Muscular Dystrophy Coordinating Committee

December 16, 2020

## Introduction and General Information

The Muscular Dystrophy Coordinating Committee (MDCC) of the National Institute of Neurological Disorders and Stroke (NINDS) met on December 16, 2020, via teleconference. Committee Chair, Diana Bianchi, MD, Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD/NIH), led the meeting, and Glen Nuckolls, PhD, served as Executive Secretary. The entire meeting was held in open session and was in accordance with the Federal Advisory Committee Act (P.L. 92-463).

**Dr. Nuckolls** acknowledged the service of Drs. Devanand Jillapalli and John Porter, who are retiring from the MDCC. Dr. Emily Freilich, Center for Drug Evaluation and Research (CDER) at the U.S. Food and Drug Administration (FDA), will replace Dr. Jillapalli on the MDCC. Dr. Nuckolls then discussed the meeting procedures required to comply with FACA committee policies and to avoid conflicts of interest. He also acknowledged NIH staff who helped to organize the meeting.

### Chair Presentation

**Dr. Bianchi** provided updates on COVID-19, key advances in muscular dystrophy research, and the NIH budget. She began with an overview of the four primary subprojects within the NIH [Rapid Acceleration of Diagnostics (RADx) Initiative](https://www.nih.gov/research-training/medical-research-initiatives/radx/radx-programs): RADx Tech, RADx-Advanced Testing Program (RADx-ATP), RADx-Radical (RADx-rad), and RADx-Underserved Populations (RADx-UP). Dr. Bianchi indicated that RADx-UP has provided [supplemental awards](https://www.nih.gov/research-training/medical-research-initiatives/radx/funding#radx-up) to existing NIH grants to improve access to testing in underserved populations. One of these awards was given to the [Intellectual and Developmental Disabilities Research Center (IDDRC)](https://iddrc.wustl.edu/) at Washington University in St. Louis to support testing for children with intellectual and developmental disabilities and staff at six special education schools. She noted that some populations of interest to the MDCC have received similar awards. Dr. Bianchi strongly advocated for testing and vaccination of vulnerable children and teaching staff more broadly so that these children can return to school safely and receive the services that they need. She also highlighted a recently funded effort to predict children at risk of suffering long-term complications from COVID-19 infection, known as [Predicting Viral-Associated Inflammatory Disease Severity in children with Laboratory Diagnostics and Artificial Intelligence](https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-20-023.html) (PreVAIL kIds). Approximately 1.5 million children have been diagnosed with COVID-19 to date, and a small fraction (< 1%) of those children develop Multi-system Inflammatory Syndrome in Children (MIS-C) or other severe post-acute sequelae. NIH is also supporting Collaboration to Assess Risk and Identify loNG-term Outcomes (CARING) for Children with COVID to build a centralized cohort of children with COVID-19 and/or MIS-C.

Dr. Bianchi next discussed several recent advances in muscular dystrophy research:

1. Analysis of cohort diversity in studies of Duchenne muscular dystrophy (DMD) (supported by NICHD, National Institute of Arthritis and Musculoskeletal and Skin Diseases [NIAMS], and National Heart, Lung, and Blood Institute [NHLBI]): <https://pubmed.ncbi.nlm.nih.gov/31929119/>
2. Quantitative morphological analysis of nerve sections that identified specific dysfunction of nerves for the tongue and diaphragm that could contribute to respiratory failure, the most common cause of death in DMD (supported by NIH): <https://www.nature.com/articles/s41598-020-65824-1>
3. Identification of biomarkers for facioscapulohumeral dystrophy (FSHD) (supported by NHLBI, NICHD, NINDS, Foundation to Eradicate Duchenne, and FSHD Society): <https://pubmed.ncbi.nlm.nih.gov/33228131/>
4. Development of a new delivery system for CRISPR-Cas9 gene editing in specific target tissues that restored dystrophin expression in a mouse model of DMD (supported by National Institute of Biomedical Imaging and Bioengineering [NIBIB], Cystic Fibrosis Foundation [CFF], American Cancer Society [ACS], and the Robert A. Welch Foundation): <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7320157/pdf/41467_2020_Article_17029.pdf>
5. Use of AAV delivery of CRISPR-Cas9 gene editing to eliminate toxic RNAs that cause repetitive sequences in myotonic dystrophy type 1 (DM1) (supported by NIH and the Muscular Dystrophy Association MDA Venture Philanthropy [MVP]): <https://www.nature.com/articles/s41551-020-00607-7>

Dr. Bianchi then discussed the NIH budget. She stated that appropriations for FY 2021 are still being negotiated and that the federal government is currently funded through December 18, 2020; a supplemental coronavirus relief package is also being considered. She also highlighted a funding opportunity to address the effects of COVID-19 on individuals with physical rehabilitation needs through the [National Center for Medical Rehabilitation Research](https://www.nichd.nih.gov/about/org/ncmrr) (NCMRR).

## Meeting Reports

**Ryan Fischer**, Chief Advocacy Officer of [Parent Project Muscular Dystrophy](https://www.parentprojectmd.org/) (PPMD), provided a summary of the PPMD 2020 Virtual Annual Conference held from July 22 to 25, 2020. For its first-ever virtual conference, two PPMD representatives hosted the conference live from a studio and presentations were delivered virtually. More than 2,500 registered participants—approximately half of which were families—received meeting content gradually over the course of months and live polling of participants was conducted during the conference to collect data, as is normally done. A [conference hub](https://www.parentprojectmd.org/2020-ppmd-virtual-conference-hub/) allowed participants to access meeting materials and connect with one another. Companies pre-recorded presentations for publication to the conference hub prior to the meeting and were invited to give brief remarks before a live interactive panel discussion. “Lunch and Learn” sessions provided an opportunity for participants to converse with representatives from [Casimir](https://casimirtrials.com/) and the [Duchenne Family Assistance Program](http://duchennefap.org/index.html). One-on-one sessions with specialists in school and behavior, genetics and registry, and physical therapy were available by appointment. The conference received positive feedback (4/4 stars from 85% and 3/4 stars from 15%), and participants appreciated the ability to attend the conference without traveling; however, many noted a lack of interaction with community members and experts relative to an in-person meeting.

## Newborn Screening for Rare Diseases

**Dr. Bianchi** introduced the main session for the meeting, titled “Newborn Screening for Rare Diseases: Current Landscape and Future Directions.” She noted the MDCC’s action plan for the muscular dystrophies includes an important objective to develop newborn screening (NBS) methods for the muscular dystrophies, explore related social and ethical issues, and develop techniques to make NBS practical. Significant progress on screening and treatment for spinal muscular atrophy (SMA) has occurred in recent years, and the MDCC hopes to see such progress for the muscular dystrophies in coming years.

**Melissa Parisi**, MD, PhD, NICHD, spoke about “The Challenges of Adding a New Condition to the [Recommended Uniform Screening Panel](https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html) (RUSP).” She provided a primer on NBS, discussed the nomination process for adding a condition to the RUSP, and described NIH tools and resources to support NBS research. NBS is a public health service that screens 4 million newborns in the United States per year for 30 to 70 serious but treatable diseases. The Department of Health and Human Services (HHS) recommends which diseases should be screened through the RUSP, although the final choice is made at the state level. Currently, the RUSP lists 35 primary conditions that HHS recommends for screening. The [Advisory Committee on Heritable Disorders in Newborns and Children](https://www.hrsa.gov/advisory-committees/heritable-disorders) (ACHDNC) assists the HHS Secretary by providing recommendations and technical information related to NBS grants, projects, policies, and priorities that will help to reduce morbidity and mortality from heritable disorders in newborns and children.

Any stakeholder can nominate a condition for addition to the RUSP if the condition meets four requirements: (1) neonatal onset, (2) validated accurate screening test, (3) available treatment that improves quality of life, and (4) completed pilot with successful identification of neonatal cases and outcomes. Recommendations must be evidence-based, demonstrate a health benefit for the infant that results from diagnosis, consider the readiness and ability of state health departments to implement the screen (including follow-up and treatment), and assess any ethical, legal, and societal implications of screening for the condition. Recommended conditions for screening should also be well-defined, which Dr. Parisi noted can be difficult in the case of rare diseases.

Dr. Parisi summarized the [decision matrix](https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/Nominate-condition/decision-matrix.pdf) (currently under review by ACHDNC) and the [review process](https://pubmed.ncbi.nlm.nih.gov/29214581/) for nominated conditions, which begins with the submission of a nomination package to the [Health Resources and Services Administration](https://www.hrsa.gov/) (HRSA) and, if successful, culminates in Secretarial action to add the condition to the RUSP. Dr. Parisi also reviewed several recent RUSP additions, including the rapid adoption of SMA screening by 32 states. Challenges to adding conditions include an imperfect review process, delays in review and approval, and a lack of pilot studies for many conditions that instill confidence in successful incorporation of a screen. There are also outstanding questions regarding how best to manage carriers, late-onset phenotypes, and treatment access.

Dr. Parisi provided an overview of NIH resources that support NBS research, including pilot studies funded by NICHD, the [Hunter Kelly Newborn Screening Research Program](https://www.nih.gov/news-events/news-releases/nih-newborn-screening-research-program-named-memory-hunter-kelly), the [Newborn Screening Translational Research Network](https://nbstrn.org/) (NBSTRN), and [the Newborn Sequencing In Genomic medicine and public HealTh](https://www.genome.gov/Funded-Programs-Projects/Newborn-Sequencing-in-Genomic-Medicine-and-Public-Health-NSIGHT) (NSIGHT). The NBSTRN provided data that supported screening for SMA and is coordinating evidence in support of adding DMD to the RUSP. She concluded by sharing funding opportunities related to NBS and acknowledging coordinated federal efforts to support NBS pilot studies.

**Kathryn J. Swoboda**, MD, FACMG, Massachusetts General Hospital, spoke about “Lessons along the way: Addition of SMA to the RUSP.” She began by providing a brief background on the biological and public health characteristics that influenced the successful addition of SMA to the RUSP. SMA is the most common inherited recessive cause of infant mortality. The identification of SMA by homozygous deletion in the *SMN1* gene (rather than through individual private mutations) and prediction of disease severity by *SMN2* copy number enabled confirmation of SMA with a relative indicator of urgency to initiate treatment in a rapid and easily accessible test. Furthermore, most cases of SMA are of the Type I (infantile) subtype, which is identifiable by *SMN2* copy number and supports the urgency of intervention in the newborn time period.

Dr. Swoboda reviewed a timeline of advances in SMA therapeutics, emphasizing the importance of the first FDA approval for an SMA treatment in 2016 to establishing justification for SMA’s nomination for NBS. The ACHDNC declined to review SMA for addition to the RUSP in 2008, largely because of the lack of approved treatments and pilot studies. Subsequent NBS pilot studies developed methods to screen for SMA that were feasible in public health laboratory settings. Following FDA approval of the first antisense oligonucleotide therapy for SMA, nusinersen, in 2016, SMA was nominated once again and ultimately added to the RUSP. Dr. Swoboda acknowledged the essential role of the Condition Review Workgroup and Technical Expert Panel in providing the best information to the ACHDNC. She listed three critical components of the review process: (1) systematic evidence review, which focuses on published data rather than expert opinion; (2) models of expected outcomes, which are primarily limited to published data and are supported by the NBSTRN; and (3) assessment of public health system impact, which the Technical Expert Panel should be prepared to address. Key elements that supported the addition of SMA to the RUSP included a CDC-developed NBS assay, the availability of pilot data from the New York State program and Taiwan pilot study, published treatment data, and the availability of at least one treatment (nusinersen) with proven efficacy.

Dr. Swoboda also shared her work on the Project Cure SMA Longitudinal Population Data Repository, which contains longitudinal data from more than 600 SMA patients from 2000 to 2015, and the SPOT SMA Longitudinal Population Data Repository, which contains longitudinal data with an emphasis on newborns identified in NBS pilot studies. To conclude, Dr. Swoboda remarked that half of all U.S. states now conduct NBS for SMA and highlighted several therapeutic successes in infants treated with nusinersen.

**Michele Caggana**, ScD, FACMG, Newborn Screening Program, Wadsworth Center, New York State Department of Health, spoke about “Considerations for Newborn Screening Pilot Studies from the Public Health Perspective.” Dr. Caggana began by introducing the many stakeholder perspectives that inform public programs for NBS pilots and stressing the importance of harmonized expectations among stakeholders. She also cautioned that NBS programs must recognize that screens rarely detect only textbook cases of a condition and often identify related or secondary conditions that may or may not be treatable. Dr. Caggana offered several practical considerations for NBS pilot studies. Timelines for pilot studies often change for a variety of reasons, including the need to establish a consent model, which is a staff-intensive and expensive effort that must navigate multiple institutional review boards (IRBs). Each pilot study must create brochures in multiple languages and with specific institutional language. Several groups must be trained to work on the pilot, including research scientists, clinicians, and hospital staff, and turnover must be managed. Moreover, parents must be educated about the study in the busy time shortly after a child’s birth. Tests must be developed and validated, and laboratory information management (LIM) systems must be prepared for timely integration of results into the NBS workflow.

Dr. Caggana described the goals of the Duchenne Consented Pilot Study, which aims to validate a high-throughput first-tier immunoassay screen for DMD using creatine kinase (CK)-MM, a marker of skeletal muscle damage that also detects other muscular dystrophies, in a high birth number state (NY) and to optimize a second-tier molecular (genetic) testing strategy that will increase test specificity. The study is designed to identify infants who will develop DMD before they exhibit symptoms so that parents may opt-in to treatments and trials, and outcomes will be tracked in coordination with NBSTRN. The study results will be used to support the nomination of DMD for addition to the RUSP. Dr. Caggana explained that validation of NBS tests involves an assay of a “reasonable” number of blinded specimens across a variety of categorizations (e.g., birth weight, age at collection, gender) to assess variability, select borderline cutoffs, and set referral levels. In the case of the DMD pilot, variability was greatest based on age at specimen collection, with newborns having higher levels of CK-MM and older infants having lower levels of CK-MM. CK-MM levels are accordingly stratified based on the newborn’s age at specimen collection; a borderline category for repeat sampling guards against false negatives. Dr. Caggana highlighted pilot studies as an opportunity to refine cutoff levels prior to universal screening and described the utility of borderline categories in refining these levels at the pilot stage. This DMD pilot study officially began in October 2019 with nine participating hospitals in New York City. From October 1, 2019, to October 31, 2020, 17,671 newborns were screened (1 in 1,039) and 17 infants were referred for evaluation of DMD. Dr. Caggana acknowledged the challenges introduced by the COVID-19 pandemic and noted that some steps taken to mitigate these challenges (e.g., through remote recruitment) may present an opportunity to enhance enrollment.

**Nikki Armstrong**, MS, CGC, NBS Pilot Program Manager, PPMD, provided a patient advocacy perspective on the Duchenne Consented Pilot Study. Ms. Armstrong stated that development of the groundwork for this pilot spanned nearly a decade and included forging relationships, curating knowledge, and building infrastructure beyond the hospital and laboratory infrastructure described by Dr. Caggana. PPMD gathered experts in NBS, DMD, and public health to form a steering committee and working groups with the goal of determining the necessary requirements to screen and care for children with DMD. Ms. Armstrong explained that, although achieving the goal to end DMD will likely require NBS, PPMD continues to pursue its mission to ensure that families of children with DMD and Becker muscular dystrophy (BMD) feel supported, receive education, and have access to care and treatments.

**Alan H. Beggs**, PhD, Boston Children’s Hospital/Harvard Medical School, spoke about newborn genomic sequencing (NGS). He began by emphasizing the power of NGS technology for understanding the medical futures of newborn children and raised the possibility that aspects of NGS might be incorporated in a future screening paradigm. He further explained that NGS encompasses a variety of technologies--including whole exome sequencing, whole genome sequencing, and genome mapping-- that assess a potential genetic condition on a genome scale, but not by sequencing the entire genome. He then distinguished NGS from NBS, particularly with regard to the strict specificity, therapeutic benefit, and timing requirements for inclusion of a condition on the RUSP. In contrast to NGS, the specificity and sensitivity of NGS are often uncertain and results can take weeks or months. At this time, no proven interventions or treatments are based on NGS, and the benefits and risks of NGS may not be clear for many years. Potential benefits include early diagnosis of affected infants, discovery of treatable pediatric disease, better management of diseases through early intervention, optimization of drug treatments, prediction of therapy response based on blood group and platelet antigens, and opportunities to provide reproductive planning information to families. Potential risks include psychological distress resulting from unexpected disease risk, increased anxiety following uncertain results, a negative impact on the parent-child relationship, early discovery by children of later-onset disease risk, stigmatization or discrimination, and discovery of nonpaternity.

Dr. Beggs mentioned the NSIGHT Consortium, a [network](https://pubmed.ncbi.nlm.nih.gov/28096516/) of four sites that launched in response to a 2013 Request for Applications (RFA) from NICHD and the National Human Genome Research Institute (NHGRI) to carefully explore how genomic information can broaden understanding of diseases identified in the newborn period. He emphasized that the RFA was not intended to be an NBS pilot. Dr. Beggs described the [BabySeq](https://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-018-1200-1) study, which was designed to determine the medical, behavioral, and economic impacts of NGS. The study had two arms: healthy newborns in the normal newborn nursery and sick newborns in the intensive care unit (ICU). Each arm had two cohorts: one received the standard of care NBS, and another received standard of care plus a Genomic Newborn Sequencing Report (GNSR). The GNSR included risk and carrier status for genes with strong evidence of association with pediatric-onset disease and high penetrance; a curated [gene list](https://pubmed.ncbi.nlm.nih.gov/28079900/) used in the BabySeq study is available. The study identified monogenic disease risk in 11 percent of whole exome sequenced infants as well as 566 recessive genes that may confer carrier status—99 percent of which would have been missed by routine care. Dr. Beggs noted several [barriers to enrollment](https://pubmed.ncbi.nlm.nih.gov/30209271/) in the BabySeq study that likely contributed to a lack of diversity and stated that future studies should address these barriers to ensure racial, ethnic, and socioeconomic diversity. To conclude, Dr. Beggs noted that sequencing newborns carries implications for the risk burden of family members.

## Closing Remarks

Walter Koroshetz, MD, Director of NINDS, acknowledged the complexity of conducting presymptomatic screening and the necessity of building flexible programs that are customized to meet the needs and wishes of parents. Dr. Bianchi summarized the meeting’s discussions, synthesized main themes, identified gaps in knowledge, and emphasized future directions and goals. Dr. Nuckolls thanked the presenters and committee members for their participation and announced that the next MDCC meeting in April or May 2021 will focus on respiratory and sleep disturbances.

**We certify that, to the best of our knowledge, the foregoing minutes are accurate and complete.**

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