Advisory Committee on Heritable Disorders in Newborns and Children

Meeting Summary
March 22, 2019

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee) meeting was convened on March 22, 2019 and adjourned on March 22. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

Committee Members

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

Susan A. Berry, M.D.
Professor and Director
Division of Genetics and Metabolism
Department of Pediatrics and Genetics
Cell Biology & Development
University of Minnesota

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

Jeffrey P. Brosco, M.D., Ph.D.
Professor of Clinical Pediatrics
University of Miami School of Medicine
Department of Pediatrics
Deputy Secretary, Children's Medical Services
Florida State Department of Health

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

Annamarie Saarinen
Co-founder, CEO
Newborn Foundation

Scott M. Shone, Ph.D.
Senior Research Public Health Analyst
RTI International

Beth Tarini, M.D., M.S., FAAP
Associate Director
Center for Translational Science
Children's National Health System

Ex-Officio Members

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

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

Food and Drug Administration
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Health Resources & Services Administration
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Maternal and Child Health Bureau

National Institutes of Health
Diana Bianchi, M.D.
Director
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National Institutes of Health

Designated Federal Official
Catharine Riley, Ph.D., M.P.H.
Health Resources and Services Administration
Genetic Services Branch
Maternal and Child Health Bureau

Organizational Representatives

American Academy of Family Physicians
Robert Ostrander, M.D.
Valley View Family Practice

American Academy of Pediatrics
Debra Freedenberg, M.D., Ph.D.
Texas Department of State Health Services

American College of Medical Genetics
Michael S. Watson, Ph.D., FACMG
Executive Director

American College of Obstetricians & Gynecologists
Britton Rink, M.D., M.S.
Mount Carmel Health Systems

Association of Maternal & Child Health Programs
Jed Miller, M.D.
Director, Office of the Office for Genetics and People with Special Health Care Needs
Maryland Department of Health Maternal and Child Health Bureau

Association of Public Health Laboratories
Susan M. Tanksley, Ph.D.
Manager, Laboratory Operations Unit Texas Department of State Health Services

Association of State & Territorial Health Officials
Christopher Kus, M.D., M.P.H.
Associate Medical Director
Division of Family Health
New York State Department of Health

Department of Defense
TBD

Genetic Alliance
Natasha F. Bonhomme
Vice President of Strategic Development
Genetic Alliance

March of Dimes
Siobhan Dolan, MD, MPH
Albert Einstein College of Medicine and Montefiore Medical Center

National Society of Genetic Counselors
Cate Walsh Vockley, M.S., CGC
Senior Genetic Counselor Division of Medical Genetics Children's Hospital of Pittsburgh

Society for Inherited Metabolic Disorders
Shawn E. McCandless, M.D.
Section Head, Genetics and Metabolism
Children's Hospital Colorado

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I. Administrative Business — March 22, 2019

Joseph A. Bocchini, Jr., M.D.
Committee Chair
Professor and Chairman
Department of Pediatrics
Louisiana State University

A. Welcome and Roll Call

Dr. Bocchini welcomed participants to the first 2019 meeting of the Advisory Committee on Heritable Disorders in Newborns and Children.

Dr. Bocchini then conducted the roll call. The Committee members in attendance were:

- Dr. Mei Baker
- Dr. Susan Berry
- Dr. Joseph Bocchini
- Dr. Jeffrey Brosco (joined the call at 11:15 a.m.)
- Dr. Carla Cuthbert (Centers for Disease Control and Prevention)
- Dr. Kellie Kelm (Food and Drug Administration)
- Dr. Melissa Parisi (National Institutes of Health)
- Dr. Cynthia Powell
- Ms. Annamarie Saarinen
- Ms. Joan Scott (Health Resources and Services Administration)
- Dr. Scott Shone
- Dr. Beth Tarini
- Dr. Catharine Riley (Designated Federal Official)

Organizational representatives in attendance were:

- American Academy of Family Physicians, Dr. Robert Ostrander (afternoon only)
- American Academy of Pediatrics, Dr. Debra Freedenberg
- American College of Medical Genetics, Dr. Michael Watson
- Association of Maternal and Child Health Programs, Dr. Jed Miller
- Association of Public Health Laboratories, Dr. Susan Tanksley
- Association of State & Territorial Health Officials, Dr. Chris Kus
- Genetic Alliance, Ms. Natasha F. Bonhomme
- March of Dimes, Ms. Rebecca Abbott
- National Society of Genetic Counselors, Ms. Cate Walsh-Vockley

B. Vote on November 2018 Meeting Minutes

By roll call vote, the minutes were approved by all Committee members who were present.

C. Opening Remarks

Dr. Bocchini thanked the many candidates who submitted applications to serve on the Advisory Committee's Workgroups. Twelve new workgroup members have been selected (see slide presentation for names and affiliations). He encouraged all those not selected this year to apply again next year.

Dr. Bocchini thanked those who applied to become organizational representatives. Selections will be made before the April 23-24 Committee meeting.

Dr. Bocchini announced that he would be stepping down as chair of the Committee after the April meeting and will be succeeded by Cynthia (Cindy) Powell who has served on the Committee since 2017.

II. Ad-Hoc Workgroup Update: Interpreting NBS Results

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

Dr. Baker provided an update on the Workgroup's initial ideas for addressing the charges they received from the Committee. The first charge was to address opportunities and challenges related to interpretation of newborn screening results, including how to communicate the strengths and limitations of these results and how to educate various audiences—providers, parents and the public. This entails making sure pediatricians and family physicians, who convey newborn screening results to families, understand and fully communicate the results (positive, abnormal, negative and normal) and the difference between screening and diagnostic testing.

The Workgroup's second charge is to draft recommendations that could help states with risk assessment, including screening cutoff establishment and monitoring. The Workgroup plans to review the document and draft recommendations for the field, with an emphasis on considering sensitivity and specificity and the need for ongoing evaluation. The Workgroup plans to draft a report and develop a peer-reviewed journal article to reach a broad audience. An educational slide deck will be developed for use by clinicians. The workgroup will incorporate work in the field, such as that of the Midwest Genetic Network's MOC 4 effort. The Workgroup hopes to complete activities by ACHDNC's Feb. 13-14, 2020 meeting.

A. Discussion

- An organizational representative noted that many of the activities this Workgroup is addressing are being addressed by other organizations that focus on newborn screening and suggested that their activities be included in the Ad-Hoc Workgroup's efforts. Dr. Baker said that feedback is helpful and warrants further discussion and exploration.

III. Public Comments

A. Ms. Annie Kennedy, Senior Vice President of Parent Project Muscular Dystrophy

Ms. Kennedy explained that Parent Project Muscular Dystrophy (PPMD) has been leading a national effort over the past four years to build a newborn screening infrastructure for Duchenne muscular dystrophy, building on a pilot study led by Dr. Jerry Mendell at Ohio State University. By the time the study ended in 2012, 60,000 infants were screened and six were found to have Duchenne, establishing evidence for a two-tier screen of newborns within the U.S. newborn screening system. In order to conduct research and implement pilot studies, PPMD convened experts from the National Institutes of Health, Health Resources and Services Administration, Food and Drug Administration, Centers for Disease Control and Prevention (CDC), and the American College of Medical Genetics and Genomics, as well as the newborn screening community. PPMD has also collaborated with CDC and the American Academy of Pediatrics to develop diagnostic tools and resources for primary care providers and families. A newborn screening pilot program was developed to validate and conduct a consented screen for infants born at select hospitals in New York State. PPMD convened a consortium of biopharmaceutical industry partners that are interested in early diagnosis and intervention in Duchenne. Two therapies for Duchenne were recently approved by the FDA and others are being developed.

B. Ms. Brittany Hernandez, Director of Advocacy for the Muscular Dystrophy Association

Ms. Hernandez explained that the Muscular Dystrophy Association (MDA) is an umbrella organization representing more than 40 neuromuscular disorders, including SMA and Pompe, both of which are on the Recommended Uniform Screening Panel (RUSP), as well as Duchenne. MDA also supports a network of more than 150 care centers nationwide that provide clinical care and access to support and provide services to families with Duchenne and other neuromuscular diseases and can also play an important role in the newborn screening continuum. MDA also collects longitudinal clinical data on multiple disorders in newborns through its neuroMuscular ObserVational Research (MOVR) data hub, to optimize clinical care and drug development. The specific emphases are on benchmarking quality of care, safety and effectiveness of new treatment, natural history of disease, and correlation between genotype and phenotype. Ms. Hernandez encouraged the Committee to consider this infrastructure that MDA has put in place when considering a Duchenne's future nomination to the RUSP.

IV. RUSP Condition Nomination and Evidence Review Process: Summary of the Expert Advisory Panel Meeting

Alex Kemper, M.D., M.P.H., M.S.
Lead, Evidence-Based Reviews
Division Chief of Ambulatory Pediatrics
Nationwide Children's Hospital
Professor of Pediatrics
Ohio State University School of Medicine

Dr. Bocchini introduced Dr. Kemper's presentation by saying that the Committee recognized the need to examine the process of determining what conditions to add to and remove from the Recommended Uniform Screening Panel (RUSP). The project is designed to collect information on how to improve the nomination, evidence-review, and decision-making processes to ensure that they reflect the most up-to-date approaches to using evidence in developing public health policies, especially for rare conditions. He noted that a draft work plan will be presented for the Committee's consideration during its April meeting.

Dr. Kemper summarized the Expert Advisory Panel (EAP) meeting on Feb. 5-6; which included representatives from HRSA and other agencies within the Department of Health and Human Services, advisory committee members, members of the Evidence-based Review Workgroup, experts from state screening programs and the field of evidence-based decision-making from the United States and Canada. The group discussed how Grading of Recommendations, Assessment, Development and Evaluation (GRADE) can be applied to rare diseases, how to assess published and unpublished evidence, strategies related to public health system impact assessment, how to determine the values of different stakeholders, and how to assess the decision matrix. Other topics included how to reconsider conditions that are already on the RUSP, the nominations process and other areas that need more research and development.

Long-term follow up methods also need to be examined. For example, should conditions continue to be considered separately or grouped together in panels (e.g., a panel of intellectual disorders)? Long-term follow up plans should be described and there should exist a framework for assessing their future quality. The EAP suggested with regard to the nominations process that it should be made more transparent and that nominators should be asked to identify critical outcomes. One recommendation was to better identify targets in general as well as primary and secondary targets and clarify incidental findings before the evidence review process begins. The EAP discussed the option of conducting a "scoping" review of available literature before conducting a full evidence review, during which the availability of—and critical gaps in—evidence would be considered but it is necessary to determine what type of review this would involve.

The EAP's suggestions and related methods discussed during the meeting will be refined in with guidance from the Committee. A manual of procedures will also be developed.

A. Discussion

- A Committee member asked whether the Committee should discuss what constitutes a critical outcome for a condition since there has been debate in the past about how to measure this—whether it should focus on survivability alone or quality of life, or improvement of motor function, for example. In short, is there a general definition of critical outcomes and how to measure them? Dr. Kemper said that Dr. Schunemann suggested that conditions have a hierarchical list of important outcomes; morbidity might be the first one in terms of importance, followed by others. He agreed that important outcomes should be determined before the review process begins. Dr. Bocchini concurred, saying that identifying critical outcomes would help the Committee to evaluate the strength of the evidence in terms of the net benefit each of the outcomes confers, which could help to standardize the approach to making decisions about additions to the RUSP.

- A Committee member asked whether the general principles the Committee has followed in deciding whether to recommend a condition for the RUSP—that the disorder must have an impact on the patient's health, be detectable through screening and be linked to an effective treatment—might change, especially if conditions are grouped into panels rather than being viewed separately? She also asked whether conditions that can be detected in newborns but may not be symptomatic until significantly later in life are being considered in the context of this discussion. Dr. Kemper said that the Committee's fundamental approach to deciding what to recommend adding to the RUSP will not change; the goal is simply to better synthesize the evidence that is used to make such decisions. He also said that whether to screen for a condition for which treatment might benefit someone past infancy is not within the purview of the evidence review process. However, the process does look for evidence that newborn screening leads to better outcomes than other forms of case detection.
- A Committee member asked about the suggestion that resource implications, which could be related to the impact on the public health system could be added to the decision matrix. He further pointed out that disorders can wind up on different places on the matrix, yet the outcome can be the same. Should the review process take this into account? Dr. Kemper replied that a discussion about this—whether the decision matrix directly affects the Committee's final RUSP recommendation or is more of a tool that is used to foster discussion—needs to be discussed more broadly as do resources that might be required to do long-term follow up.
- A Committee member pointed out that the Newborn Screening Translational Network has been thinking about whether it might be useful to issue a provisional approval to the process the Committee uses to recommend conditions to the RUSP, which would permit more study of issues surrounding it and better inform the Committee's decisions.
- An organizational representative said that it is hard at the population level to generate any sort of data on rare diseases. However, FDA does allow provisional approval of newly developed drugs for rare conditions, followed by data-sharing from drug development studies and post-market surveillance. A well-organized prospective process with controlled data collection for provisional approval might be useful and will be discussed at the Committee's April meeting.
- A Committee member said that provisional approval would permit the collection of more data before making a decision about a RUSP nominated condition and might prevent the need to reassess a decision later that had been based on more limited data.
- A Committee member said that she was more concerned about whether the matrix can account for late onset conditions that can be picked up through newborn screening. She said she was pleased to see panels mentioned that might focus on conditions that could cover multiple disorders or be discovered through emerging screening methods such as genetic or whole genome sequencing.

V. Analyzing the Impact of Adding Conditions to the RUSP: Drafting an Approach

Alex Kemper, M.D., M.P.H., M.S.
Lead, Evidence-Based Reviews
Division Chief of Ambulatory Pediatrics
Nationwide Children's Hospital
Professor of Pediatrics

Ohio State University School of Medicine

Dr. Bocchini introduced this presentation by explaining that Dr. Kemper and his team were asked to conduct a retrospective analysis of how well the process of implementing screening for conditions recently added to the RUSP has gone and the impact on state newborn screening programs and the newborn screening system.

Dr. Kemper provided an outline for the report and asked the Committee to provide input on the review's overall approach to reviewing implementation of newborn screening for the five conditions that were added to the RUSP from 2010 through 2017: Severe Combined Immunodeficiency, CCHD, Pompe Disease, Mucopolysaccharidosis I and *X*-linked adrenoleukodystrophy. This review also provides an opportunity to develop standard review methods to address screening implementation and outcomes after a condition is added to the RUSP. The project will cover state implementation, public health implications and clinical outcomes and the system impacts of adding these conditions to the RUSP. The review will involve interviews, literature reviews and consideration of previous reports and Committee deliberations.

Separately, the team will also review and issue a slightly different report on spinal muscular atrophy (SMA) screening implementation, which the Secretary of Health and Human Services requested in response to the Committee's recommendation. This review, which will be conducted by a technical expert panel, will examine what activities the states have conducted to implement screening, the extent of knowledge about clinical outcomes in infants who were treated early and about potential harm to infants who are diagnosed with SMA.

A. Discussion

- A Committee member suggested that, in addition to the information Dr. Kemper already mentioned, data on how many infants are affected by the screening for these conditions would be helpful as well, to give a sense of what impact screening has in various states. He agreed and said he would discuss it with NewSTEPs.
- An organizational representative indicated the Follow-up and Treatment Workgroup has discussed longitudinal follow up for RUSP conditions. A Committee member asked how this work fits into long-term follow up for newborn screening at the state level. Dr. Kemper said that it will hinge in part on what type of longitudinal follow up data are available but being able to track it would help the Committee to better understand the impact of the decision making process and how successfully the report predicts issues that will arise in the future. Another Committee member said that long-term follow up should be part of the planning behind adding all conditions to the RUSP and this priority should be reflected in the decision matrix. Dr. Bocchini concurred, saying that the goal of this review is to determine, not just how many states are screening and how long it took to implement, but the effect on the states' public health systems and the children screened.
- An organizational representative asked what pursuing implementation means specifically: does it mean pursuit of enabling legislation or that states or advocates are pushing for screening? Dr. Kemper asked Marci Sontag of New Steps to weigh in. She offered clarification that such activity, conducted by the public health program, could consist of lobbying for relevant legislation, working with the Advisory Committee, seeking fee changes or acquiring new equipment. She indicated that APHL will discuss this during a future meeting.

- A Committee member asked whether anyone is collecting information on the barriers state newborn screening programs face in adopting/implementing a new screen (e.g., lack of enabling legislation, equipment or knowledge or financial support). Dr. Kemper confirmed that the team would try to collect this information.
- A Committee member offered that a possible way of surmounting some barriers is for states to collaborate and use technology to overcome hurdles. It would be helpful if Dr. Kemper's team could identify mechanisms and strategies to overcome barriers. Dr. Kemper agreed.
- An organizational representative said that she hoped it would be possible to explore the possibility of using some of the data in the longitudinal pediatric data resource (LPDR). These data may be useful in identifying outcomes in SMA and other conditions added to the RUSP. Examining best practices for long-term follow-up would also be helpful, especially given the different strategies and screening systems various states are employing. Dr. Kemper agreed.
- An organizational representative said that barriers and facilitators to implementing new screening should be considered when the Committee is considering future funding opportunities or other recommendations about how funding opportunities should be structured. Dr. Kemper agreed.
- A Follow-up and Treatment Workgroup member pointed out that, although all states are implementing critical congenital heart disease (CCHD) screening, approaches vary and there is no way to report how well it is being done. Hospitals have a legislative mandate to do the screening but no funding was provided to support reporting requirements to ensure compliance. Dr. Kemper agreed, saying that such limitations and the fact that this is a point-of-care screen makes it hard to collect relevant data and the team will be examining this issue.
- A Committee member noted that Dr. Kemper had discussed as factors that support or impede screening adoption, public activities, grant support, advocacy, and involvement of payers and clinicians, but not a state's fundamental disagreement with adding a new condition to the RUSP. He thought it would be helpful to gauge the attitudes of state advisory committees on the Advisory Committees' recommendations to add a condition to the RUSP. Dr. Kemper agreed.

VI. Resources for Facilitating Rare Disease Research – PANEL

Dr. Bocchini explained that the Committee has been discussing what data resources might be useful in considering conditions nominated for the RUSP and in assessing long-term outcomes. These resources could also be useful in assessing the nomination evidence review process. The panel will provide an overview of available resources and start a conversation that will continue during the April meeting. He asked the Committee to think about what it can do to encourage rare disease research through the development of additional data resources and through identification of ways to increase synergy between already available resources.

James O'Leary, M.B.A.
Strategist/Community Builder
Formerly, Chief Innovation Officer
Genetic Alliance

The Committee is aware of the need to accelerate research into rare diseases. There are many available resources, ranging from data to internal and external expertise, to information and technology platforms. The discussion focused primarily on registries. They are decentralized and tend to be disease

or institution specific. As a result, there are thousands of registries that focus on different aspects of disease tracking to clinical and health care outcomes. Therefore, it can be difficult to build broadly useful tools.

It is important to determine the registry's purpose—do they collect data on biological specimens? Do they contain data collected from patients, clinicians, apps, tests or insurance companies? Other factors include the type of data and samples that will be collected and from whom and how the data will be used. Will it focus on natural history, bio marker identification, trial recruitments or surveillance? Does it contain the information and context to do what it was designed to help accomplish? For example, an organization was asked to dovetail its registry with its desire to have the condition for which data is being collected added to the RUSP, but they lacked information on how to do that. They didn't know what validated questions to ask and what baselines were needed.

It is also important to establish strong levels of trust and security to ensure that the process of collecting data and its ongoing availability is reliable. Other factors to consider are whether the data are longitudinal and whether they will be de-identified. If the registry is developed at a national level, it may be difficult to move it into the international realm. How the registry will be governed needs to be determined as well. Who owns the data—the collecting agency, the government or the individual—must also be determined. Registry platforms need to be tailored to the people who will use them. Who asks the questions is as important as are what types of questions will not be asked. Policy and regulatory restrictions may also pose barriers that must be overcome and funding is often an issue. Community registries that have been started and maintained with industry funding may lose this support because they are hard to maintain and there is a risk of loss of integrity if the industry partner is no longer asking the questions and ensuring that the information is useful to both parties. Other challenges include policy and regulatory barriers.

Leadership is needed in identifying the need for a registry, creating a neutral space in which collaboration can occur and in defining what questions and data types that will be most useful.

Tiina Urv, Ph.D.
Program Director
Office of Rare Diseases Research
National Center for Advancing Translational Sciences
National Institutes of Health

Dr. Urv delivered a presentation on the Office of Rare Diseases Research's (ORDR) resources and activities. About 7,000 diseases are classified as rare and about 230 per year have been added for the past several years. About 30 million people in the U.S. have a rare disease. Identification of rare disease is difficult due to the small number of patients, lack of knowledge about these diseases, likelihood of phenotypic diversity within the disease and geographic dispersal of patients. As a result, only about 5 percent of rare diseases have a regulatory-approved treatment and development of about three to five treatments for newly treatable diseases per year are underway.

ORDR, which is part of the National Institutes of Health's National Center for Advancing Translational Sciences, facilitates coordination between multiple stakeholders in the rare diseases community, including scientists, clinicians, patients and patient groups. The office provides several tools to convey knowledge and information: The online Genetics and Rare Diseases (GARD) Information Center provides comprehensive plain language information on rare diseases that is available to the public. GARD

maintains a website, a database containing information on rare and genetic diseases, which can include newborn screening information.

ORDR developed a Toolkit for Patient-Focused Therapy Development that includes the new rare diseases registry (RaDaR), which is designed to provide an easy-to-use educational tool to help new patient advocacy groups adopt good quality practices early in their development of disease registries. The toolkit includes tools for discovery, how to prepare for clinical trials for FDA review and what actions to take after the trials have been completed, thus making them part of the process.

To foster and support research and collaboration, ORDR has developed the Rare Diseases Clinical Research Network, which was introduced through public law and calls for the establishment of rare disease clinical research consortia of excellence. The network recruits applications through competitions held every five years. The network started with seven and now has 22 consortia of researchers and patient and advocacy groups that work to advance the diagnosis, management and patient-centric treatment of rare diseases with a focus on reaching clinical trial readiness. The consortia promote collaborative, multi-site patient-centric translational clinical research to address unmet clinical trial readiness needs. The network covers 238 disorders and has more than 40,000 participants.

ORDR also has created the Therapeutics for Rare and Neglected Diseases program and the Bridging Interventional Development Gaps program, both of which work with outside laboratories with disease-area/target expertise to help move drugs from the laboratory to clinical trial. Their focus is on developing data that will lead to an investigational new drug application. The goal is to ensure data collected use standards that will be usable in the future, for example, natural history studies in connection with adding conditions to the RUSP.

Vanessa Boulanger, M.Sc.
Director of Research
National Organization for Rare Disorders

Dr. Boulanger provided an overview of the nonprofit National Organization for Rare Diseases' (NORD) IAMRARE Registry and its Patient Centered Research Program. NORD is an independent nonprofit (501 (c) 3) organization that is focusing on improving the lives of patients with rare disease and their families. NORD's research efforts encompass its registry program, which partners to develop patient natural history studies that provide research grants and publish original research**.**

NORD works with a committee of stakeholders, including NIH, FDA, community organizations, patients, researchers and clinicians to design, develop and maintain its program. The goal was to develop a registry platform that is available to the rare disease community and keeps data ownership in the hands of the disease-specific communities. NORD also forges partnerships to help patient organizations to become data stewards and experts for their communities.

Through a cooperative agreement with FDA, NORD moved from working with five pilot groups to subsidizing 20—and now 34—partners that use the organization's registry platform to store data collected from surveys on a variety of rare diseases. The data these surveys collect consists of patient-reported outcomes and experience data, including information on 1. diagnosis and treatment; 2. insurance, medical costs; 3. transitions in care; 4. disease progression over time; 5. heterogeneity of disease expression; 6 quality of life and; 7. lived experience. The platform employs a common infrastructure for longitudinal data collection. Data elements are pulled from the Global Rare Disease

Registry Repository. This core set of surveys remain the same across registries it hosts to support cross-disease analysis but the platform also has the flexibility to support customized, disease-specific surveys. NORD also provides training, user and instruction guides, best practices, recommendations and guidelines. Users can also access consent, marketing, and institutional review board (IRB) protocol templates. Registry leaders communicate with each other to share resources and meet once a year.

NORD and FDA also have a memorandum of understanding to support patient-listening sessions, which consist of a portal through which patients and caregivers can submit a question to, or request a meeting with FDA.

A. Discussion

- A Committee member expressed concern that economically disadvantaged families may have trouble participating in or accessing registries or obtaining access to other tools and asked how that obstacle could be overcome. Mr. O'Leary suggested technology fixes such as iPads containing registry surveys at clinics or having registries partner with Medicare navigators or community liaisons. He acknowledged better solutions are needed. Dr. Boulanger said that NORD is trying to achieve better representation in its registries in terms of racial distribution and socioeconomic status.
- A Committee member said that, although it is necessary to focus on patient-centered outcomes, clinicians and other experts have roles to play in registries, which tend to be compromised in the long run by varying degrees of sustainability. Artificial intelligence technology does not seem to have addressed this and allocation resources is an issue as well; more money seems to go to cancer research than to this collective group of diseases. Dr. Urv said that ORDR is trying to convey the message that "rare" diseases, when considered collectively, are not that rare and that they should be viewed as a group in terms of their impact, as cancer often is. This could lead to a trend away from many individual registries to a more cooperative effort across disease types, which is what the Rare Diseases Clinical Research Network is trying to achieve. This is the best way to attract funding. Mr. O'Leary said that coming up with a uniform platform on which to do this would be difficult. It may be necessary to build another system entirely on top of what exists to make it happen. He said that the Parent Project Muscular Dystrophy is a good example of a group that already is successful at collecting patient-reported data but also focuses on funding clinical sites to collect that data, which includes setting requirements for entering structured data and then coordinated these two data sources together, however, this is an expensive undertaking.
- A Committee member said that Shawn McCandless is spearheading an effort on behalf of the Society for Inherited Metabolic Disorders (SIMD) to bring clinicians in the metabolic disease care community together to consider how to better share information. Dr. Urv said that some NIH institutes, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and FDA also have initiatives to bring groups together to start collecting natural history data.
- A Committee member pointed out that a very enthusiastic family might try to sign up for more than one registry or trial and that it may be difficult to preserve patient confidentiality while ensuring that patients are not reflected in more than one registry. Dr. Boulanger said that NORD's platform tracks participants by giving each one a globally unique identifier (GUID), which allows them to be tracked across registries but this is a limited tool.
- A Workgroup member said that in his experience as a chief medical officer in a large health care system, they could not financially support electronic connections to multiple registries. This is

also true of hospitals and physician practices in which he has worked. Clinicians are also frustrated that they have to enter data manually. If rare disease and newborn screening registries are to get clinical data from medical providers, there needs to be one place where these organizations can report and one place to send data for storage in a dual registry. He noted that the American Academy of Pediatrics is beginning to consider a "report once, distribute to many" model.

- A Committee member said that these themes also emerged during recent meetings of the Muscular Dystrophy Coordinating Committee meeting. She added that NICHD has a program announcement with review for newborn screening conditions and natural history studies but it is difficult to coordinate data from different studies in a useful way. It is also difficult to combine data from disparate sources but Parent Project Muscular Dystrophy is trying to develop a template for doing so in a HIPAA-compliant and useful way.

Dr. Bocchini summarized that the Committee would like to keep in touch with the panel members and their organizations. The Committee will begin to examine some individual registries with an eye toward using them to conduct long-term follow up.

VII. New Topics

Joseph A. Bocchini, Jr., M.D.
Committee Chair
Professor and Chairman
Department of Pediatrics
Louisiana State University

Dr. Bocchini asked for new topics the Committee should consider.

Dr. Ostrander said that direct-to-consumer screening for rare diseases has become a concern. It involves ordering a kit, with a questionnaire, and getting a swab from the infant. The doctor reviews the questionnaire and enters the order to comply with FDA. This has the potential to cause harm and confusion. Dr. Ostrander has been working with the American Academy of Family Physicians to develop a policy statement about setting minimum requirements for these tests that would cover ethics, informed consent, interactive pre- and post-test counseling and other considerations.

Dr. Baker brought up carrier screening and said that it would be helpful if we could have more of a connection with obstetrician and gynecologist groups.

VIII. Adjourn

Dr. Bocchini thanked everyone for participating, reminded everyone that the next meeting will be held April 23-24 at HRSA headquarters in Rockville, Md. and adjourned the meeting.