrogenase deficiency		X			
M/SCHAD	Medium/short-chain L-3-hydroxyacyl- CoA dehydrogenase		X			
GA2	Glutaric acidemia type II		X			
MCAT	Medium-chain ketoacyl-CoA thiolase deficiency		X			
DE RED	2,4 Dienoyl-CoA reductase deficiency		X			
CPT IA	Carnitine palmitoyltransferase type I deficiency		X			
CPT II	Carnitine palmitoyltransferase type II deficiency		X			
CACT	Carnitine acylcarnitine translocase deficiency		X			
ARG	Argininemia			X		
CIT II	Citrullinemia, type II			X		
MET	Hypermethioninemia			X		
H-PHE	Benign hyperphenylalaninemia			X		
BIOPT	Biopterin defect in cofactor biosynthesis			X		
BIOPT	Biopterin defect in cofactor regeneration			X		
TYR II	Tyrosinemia, type II			X		
TYR III	Tyrosinemia, type III			X		
Var Hb	Various other hemoglobinopathies				X	
GALE	Galactoepimerase deficiency					X
GALK	Galactokinase deficiency					X
	T-cell related lymphocyte deficiencies					X

1. Selection of conditions based upon "Newborn Screening: Towards a Uniform Screening Panel and System." *Genetic Med*. 2006; 8(5) Suppl: S12- S252" as authored by the American College of Medical Genetics (ACMG) and commissioned by the Health Resources and Services Administration (HRSA).
2. Disorders that can be detected in the differential diagnosis of a core disorder.
3. Nomenclature for Conditions based upon "Naming and Counting Disorders (Conditions) Included in Newborn Screening Panels." *Pediatrics*. 2006; 117 (5) Suppl: S308-S314.

Appendix B: ACHDNC Recommendations and Secretary Response, 2013-2017

In 2013, the ACHDNC recommended adding Pompe (Letter to Secretary recommending RUSP to include Pompe Disease) disease to the Recommended Uniform Screening Panel (RUSP). The Secretary requested additional review (The Secretary of Health and Human Services response regarding Pompe) by the Interagency Coordinating Committee on Screening in Newborns and Children, and then accepted the recommendation (The Secretary of Health and Human Services final response regarding Pompe) on March 2, 2015.

In 2014, the ACHDNC recommended the Secretary (Letter to Secretary recommending RUSP to include Tyrosinemia type I) should facilitate a national dialogue among federal and state stakeholders on the benefits of measuring succinylacetone in dried blood spots to improve the specificity of newborn screening for Tyrosinemia type I, a condition on the RUSP. The Secretary accepted the recommendation (The Secretary of Health and Human Services response regarding Tyrosinemia type I) and tasked the Centers for Disease Control and Prevention with implementing a national discussion to address technical and practice issues in measuring succinylacetone for screening newborns.

In 2015, the ACHDNC recommended including mucopolysaccharidosis type I (MPS 1) (Letter to the Secretary recommending RUSP to include MPS 1) on the RUSP and providing federal funding to State newborn screening programs to implement screening of MPS 1, including defining the most appropriate test platform and laboratory protocol and establishing short and long term follow-up procedures. The Secretary accepted the recommendation (The Secretary of Health and Human Services response regarding MPS 1) to expand the RUSP to include MPS 1, but did not accept the recommendation to provide additional funding. The Secretary encouraged federal agencies to provide technical expertise and support states with existing resources and activities.

In 2015, the ACHDNC recommended adding adrenoleukodystrophy (X-ALD) (Letter to the Secretary recommending RUSP to include X-ALD) to the RUSP and providing federal funding to State newborn screening programs to implement screening of X-ALD and collect data and disseminate information that defines short and long term follow-up procedures for pre-symptomatic infants diagnosed with X-ALD. The Secretary accepted the recommendation to add X-ALD (The Secretary of Health and Human Services response regarding X-ALD) to the RUSP and asked federal agencies to consider ways within existing research and technical assistance resources to support state programs as they implement screening for X-ALD.

Appendix C: ACHDNC Members for 2017

ACHDNC members are appointed by the Secretary or designee, and shall not exceed 15 voting members, including the Chair and Federal Ex-Officio members. The Committee may also include up to 15 non-voting organizational representatives, as the Secretary determines necessary.

The Designated Federal Official from HRSA's Maternal and Child Health Bureau serves as the government's agent for matters related to the management of the ACHDNC's activities, and ensures all procedures are within applicable statutory, regulatory, and HHS General Administration Manual directives.

The following is a list of the 2017 ACHDNC members.

Mei Wang Baker, MD
Professor of Pediatrics
University of Wisconsin School of Medicine and Public Health
Co-Director, Newborn Screening Laboratory
Wisconsin State Laboratory of Hygiene
Term End Date: June 30, 2020

Susan A. Berry, MD
Professor and Director
Division of Genetics and Metabolism
Departments of Pediatrics and Genetics,
Cell Biology & Development
University of Minnesota
Term End Date: June 30, 2021

Joseph A. Bocchini, Jr., MD (Chairperson)
Professor and Chairman
Department of Pediatrics Louisiana State University

Jeffrey P. Brosco, MD, PhD
Professor of Clinical Pediatrics
University of Miami School of Medicine
Department of Pediatrics
Deputy Secretary, Children's Medical Services
Florida State Department of Health Term End Date: June 30, 2020

Dietrich Matern, MD, PhD
Professor of Laboratory Medicine,
Medical Genetics and Pediatrics
Mayo Clinic
Term End Date: June 30, 2018

Cynthia M. Powell, MD
Professor of Pediatrics and Genetics
Director, Medical Genetics Residency Program
Pediatric Genetics and Metabolism
The University of North Carolina at Chapel Hill
Term End Date: June 30, 2021

Annamarie Saarinen
Co-founder, CEO
Newborn Foundation
Term End Date: June 30, 2020

Scott M. Shone, Ph.D.
Senior Research Public Health Analyst
RTI International
Term End Date: June 30, 2021

Beth Tarini, MD, MS, FAAP
Associate Professor and Division Director
General Pediatrics & Adolescent Medicine
University of Iowa Hospitals & Clinics
Term End Date: June 30, 2020

Catherine A. L. Wicklund, MS, CGC
Northwestern University Feinberg School of Medicine Center for Genetic Medicine Term End Date: June 30, 2018

Ex-Officio Members –

Agency for Healthcare Research and Quality
Kamila B. Mistry, PhD, MPH
Senior Advisor
Child Health and Quality Improvement

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

Food and Drug Administration
Kellie B. Kelm, PhD
Chief, Cardio-Renal Diagnostic Devices Branch,
Office of In Vitro Diagnostic Devices Evaluation & Safety

Health Resources and Services Administration
Laura Kavanagh, MPP
Acting Associate Administrator
Maternal and Child Health Bureau

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

Designated Federal Official –
Catharine Riley, PhD, MPH
Health Resources and Services Administration
Maternal and Child Health Bureau

Appendix D: Glossary

Term	Definition
X-linked Adrenoleukodystrophy (X-ALD)	A genetic disorder that affects the nervous system and the adrenal glands, where the fatty covering (myelin) that insulates nerves in the brain and spinal cord is prone to deterioration (demyelination), which reduces the ability of the nerves to relay information to the brain. In addition, damage to the outer layer of the adrenal glands (adrenal cortex) causes a shortage of certain hormones (adrenocortical insufficiency). Adrenocortical insufficiency may cause weakness, weight loss, skin changes, vomiting, and coma.
Heritable Disorders	Group of genetically inherited conditions present at birth that, undetected, can cause intellectual/physical disabilities and life-threatening illnesses.
Mucopolysaccharidosis Type I (MPS I)	A genetic disorder caused by a deficiency of the enzyme alpha-L-iduronidase which prevents effective metabolic processing and leads to accumulation of materials in cells resulting in poor cell performance and progressive damage throughout the body.
Newborn Screening (NBS)	Practice of testing babies for heritable disorders and conditions that can hinder their normal development, enabling early detection/treatment and preventing intellectual/physical disabilities and life-threatening illnesses.
Pilot Study	Systematic investigations or public health activities that are designed to evaluate the efficacy and safety of incorporating a new test or condition on a population-based level into state newborn screening programs.
Pompe disease	An inherited disorder caused by the buildup of a complex sugar called glycogen in the body's cells. The accumulation of glycogen in certain organs and tissues, especially muscles, impairs their ability to function normally.
Recommended Uniform Screening Panel (RUSP)	Standard guideline for the newborn screening of heritable conditions, consisting of a list of conditions referred to as a screening panel. This panel provides guidance to the states regarding the latest evidence-based medical recommendations for newborn screening.

Appendix E: Acronyms

ACHDNC	Secretary's Advisory Committee on Heritable Disorders in Newborns and Children
AMCHP	Association of Maternal and Child Health Programs
APHL	Association of Public Health Laboratories
CDC	Centers for Disease Control and Prevention
CoIIN	Collaborative Improvement and Innovation Network
CCHD	Critical Congenital Heart Defects
CRW	Condition Review Workgroup
CAW	Cost Assessment Workgroup
CLIR	Collaborative Laboratory Integrated Reports
CONPLAN	National Newborn Screening Contingency Plan
GAO	Government Accountability Office
GAMT	Guanidinoacetate methyltransferase
HHS	U.S. Department of Health and Human Services
HRSA	Health Resources and Services Administration
IEM	Inborn Errors of Metabolism
IRB	Institutional Review Board
MPS-I	Mucopolysaccharidosis type I
NewSTEPS	Newborn Screening Technical Assistance and Evaluation Program
NBS	Newborn Screening
NIH	National Institutes of Health
NCHVS	National Committee on Vital and Health Statistics
PCR	Polymerase Chain Reaction
PKU	Phenylketonuria
RUSP	Recommended Uniform Screening Panel
RWJ	Robert Wood Johnson Foundation
R4S	Region 4 Stork

SACHRP	Secretary's Advisory Committee on Human Research Protections
SMA	Spinal Muscular Atrophy
SCID	Severe Combined Immunodeficiency
USPSTF	U.S. Preventive Services Task Force
X-ALD	X-linked Adrenoleukodystrophy

Appendix F: Decision Matrix

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

<table>
<tr><th colspan="3" rowspan="2">NET BENEFIT/ CERTAINTY</th><th colspan="3">READINESS</th><th colspan="2" rowspan="2">FEASIBILITY</th></tr>
<tr><th>Ready</th><th>Developmental</th><th>Unprepared</th></tr>
<tr><td rowspan="3">SIGNIFICANT Benefit</td><td rowspan="3">Certainty</td><td>HIGH</td><td>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.</td><td>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.</td><td>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.</td><td rowspan="2">Feasibility</td><td>HIGH or MODERATE</td></tr>
<tr><td>LOW</td><td colspan="3">A4
There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.</td></tr>
<tr><td>MOD</td><td colspan="3">B 1-4
There is moderate certainty that screening would have a significant benefit.</td><td colspan="2">---</td></tr>
<tr><td>Small to ZERO Benefit</td><td rowspan="3">Certainty</td><td rowspan="2">MOD/HIGH</td><td colspan="3">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.</td><td colspan="2">---</td></tr>
<tr><td>NEG Benefit</td><td colspan="3">D 1-4
There is high or moderate certainty that adoption of screening for the targeted condition would have a negative net benefit.</td><td colspan="2">---</td></tr>
<tr><td>---</td><td>LOW</td><td colspan="3">L 1-4
There is low certainty regarding the potential net benefit from screening.</td><td colspan="2">---</td></tr>
</table>