Health Resources and Services Administration
Advisory Committee on Heritable Disorders
in Newborns and Children
Brief Summary of Committee Meeting
May 4-5, 2023

Introduction

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) met on May 4-5, 2023 to discuss various topics related to newborn screening and genetic disorders. The committee heard presentations from experts and stakeholders on the evidence review process, the nomination and prioritization of conditions, the implementation of screening programs, and the long-term follow-up of patients. The meeting was open to the public and public comments were allowed.

Newborn Screening and Early Intervention

Don Bailey and Elizabeth Reynolds from RTI International presented research on the link between Early Intervention (EI) and Newborn Screening (NBS) programs for infants and toddlers with disabilities. The subjective nature of "net benefit" as a criterion for decision making in NBS was discussed. An argument was made that EI should be considered as a potential net benefit for NBS, and that EI and NBS should be coordinated to ensure earlier intervention services for children identified through NBS.

A matrix was presented that can be used to assess which NBS conditions put children at risk for developmental delay. They concluded by suggesting that federal guidelines could adopt definitions and standards for established conditions, and that the committee should include EI when weighing net benefit for NBS.

Committee Discussion

a. A committee member asked how gathering evidence of net benefit works for more common conditions. The difficulty of performing randomized controlled trials for common conditions was acknowledged. The committee member raised the concern that EI is not always available.
b. A question was posed about why the presented decision matrix had classified Phenylketonuria (PKU) in a yellow zone in terms of suggesting EI for this condition. It was clarified that PKU was discussed separately, and the efficacy of dietary treatments established PKU as a condition that did not need to automatically suggest EI. It was brought up that medical treatment adherence is not a factor.
c. A committee member initiated a discussion about the effect of genetics vs environment, using Fragile X syndrome as an example of a condition that has a cap to the potential of EI, but progress can still be made.
d. A question was raised if there are any exemplar states that have established a connection between NBS and EI. Two states were brought up that auto-enroll NBS cases for EI. The need to collaborate and communicate between the two paths was stressed. A study on caregiving was also mentioned, as well as a potential project to examine the barriers and facilitators for connecting NBS and EI in other states.
e. A question was raised if parents can self-refer to early intervention (EI) services. The ability of parents to self-enroll was acknowledged, however eligibility and developmental delay qualifications must still be met.

f. A question was raised about the scoring methods used. Specifically, a clinical metric was valued at 2 points while a parent factor was valued at 1 point. It was explained that the parental factor was added because some disorders lack clinical guidelines.
g. A question was raised about how to practically make changes. The effectiveness of legislative change to ask states to include a condition was indicated. Alternatively, an advisory committee could be established focused on EI. Failing these efforts, state-level work would be indicated.
h. A committee member proposed that EI enrollment could be more flexible, allowing children to catch up and then be taken off the program if not needed anymore. The difficulty of removing a child from EI once they have an established condition was stressed.
i. A committee member asked how resources could be spent wisely given that programs are run at a more local level. There was an agreement that EI programs are run by counties and schools, but they are following the standards set by the state.
j. A committee member asked if the current federal supplement would be sufficient. It was indicated that a combination of funding sources would be required, including private insurance, Medicaid, and state supplements.
k. A committee member brought up factors, such as publication bias or a link between the efficacy of developmental delay treatment and medical complexity. The committee member then asked how to bring in the availability of services with the calculation of net benefit. Focus was put on the "magnitude" portion of the question and an analogy was made with care of patients with Zika virus. The value of helping parents as a way to help children was raised.
l. A question was raised about the timing of EI and whether there is a method to study the benefit of timing. The use of sibling studies was emphasized.

Potential for Harm with Uncertain Prognoses

Dr. Beth Tarini from Children's National Research Institute presented research about the harms of newborn screening (NBS), especially the psychosocial effects of false positive and uncertain results on parents and children. Harm, defined as any negative effect perceived by patients or significant others resulting from screening compared with not screening, was categorized into four domains: physical, psychosocial, financial strain, and opportunity costs. The existing literature on the topic, which is limited in scope and inconsistent, was reviewed and ongoing research projects were described that aim to quantify and understand the harms of NBS using a multi-site prospective observational cohort study and a mixed-method study.

Committee Discussion

a. A committee member asked to speculate about the false positive group. An analogous situation was raised with genetic sequencing false positives where truly adverse outcomes affect only a small percentage of patients, and typically occurs with patients already struggling with mental health. The issue of a subgroup of mental health affected individuals was acknowledged as a cohort that may be missed in aggregate studies.
b. A committee member pointed out that uncertainty with diagnostic results is a prevalent issue across medicine and not specific to a screening context. Differences that were highlighted include communication issues with parents and the lack of clinical training related to screening results.
c. A question arose if more diseases could be included in studies looking at harm with uncertain prognoses. Financial and practical constraints were raised.

d. A question about the ability to compare the results of mandatory public health screening programs and consented research projects. An inability to directly compare was brought up due to the use of different instruments. However, qualitative experience results could be compared.
e. A committee member asked how the messaging to the parents is being controlled. The challenge of formulating effective messaging was acknowledged. A proposition was made that in the long run, the state may need to take over the communication process.
f. A committee member praised the goal of collecting evidence to measure the magnitude of harm.
g. A comment was made that the time spent discussing harms is overstated and is done at the exclusion of a discussion of the benefits. The benefit of gathering evidence to ensure the discussion is two-sided was stressed.
h. A question was raised about what the results could look like if the study continued to 4 years of age instead of the current 2 years. The effort required to build a cohort was stressed and it was agreed that there may be interesting results over a longer timescale. The difficulty of getting unconfounded results was also mentioned.
i. A question was raised about how the state and primary care physician roles would change based on the paradigm shift being proposed. The paucity of data was brought up as evidence is needed to inform how best to proceed. It was made clear that the goal is not to cut out the primary care physician.

Agency Collaboration

Sickle Cell Data Collection (SCDC) Program, CDC

A summary of the SCDC Program was provided. The SCDC collects and uses data from multiple sources to help sickle cell patients in 11 states. The data is kept confidential and only shared in aggregate form. The program has found that the NBS offered is not sufficient and that surveillance data can improve health care in various ways.

Implementing the Blueprint: Implications on Newborn Screening, MHCB

A summary of eight papers describing a blueprint for change was described. The overall goal is to ensure that children identified with NBS can get access to treatment. To address this issue, the need for appropriate metrics was conveyed. The overall goal of the blueprint is to ensure that every child gets the services they need so they can play, go to school, become a healthy adult and that families are thriving also. Measuring what matters was emphasized as a key approach to assist in achieving this goal. The speaker used hemophilia as an example with outcomes such as the percentage of patients who graduate from high school. It was concluded that it was important for federal partners to work together to create an integrated data system to measure whether programs are actually working for children.

CDC's ED3N Project, CDC

The Enhancing Data-driven Detection in Newborns (ED3N) data platform was described as aiming to improve risk assessment with newborn screening that would allow for more timely diagnosis and intervention; and decrease disparities across newborn screening programs. The background, goals, challenges, and the timeline for the project's implementation were presented. The three essential modules (Evaluate, Explore, and Educate) were demonstrated.

Committee Discussion

a. A committee member with experience across federal agencies stated that NBS is being executed well as demonstrated by the level of federal government agency collaboration.

b. A committee member asked if ED3N will support cooperative agreements with states. It was clarified that ED3N is building the infrastructure and partnerships will help fund the state initiatives.
c. A question was raised about how measurements will be done concerning disparities across state programs and the family experience. It was brought up that the scope of ED3N is data-analytics, but there is a broader focus to use the data to select strategies.
d. A question was raised on how a data focus on implementing the blueprint would address concerns related to newborn screening outside the state lab such as lawsuits and educational needs. There was clarification that the blueprint is for all children with special needs and that measuring the things that matter (ex. family well-being, child well-being, etc.) will help address some of the concerns outside the state lab.
e. A committee member asked about lessons learned from the sickle cell data collection program and what ED3N is planning. It was conveyed that the sickle cell data program has focused on determining if the data being used is appropriate for over a decade and has worked with outside organizations to help learn what data is important. The ED3N project has focused on diagnostic data and hasn't worked specifically on long-term follow-up data. But, there is a plan to leverage information from other sources.
f. A committee member asked about data linkage, and specifically if the ED3N data is meant to supplant the need for data linkage data in the state. It was clarified that the goal is not to supplant, but to provide a resource for states to use.
g. A comment was made that ED3N may benefit by coordinating bi-directionally with databases like ClinVar. It was clarified that the unidirectional arrow shown should have been bidirectional, and that the current relationship is bidirectional.
h. A question was raised how clinical outcomes have improved with the sickle cell data collection system. Specifically, a metric was shown about sickle cell patients not seeing a hematologist, and whether this metric could be used by more states. It was clarified that the goal is to get more sickle cell patients into care. The specific metric was described as useful because it was used to find geographical areas in which no hematologists are available.
i. A comment was made that EI data is not easily accessible via the collaborations described from Ed3N and HRSA. The response was that there is an ongoing project with Part C projects to figure out how to get EI data.
j. A question was raised if ED3N is FISMA-compliant. It was clarified that ED3N is FISMA moderate compliant.
k. A committee member made a comment about the importance of hearing from a patient advocacy organization about the patient experience in accessing care and stressed that there are insurance barriers to seeing an expert in different locations in a state or across state lines.
l. A committee member asked if there are any plans to expand the sickle cell framework for other states across the country to examine how patients are doing overall. There was agreement that the level of care is an important factor and that the program should be national in scope.
m. A question was raised about how partners can specifically help to continue to push forward programs. One area brought up that could be helpful is for partners to help with data use agreements.

Public Comment

Public comments were made by 17 people, representing individual parents, parent advocacy groups, as well as medical researchers. Several people shared their personal stories of having children with Krabbe disease or congenital CMV and advocated for including these conditions in the screening list. Some

people also questioned the committee's decision-making process and bylaws and suggested improvements. Others argued for having consistent screening across states.

Kathleen Smith

Ms. Smith had her daughter, Lily, with her, and spoke of Lily's journey to be diagnosed with Krabbe disease. Lily was not diagnosed through newborn screening, but through observation around five months old. Lily was able to receive a transplant and is able to communicate with an eye gaze device that lets her personality shine. However, had Lily been diagnosed earlier, her outcomes could be even better than what they currently are.

Anna Grantham

Ms. Grantham is Director of Newborn Screening for the Hunter's Hope Foundation, one of the organizations that nominated Krabbe, both in 2009 and 2022. She discussed why Krabbe was not added to the RUSP in 2009, per the Committee's decision. The Foundation and the experts consulted felt that all the issues with the 2009 nomination package had been addressed when they resubmitted Krabbe disease. She highlighted some specific concerns from the prior package and how different Krabbe screening and treatment is over a decade later.

Vanessa Werner

Ms. Werner spoke about her son, DJ, who was diagnosed with Krabbe via newborn screening. She shared that she and her husband struggled with fertility issues and choose to have DJ via IVF; while IVF often includes genetic testing, it does not always test for rare diseases like Krabbe. While DJ has some developmental delays and requires medication and tube feeding, Ms. Werner emphasized how happy DJ and her family are.

Stacey Pike- Langenfeld

Ms. Pike-Langenfeld spoke as the President of Krabbe Connect. She focused her public comments on concerns about the Committee's operations. She referenced the Committee's charter and bylaws on procedures that can occur should a tie happen. In addition, she expressed concern that the Committee did not pause before voting to ensure all the questions by members were fully answered.

Joanne Kurtzberg

Dr. Kurtzberg is a pediatric transplant physician who pioneered unrelated cord transplant for treatment of Krabbe disease. She spoke on the effectiveness of transplant, regardless of if the child was diagnosed via sibling or via NBS. While attending the February meeting, Dr. Kurtzberg felt that several of the questions Committee members had during deliberation could have been answered by data or experts that were not a part of the Evidence-Based review. She asked that the nomination package be reconsidered without it having to go through another ERG and voted on again.

Matt Blum

Mr. Blum and his wife have a daughter, Chloe, with congenital cytomegalovirus (CMV). She was diagnosed after her six-month checkup showed signs of delays. After four more months, they were able to get the diagnosis. At 17 months old now, Chloe is thriving, despite the issues caused by CMV. Mr. Blum feels blessed with how well Chloe is doing, but was clear that Chloe is not an average case and most children diagnosed after 21 days do not do as well as her.

Pamela Jinsky

Ms. Jinsky spoke about her daughter, Pella, who has CMV. Pella had a long diagnostic odyssey, despite Ms. Jinsky's perinatologist noting that she had markers for CMV. Doctors gave many answers for Pella's increasing disabilities before finally getting the correct diagnosis of CMV after she was one year old, which is very late to start treatment.

Danae Barke

Ms. Barke is the Executive Director of HCU Network America. She applauded the CDC's efforts in revising newborn screening protocols for classic homocystinuria. She also wanted to make the Committee and participants aware of HCU Network America's upcoming newborn screening update and roundtable discussion on Monday, May 22, 2023.

Dean Suhr

Mr. Suhr is the President and Co-Founder of MLD Foundation. He provided updates on research and therapies for metachromatic leukodystrophy (MLD), which the MLD Foundation is planning to nominate for the RUSP during 2023.

Niki Armstrong

Ms. Armstrong is the Newborn Screening Program Manager for Parent Project Muscular Dystrophy. She spoke about the February meeting's vote on Duchenne muscular dystrophy (DMD). After the Committee's vote, PPMD is updating the nomination package and plans to resubmit in May 2023. She highlighted the difference between DMD and other current RUSP conditions and noted that while there is not a cure yet, there are therapies that are very successful in elongating and improving lives.

Paul Melmeyer

Mr. Melmeyer is Vice President of Public Policy and Advocacy of the Muscular Dystrophy Association. He addressed specific points that were raised during the February meeting during discussion on DMD, which will also be addressed in the updated nomination package.

Elisa Seeger

Ms. Seeger is the Founder of the ALD Alliance. She spoke about "death by zip code," which means that depending on where a baby is born, they will be tested for different conditions across the country; she supports the initiative to get all RUSP conditions tested for in all 50 states. She also expressed concern about the transparency of the Committee's onboarding process and vote on Krabbe in February.

Lesa Brackbill

Ms. Brackbill had a daughter, Victoria, who died from Krabbe in 2016. She criticized the Committee's vote on Krabbe, as she believes all of the Committee's questions were answered in the nomination package, and that there should be a new vote. She also listed the names of nearly 30 children with Krabbe who were able to get a transplant and are currently living.

Annie Kennedy

Ms. Kennedy is the Chief of Policy Advocacy and Patient Engagement for the EveryLife Foundation for Rare Diseases. After discussing the importance of patient advocacy groups, she requested that an expert member of the nominated conditions community be present in every discussion of Evidence-Based review.

Michael Gelb

Dr. Gelb, professor of Chemistry at University of Washington, provided comment on the requirement to find at least one confirmed newborn with a disease in a perspective pilot study and for the patient to go on to receive treatment, N of 1 Rule. While he thinks the rule can have its uses, it should not be a strict requirement.

Susan Tanksley

Dr. Tanksley is the Committee's organizational representative for the Association of Public Health Laboratories. Her comments focused on creating a new framework for how to count what states are testing for. For example, NewSTEPS says Texas is testing for 33 conditions, but HRSA would say Texas is screening for 57 conditions. She defined what "testing for" should mean and that core and secondary conditions should be counted separately, to reduce confusion. In addition, the RUSP should be updated to reflect the difference between core and secondary conditions, as well as be updated to have the most current names for diseases.

Prioritization and Capacity Workgroup Update

The Prioritization and Capacity Workgroup Update focused on three aspects: 1) To explore an alternative strategy for soliciting nominations, 2) To develop an approach to prioritization that accounts for having more than one condition at a time, and 3) To provide input to the Committee about potential revisions to the nomination form. An alternative strategy based on the US Preventative Services Task Force approach was proposed, which would allow for simpler nominations with less information. A prioritization method based on a point system that considers the potential public health impact of each condition was also described. Results of a pilot test that ranked SCID and Krabbe disease at opposite ends of the prioritization spectrum were shown.

Committee Discussion

a. A committee member asked if a streamlined nomination process that reduces the burden on advocates would make advocates feel like the application is out of their hands. It was described that it would need to be an inclusive process with frequent updates to the nominators throughout.
b. A question was raised about the number of nominations the committee has received at one time. It was clarified that the group has never had more than two nominations at once.
c. A question was raised about rare diseases scoring lower based on the proposed scoring matrix. It was clarified that the process is focused on prioritization and that the condition would not languish, but instead would be addressed somewhat less rapidly.
d. A committee member cautioned that changing the process may be framed as "moving the goal post" by advocates. But, this process has been evolving over time. The committee member also emphasized that the presented process addresses prioritization but not address the problem of the timeline and the capacity for evidence review.
e. A committee member suggested that a partnership with nominators is needed to reduce the burden nominators may feel.
f. A committee member asked why the range used was 1 through 5. The response was that the point system wasn't scientifically designed but that the ratings it produces are functional. It may be refined further.
g. A committee member had a question about the feasibility of screening. The response was that feasibility was a small part of the overall score and for the sample conditions used, it did not make a big difference in prioritization.

h. A comment was made that the simpler nomination proposal packet would allow lower-resources groups to be involved.
i. There was a question raised if health equity could be considered to help determine priority. It was explained that there was not a meaningful way to add this information in, but the process could be amended if an approach is found.

Decision Matrix

A presentation was given that provide the history of the decision matrix and considerations for improving the decision matrix.

Committee Discussion

a. A committee member expressed that the decision matrix was not intended for all Committee members to agree. Individuals may use a decision matrix to make their votes and that a consensus may not be needed.
b. A committee member argued that "feasibility" and "readiness" have two different meanings and that "feasibility" should remain a part of decision-making process. It was argued that "feasibility" should be discussed earlier on in the process, perhaps in the nomination and prioritization process.
c. A committee member asked what differentiates a grade of "C" and "I". It was clarified that a grade of "C" indicates that there is moderate certainty of the net benefit whereas a grade of "I" you do not have certainty of the net benefit.
d. A comment was made about challenges for state labs to test for conditions that are outside the dry blood spot matrix.
e. There was a concern raised that the revised decision matrix is built on subjective terms like "net benefit" and "certainty" that do not have agreed upon definitions.
f. A committee member expressed concern about ableism becoming a factor in decision-making.
g. There was a concern raised that a condition that received a grade of "I" may languish. Examples were provided from the United States Preventive Task Force (USPSTF) where a condition received a higher grade once evidence accumulated.
h. A question was raised whether the committee's charter includes consideration of state-by-state abilities.
i. A committee member summarized the discussion as follows: the committee desires to move away from the existing decision matrix; feasibility is an important consideration for implementation; and a grading system may not be the approach the committee wants to adopt. There was a decision to form an ad hoc topic workgroup to discuss the decision-making process for voting to recommend conditions to the RUSP.

New Business

1. There was a desire to move from standing work groups to ad hoc topic workgroups.

2. An ad hoc topic workgroup will be formed to discuss the decision-making process for recommendations to the RUSP.

3. A committee member presented a proposal to address conflicts of interest (COI) among the committee members and organizational representatives (ORs).

Committee Discussion

a. There was a suggestion to include federal grants and contracts in the financial disclosure, and that COI should be considered for ad hoc group membership. It was clarified that information should be prepared before each meeting, and that a slide would need to be added to all presentations when presenting to the committee.
b. A committee member asked if the COI changes would apply to expert panels. It was clarified that the ad hoc topic workgroup could consider this issue.
c. A question was raised whether the disclosure of grants would be applicable to personal grants or any received by the member's institution. It was clarified that the ad hoc topic workgroup could consider this issue.
d. A committee member commented on the need for the committee to rely on experts and expressed concern about how a COI policy could affect their input.
e. A committee member emphasized that the intent of addressing COI is to build the legitimacy of the committee's decision-making process and transparency.

4. The committee revisited the previous ACHDNC workgroups:
   - Education and Training
   - Follow-Up and Treatment
   - Laboratory Standards and Procedures

Committee Discussion

a. A suggestion was made that a workgroup wasn't needed for Follow-Up and Treatment because this topic was being covered by HRSA in implementing the *Blueprint for Change* in partnership with CDC.
b. Multiple committee members stated that topics related to the Laboratory Standards and Procedures workgroup is important to address, especially second-tier testing and secondary targets.
c. A suggestion was made to include the activity of counting conditions in the Laboratory Standards and Procedures workgroup. It was suggested that a broader set of experts would better serve this issue. A committee member stressed that there should be a separate ad hoc group for second tier testing and counting conditions.
d. A committee member proposed including Early Intervention and ideas introduced by Don Bailey's presentation into the collaborative work to implement the *Blueprint for Change*.

5. A committee member proposed considering other population-based screening opportunities that could occur on a voluntary basis. The committee member expressed that there may be a condition that does not meet the evidence requirements for the RUSP, but there may be a more appropriate time for screening outside the newborn period. A committee member referred to a program that fulfills this purpose, Bright Futures, that could be an audience for recommendations. It was brought up that this issue has come up before the committee in the past. There was a decision to review past work and summarize this in the next meeting.

6. A committee member brought up the concept that reconsideration of a condition when evidence review has been done recently. There was a proposal that if new evidence was provided within one year, then the entire review process did not have to be redone, and that only the new material could be reviewed and added. The topic will be put on the agenda for the next meeting for a formal vote.

7. A committee member put a motion to approve the minutes from the past meeting. A committee member provided edits that were factual in nature. The motion to approve the minutes with the factual edits was moved and seconded.

Committee Votes

The minutes from the previous meeting were approved.

Committee Decisions

The minutes from the previous meeting were approved.