Health Resources and Services Administration
Advisory Committee on Heritable Disorders
in Newborns and Children

Brief Summary of Committee Meeting
May 9-10, 2024

Introduction

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) met on May 9-10, 2024, to discuss various topics related to newborn screening and genetic disorders. The meeting was open to the public, and public comments were allowed.

Regulatory Process for the Review of Drugs for Rare Diseases

Anita Zaidi, MD

Dr. Zaidi presented the regulatory process for drug review for rare diseases and covered the definition and evaluation framework for orphan drugs. The presentation addressed the unique challenges in developing drugs for rare diseases, such as the small patient populations, which pose difficulties in study design. The talk also detailed the U.S. evidentiary standards for drug approval, which require substantial evidence from well-controlled studies. Additionally, the FDA's benefit-risk framework was discussed, emphasizing the importance of patient input in the decision-making process for drug approvals.

Committee Discussion

Committee members deliberated on several key issues related to the regulatory process for drug approval for rare diseases. The differences between FDA "traditional approval" and "accelerated approval" were discussed. With traditional approval, there is confirmation that a drug has clinical benefit, whereas with accelerated approval, a surrogate endpoint for clinical response can be used. Under accelerated approval, there is an assumption that a drug will undergo additional clinical trials to establish clinical benefit, but there is no explicit deadline for these studies. The Committee explored the challenges of designing effective studies with small patient populations and the need for reliable outcome measures and biomarkers. Additionally, organizational representatives highlighted the importance of incorporating patient input into the benefit-risk assessment framework, emphasizing how it informs regulatory decisions within the context of rare diseases.

Duchenne Muscular Dystrophy Evidence-Based Review: Update

Alex R. Kemper, MD, MPH, MS

Dr. Kemper provided an update on Duchenne Muscular Dystrophy (DMD). The presentation detailed the ongoing efforts to assess the effectiveness of therapies, such as deflazacort, eteplirsen, and golodirsen, through expert consultations and literature reviews. A significant portion of the talk was dedicated to the public health impact assessment, revealing that a majority of public health programs surveyed would take 2-3 years to implement after they receive authority to screen. The discussion mentioned three states planning to commence DMD screening in 2024.The clinical course of DMD was thoroughly examined, noting that symptoms typically begin by age three, with progression to wheelchair dependency by early teens and serious cardiac and respiratory complications arising by late teens.

Committee Discussion

The committee discussion addressed topics such as the prevalence of the disorder, focusing on symptomatic cases rather than carriers, and the strength of evidence regarding DMD's clinical impact. Discussions delved into the variability of Creatine Kinase (CK) levels in newborns and referral implications, noting that only those with consistently high levels should be referred for further diagnosis. The conversation explored treatments like exon-skipping, which does not cross the blood-brain barrier, and the complexities of gene therapy, including risks that may limit future treatments. The discussion also recognized the complex and variable nature of DMD progression and treatment response, along with concerns about early physical therapy in the absence of a definitive diagnosis of DMD (which may further damage delicate muscles in kids with DMD) and Adeno-Associated Virus (AAV) antibody handling in treatments.

ACHDNC Decision Matrix Tool: Public Health System Assessment

Ned Calonge, MD, MPH

Dr. Calonge presented a potential update to the Public Health Impact Assessment (PHIA) portion of the ACHDNC Decision Matrix Tool. The Public Health Impact Assessment (PHIA) process involves separating evidence assessment from the public health impact evaluation. During the PHIA process pilot states are surveyed to gather screening, testing, diagnosis, and first-year treatment data. These surveys assess the resources and barriers to implementing new screening programs within two years. The information collected will be used to inform the ACHDNC's recommendation to the Secretary of Health about whether to include or not include a condition to the Recommended Uniform Screening Panel (RUSP).

Committee Discussion

Committee members discussed various aspects of the PHIA process. They emphasized the importance of clinician support, the integration of components for decision-making, and the implications of the letter grade system on recommendations. Additionally, the discussion addressed the role of public health impact in recommendations to the Secretary, the potential influence of the National Academies' report, and the necessity of considering both individual and public health benefits. Organizational representatives highlighted the challenges of state legislative language and implementation timelines, with some questioning the utility of previous public health impact assessments.

Qualitative Evidence Synthesis: GRADE-CERQual Approach For Assessing the Confidence in Synthesized Findings

Jane Noyes, MD, MPH

Dr. Noyes explained the GRADE-CERQual approach for assessing confidence in synthesized qualitative findings. The presentation highlighted the importance of including qualitative evidence in the decision-making process, especially in the context of heritable disorders. It covered key aspects such as methodological limitations, relevance, coherence, and adequacy, which are crucial for evaluating the quality of qualitative studies. Dr. Noyes' key message sought to provide a systematic and transparent method for assessing confidence in qualitative evidence, aiding decision-makers in making informed choices.

Committee Discussion

Committee members discussed issues like the imbalance of voices, sample sizes, synthesizing data, biases in peer review, and interviewing children. An organizational representative inquired about using flawed data, and it was noted that such data can sometimes be useful.

ACHDNC Nomination and Evidence Review Process

Ned Calonge, MD, MPH

Dr. Calonge covered the updates to the ACHDNC condition nomination process. The revision aimed to simplify the nomination process while ensuring appropriate information is received for the evidence review. Feedback from various stakeholders and public comments were considered in the revision process he shared. The new approach introduced a preliminary nomination step to ensure sufficient information is available for the Committee to assess during the nomination and prioritization review, enhancing the efficiency of the overall process.

Committee Discussion

The discussion covered various aspects of the revised ACHDNC nomination process. Committee members debated the necessity and challenges of requiring a prospective pilot study. Their suggestions included exploring alternatives, like retrospective pilots and less rigorous prospective methods, and clarifying and possibly reordering the criteria to prioritize effective treatment. Committee members emphasized defining the purpose of newborn screening and ensuring that criteria reflect the potential for presymptomatic treatment to improve outcomes. Organizational representatives highlighted the practical difficulties and advocated for adjustments to facilitate the process.

Newborn Screening Ad Hoc Topic Groups: Updates and Committee Discussion

Jelili Ojodu, MPH

The Newborn Screening Technical Assistance and Evaluation Program (NewSTEPs) provided an update on their various workgroups and initiatives.

Advancing Health Equity in Newborn Screening: Community of Practice

This community of practice addresses health disparities within the newborn screening system. This initiative aims to enhance understanding of systemic inequities and foster actionable change, with the support of data analysis to identify and address disparities. NewSTEPs collaborates with the Racial Equity Institute to plan health equity training for the newborn screening community.

Committee Discussion

Committee members discussed the funding of the program by HRSA as part of efforts to promote equity within the newborn screening system.

Follow-Up and Education Subcommittee

The Follow-Up and Education subcommittee aims to strengthen the newborn screening (NBS) system by providing guidance and technical assistance on follow-up procedures. The subcommittee offers a platform for networking and collaboration among follow-up staff from regional and state NBS programs, focusing on short-term and long-term follow-up. The subcommittee also developed a landscape survey for long-term follow-up (LTFU), defining essential elements, and creating fact sheets and quality indicators. The subcommittee plans to engage families, assess ongoing needs, and perform outreach to underserved communities.

Committee Discussion

The discussion covered definitions of short-term follow-up as immediate post-screening actions, and long-term follow-up as ongoing care, with an effort to redefine it as a longitudinal follow-up. Organizational representatives emphasized the need for a cultural shift and understanding of regional

variations in follow-up care. The Clinical and Laboratory Standards Institute (CLSI) developed specific terminology for newborn screening, and this feedback will be taken back to the workgroup.

Higher-Tier Testing Workgroup

The Higher Tier Testing Workgroup update focused on the necessity of higher-tier testing for certain newborn screening disorders and the challenges faced by states with lower birth rates in implementing these tests. The group aimed to develop model practices for cross-program collaboration, identify barriers, and prioritize support for programs most in need. Key activities included defining tiered testing, scheduling meetings, and planning surveys and webinars to understand and address the challenges of implementing higher-tier testing.

Committee Discussion

Committee members and organizational representatives discussed various aspects of higher-tier testing. They addressed the challenges states face in negotiating better rates for uncommon tests and the difficulties of the contract process, highlighting that varying terms and conditions hinder cross-jurisdictional agreements. They also discussed the impact of the FDA's recent rule change on test availability and the challenges of obtaining coverage for tests not included in newborn screening programs. Additionally, the potential need for a workgroup focusing on the interface of molecular diagnostics with clinical care was noted.

Condition Counting ad hoc Topic Group

The Condition Counting Taskforce was formed to address inconsistencies in how states count conditions on their newborn screening (NBS) panels. The ad hoc topic group developed a framework for standardizing condition counting and defining screening, involving various stakeholders. The group aims to achieve national standardization of condition counting and naming. Its objectives are to present its final considerations to the ACHDNC and develop a communications plan.

Committee Discussion

A committee member inquired about secondary conditions and their applicability after second-tier testing, citing hemoglobinopathy variants as an example where states may count each hemoglobin phenotype tested. An organizational representative clarified that guidelines are being developed to standardize what is tested for. Another organizational representative noted that states, rather than advocacy groups, have the most uncertainty about these efforts, questioning the value if states do not adopt the guidelines, and expressed openness to suggestions for state adoption.

Other NBS Related Updates: Brief State of the States

The talk provided an overview of the United States Newborn Screening Programs, highlighting 53 programs and 36 laboratories, with some states outsourcing screening. It detailed the number of core RUSP disorders screened by states as of March 2024, ranging from 31 to 37 disorders. Updates on implementing the newest RUSP disorders and newborn screening fees were also discussed. Additionally, the talk mentioned FDA regulations on lab-developed tests, upcoming legal cases and the October NBS Symposium.

Public Comments

On the first day of public comments, seven oral comments were provided to the committee. Commenters included representatives from National MPS Society, EveryLife Foundation for Rare

Diseases, Kindness Over Muscular Dystrophy, Parent Project Muscular Dystrophy, Muscular Dystrophy Association (MDA), as well as parents with children with a genetic condition, and medical practitioners. Topics covered included the scientific basis of the N=1 rule, health justice and equity, as well as relating personal and professional experiences with Duchenne muscular dystrophy (DMD).

On the second day of public comments, four oral comments were provided to the committee. Commenters included representatives from Cure MLD, MLD Foundation, as well as parents with children with a genetic condition, and medical practitioners. Topics covered included personal and professional experiences with Metachromatic Leukodystrophy (MLD) and Biliary Atresia.

New Business

- The committee discussed the ability to notify the Secretary about funding for Propel and Co-Propel.
- A funding opportunity for Rare Diseases Clinical Research Consortia for the Rare Diseases Clinical Research Network was announced, with a deadline of August 13th.
- The timeliness of results was highlighted as a critical issue, and a disorders workgroup was introduced to address the issue.
- There was also a discussion on the importance of maintaining the ACT Sheets for newborn screening and genetics in general.
- The next meeting is scheduled for August 8th and 9th.

Awards and Acknowledgments

The Committee acknowledged and thanked Lisa Prosser for her contributions, as she will no longer be with the evidence review group. Additionally, Shawn McCandless was recognized for completing his term as a committee member.

Committee Votes

Motion #1: (Phornphutkul / Kwon) Motion to postpone vote to recommend inclusion of DMD on the RUSP based on the letter from the nominators until additional information is available to make an evidence-based decision for no later than one (1) year.

13 in favor / 0 opposed. Motion carries.

Motion #2: (Caggana / Brosco) Motion to approve the meeting summary from the meeting on January 29-30, 2024.

13 in favor / 0 opposed. Motion carries.