EDITORIAL

*Muscle Nerve* **53:** 839–841, 2016

# THE MUSCULAR DYSTROPHY COORDINATING COMMITTEE ACTION PLAN FOR THE MUSCULAR DYSTROPHIES

**HEATHER I. RIEFF, PhD,[1] JONELLE K. DRUGAN, PhD, MPH,[2] THOMAS R. CHEEVER, PhD,[2] ASHLEE VAN'T VEER, PhD,[1] GLEN H. NUCKOLLS, PhD,[1] and STEPHEN I. KATZ, MD, PhD[2]**

[1] National Institute of Neurological Disorders and Stroke, National Institutes of Health, 6001 Executive Boulevard, Neuroscience Center, Room 2203, Bethesda, Maryland 20892, USA

[2] National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland, USA

*Accepted 18 March 2016*

The muscular dystrophy research community is at a watershed moment. Our understanding of the molecular, cellular, and physiological underpinnings of the muscular dystrophies continues to increase and has revealed several therapeutic targets. For the first time, investigational therapies are reaching the final stages of review by United States regulatory agencies. Yet, as we learn more about these diseases and the ongoing efforts to treat them, we are more aware of the critical work that remains. In this editorial we describe the work of the collaborative Muscular Dystrophy Coordinating Committee (MDCC), a congressionally mandated consortium of federal agencies and patient advocates tasked with identifying the many challenges confronting patients and their families and coordinating efforts to address them. Recently, the MDCC released an updated version of its Action Plan for the Muscular Dystrophies, a comprehensive document outlining the needs and priorities of the muscular dystrophy patient, family, and research communities. Our hope for the scientific community is that it will facilitate strategic planning and identification of common goals among funders, encourage researchers both inside and outside of the muscular dystrophy field to investigate the Plan's focus areas, and foster activities to further strengthen the training and career development of the next generation of researchers in the muscular dystrophies.

The muscular dystrophies comprise a heterogeneous group of genetic disorders that involve progressive weakness and degeneration of skeletal muscle. There are dozens of genetically distinct types.[1] Most also involve cardiac and smooth muscle, and some involve the brain, skeleton, and other organ systems. Efforts over the past 10 years have led to significant advances in knowledge about the muscular dystrophies and a great expansion in therapy development efforts (see reviews[2–4]). Although no treatments are available to stop disease progression, several candidate therapeutics are being tested in clinical trials, and anticipation for new medications is high.

## WHAT ARE THE MDCC AND THE ACTION PLAN FOR THE MUSCULAR DYSTROPHIES?

Accelerating advances in understanding the causes of the muscular dystrophies, developing therapies, and reducing the personal and societal impacts of the diseases require a coordinated effort from stakeholders, including patient advocacy groups, government agencies, researchers, and physicians. As part of these efforts, the Muscular Dystrophy Community Assistance, Research and Education Amendments of 2001 (MD-CARE Act, Public Law 107-84) guided the National Institutes of Health (NIH) to establish the MDCC.[5] With reauthorization of the Committee and the addition of members through the MD-CARE Acts of 2008 and 2014, the MDCC now includes representatives from 4 NIH institutes and other government agencies, including the Agency for Community Living, the Centers of Disease Control and Prevention, the Department of Defense, the Department of Education, the Food and Drug Administration, the Health Resources and Services Administration, and the Social Security Administration. In addition to federal agency members, one third of MDCC members represent the perspectives of patients, family members, or health-care providers. The current roster can be found at the MDCC website.[6]

In 2005, the MDCC approved the first Action Plan for the Muscular Dystrophies, which defined important research objectives and other goals, based on the recommendations of experts in the field.[7] The 2005 Action Plan guided the activities of the NIH and other MDCC member

Additional Supporting Information may be found in the online version of this article.

**Correspondence to:** G. Nuckolls; e-mail: glen.nuckolls@nih.gov

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Published online 25 April 2016 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/mus.25111

organizations to advance knowledge, develop treatments, and improve patients' and their families' lives. After 10 years of progress in the muscular dystrophy field, the MDCC updated the Action Plan.[8] Similar to the process used in 2005, the revised Action Plan was developed with the input of experts in basic, translational, and clinical sciences; clinical care; and health-related services for the muscular dystrophies (for a list of contributors to the Action Plan, refer to Table S1 in the Supplementary Material, available online). Reflecting the current thinking of the muscular dystrophy field, it includes significant research objectives as well as administrative, policy, and organizational goals that could decrease the impact of the muscular dystrophies on patients, families, and communities. All but a few of the 2005 Plan's objectives were carried forward, although several topics evolved to reflect research advances, a better understanding of the obstacles to treatment development, and improved care. New objectives also were added. In general, the revised Action Plan better emphasizes the commonalities across the different muscular dystrophies and reflects the importance of including patient perspectives in therapy development activities and when addressing access to services.

## RESEARCH PRIORITIES OF THE MDCC ACTION PLAN FOR THE MUSCULAR DYSTROPHIES

**Understanding Causes.** In the area of disease mechanisms, the Plan includes mechanisms related to specific types of muscular dystrophy and also highlights the need to understand shared mechanisms across dystrophies, despite differences in their underlying genetic causes. Specific objectives focus on understanding the structural links and signaling components connecting the muscle extracellular matrix across the sarcolemma and to the myonuclei, the mechanisms of membrane repair, the roles of different cell types in pathophysiology, the relative contribution of inflammation and other immune responses, and the effects of missing or aberrantly expressed gene products. Deciphering the causes of variations in disease course among patients with the same mutations, as well as variations in disease manifestations among muscles and other organs within individuals, may facilitate the development of therapies.

**Screening and Diagnosis.** Accurate and timely diagnosis and screening systems and useful biomarkers continue to be challenges for the muscular dystrophies. Advances in genetic testing and imaging approaches, such as MRI, are providing useful data in clinical trials and are decreasing the need for invasive muscle biopsies. Although there are many promising candidate biomarkers, additional studies are necessary to validate their use for identifying appropriate participants for clinical trials and for measuring the effects of candidate therapeutics. Effective newborn screening efforts for the dystrophies will depend on policy changes as well as continued research.

**Developing Treatments.** Since the original Action Plan in 2005, the number, quality, and level of innovation of preclinical translational studies have expanded immensely, as researchers have explored many new avenues that may lead to treatments. The revised action plan emphasizes the value of new tools, the opportunities afforded by the identification of targets, and the continued importance of rigor and reproducibility in studies that inform clinical testing. Although the development of therapies that address the root causes of muscular dystrophies, such as gene replacement or strategies to normalize gene expression, is still a priority, there is growing interest in targeting events downstream of the primary mutations. Such approaches may be applicable to a larger number of patients instead of being limited to those with a specific gene mutation. New technologies are available for gene- and cell-based interventions, and additional research could harness these technologies to overcome the remaining obstacles to their clinical use. Animal models that replicate aspects of the human diseases have helped advance preclinical studies in some types of dystrophy, but other dystrophies would benefit from well-characterized models that more closely mimic human disease and additional, standardized endpoints to allow comparisons across studies. As more candidate therapeutics are approaching readiness for clinical trials, there is growing interest in preclinical testing of combinations of interventions that may provide additive or synergistic effects.

**Preparing for Clinical Trials.** The 2015 Action Plan emphasizes the continued need to accelerate the testing of candidate therapeutics while incorporating the viewpoints of patients and their families. Patients and caregivers are providing their perspectives on priorities for treatments and symptom management as well as assessing risks and benefits to guide therapy development. As therapy development proceeds, additional knowledge will be needed regarding the involvement of organ systems beyond skeletal muscle, including the cardiovascular, respiratory/pulmonary, digestive, endocrine, nervous, and skeletal systems. Sleep disorders and sleep concerns among patients warrant attention as well. In addition to the development of novel therapeutics, drugs or biologics approved for treatment of other conditions potentially could be repurposed. Experts who contributed to the revised plan stressed that, in addition to the biomarker research activities noted above, validation of additional

clinical outcome assessment measures and thorough characterizations of disease progression would accelerate progress toward approval of treatments. As more candidate therapeutics move into clinical trials, there is an increasing need for physician-scientists and other clinical researchers capable of contributing to the leadership and conduct of these trials. The updated Action Plan supports the continued training and mentoring of these researchers and clinicians and highlights the need for growth in this critical part of the muscular dystrophy workforce.

**Providing Care, Management, and Access to Services.** Although advances in diagnosis and therapy development are essential, the revised Plan encourages other approaches to reduce the impact of muscular dystrophies. Contributors recommended actions to better assess and address the changing needs of patients, caregivers, families, and communities. Further development of disease-specific quality-of-life measurement tools and strategies to assess the impacts of neuropsychological and neurobehavioral impairments will be important for identifying the effectiveness of interventions. Better understanding of the prevalence and severity of secondary conditions for muscular dystrophy patients can contribute to development of management strategies to improve patients' lives. Advances over the past decade regarding care for patients with childhood-onset dystrophies have led to an increased lifespan for some patients and the growing need for improved strategies for integrating them into all levels of the educational system and the workforce. The revised Action Plan also explains the importance of understanding the diseases' economic impacts, because this knowledge could inform policy decisions and resource allocations.

**Investing in Research Infrastructure and the Workforce.** The new Action Plan describes infrastructure needs for the research and patient care communities, including strategies to facilitate access to biospecimens and animal models, enhance the value of information in patient registries, and organize and support international clinical research networks. Continued training, quality mentoring, and career development for researchers and health-care providers already working in the muscular dystrophies as well as those new to the field are fundamental for achieving the research objectives in the 2015 Plan. The MDCC provides a forum for member organizations to discuss ways to encourage training and career development across the spectrum of biomedical research and social service needs, to support ongoing research in today's funding climate, and to ensure that patients and their families have access to services.

## RECOMMENDATIONS ON THE USE OF THE MDCC ACTION PLAN

The 2015 MDCC Action Plan serves as a compilation of research objectives and other priorities for the overall muscular dystrophy field. The Plan's value lies in its comprehensive scope and the broad range of expertise that contributed to its development. The efforts of all stakeholders in the muscular dystrophies are required to address the objectives and goals described in the Plan. The funding organizations directly represented on the MDCC and other public and private organizations are encouraged to consider this Action Plan when developing their own strategic plans, creating specific initiatives, and making award decisions. The MDCC will continue to collect information from its member organizations about grants and other supported activities relative to the Action Plan and will make this information available to the research and patient communities via the MDCC website.[5] This information will facilitate the analysis of progress toward the Plan's priority areas, while continuing to identify gaps and avoid redundancy. The MDCC encourages researchers to use the 2015 Action Plan to explore opportunities for collaborations outside their immediate discipline or research area. The Plan should be required reading for investigators who are new to the muscular dystrophies so they can better understand how their research fits into the field's current landscape and future directions. In addition, the Plan's range of basic, translational, clinical, and societal objectives should inspire scientists of any discipline to pursue research in the exciting and rapidly advancing field of the muscular dystrophies.

The authors thank the MDCC Action Plan Working Group members and all who provided comments on the document; John D. Porter for leading efforts to develop the action plan; and Alan E. Guttmacher, chair of the MDCC during the revision of the plan.

## REFERENCES

1. Cohn RD, Campbell KP. Molecular basis of muscular dystrophies. Muscle Nerve 2000;23:1456–1471.
2. Kanagawa M, Toda T. The genetic and molecular basis of muscular dystrophy: roles of cell–matrix linkage in the pathogenesis. J Hum Genet 2006;51:915–926.
3. Flanigan KM. The muscular dystrophies. Semin Neurol 2012;32:255–263.
4. Kang PB, Griggs RC. Advances in muscular dystrophies. JAMA Neurol 2015;72:741–742.
5. National Institutes of Health. http://mdcc.nih.gov/. Accessed February 2, 2016.
6. National Institutes of Health. MDCC membership. http://mdcc.nih.gov/membership/mdcc-roster.htm/. Accessed March 16, 2016.
7. U.S. Department of Health and Human Services. Muscular Dystrophy Coordinating Committee. 2005. Action Plan for the Muscular Dystrophies. http://mdcc.nih.gov/action_plan/mdcc-action-Plan-2006.pdf/. Accessed February 2, 2016.
8. U.S. Department of Health and Human Services. Muscular Dystrophy Coordinating Committee. 2015 MDCC Action Plan for the Muscular Dystrophies. http://mdcc.nih.gov/action_plan/index.htm. Accessed February 2, 2016.