DEPARTMENT OF HEALTH AND HUMAN SERVICES

Muscular Dystrophy Coordinating Committee

2015 MDCC Action Plan for the Muscular Dystrophies

Plan developed by:

Muscular Dystrophy Coordinating Committee
Action Plan Working Group
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Approved by:

Muscular Dystrophy Coordinating Committee
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2015 MUSCULAR DYSTROPHY COORDINATING COMMITTEE ROSTER

The 2015 Action Plan for the Muscular Dystrophies was reviewed and discussed by the Muscular Dystrophy Coordinating Committee (MDCC) at its meeting on March 17, 2015. Edits recommended by the MDCC members and from a Request for Information from the public on February 13-March 10, 2015 were incorporated into the final document, which was approved by the committee on November 13, 2015. The 2015 Committee membership roster responsible for approval of the Action Plan includes:

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INTRODUCTION

This 2015 Action Plan for the Muscular Dystrophies has been developed under the auspices of the U.S. interagency Muscular Dystrophy Coordinating Committee. As an outline of the priority needs to improve treatments and reduce the disease burden for all types of muscular dystrophies, it is intended to be a blueprint for the entire muscular dystrophy community. All stakeholders, including academic researchers, companies, government agencies, patient advocacy groups, and patients and their families, have a shared responsibility for meeting the needs described herein, and thereby improving the lives of people living with muscular dystrophy. While the Action Plan includes some objectives for specific types of muscular dystrophies, most objectives address shared needs of the field as a whole. The 2015 MDCC Action Plan for the Muscular Dystrophies has added value in that it can serve as both a starting point and a guide for individual disease communities to tailor strategic plans for their specific types of muscular dystrophy.

The Muscular Dystrophies

The muscular dystrophies are a group of more than 30 genetic diseases characterized by progressive degeneration of skeletal muscles, which includes muscles of respiration. The muscular dystrophies differ in their age of onset, penetrance, severity, and pattern of muscles affected. Many dystrophies also affect other organ systems such as the heart, brain, blood vessels, and gastrointestinal tract. Some forms occur in infancy or childhood, whereas others usually do not appear until middle age or later.

- *Congenital muscular dystrophies (CMD).* The CMDs are a group of muscular dystrophies with different genetic causes that cause weakness at birth. Muscle degeneration can be mild or severe, and may be restricted to skeletal muscle, or paired with effects on the brain and other organs. Several forms of CMD are caused by defects in the interactions of muscle cells with the surrounding protein matrix.

- *Duchenne and Becker muscular dystrophies (DMD, BMD).* DMD is an X-linked recessive disease and is the most common childhood form of muscular dystrophy. DMD usually becomes evident when a child begins walking. Because it is carried on the X chromosome and its effects are masked by the normal gene, it primarily affects males. Women are carriers and may be affected due to patterns of X-inactivation. About 1/3 of cases are spontaneous with no prior family history. Boys who have DMD lack the protein dystrophin, which muscle cells need to function properly. BMD, a less severe disease, typically first manifests around 12 years; some patients have no symptoms until much later in life. BMD is a consequence of dystrophin mutations that do not eliminate protein expression, but instead result in the production of truncated forms of dystrophin that are only partially functional.

- *Facioscapulohumeral muscular dystrophy (FSHD).* FSHD often affects muscles of the face (facio), shoulders (scapulo), and upper arms (humeral), and may affect any skeletal muscle in the body, including the trunk and legs. Symptoms are highly variable, with weakness appearing from infancy to late in life, but typically in the second decade. Disease progression is typically slow and often results in significant impairment; 20% of patients over 50 years of age lose ambulation. FSHD exhibits autosomal-dominant inheritance, and most cases of FSHD1 are associated with deletions of tandem repeats, termed D4Z4, in a distal region of chromosome 4 (4q35). FSHD2 is caused by mutations in SMCHD1.

- *Limb-girdle muscular dystrophies (LGMDs).* LGMDs show a similar distribution of muscle weakness, affecting both upper arms and thighs. Scientists have identified more than 25 forms of LGMDs; they can have a childhood onset, although more often symptoms appear in adolescence or young adulthood. Several forms are due to mutations in a component of the dystrophin-glycoprotein complex or in defects in proteins that associate with the complex. However, many of the LGMDs are due to mutations in genes that have functions unrelated to the dystrophin-glycoprotein complex and in some cases the gene function is not yet known. LGMDs exhibit autosomal dominant (designated LGMD1) or autosomal recessive (LGMD2) inheritance patterns.

- *Myotonic dystrophy (DM).* DM is commonly an adult form of muscular dystrophy, although forms of this disease can affect children, including newborns. It is marked by myotonia (an inability to relax muscles after they contract) and muscle wasting and weakness. DM varies in severity and symptoms. It affects body systems in addition to skeletal muscles which commonly includes symptoms such as day-time sleepiness, gaps in executive function and follow through, central fatigue, and gastrointestinal symptoms. DM type 1 and type 2 are caused by nucleotide repeat expansions in the affected genes, DMPK and CNBP, respectively.

Other forms of muscular dystrophy include oculopharyngeal muscular dystrophy (OPMD), distal muscular dystrophy, and Emery-Dreifuss muscular dystrophy.

Currently, no treatment can stop or reverse the progression of any form of muscular dystrophy. Treatments such as physical therapy, use of appliances for support, corrective orthopedic surgery, and drugs can reduce symptoms and improve quality of life for some individuals. Corticosteroids are often used in DMD for symptomatic treatment, but do not alter the ultimate course of the disease and have undesirable side effects. Therapy development is underway for several forms of muscular dystrophies, and several potential therapies have either moved into clinical trials or are nearing readiness for clinical trials.

The Muscular Dystrophy Coordinating Committee (MDCC)

MDCC Authorization: The Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (MD-CARE Act; P.L. 107-84) authorized the establishment of the MDCC, with members appointed by the Secretary of the Department of Health and Human Services, in order to coordinate activities across the National Institutes of Health (NIH) and with other Federal health programs and activities relevant to the various forms of muscular dystrophy. The MDCC was subsequently re-authorized in the Paul D. Wellstone Muscular Dystrophy Community Assistance, Research and Education Amendments of 2008 and 2014 (MD-CARE Acts of 2008, P.L. 110-361, and 2014, P.L. 113-166), with changes in its composition with each re-authorization.

MDCC Composition: The most recent version of the MDCC Charter, based upon the MD-CARE Act of 2014, stipulates that:

> "...the Committee will consist of not more than 18 members, including the Chair, appointed by the Secretary. Two-thirds of the members will represent governmental agencies, including the directors or their designees of each of the national research institutes involved in research with respect to muscular dystrophy and representatives of all other Federal departments and

agencies whose programs involve health functions or responsibilities relevant to these diseases, including the Centers for Disease Control and Prevention (CDC), the Health Resources and Services Administration (HRSA), the Food and Drug Administration (FDA), the Administration for Community Living (ACL), and representatives of other governmental agencies including the Department of Education (DoEd) and the Social Security Administration (SSA). One-third of the members will represent the public, including a broad cross section of persons affected with muscular dystrophies, including parents or legal guardians, affected individuals, researchers, and clinicians."

Taken together, the new legislation authorizes three additional members (ACL, SSA, and an additional Public Member/Special Government Employee), to be added during 2015—these new members will join those listed in the roster on page 2 of this document.

MDCC Mission: According to the MDCC Charter, the:

"Committee will develop a plan for conducting and supporting research and education on muscular dystrophy through the national research institutes, and will periodically review and revise the plan. The plan will (a) provide for a broad range of research and education activities relating to biomedical, epidemiological, psychosocial, and rehabilitative issues, including studies of the impact of these diseases in rural and underserved communities; (b) identify priorities among the programs and activities of the NIH regarding these diseases; and (c) reflect input from a broad range of scientists, patients, and advocacy groups. In developing this plan, the Committee may evaluate the potential need to enhance the clinical research infrastructure required to test emerging therapies for the various forms of muscular dystrophy by prioritizing achievement of the goals related to this topic."

MDCC Planning Efforts: The MD-CARE Act of 2001 directed the MDCC to develop a plan for conducting and supporting research and education on muscular dystrophy through the national research institutes, and to submit this plan to Congress within the first year of the establishment of the MDCC. This first planning stage led to the Muscular Dystrophy Research and Education Plan for NIH, which was submitted to Congress in August 2004. This initial plan formed the basis for a subsequent, more intensive planning process that produced the 2005 MDCC Action Plan for the Muscular Dystrophies (http://www.ninds.nih.gov/about_ninds/groups/mdcc/MDCC_Action_Plan.pdf), which was approved by the MDCC in December 2005. The 2005 MDCC Action Plan contains specific objectives that are appropriate to the missions of MDCC member agencies and organizations and has served as a central focus for coordination of efforts in muscular dystrophy. The next stage in planning is described in this document, the 2015 MDCC Action Plan for the Muscular Dystrophies.

The Path Forward for the Muscular Dystrophies

In the decade since the development of the 2005 MDCC Action Plan for the Muscular Dystrophies, there has been tremendous progress in several (but not all) areas, including mechanistic understanding of these disorders, development of therapeutic strategies, with multiple candidate therapies progressing to clinical trials, and improvements in clinical management and quality of life for people living with muscular dystrophy. Much of this progress has come about through improved partnering across the advocacy-academic-company-government stakeholders in the field.

There is, as yet, no cure for any type of muscular dystrophy. Moreover, no one party has the resources to produce a novel therapy on their own. As the prospects for efficacious therapies improve for all of

the muscular dystrophies, it is clear that the opportunities and challenges that the field faces are only increasing—issues such as newborn screening, pediatric patients living into adulthood, and reimbursement for very expensive drugs were not on the horizon ten years ago. This is reflected in the 2015 MDCC Action Plan in the form of recommendations for: deeper understanding of disease mechanisms and more careful vetting of therapeutic targets; better aggregation of mutation/polymorphism, patient sample, and genotype-phenotype data to improve diagnostics, to identify people with muscular dystrophy earlier and with more reliability, and to qualify biomarkers; improvement of the efficiency of preclinical and clinical vetting of candidate therapeutics in order to avoid failures in late stages of clinical trials that can be catastrophic to the field; and increasing the efforts and urgency to address the quality of life, education, and employment of people living with muscular dystrophies.

Taken together, the muscular dystrophy landscape is considerably more complex, and adequate solutions to the myriad of problems will require a new, considerably higher level of cooperation among stakeholders in the field, and collaborations with new partners. The 2015 MDCC Action Plan for the Muscular Dystrophies provides a roadmap for those collaborations.

2015 MDCC ACTION PLAN PROCESS

The process for undertaking the 2015 MDCC Action Plan for the Muscular Dystrophies was approved at the August 26, 2013, meeting of the MDCC. Recommendations for experts in basic, translational, and clinical science of the muscular dystrophies were solicited from MDCC membership, and the MDCC Action Plan Working Group was appointed. Participants were selected to ensure that all of the major types of muscular dystrophy were represented, and that there was sufficient expertise relevant to the major Action Plan topics. Thirty-four muscular dystrophy experts participated in the Action Plan Working Groups. Working Groups were formed to evaluate needs in **five topic areas: Mechanisms of Muscular Dystrophy; Diagnosis, Screening, and Biomarkers for Muscular Dystrophy; Preclinical Therapy Development for Muscular Dystrophy; Clinical Therapy Development for Muscular Dystrophy; and Living with Muscular Dystrophy**. Objectives developed by the five Working Groups that addressed **cross-cutting support structure were subsequently compiled into a sixth topical area, Infrastructure for the Muscular Dystrophies**.

The Action Plan Working Groups (see 2015 MDCC Action Plan Process Participants), working in coordination with NIH, CDC, and DMD Research Program (DMDRP)/Department of Defense (DoD) staff (Working Group Liaisons), developed the 2015 MDCC Action Plan for the Muscular Dystrophies. Working Groups evaluated the status of objectives from the 2005 Action Plan, either revising or eliminating them, and developed new objectives to address priority gaps in each topic area. Objectives that were revised or newly developed by each Working Group were presented and vetted at a face-to-face meeting on July 28-29 at the NIH. Participants at this meeting included MDCC members, patient advocacy groups, and individuals living with muscular dystrophy or their family members. NIH staff then consolidated the overall MDCC Action Plan. This included combining similar objectives from the different Working Groups and moving some objectives to a separate Infrastructure for the Muscular Dystrophies section. The assembled 2015 Action Plan then was made available for public comment, prior to discussion at an MDCC meeting in March 2015. Public comments received through a Request for Information were compiled and coded as to the topic area discussed. All attempts were made to incorporate these suggestions into the final version of the 2015 Action Plan.

Comparisons between the 2005 and 2015 Action Plans

To provide historical consistency for the Action Plan process, we compared the structure and individual objectives in the 2005 Plan to the final recommendations for the 2015 Plan. All but a few of the 76 objectives in the 2005 Action Plan have been carried forward, although the topics have evolved due to research advances and better understanding of the problems and obstacles. The overall structure remained largely the same, with the section on Therapy of Muscular Dystrophy in the previous plan being expanded to the two sections on Preclinical Therapy Development and Clinical Therapy Development, since these are the areas of research that have seen the greatest growth over the past ten years. Previous topics in Mechanisms of Muscular Dystrophies that focused on a single disease, such as signal transduction or epigenetic regulation, were expanded to other dystrophies, reflecting advances in understanding of common features of disease pathophysiology. A notable new objective in the Mechanism section is focused on understanding the causes of variation in the course of disease in patients with the same mutations. The Diagnosis and Screening section was expanded with the addition of biomarkers suitable for use in future clinical trials. A previous objective encouraging support for disease-specific registries has evolved to promote cross-communication and strategies for harmonization among registries. Three objectives on optimizing the research use of muscle biopsy material were condensed into one, which corresponds with a shift in the field to focus more on non- or minimally-invasive approaches for patient diagnosis. Objectives on cell and gene therapy and genome editing in the Therapy of Muscular Dystrophy section have been carried over and consolidated in the revised Plan, as some obstacles have been overcome while others have been revealed. The 2015 Plan has an increased emphasis on improving the process of preclinical translation, with new objectives on assay development, effective use of animal models, standardizing outcome measures and exploring combination therapies. The Clinical Therapy Development section expands on the theme of drug repurposing opportunities to address inflammation, fibrosis and other components of the pathology of muscular dystrophies. This section also carries over and further emphasizes the need for studies on the systemic consequences of the muscular dystrophies including effects on the skeleton, nervous, endocrine, digestive, cardiovascular and pulmonary systems. The topic of cardiopulmonary consequences of the dystrophies has been reinforced and separated into cardiac and respiratory/pulmonary, with new emphasis on sleep-related breathing disorders. In the section on Living with Muscular Dystrophy, several objectives were carried over from the previous Plan for continuing to advance understanding of the determinants of patient quality of life and disease burden, and additional research on secondary conditions. Objectives were also carried over and reinforced on the integration of people living with muscular dystrophies into the education system and strategies for improving vocational outcomes. A new objective emphasizes the need for additional studies to measure the economic impact of the dystrophies on patients, families and society. An objective from the original Plan for establishing educational conferences for patients and families was dropped from the 2015 plan, since this has largely been accomplished by advocacy groups and clinicians working together with the patient communities. The Infrastructure section underwent the most change, with several objectives eliminated and new objectives added. Several objectives from the 2005 plan on quality of life, rehabilitation and educational assessment moved to the Living with Muscular Dystrophy section of the 2015 plan. Dropped were Infrastructure objectives on publicizing available research resources and training opportunities, and establishing a conference series to promote international communication. The breadth and quality of communications within the dystrophy communities has significantly advanced since 2005 and the Working Group participants did not consider it necessary to further emphasize these activities. There is significant emphasis on infrastructure for clinical trial readiness in the 2015 Plan, including clinical research networks, registries, facilitating international trials and training

the next generation of researchers. Overall, few of the objectives of the 2005 Action Plan can be considered completed. This is due to the ambitious nature of the objectives identified by the Working Groups, which will require decades of effort to overcome. Advances in understanding disease mechanism, development of many innovative candidate therapeutics and the early advances in clinical trials have all uncovered some new challenges. The efforts of all of the organizations that participate in the MDCC will be required to address the objectives and goals described in this Plan.

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SUMMARY LISTING OF OBJECTIVES

Mechanisms of Muscular Dystrophy

Mechanisms of disease common to several types of muscular dystrophy:

1. Define the disease mechanisms associated with disorders caused by defects in extracellular matrix (ECM)-membrane-cytoskeletal adhesion and signaling

2. Elucidate the triggers and mechanisms of abnormal cellular physiology, including apoptosis, necroptosis, oxidative- and endoplasmic reticulum-associated stresses, in the muscular dystrophies

3. Evaluate the interactions among calcium homeostasis, excitation-contraction coupling, and muscular dystrophy pathogenesis

4. Define the biochemical mechanisms involved in sarcolemmal membrane repair

5. Define the roles of different cell types in the pathophysiology of the muscular dystrophies and their influences on one another in normal and failed muscle regeneration

6. Define the pathogenic roles of immune responses to muscle and muscle inflammation in various muscular dystrophies

7. Understand the impact of newly created or abnormally expressed proteins on cellular functions and lymphocyte responses

8. Better characterize the effects of muscular dystrophy-associated genetic mutations, and epigenetic dysregulation, both directly on the nervous system and indirectly as a consequence of lost muscle function

9. Determine the causes of variation in age of onset and phenotypic severity of skeletal muscle, heart, and central nervous system symptoms across diseases and among individuals with the same mutations

10. Identify and characterize gene mutations or epigenetic dysregulations associated with understudied forms of muscular dystrophy

Mechanisms relating to specific types of muscular dystrophy:

11. Define the mechanisms by which unstable genetic repeats and abnormalities in protein and RNA expression and function lead to brain, muscle, and other tissue phenotypes in DM and develop therapeutic strategies to block these effects

12. Further define the molecular pathogenic mechanisms of FSHD, and establish animal and cellular models for testing hypotheses regarding these mechanisms and for the development of interventions

13. Further define the disease mechanism of Emery-Dreifuss and other laminopathy muscular dystrophies

14. Define the molecular pathways by which mutant PABPN1 causes oculopharyngeal muscular dystrophy (OPMD)

15. Define pathogenic mechanisms underlying CMDs due to abnormalities in dystroglycan and its processing (dystroglycanopathies)

Diagnosis, Screening, and Biomarkers for Muscular Dystrophy

Technology and other resources for diagnostic testing:

1. Develop definitive tests for muscular dystrophies for which genetic testing is not yet available

2. Develop minimally invasive diagnostic techniques for muscular dystrophies

3. Establish the specificity and sensitivity of diagnostic tests for the muscular dystrophies

4. Advance knowledge of genotype/phenotype correlations and implement this knowledge in patient care.

5. Establish mechanisms for muscular dystrophy patients to obtain accurate genetic counseling

Data sharing/optimal use of information and materials:

6. Encourage submission of new mutation and polymorphism data for muscular dystrophy genes to public databases

7. Further optimize utilization of muscle biopsy materials for diagnostics and research

8. Support a web-based, non-commercial resource to assist the clinician with identifying and choosing a diagnostic approach for muscular dystrophies

Population screening for muscular dystrophy:

9. Establish current and accurate incidence and prevalence data for genetically confirmed forms of diagnosed muscular dystrophy

10. Develop methods for newborn screening of the muscular dystrophies; explore the social and ethical issues involved in offering neonatal screening for muscular dystrophy and develop techniques that would make screening practical

11. Establish and implement guidelines for screening family members and potential carriers of muscular dystrophies and provide appropriate clinical care and counseling

Development of biomarkers:

12. Develop and validate the role of muscle imaging in diagnostic evaluation of the muscular dystrophies, or as a biomarker or endpoint measure for clinical trials

13. Foster the development of prognostic, predictive, pharmacodynamic, and efficacy-response molecular/biochemical biomarkers to facilitate design, conduct and decision making in clinical trials in muscular dystrophy; establish data in support of FDA biomarker qualification

Preclinical Therapy Development for the Muscular Dystrophies

Modulation of muscle biology:

1. Identify mechanisms of positive and negative regulators of muscle growth and repair and establish their potential as therapeutics through preclinical testing in animal models of various types of muscular dystrophy

2. Examine the efficacy of existing drugs for targets downstream of the primary genetic lesion in the pathogenesis of muscular dystrophy

Cell and gene therapy/editing:

3. Overcome barriers to muscle stem cell transplantation

4. Improve the efficiency and efficacy of gene therapy delivery in the muscular dystrophies, while minimizing the immune response to both gene product and delivery vehicle

5. Evaluate the safety and efficacy of agents that promote stop codon read-through or exon skipping using cell or animal models of muscular dystrophy

6. Develop novel agents to improve efficacy of current gene repair strategies or to facilitate new strategies

7. Evaluate the safety and efficacy of targeted gene silencing as a therapeutic strategy for muscular dystrophy

Improving the process of therapy development:

8. Identify new strategies to implement translational research projects for muscular dystrophy

9. Facilitate research (discovery, validation, and dissemination) of the biochemical pathways involved in muscular dystrophy

10. Encourage the development of target-directed and phenotypic assays suitable for screening or validation of compounds to identify therapeutic candidates for the muscular dystrophies

11. Develop the animal models, assays, and tools necessary for preclinical translational research projects that focus upon rapidly moving the accumulated mechanistic knowledge into clinical trials

12. Establish standardized endpoints for preclinical trials in mouse and dog models, and ensure that facilities are available that enable testing of drugs and other therapeutic approaches

13. Develop preclinical strategies for selecting, testing and prioritizing combination therapies.

Clinical Therapy Development for the Muscular Dystrophies

Optimizing available therapies:

1. Optimize the use of corticosteroids as a treatment for DMD

2. Determine the mechanism of action of the corticosteroids in muscular dystrophy in order to develop new, potentially more efficacious agents

3. Examine the efficacy of existing immune-modulating and anti-fibrotic drugs for treatment of muscular dystrophy

4. Evaluate the efficacy of existing therapies for myotonic dystrophy symptoms affecting disease burden.

Cell and gene therapy/editing:

5. Improve the efficiency of gene therapy delivery in the muscular dystrophies, while minimizing the immune response to both gene product and delivery vehicle, in patients

6. Evaluate the safety and efficacy of gene repair, stop codon readthrough, upregulation of compensating genes and exon skipping agents through additional translational studies and clinical trials

Improving the processes and resources for patient care:

7. Improve treatment for systemic consequences in muscular dystrophy patients: developing guidelines based on evidence and/or current practice standard of care and continually updating guidelines for multi-disciplinary aspects of these diseases

8. Improve treatment for cardiac consequences in muscular dystrophy patients: establishing evidence for use of FDA-approved agents and advancing new and more targeted therapies to treat the hearts of dystrophy patients.

9. Improve treatment for respiratory and pulmonary consequences of muscular dystrophies and address sleep disturbances.

10. Monitor, coordinate, and communicate the rehabilitation and educational assessment activities of the various Federal agencies, voluntary, and patient advocacy groups to identify clinical research needs and improve clinical outcomes

Improving the process of therapy development:

11. Evaluate the endpoints needed for clinical trials in the muscular dystrophies

12. Improve understanding of disease burden, quality of life, cognitive, and central nervous system function for the muscular dystrophies through continued development and use of standardized instruments.

13. Better establish readiness for clinical trials in all types of muscular dystrophy and initiate clinical trials in rare muscular dystrophies

14. Be rigorous and systematic about the de-risking process of drugs and biologics that are advanced into clinical trials

Living with Muscular Dystrophy

Quality of life and burden of disease measures:

1. Identify and evaluate the quality of life and burden of disease measurement tools that are currently available

2. Develop disease-specific quality of life and burden of disease measures where gaps in existing measures are found

3. Assess the cognitive, neuropsychological, and neurobehavioral profiles that most impact quality of life of people living with various forms of muscular dystrophy and identify interventions and supports to positively impact quality of life

4. Advance research into reproductive health issues in the muscular dystrophies

5. Conduct studies to determine the economic impact of the muscular dystrophies on patients, families and society.

Prioritizing and facilitating clinical trials:

6. Determine the sensitivity of clinical endpoints to changes in disease severity and the magnitude of changes in endpoints which are clinically meaningful to patients and family members

7. Develop standardized data collection approaches nationally using clinically meaningful, readily obtainable parameters; develop a minimum data set for national data gathering efforts; complete and maintain common data elements (CDEs) for muscular dystrophies across life span

8. Determine the benefits and risks of varied exercise approaches in the muscular dystrophies and develop scientifically based recommendations concerning optimal exercise, physical activity, and recreation; examine nutrition both in relationship to exercise, and as an independent variable in improving the lives of those living with muscular dystrophy

9. Assess the prevalence of secondary conditions in muscular dystrophy using existing longitudinal data collection efforts; assess the effectiveness of clinical management approaches to prevent and treat secondary conditions

10. Newborn screening and infant identification: a need for a national outreach, care, information, and support delivery model

Lifestyle, education, and employment issues:

11. Using novel partnerships and research approaches, identify strategies to improve patient integration into educational systems and employment

12. Empowering autonomy, independent living, and employment through exploration of alternate resource models for men and women living with muscular dystrophy

13. Address mental health needs and opportunities for improving social connectedness throughout the life-span of individuals and their family members

14. Create a national formalized assessment of vocational outcomes for adults transitioning from terminal education and training to workplace as a basis to identify strategies to improve vocational outcomes

15. Educate and empower people with muscular dystrophy in self-management strategies and educate their family members and primary care providers to promote and reinforce these strategies.

Infrastructure for the Muscular Dystrophies

Facilitating mechanistic and preclinical studies:

1. Establish additional mouse and other large animal models to facilitate advances in understanding disease mechanisms, to develop candidate therapeutics, and to identify and characterize disease modifying genes

2. Establish invertebrate, other vertebrate, and alternative model systems to study pathogenetic mechanisms of gene/RNA/protein defects that cause muscular dystrophies in humans

3. Facilitate studies of human disease mechanisms and the translation of discoveries of pathogenic mechanism from animal models to humans by increasing the availability of well characterized, high quality tissues/cells/serum and clinical data from muscular dystrophy patients

4. Define the most efficient mechanisms to generate skeletal and cardiac muscle stem cells, as well as other relevant cell types, from embryonic and induced pluripotent cells; create iPS and ES cell lines from all the different forms of muscular dystrophy

5. Create a mechanism to maintain mouse models of muscular dystrophy at approved vendors in a live or cryopreserved state, available for easy and rapid importation into academic colonies

Facilitate clinical trial readiness:

6. Explore the benefits of harmonization of the existing clinical trial networks that conduct research on the muscular dystrophies

7. Support and foster cross-communication among neuromuscular registries and consider strategies to harmonize registries across neuromuscular disorders

8. Address the issues of setting up multinational trials especially in the academic arena relating to trial set up and administrative burden

9. Prioritize the development of therapies that may be applicable across the various types of muscular dystrophy

10. Continue to provide high quality mentoring and support for training and career development for researchers new to the muscular dystrophies and throughout their careers.

11. Develop and propose revised International Classification of Disease (ICD) codes for the muscular dystrophies

MECHANISMS OF MUSCULAR DYSTROPHY

The Mechanisms of Muscular Dystrophy Working Group focused on gaps in knowledge about the cellular, biochemical, and molecular mechanisms underlying the muscular dystrophies. It is important to note that although several potential therapies for some muscular dystrophies are on the horizon, there is still much that we do not understand about the pathological mechanisms underlying all of the muscular dystrophies. Elucidating these mechanisms for specific types of dystrophies could contribute to our understanding across many other forms of dystrophy and perhaps other neuromuscular diseases. A continued investment in the basic and fundamental understanding of these processes is critical for the identification and validation of new therapeutic targets. Without it, important drug targets may be missed and/or poor choices of drug development targets could be made that are destined to fail. The following objectives address barriers to disease characterization, therapeutic development, and patient care as we understand them currently.

Mechanisms of disease common to several types of muscular dystrophy:

1. **Define the disease mechanisms associated with disorders caused by defects in extracellular matrix (ECM)-membrane-cytoskeletal adhesion and signaling**

   Muscular dystrophies can arise from mutations in genes coding for proteins that impact the structural connections and signaling from the ECM, through the muscle cell membrane, to the cytoskeleton. These dystrophies arise from loss of function mutations in 3 main categories of genes: (1) genes encoding the cytoskeleton- and membrane-associated dystrophin-glycoprotein complex (e.g., dystrophin, sarcoglycans, dystroglycans), (2) genes encoding proteins that glycosylate alpha-dystroglycan and affect interaction with laminin (e.g., FKRP, LARGE, fukutin, POMGnT1, POMT1, ISPD, B3GALNT2, GDP mannose phosphorylase B, DPM1), and (3) genes encoding proteins in the basement membrane that interact with the extracellular side of the sarcolemma (e.g., collagen VI and laminin). Because the normal functions of the dystrophin-glycoprotein complex and its interactions with other proteins are not fully understood, studies of the basic biology of this complex will complement studies of the effects of genetic mutations that cause muscular dystrophies.

   The cytoskeleton is also associated with components of the nuclear envelope and nuclear skeleton. Research objectives related to the muscular dystrophies that are caused by defects in nuclear components are discussed below.

   The loss of the ECM-membrane-cytoskeleton link may cause dystrophic changes in muscle directly due to weakened connections, or due to defects in signal transduction that is associated with these structures. Additional studies are needed to enhance understanding of the role of the dystrophin-glycoprotein complex in maintaining membrane stability and of how defects in this complex lead to abnormal signaling, calcium entry, and muscle degeneration. For example, the loss of neuronal Nitric Oxide Synthase (nNOS) from the dystrophin-glycoprotein complex results in defects in signaling from the muscle to neighboring blood vessels. However, the impact of loss of NO signaling on pathogenic progression is not clearly delineated. Progress in therapy development can be accelerated by a better understanding of how nNOS impacts dystrophic pathology. Several areas have been explored, including inflammation, vasodilation, and satellite cell function, but it is still unclear whether disruption of any of these NOS-mediated

events impact pathogenesis. It will be important to understand this area, in light of the fact that the truncated dystrophins generated through at least two therapeutic strategies, exon skipping and gene therapy, will often omit the NOS binding site.

ECM-membrane-cytoskeletal links in muscle cells may have other important signaling roles that have been incompletely explored. Various pathways may converge on a smaller set of downstream targets. The mechanisms by which disrupted muscle cell adhesion to the ECM leads to apoptosis and altered mitochondrial function need to be more thoroughly characterized. Efforts directed toward defining the downstream signaling pathways controlled by components of the dystrophin-glycoprotein complex, other matrix receptors, and signaling complexes involved in other muscular dystrophies should identify commonalities in these pathways and downstream targets. Such knowledge may be especially valuable in identifying therapeutic approaches that can be applied to different types of muscular dystrophies.

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2. Elucidate the triggers and mechanisms of abnormal cellular physiology, including apoptosis, necroptosis, oxidative- and endoplasmic reticulum-associated stresses, in the muscular dystrophies

The pathology of several dystrophies includes changes in muscle cell physiology due to defects in membrane-ECM interactions, ion gradients, or the turnover of proteins and organelles. Further characterization of these physiological processes may lead to novel biomarkers and additional candidate therapeutics. Apoptosis has been identified as a secondary disease mechanism in several muscular dystrophies, including DMD, sarcoglycanopathies, some types of CMD (e.g., MDC1A and Ulrich's CMD), and FSHD. Interventions designed to reduce/diminish apoptosis have led to improved histopathology, improved force generation and prolonged survival in animal models. Pathways of the ubiquitin-proteasome system, autophagy, apoptosis and necroptosis are interwoven, and additional studies are needed to determine not only their individual roles in different muscular dystrophies, but also their interplay amongst all of the muscular dystrophies. Oxidative stress, endoplasmic reticulum (ER) stress or defects in cell adhesion signaling may be triggers for regulated cell death in some muscular dystrophies. There are needs for further preclinical and clinical testing of candidate therapeutics that address abnormal apoptosis or necroptosis.

Identification of the disease mechanisms leading to oxidative or ER stress and targets for restoring normal activity in the ubiquitin-proteasome system and autophagy pathways is also important. Further understanding of signaling associated with cell adhesion, the dystrophin-glycoprotein complex, the cytoskeleton and the nucleus, which is the focus of other research objectives in this section, would contribute to an understanding of the causes and mechanisms of altered cellular physiology associated with the muscular dystrophies.

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3. Evaluate the interactions among calcium homeostasis, excitation-contraction coupling, and muscular dystrophy pathogenesis

Muscle calcium levels are tightly regulated in order to maintain a key calcium gradient between the sarcoplasm and sarcoplasmic reticulum (SR), the major muscle calcium reservoir. One primary role for calcium in the muscle is during excitation-contraction coupling, where release

of calcium from the triad (a muscle fiber component that consists of the transverse-tubule and a pair of terminal cisternae of the sarcoplasmic reticulum), and specifically from the ryanodine receptor into the sarcoplasm, initiates cycling of the actin-myosin cross bridge and generates muscle contraction. Altered calcium homeostasis can have several consequences for the muscle fiber. Inappropriate sarcoplasmic calcium levels can alter excitation-contraction coupling and can lead to excessive oxidative stress or other toxic responses.

The relationship between calcium homeostasis, excitation-contraction coupling and muscular dystrophy is an emerging area of research. There is evidence that the loss of membrane integrity associated with several muscular dystrophies results in inappropriate changes in sarcoplasmic calcium levels, which, in turn, has toxic downstream consequences, including oxidative stress, apoptosis, and autophagy. There is also evidence that muscular dystrophies can directly affect the triad. For instance, in dystrophinopathies and sarcoglycanopathies there is preclinical evidence that the ryanodine receptor is hypernitrosylated, leading to chronic sarcoplasmic reticulum calcium leak, which impairs excitation-contraction coupling and causes toxic accumulation of cytoplasmic calcium. Also, several muscular dystrophy-associated proteins (dysferlin, caveolin-3, dystrophin, and calpain-3) have been found to be components of the triad. The exact role of these proteins at the transverse-tubule, however, is still unclear. Finally, in DM1 there is mis-splicing of key components of the excitation-contraction coupling machinery (including BIN1, RYR1, and DHPR), and this is hypothesized to lead to impaired excitation-contraction coupling and to be responsible in part for altered force generation in this condition.

Abnormalities in calcium homeostasis are a ripe subject for therapy development. Overexpression of SERCA, the enzyme responsible for bringing calcium back into the SR from the sarcoplasm, improves the dystrophic phenotype of both mdx and sarcoglycan deficient mice. Treatments with RyCals, drugs that reduce ryanodine receptor type 1 leakiness, improve muscular dystrophy pathology in the same models. Lastly, genetic approaches or drugs that target oxidative stress seem to improve preclinical model phenotypes.

Key future directions related to this area of study include establishing more firmly the mechanistic link between specific gene mutations and alterations in calcium homeostasis and/or triad structure and function. Also, it is important to understand if different muscular dystrophies are affecting the excitation-contraction coupling machinery differently, as treatment approaches can be tailored based on what aspect of calcium homeostasis is affected.

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4. Define the biochemical mechanisms involved in sarcolemmal membrane repair

Membrane repair is necessary to maintain muscle health, and defects in membrane repair negatively impact muscle maintenance and regeneration. Membrane resealing is a dynamic process, regulated by calcium signaling and involving vesicle transport and protein complexes including dysferlin, calpains 1 and 2, annexins, synaptotagmin, Trim72 (MG53), and caveolin 3.

A subset of muscular dystrophies involves gene defects, namely in the genes for dysferlin or caveolin 3, that lead to delayed or incomplete muscle membrane repair. Dysferlin deficiency leads to autosomal recessive LGMD type 2B (LGMD2B/Myoshi myopathy or dysferlinopathy) while caveolin 3 mutations lead to autosomal dominant LGMD1C as well as three other myopathies (hyperCKemia, distal myopathy, and rippling muscle disease). Studies have directly

demonstrated that membrane repair mechanisms are compromised in muscle lacking dysferlin. Mutations in caveolin 3 that disrupt interactions with dysferlin and MG53 can disturb the repair process in vitro.

Defects in membrane repair can set off a variety of downstream disease mechanisms, including increased intracellular calcium and the abnormal accumulation of muscle cell components in the extracellular space leading to activation of a strong inflammatory response.

Progress has been made in identifying key components and events in muscle membrane repair, but additional studies are needed to fully define the normal and disease associated mechanisms of skeletal muscle repair. Further characterization of the protein-protein and protein-phospholipid interactions, as well as the physiological and biophysical effects of gene mutations, will facilitate the identification of potential therapeutic targets.

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5. **Define the roles of different cell types in the pathophysiology of the muscular dystrophies and their influences on one another in normal and failed muscle regeneration**

Skeletal muscle is composed of fibroblasts, endothelial cells, adipocytes, fibro-adipogenic progenitor cells, cells of the immune system, and Schwann cells and neurites, in addition to muscle fibers and satellite cells. Many of the pathological features of muscular dystrophies arise or may arise from disturbances in the normal interactions and communications among the various cell types (including within muscle types like skeletal and cardiac), in addition to the cell-autonomous effects of gene mutations or epigenetic dysregulations.

Various cell types work in concert during muscle regeneration in response to injury or disease. Some CMDs are caused by defects in extracellular matrix, secreted by fibroblasts, which result in abnormal adhesion and signaling in muscle cells. Factors secreted by macrophages promote tissue fibrosis in various muscular dystrophies, and eosinophils regulate the fate of fibro-adipogenic progenitor cells. The failure of muscle regeneration to keep pace with the loss of muscle fibers in the muscular dystrophies may reflect limitations in the proliferation and maintenance of the satellite cell pool or defects in their activation, migration, differentiation or fusion with existing fibers – all influenced by other muscle cell types. Better understanding of the normal interaction and communications of different cell types in muscle and the changes in these activities in dystrophic muscle may lead to novel treatment strategies.

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6. **Define the pathogenic roles of immune responses to muscle and muscle inflammation in various muscular dystrophies**

Emerging data support a role for inflammation in the downstream pathogenesis of at least some of the muscular dystrophies. In other forms of muscular dystrophy, primary immune responses, such as muscle-specific lymphocyte responses, may be direct contributors to the pathophysiology. Further advances in this field will require the identification of the specific immune effectors that contribute to pathogenesis and the characterization and verification of specific therapeutic targets.

The persistent inflammatory milieu of dystrophic muscle due to degeneration and failed regeneration elevates the levels of numerous immune cell-derived cytokines and chemokines. Among these, the cytokine TGF-beta is strongly associated with muscle fibrosis in dystrophinopathies. Furthermore, variations in genes encoding modulators of TGF-beta activity (LTBP4 and osteopontin) are disease modifiers for dystrophinopathies, which demonstrates the importance of immune cells and their secreted factors in disease progression. In other forms of muscular dystrophy, such as FSHD, pathogenic mechanisms may also involve the interactions of infiltrating lymphocytes with muscle cells. The presence of immune cells in muscle and inflammation is also important for normal muscle repair and immune surveillance. Therefore, targets for treating muscular dystrophy-associated inflammation and immune responses must be chosen carefully. Identification of optimal targets is complicated by the dual roles played by many of these mediators.

High priority research topics in this area include the identification and thorough characterization of specific immune cell populations invading dystrophic muscle during disease progression and in response to candidate therapeutic interventions. Achieving this goal may require improved methods to isolate and evaluate immune cells in muscle. There is a need for further characterization of the cytokine profiles in the different types of muscular dystrophy and the effects of these cytokines on cell processes such as extracellular matrix production by fibroblasts or cell fate determination of progenitor cells. Potential immune modulators should be evaluated in long-term in vivo studies, and in parallel with studies of muscle fibrosis and regeneration to reveal any potential adverse effects or induced autoimmunity.

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7. Understand the impact of newly created or abnormally expressed proteins on cellular functions and lymphocyte responses

The disease-causing muscular dystrophy mutations themselves and corresponding therapies can result in the generation of proteins that are not normally found in nature or are expressed at an abnormal time or place. The impact of these new protein species on normal cellular and tissue functions, as well as the immune response to these abnormally expressed proteins, has not been fully explored. For example, the germline transcription factor, DUX4, is mis-expressed in FSHD muscle. Its presence abnormally activates transcripts in adult skeletal muscle, including cancer testis antigens, which may elicit an immune response. Several lines of evidence suggest an active involvement of these antigens in the disease mechanism of FSHD.

Studies are needed to further characterize the repertoire of proteins abnormally expressed in dystrophic muscle and other tissues, and the impact of these proteins on normal physiologic function and lymphocyte activity. Examples include:

- In-frame, deleted dystrophins (created by exon skipping and microdystrophins) and their impact on sarcolemmal stability, calcium channel and microtubule function and signaling roles of the dystrophin-glycoprotein complex.
- Abnormally expressed gene products as a result of repeat expansion and disrupted splicing activity in DM.
- DUX4 and abnormally expressed gene products that are downstream targets of this transcription factor in FSHD.

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8. **Better characterize the effects of muscular dystrophy-associated genetic mutations, and epigenetic dysregulation, both directly on the nervous system and indirectly as a consequence of lost muscle function**

   Muscular dystrophies are associated with central nervous system changes, including brain structural abnormalities, peripheral nerve and neuromuscular junction defects, as well as functional deficiencies in cognition and behavior. These can be a combination of direct effects of gene mutations or epigenetic dysregulation in the nervous system, or secondary effects due to altered systemic metabolism (e.g., myokine production, glucose or oxygen uptake) or disrupted communications between dystrophic muscle and the nervous system. Alterations in the extracellular matrix of dystrophic muscle may affect the neuromuscular junctions and Schwann cells. Reduced muscle strength and altered muscle proprioception also may lead to changes in the brain due to altered sensory input or compensatory motor control. Additional studies are needed to understand the involvement of the central and peripheral nervous systems in the muscular dystrophies. Treatments that target only muscle may be insufficient to restore patient function and quality of life without also addressing nervous system symptoms. Therefore, characterizing nervous system abnormalities and distinguishing primary and secondary effects of the muscular dystrophies may open new directions for therapy development.

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9. **Determine the causes of variation in age of onset and phenotypic severity of skeletal muscle, heart, and central nervous system symptoms across diseases and among individuals with the same mutations**

   Muscular dystrophies comprise a heterogeneous group of genetic diseases often characterized by multi-systemic effects and distinct patterns of muscle involvement. While a characteristic pattern of muscle weakness has traditionally been used to define the different subtypes of muscular dystrophy, the cause for the regional distribution of muscle weakness, often with sparing of specific muscle groups, has largely remained unresolved. Moreover, many muscular dystrophies show noticeable variation in disease onset and progression, both between as well as within families.

   Involvement of the diaphragm and muscles of respiration often proceeds at a rate different from other striated muscles. Loss of diaphragm function and impaired respiration is a leading driver of morbidity and mortality in the muscle diseases, and therefore requires additional study in all of the muscular dystrophies.

   Studies in mice and humans have provided some evidence for genetic modifiers of disease onset, presentation and progression, but a comprehensive explanation for the observed differences in muscle, heart and brain involvement and disease progression is currently lacking. Disease penetrance may be affected by genetic background or gene-environment interactions. Future studies on the identification and validation of such factors, both genetic and non-genetic (off target effects of drugs, diet, exercise, other health factors, lifestyle, etc.), may provide insight into strategies that delay disease onset, prevent off-target effects of drugs and improve quality of life.

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10. **Identify and characterize gene mutations or epigenetic dysregulations associated with understudied forms of muscular dystrophy**

    The discovery of causative genetic or epigenetic factors would facilitate research into the pathogenic mechanisms of many understudied muscular dystrophies. For example, only about 40 percent of LGMD cases show linkage to a known disease gene. Similarly, some patients with Emery-Dreifuss muscular dystrophy-like phenotypes do not have mutations in the known causative genes. These data support the importance of linkage analysis, positional cloning efforts, candidate gene approaches, and chromatin modification and non-coding RNA expression studies to identify novel muscular dystrophy genes or epigenetic dysregulations associated with these conditions. Classical gene identification methods can be complemented by whole exome sequencing of affected individuals and family members, which could lead to the identification of many rare variants that may only be present in a few affected people. Care must be taken to discern actual disease-causing mutations from non-pathogenic polymorphisms when there are only anecdotal cases or small series of patients, especially when clear segregation of the mutation and the disease is not observed in several families. These genomic and epigenomic analyses should be conducted as international collaborations to speed verification of findings and applicability to various subpopulations. Importantly, the functional consequences of putative rare muscular dystrophy-causing mutations or epigenetic changes must be studied in cellular and animal models to confirm pathogenicity and decipher pathogenic mechanisms.

Mechanisms relating to specific types of muscular dystrophy:

11. **Define the mechanisms by which unstable genetic repeats and abnormalities in protein and RNA expression and function lead to brain, gastrointestinal, muscle, and other tissue phenotypes in DM and develop therapeutic strategies to block these effects**

    The roles of RNA processing abnormalities, bidirectional transcription, and repeat associated non-ATG (RAN) translation in DM as they relate to abnormalities of skeletal muscle, the brain (cognitive impairment, hypersomnolence, effects of personality and behavior), endocrine/other systems (frontal balding, hypogammaglobulinemia), the visual system (cataracts), the gastrointestinal tract, cardiac muscle, and the skeleton (talipes) should be clarified. Understanding the contribution of repeat instability in disease and the roles of DNA mismatch repair, recombination, and replication in repeat expansion is also relevant to dissecting the mechanisms of DM. Diverse therapeutic strategies to prevent or reverse the impact of RNA, protein and repeat instability mechanisms are needed.

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12. **Further define the molecular pathogenic mechanisms of FSHD, and establish animal and cellular models for testing hypotheses regarding these mechanisms and for the development of interventions**

    There have been significant advances in recent years in understanding the genetic, epigenetic, and molecular disease mechanisms of FSHD. There is strong evidence that FSHD is caused by incomplete repeat-mediated epigenetic repression of DUX4 located in the D4Z4 repeat array. In FSHD1, this is caused by contraction to an array of 1-10 units; in FSHD2, the majority of cases are

due to mutations in SMCHD1. FSHD requires a specific background of chromosome 4 (4A but not 4B) that contains a polymorphic DUX4 polyadenylation signal. Contractions on chromosomes that do not have a DUX4 polyadenylation signal do not cause FSHD. The changes in D4Z4 chromatin structure in FSHD are partly identified. Follow-up studies should further identify the genetic and epigenetic requirements of FSHD, including additional FSHD2 disease genes, as well as other epigenetic modifiers of D4Z4 in somatic cells (whether proteins or RNA molecules or their modifications), and the role of other genetic variants that consistently differ between 4A and 4B alleles that might affect the D4Z4 chromatin structure or D4Z4 RNA processing. DUX4 is a germline transcription factor normally silenced in somatic tissue. Ectopic expression of DUX4 in skeletal muscle triggers the expression of a plethora of coding and non-coding RNAs, including those involved in germline biology and early development, as well as the immune system. How these altered expression patterns lead to muscle pathology should be further investigated.

There is a strong need for generating, characterizing, and distributing cellular and animal models. Models of FSHD can facilitate further study of the pathogenic pathways and can accelerate the development and testing of evidence-based therapeutic strategies to either prevent the onset or reverse symptoms. The FSHD disease mechanisms are unique among the muscular dystrophies, and the generation of model systems is challenging because of these unique mechanisms and the hominoid-specific features of the FSHD locus. Nevertheless, gene-specific models may be useful for the study of clinical phenotypes; xenotransplantation models may overcome some of the hominoid-specific features of the disease; and genomic models may facilitate study of the epigenetic and other features of the disease.

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13. Further define the disease mechanism of Emery-Dreifuss and other laminopathy muscular dystrophies

Laminopathies are a broad range of diseases caused by mutations in the genes encoding lamin A/C and other nuclear envelope proteins. While the encoded proteins are expressed in most somatic cells, mutations can cause tissue-selective diseases, often affecting striated muscle in the form of muscular dystrophy and cardiomyopathy. While advances have been made in the genetics of these disorders, progress has been limited in deciphering pathogenic mechanisms, which could lead to the development of specific treatments. Much of the basic biology of these disorders remains undiscovered. There is a need to define the multiple divergent effects that single mutations in genes encoding nuclear envelope proteins exert on different tissues and how these mutations trigger detrimental effects. Elucidation of the three-dimensional structures and structure-function relationships of nuclear envelope proteins, particularly those altered in human diseases, will aid in the understanding of pathogenic mechanisms. Likewise, high-resolution imaging studies of nuclei and nuclear migration in cells with lamin A/C and other nuclear envelope protein alterations during development and in response to mechanical or oxidative stress may provide critical insights. It will also be important to determine the downstream cellular responses that are caused by mutations in the genes encoding lamins A/C and other nuclear envelope proteins. Connections between the nuclear envelope and the cytoskeleton are important for conveying signals to the nucleus that originate from the ECM or neighboring cells. Nuclear envelope proteins also participate in other intracellular signaling pathways. Studies in mouse models of Emery-Dreifuss muscular dystrophy have already demonstrated that restoring normal signaling can improve function and prolong survival. This knowledge can provide justification for future clinical trials. Finally, statistically meaningful,

exploratory studies of alterations in the transcriptome, proteome and protein interactome of various cell types and tissues from animal models and people with mutations in lamin A/C and other nuclear envelope genes could help identify pathogenic mechanisms not yet uncovered by other approaches.

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14. Define the molecular pathways by which mutant PABPN1 causes oculopharyngeal muscular dystrophy (OPMD)

OPMD is caused by a small polyalanine expansion in the ubiquitously expressed nuclear protein PABPN1, which plays key roles in post-transcriptional regulation of gene expression. Critical questions that need to be answered in order to understand the disease mechanisms of OPMD include, "Why does a mutation in a ubiquitously expressed protein lead to a muscle-specific disease?", "Why is a specific subset of muscles affected in OPMD?", "What are the cellular and molecular events that trigger myofiber death and atrophy in OPMD?" and "Why is OPMD a late-onset disease?" Studies of the regulation of PABPN1 levels and its RNA and protein interactions in skeletal muscle are needed to answer these questions. Furthermore, comparisons of the expression and function of PABPN1 in craniofacial and other muscles, in young and old patients or animal models, may be necessary for understanding the late-onset pathology in specific muscles. Animal models are needed to help determine whether OPMD results from gain or loss of function, or both, and such models could also contribute to biomarker identification and therapy development.

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15. Define pathogenic mechanisms underlying CMDs due to abnormalities in dystroglycan and its processing (dystroglycanopathies)

The dystroglycanopathies are an expanding group of CMD and LGMD caused by a mutation in the dystroglycan gene or (more commonly) secondary abnormalities in the glycosylation of dystroglycan. Numerous recent advances in understanding regarding the genes that lead to dystroglycanopathies are providing a much more comprehensive view of glycosyation's critical role in muscle structure and function. Discovery of new causes of dystroglycanopathies has been aided by Next Generation (Next Gen) sequencing and novel phenotyping strategies [based on biopsies, magnetic resonance imaging (MRI), and dystroglycan glycosylation patterns]. At least 14 genes affect proper glycosylation of alpha-dystroglycan. Mutations in any of these genes lead to a variety of muscular dystrophies (including LGMD2M, 2N, 2O, 2P, MDC1C, MDC1D, Muscle Eye Brain Disease and Walker-Warburg Syndrome).

Progress has been made in developing zebrafish and murine models for many of the gene mutations that cause dystroglycanopathies. Although these disorders have been, in general, difficult to study in the mouse due to the severity of whole animal knockout phenotype, newer models should aid greatly in therapy development. Since defects in glycosylation associated with the dystroglycanopathies results in structural and functional abnormalities in skeletal muscle, the brain, eyes and other organs, studies of the developmental defects in these animal models can advance understanding of the common pathways involved in these different organs and the regulation of these pathways by membrane protein glycosylation, which could be applicable to other forms of dystrophy.

The importance of dystroglycan studies goes beyond the dystroglycanopathies; secondary changes in dystroglycan function occur in other muscular dystrophies. Data has shown that increasing glycosylation of dystroglycan with Galgt2 improves the phenotype in the mdx model of DMD. Results from further translational studies in mice and non-human primates provide justification for clinical testing of gene transfer of GALGT2 to skeletal muscle in DMD patients, and this strategy may also be applicable to other forms of dystrophy.

There is a need for additional studies aimed at characterizing the fundamental biology and function of dystroglycan post-translational modification, as well as the disease mechanisms of dystroglycanopathies. Additional animal models of these diseases will facilitate studies of disease mechanisms and therapy development. The potential efficacy of strategies to improve glycosylation also should be explored in the context of other muscular dystrophies.

DIAGNOSIS, SCREENING, AND BIOMARKERS FOR MUSCULAR DYSTROPHY

The Diagnosis, Screening, and Biomarkers for Muscular Dystrophy Working Group addressed the needs for efficiently and accurately identifying and distinguishing dystrophies in human populations and measuring disease related parameters. Muscular dystrophy patients and their families often encounter a long delay between their first contact with a physician regarding their condition and an eventual accurate diagnosis, with the various missteps referred to as the "diagnostic odyssey." More advanced tests and improvements in healthcare systems utilizing the tests could decrease or eliminate this experience. Diagnostic tools help the physician, family, and patient understand the disease. Screening tools facilitate early detection, management, and, as targeted therapies become available, earlier (and potentially more efficacious) intervention in the disease. Population-based screening can provide data important for the allocation of healthcare resources. Biomarkers facilitate the therapy development process by providing an early signal of safety or efficacy of candidate therapeutics. Some biomarkers can become qualified as outcome measures or surrogate endpoints for clinical trials.

Technology and other resources for diagnostic testing:

1. **Develop definitive tests for muscular dystrophies for which genetic testing is not yet available**

   The 'molecular diagnostic odyssey' facing many patients and their physicians, where an expanding number of causative genes are tested individually in different clinical and research labs, is being largely solved by Next Gen (highly parallel) sequencing. Both targeted panels of muscular dystrophy genes and complete exome studies can provide for a molecular diagnosis in an increasing proportion of patients and their families. However, it is becoming apparent that the wealth of riches in terms of obtaining sequence data also leads to challenges in interpreting this data, with a particular problem of 'over-interpretation' or false positive interpretation (e.g., interpreting a DNA variant in a patient as 'pathogenic' when instead it may in fact be a rare benign polymorphism). The assignment of pathogenicity depends on phenotype/genotype correlations that are increasingly stratified and complex (e.g., specific changes in MRI patterns, syndromic presentations, and other features that assist the astute neurologist in interpreting the plethora of DNA variants reported on a patient). Another issue is detection of genetic variants of unknown significance; this impacts both diagnostics and mechanistic research and a consensus should be reached as to how such variants are to be collected and shared. It will be more important to have centralized or coordinated interpretation facilities or forums. Furthermore, data filtration programs for whole exome sequencing (e.g. XBrowse) should be encouraged to be open to iterative feedback to improve the platforms and provide the ability for the muscular dystrophy community to filter the data sets. Such ability to filter may be key to identifying pathogenic variants, especially in conditions with new phenotypes and genes. Another strategy that may aid in identifying pathogenic disease mutations would be to increase the interactions of the muscular dystrophy field with the NIH Undiagnosed Diseases Program. It would also be important to develop and improve algorithms to help determine pathogenicity based on the clinical presentation as was recently done for LGMD.

   Some relatively common muscular dystrophies are not easily diagnosed by Next Gen sequencing (e.g., DM and FSHD). Progress has been made in publication of larger cohorts in FSHD and DM, and defining genotype/phenotype relationships. Sharing of the phenotypic data in all diseases is especially important, as classification of muscular dystrophies is going to be fundamentally challenged by findings of DNA sequencing.

New challenges have emerged in interpreting particularly large genes causing muscular dystrophy, with the many possible pathogenic variants often reported from exome or targeted re-sequencing studies (e.g., titin, nebulin).

Better, and importantly affordable, diagnostic tests are needed for both research and clinical care. Increasing the fraction of patients who have accurate genetic diagnosis will increase the available pool for research studies and increase the quality of data from those studies. Accurate diagnosis can also improve clinical care and decrease disease burden. Investment is also needed to support genetic testing in research and clinical trials in order to better assess disease modifier genes to facilitate stratification and data interpretation. Demonstrating the economic benefit of these tests through better diagnosis, better targeting of treatment, and accelerated research will provide positive feedback for the development of more and even better tests.

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2. Develop minimally invasive diagnostic techniques for muscular dystrophies

Whereas patient muscle biopsies were, at one time, essential for the process of diagnosing DMD, physicians can now use a minimally invasive test, such as genetic testing of small blood samples or buccal swabs, to diagnose DMD. There continues to be a need to develop quick, minimally invasive diagnostic tests for other muscular dystrophies. In addition to genetic tests, imaging methodology such as MRI may in the future provide a means to narrow down a diagnosis which could then be followed by genetic tests when available. Developing improved, rapid and minimally invasive diagnostic tests for all muscular dystrophies, and implementing them in healthcare systems would reduce the disease burden and improve healthcare cost-effectiveness. Such tests would also facilitate newborn screening. Developing and validating new tests will require confirmation using traditional methods, including archived or new muscle tissue or skin-based specimens to interpret test results. Even as gene panels are becoming more widespread, minimally invasive techniques will also be necessary to follow-up and interpret these results to attain an accurate diagnosis. Having standardized clinical scales would also help in guiding the use of diagnostic tests.

There also are continuing barriers in access to genetic testing for the muscular dystrophies; barriers include physicians not ordering genetic testing and state-to-state variability in reimbursement rates. Often insurance will reimburse for more expensive muscle biopsies and not for genetic testing. These barriers could be addressed through education (of both physicians and affected people and their families) and innovative ways to help alleviate obstacles to reimbursement.

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3. Establish the specificity and sensitivity of diagnostic tests for the muscular dystrophies

As DNA sequencing costs continue to be reduced, and throughput and accessibility increased, DNA testing continues to displace protein testing with the (often) requisite muscle biopsy. However, the diagnostic accuracy of standardized commercially available tests is often not known. Therefore, a priority is to establish the specificity and sensitivity of these diagnostic tests so that patients and providers know, not only what they cover, but also what the likelihood of a correct diagnosis is, based on the false positive and false negative rates. This may be

accomplished through large studies to confirm the validity of new and currently available tests, and establish standards, particularly for large genes with a lot of variation (e.g., titin, nebulin), through aggregation of data that allows the generation of sensitivity and specificity data comparable to what's known for protein analysis from muscle biopsy. Acquisitioning members of the families that are not showing any signs of the disease will also provide important data for determining sensitivity and specificity.

The interpretation of Next Gen sequencing will likely require additional data from disease-related biomarkers. This may involve use of antibody-based diagnostic techniques on muscle biopsies, which are valuable and currently available, but invasive. Alternatively, there is increased research on serum biochemical biomarkers (e.g., protein or nucleic acids) in the context of drug development for muscular dystrophies. The potential applicability of serum biomarkers as an aid in interpreting Next Gen sequencing variants should be further investigated.

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4. Advance knowledge of genotype/phenotype correlations and implement this knowledge in patient care.

Improvements in genetic testing for the muscular dystrophies will increase the number of patients for whom the specific DNA sequence changes causing the disease is characterized. Furthermore, characterization of the course of disease in these patients, using standardized clinical outcome assessments, will provide the data needed to inform more accurate prognoses. In addition to the causative gene mutation, other genetic factors contribute to the disease mechanisms and are modifiers of disease progression. Testing for these genetic modifiers will provide additional information predictive of disease progression. Collection and analysis of data on genotypes and phenotypes could lead to improvements in the standard of care. For example, if specific genotypes are known to be associated with more severe or rapidly progressing cardiomyopathy, aggressive therapies could be started in patients with those genotypes, even before the onset of cardiac symptoms.

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5. Establish mechanisms for muscular dystrophy patients to obtain accurate genetic counseling

The availability of genetic counseling services in the clinic varies enormously from very sophisticated to very basic. Furthermore, genetic information in muscular dystrophy is very complex (see objective 3), so even highly trained geneticists may not have the expertise to interpret the results accurately. Therefore, it is critical that the timing and purpose of genetic counseling be defined. Differences in the information to be shared at during preconception, prenatal and diagnostic counseling need to be better understood. The ethical, legal, and social impacts of genetic testing and counseling for the muscular dystrophies should be considered in healthcare practice.

In addition to the need to train geneticists in the specifics of muscular dystrophies, better tools to share information would be valuable. For instance, some countries (e.g., The Netherlands) have good centralization of databases and diagnostic testing that, if adopted in the United States, may help relay knowledge to doctors and counselors. These methods would be most beneficial to centers in highly populated areas, but alternative methods may be more

appropriate for areas with a lack of access to adequately trained personnel. In these instances, telemedicine centers could provide information and services to patients and their families. Such national call centers could be developed with engagement of appropriate professional associations. Although there are state regulations limiting such options, an exemption for rare diseases for a national counseling network may be feasible given the limited resources for care in some areas. Such efforts are necessary in order to provide accurate genetic counseling to all.

Efforts to support additional training are also important, as there are too few genetic counselors and geneticists. The training of these specialties is central to better access in the future. An effective way to increase the number of well-qualified counselors may be to provide a specialized year in genetics leading to formal certification at the conclusion of a neurology training program, as is being considered by the American College of Medical Genetics and the neurology community.

Data sharing/optimal use of information and materials:

6. **Encourage submission of new mutation and polymorphism data for muscular dystrophy genes to public databases**

   As more patients receive genetic testing for clinical diagnosis, and research projects conduct genetic screening on participants, there is an opportunity to collect the data in public databases to serve as a research resource. In addition to mutation and polymorphism data, it is important to include phenotypic data using currently available Common Data Elements. Although there are several existing public databases, the NIH National Center for Biotechnology Information has developed a central, national database called ClinVar. Data in ClinVar is curated by a team at ClinGen, who analyze the data and decide its relevance to human disease with the goal of determining which genetic variants are most informative for patient care. This serves the critical function of helping to make the process of mutation identification and determination of pathogenicity more standardized. ClinVar currently lists some of the variants for many of the genes associated with muscular dystrophies, and this data continues to accumulate. This and other databases provide an opportunity for further investigation of genotype/phenotype correlations for the muscular dystrophies.

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7. Further optimize utilization of muscle biopsy materials for diagnostics and research

   Muscle biopsies from dystrophy patients and controls, provides essential materials for testing hypotheses regarding mechanisms of disease and for measuring tissue and cellular responses to experimental interventions. However, invasive procedures directed at already compromised muscle tissue are understandably of great concern to patients and their families. Advancing technologies to conduct more analysis while decreasing the amount of tissue required, will facilitate research advances and decrease the discomfort to patients. The utilization of pooled cryosections of biopsies for protein or mRNA evaluation is available on a research basis in a variety of locations. For example, dystrophin and some LGMD-associated proteins may be evaluated by western blotting and mRNA may be evaluated by expression profiling or RNA sequencing (RNA-seq). Mass spectrometry approaches have also been developed. However, for

the most part, these techniques are not readily available in CLIA-certified diagnostic laboratories.

Continued advances in the development of assays that derive more information, and more accurate information from smaller samples, will accelerate research, increase the efficiency of clinical trials, and reduce the discomfort of patients during the sample collection procedure. The community is strongly encouraged to maximize the utility of biopsy material that is necessary by ensuring it is available for research purposes. However, the community should also strive to reduce the need for biopsies in general, and specifically in clinical trials.

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8. **Support a web-based resource to assist the clinician with identifying and choosing a diagnostic approach for muscular dystrophies**

Availability of algorithms to guide efficient diagnosis of the muscular dystrophies has been evolving. While some muscular dystrophies already have web-based tools available to facilitate diagnosis (see the Automated LGMD Diagnostic Assistant, or ALDA, developed by the Jain Foundation), many others do not. Next Gen sequencing panels are rapidly changing the landscape and potentially represent the most cost effective approach to diagnosis. Diagnosis of muscular dystrophies would be facilitated by the availability of a resource similar to GeneTests (https://www.genetests.org/), which hosts a list of CLIA-approved commercial or research labs offering testing for a disease or group of diseases. Ideally, this would be implemented as a single site, with tables that would include (at a minimum) the CLIA-approved lab with web link, test name, genes tested, sensitivity of the tests, diseases associated with those genes, and, ideally, some estimate of cost.

Since much of the genetic testing for the muscular dystrophies is referred to commercial labs (volume is high; approximately 900 tests/year)—these data represent a considerable resource that is currently untapped. The ability of researchers to leverage data from these commercial testing resources would accelerate both research and therapeutic development for the muscular dystrophies; issues inhibiting such data sharing and strategies for resolving them should be explored.

Population screening for muscular dystrophy:

9. **Establish current and accurate incidence and prevalence data for genetically confirmed forms of diagnosed muscular dystrophy**

Accurate incidence and prevalence data is important for decision making in allocating healthcare resources by public and private organizations. Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet), a research effort funded by the CDC, has presented incidence and prevalence figures for childhood-onset DMD/BMD. However, these data are from a cohort with largely northern European ancestry. Thus, further efforts to obtain accurate data across different racial and ethnic groups are needed so that the numbers better represent the general population. The CDC is aware of this and is working to update these figures for DMD/BMD. Data collection has been expanded to several other forms of muscular dystrophy, and it is important to ensure inclusion of a diverse sample in all such studies which ideally would be conducted

using population-based screens. As mutation-specific treatment becomes feasible, epidemiology based on genotype is desirable.
The potential implementation of newborn screening would greatly improve the ability of accurate and current incidence and prevalence data through population screening.

It is likely that there are many individuals affected by a muscular dystrophy, yet they remain undiagnosed. Sometimes an older patient seeks care for weakness, and this becomes the first indication of a family cluster of undiagnosed muscular dystrophy. Advances in newborn genetic screening may eventually lead to more consistent detection and diagnoses.

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10. Develop methods for newborn screening of the muscular dystrophies; explore the social and ethical issues involved in offering neonatal screening for muscular dystrophy and develop techniques that would make screening practical

The addition of a disorder to the Recommended Uniform Screening Panel (RUSP) requires the approval of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, and the Secretary of the Department of Health and Human Services. Disorders are chosen based on evidence that supports the potential net benefit of screening; included among the criteria is the existence of a cost effective test that is easily adaptable to state screening labs, and evidence of the availability of an effective treatment or intervention. There is a high threshold for addition of tests to the RUSP. Achieving this goal for muscular dystrophies will require the cooperative work and funding of many partners within the MDCC.

Even in the absence of an approved therapy (and therapies are only starting to receive conditional approval for one type of muscular dystrophy, DMD), newborn screening is important when early diagnosis results in improved clinical management. But, it is also important to begin to evaluate the feasibility of newborn screening for muscular dystrophies without current management paradigms. First, this proactive approach should be a parallel activity to therapy development, as the development of newborn screening programs can take considerable time. Screening approaches that allow for identification early in infancy may enable children to receive treatments while they are still asymptomatic. Second, newborn screening provides actionable information for families at an early stage (and avoids the diagnostic odyssey). With the implementation of newborn screening programs it is crucial to establish a system of long-term follow up of the children identified. Such a system would lead to greater understanding of the disorders.

There are multiple newborn screening technology platforms being developed, and it is critical to have as accurate testing as possible done in the first tier, to avoid false positives, but also to exclude those with genetic changes that are not clinically significant. At this time it is likely that newborn screening paradigms that assess enzyme activity or protein level will have to be combined with a second tier of gene sequencing.

As part of newborn screening initiatives in the area of muscular dystrophy several ethical, legal and societal implications must be taken into consideration. How and when to report conditions that are currently non-actionable or have a late onset must be explored. It is important for education and outreach include patients, parents and providers.

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11. **Establish and implement guidelines for screening family members and potential carriers of muscular dystrophies and provide appropriate clinical care and counseling**

    Often times the diagnosis of a muscular dystrophy patient leads to the realization that other living family members are potential carriers or have the disease, but are less severely affected. For X-linked muscular dystrophies, mothers of affected boys and other female family members may be carriers, and can be predisposed to cardiac disease and other phenotypes. The disease burden on the family can be reduced by screening members for previously undiagnosed dystrophy and comprehensive phenotyping to detect subclinical symptoms. Access to genetic counseling should also be provided (see Objective 5 above). Guidelines for screening family members and symptoms to look for in carriers could be included in the web-based resource to assist the clinician with identifying and choosing a diagnostic approach described in Objective 8 above.

Development of biomarkers:

12. **Develop and validate the role of muscle imaging in diagnostic evaluation of the muscular dystrophies, and as a biomarker or endpoint measure for clinical trials**

    The field of muscle imaging in muscular dystrophies has evolved significantly and has moved from qualitative evaluation of patterns to quantitative imaging. While the role of muscle imaging in diagnostics remains limited, the potential value for quantitative muscle imaging in research is high. A number of groups have demonstrated that specific imaging modalities (MRI and ultrasound) can detect muscle pathology and are sensitive to disease progression in muscular dystrophies (e.g., CMD, DMD, FSHD and LGMD), and, recently, it has been shown that MRI can detect the therapeutic effect of corticosteroids in DMD. Given the limitations of current outcome measures for clinical trials in muscular dystrophies, there is an urgent need to validate the potential of imaging strategies, both as a biomarker and an endpoint for clinical trials. To date, MRI has been incorporated in only a handful of clinical trials in dystrophies. However, the emerging data supports a much expanded future utilization of muscle imaging in clinical trials. Muscle imaging strategies may potentially be used at different stages of the clinical trial process as prognostic, predictive, or pharmacodynamics biomarkers. This will require an increased focus on quantitative imaging strategies, quality control procedures, and standardized data collection across sites.

    The study of quantitative muscle imaging should be expanded to qualify these measures as biomarkers and validate them as outcome measures in clinical trials. To help manage variability introduced by differences in technology and analytic software, consideration should also be given to the development of standardized data collection and quality control procedures for imaging studies in the muscular dystrophies, and perhaps centralized testing and/or analysis facilities for the conduct of these studies.

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13. **Foster the development of prognostic, predictive, pharmacodynamic, and efficacy-response molecular/biochemical biomarkers to facilitate design, conduct and decision making in clinical trials in muscular dystrophy; establish data in support of FDA biomarker qualification**

There has been significant effort in identifying molecular biomarkers for the muscular dystrophies. For DMD, studies have identified serum proteins (e.g., creatine kinase, fibronectin and MMP-9) and microRNAs (e.g., MiR-1, MiR-133, and MiR-206) that are candidate disease biomarkers. For FSHD, transcriptional profiling has identified a 'molecular signature' of 15 genes, and serum/urine protein biomarker studies are in progress. However, additional data is needed to advance the qualification and value of biomarkers for use in clinical trials for the dystrophies.

Skeletal muscle is an abundant tissue and serum biomarkers may predominantly reflect the disease state of this type of muscle. Availability of biomarkers specific for cardiac muscle involvement in muscular dystrophy has been a particularly acute gap in knowledge. Dystrophy-relevant biomarkers of other organs and tissues such as bone, brain and smooth muscle are also needed.

Knowledge of disease mechanisms further reinforces the need for specific validated and qualified biomarkers for use in clinical trials that can provide critical information on target engagement and other proximal pharmacodynamics. Methods such as Western blotting or immunostaining of tissue sections are widely used in research labs for detecting and quantitating proteins. But, the accuracy, specificity and linearity of quantification using these methods may not be sufficiently characterized to support the level of data collection needed for the regulatory approval of therapeutics. There remains a need to qualify dystrophin as a biomarker for use in trials of candidate therapeutics that are aimed at restoring dystrophin expression. Validation and qualification of dystrophin in DMD and other key proteins such as dux4 in FSHD or ClC-1 in myotonic dystrophy may accelerate progress in the development and approval of therapeutics. The FDA's Biomarker Qualification Program offers a formal process to guide submitters as they develop biomarkers and rigorously evaluate them for use in the regulatory process.

Multiple issues remain to be resolved before molecular biomarkers can be qualified for use in clinical trials in the muscular dystrophies, including assessment of the sensitivity, specificity and linearity of candidate biomarkers, and their responsiveness to disease progression and/or therapeutic interventions. There also is a clear need for development and validation of tools essential to evaluation of biomarkers, particularly valuable would be international agreement upon standard operating procedures (SOPs) for biomarker assessment and centralized resources for probes and standards as steps toward insuring reproducibility/comparability of data. Resolving these issues will require data sharing and coordination among a growing number of international groups. A commitment to include molecular measures among the exploratory measures included in all clinical trials in muscular dystrophies would be an important step.

PRECLINICAL THERAPY DEVELOPMENT FOR THE MUSCULAR DYSTROPHIES

The focus of the Preclinical Therapy Development for the Muscular Dystrophies Working Group was on the identification of high priority objectives that address both the process of therapy development and specific candidate therapy strategies. The landscape for therapy development has undergone significant changes in the last decade and there is now an emphasis on careful determination of the potential of a given therapeutic strategy and the safety/efficacy of each specific candidate drug/biologic within each therapeutic modality. Given the high number of candidate therapeutics, preclinical development must focus upon unbiased determination of both the strengths and weakness of each candidate and consider the landscape of other relevant candidates, before making the go/no go decision on launching clinical trials.

Modulating muscle biology:

1. **Identify mechanisms of positive and negative regulators of muscle growth and repair, and establish their potential as therapeutics through preclinical testing in animal models of various types of muscular dystrophy**

   An expanded focus on identifying and understanding positive regulators of muscle growth and repair, and their interactions with IGF-I and myostatin and related downstream signaling pathways, is needed. Preclinical efforts need to include development of reagents that will be used to evaluate target engagement in subsequent clinical trials.

   Preclinical efforts supporting major industry initiatives have centered on myostatin, the negative regulator of muscle growth and repair. Industry interest in this mechanism spans a number of muscular dystrophies and likely relates to potentially broader target diseases, such as age-related sarcopenia, disuse atrophy or cachexia. Importantly, it is not yet clear what types of muscular dystrophies will benefit from this approach—in some types, the approach could be detrimental, necessitating careful animal testing before moving forward.

   There are a number of ongoing trials at the time of this assessment, including: using antibodies to inhibit either myostatin or its signaling receptor; approaches using proteins that can inhibit myostatin signaling; and a gene therapy trial to inhibit myostatin through expression of follistatin. Selectivity or specificity may be very important since modulating the signaling of other activin-related proteins can also be impacted, with unknown long-term consequences in humans. The mouse models used in preclinical studies have failed to reveal the off-target effects of impacting other activin-related proteins, a deficiency that has resulted in at least one failed clinical trial. Thus, extensive preclinical work to understand potential off-target effects and the roles of signaling proteins that are related to myostatin is needed. Additional preclinical studies in animal models of a variety of muscular dystrophies may delineate the forms of disease that are likely to benefit from this type of therapy, and importantly, identify which forms of disease may be made worse by this approach.

   IGF-I has received focus as perhaps the most important positive regulator of muscle growth and repair, and is part of a signaling pathway that is subject to negative regulation by myostatin. There has been slow progress on achieving the translation of IGF-I preclinical results into a successful therapy for the muscular dystrophies. The initial trials with IGF-I bound to its binding protein 3 (Iplex) in DM1 did not demonstrate clear benefit. However, it would be anticipated

that IGF-I would show greater benefit in muscular dystrophies where there is extensive ongoing degeneration and regeneration, such as DMD. The primary obstacles to developing IGF-I as a therapeutic are targeting its delivery to/production in skeletal muscle and avoiding deleterious off-target effects in other tissues. These goals may be accomplished (from a vector engineering standpoint) with adeno-associated virus (AAV) delivery. IGF-I delivery may be considered in combination with other therapeutic genes, as well as with pharmacological interventions, such as nonsense suppression and exon skipping. There has not been much progress on developing a drug that can upregulate IGF-I specifically in muscle, but this is still a goal worth pursuing.

There are a number of other positive regulators of muscle growth that need to be evaluated for their target potential in the muscular dystrophies, including bone morphogenetic protein (BMP) family members that interact with myostatin signaling in ways that are not yet fully characterized.

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2. Examine the efficacy of existing drugs for targets downstream of the primary genetic lesion in the pathogenesis of muscular dystrophy

There are opportunities for both the repurposing of drugs, as well as directing compounds under clinical development into the muscular dystrophies when their targets are downstream of the primary muscular dystrophy mutation. For many of the muscular dystrophies in which the primary defect leads to muscle cell damage and/or loss, the muscle regeneration process itself is a potential therapeutic target. Putative targets include cytokines and signaling pathways that control the inflammatory component of repair, the fibrotic response, and the specification of both new myogenic cells and vascular cells. Considerable efforts have gone into assessing partial inhibition of NFκB as a means of dampening, but not blocking, the inflammatory response, or have focused on anti-fibrotic agents. Researchers are investigating other anti-inflammatory pathways as targets. One strategy is to use neutralizing antibodies to specific inflammatory cytokines. It is as yet unclear how and where to optimally intervene in the cascade of downstream events in the muscular dystrophies.

By contrast, there are muscular dystrophies that do not involve significant degeneration; instead, muscle weakness results from either a failure to grow normally or is due to atrophy. Better understanding of the basis of muscle weakness through study of appropriate animal models can lead to possible therapeutic interventions for these types of muscular dystrophy.

A number of potential therapies directed at downstream targets are either in or about to enter the clinic. Pending those initial trial outcomes, continued investigation of mechanisms that can lead to more successful regeneration and/or counter muscle weakness is warranted.

Several epigenetic drugs targeting DNA methylation and histone deacetylation enzymes have been tested in clinical trials for other disorders. These should be evaluated in relevant muscular dystrophies, such as FSHD.

A long-term, preclinical strategy to optimizing treatments is to identify a number of compounds that are disease modifying for a given muscular dystrophy and then combine them in animal models to identify the most synergistic agents. This is one approach to prioritize the most promising combinations to be evaluated in humans, either following evaluation of the drugs

individually or initially in combination. Drugs targeting downstream pathogenic mechanisms likely will be an important part of combinatorial therapy for muscular dystrophy. Many other diseases are managed by treatment with multiple drugs that are synergistic or address various downstream symptoms.

Cell and gene therapy/editing:

3. **Overcome barriers to muscle stem cell transplantation**

Recent advances in ex vivo muscle cell expansion and establishing immune tolerance to transplanted cells have further supported the potential for pre-clinical and clinical uses of muscle cell transplantation. These applications range from preclinical studies of mice xenografted with human muscle tissues, or cell lines derived from control and muscular dystrophy patients, to clinical studies of regional muscle replacement in humans. Proof-of-principal studies have shown that inducing immune tolerance can result in long-term engraftment of the transplanted cells, and freshly derived donor muscle cells have been shown to engraft efficiently in model systems and thereby contribute to the satellite cell population. For FSHD, where development of phenotypic mouse models has been difficult, human to mouse xenografts of muscle fibers or myogenic cells derived from patient biopsies may provide an important model for preclinical therapy development. Taken together, the preclinical work with cell-based strategies for the muscular dystrophies is advancing and encouraging for human therapy development studies.

Remaining barriers to cell-based therapies for muscular dystrophy include: development of methods to expand muscle stem cells ex vivo and maintain their engraftment potential without increasing genetic instability or tumor risk; determination of optimal conditions for survival of transplanted muscle stems cells in vivo; the need for improved methods to induce immune tolerance in allogeneic transplants and to autologous transplants that might have acquired novel antigens from ex vivo expansion or genetic manipulation; and development of delivery methods that improve the distribution of engrafted cells throughout a specific muscle or to multiple muscle groups. Because of the complexity of this therapeutic class, early dialog with regulatory authorities is critical for the development of cell-based therapeutics. In the United States, the FDA's Center for Biologics Evaluation and Research oversees the review of cell-based therapies and has released several guidance documents that investigators can use to help enable therapy development.

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4. **Improve the efficiency and efficacy of gene therapy delivery in the muscular dystrophies, while minimizing the immune response to both gene product and delivery vehicle**

Gene therapies for genetic disorders are beginning to show successes in the clinic and one vector drug has been approved for sale in Europe for a non-muscular dystrophy indication. Although there is significant potential for developing gene therapy treatments for the muscular dystrophies, several preclinical goals remain to be met. Current approaches have advanced to the stage of using regional limb delivery for gene transfer to skeletal muscles of the limbs, and in some cases for localized infusion into the heart. Therapeutic success for the muscular dystrophies requires that these approaches be expanded in scope to target all the major striated

muscles involved in muscular dystrophy, with a longer term goal of targeting smooth muscles and the central nervous system.

Several AAV serotypes show great promise for gene transfer to human muscle, but identification of an optimal vector type has proven elusive. Comparative studies have been conducted in rodent, canine, porcine, and non-human primate models and some vector types have been evaluated in human clinical trials. Vector optimization through preclinical studies is complex, in part because of: (1) considerable species-specific variation in results; (2) differences in vector production and titering methods; (3) optimal serotype differences between cardiac and skeletal muscles, and even across different types of skeletal muscles; and (4) the discovery of new serotypes both in nature and through random and targeted mutation strategies, as there is a critical need to benchmark the new serotypes against existing ones. Additional challenges are posed by some therapeutic genes that are too large to fit in a single AAV vector. Alternative strategies to deliver these larger therapeutic genes are currently being explored and remain a research challenge. An important resource for the community would be large-scale, vector production facilities to make GLP-grade vector available for testing in different labs and model systems.

Head-to-head comparisons of novel AAV capsid serotypes in rodents could inform large-animal tests of gene-delivery approaches. Indeed, rodents may be the best locus for studies intended to further explore mechanisms or traits of the vector and transgene. Due to limited availability and greater expense of the larger animal models of muscular dystrophy, comparative studies of vector efficiency, cell-type targeting, and delivery strategies that require larger animals could first be performed in normal animals. Only those vectors with the greatest therapeutic promise would then move into the larger animal disease models, that might more closely predict human application, and subsequently into clinical trials. Other priorities in vector development include evaluation of non-viral vectors, development of regulatory cassettes that lead to higher levels of gene expression in the full range of striated muscles but are silent in non-muscle cells, and an improved cassette design via optimization of codon/splice site/polyadenylation.

The majority of gene therapy development studies have focused on targeting of limb skeletal muscle. Important gaps remain in how to best achieve cardiorespiratory muscle targeting, avoid tissues where expression is undesirable (e.g., liver, immune effector cells, etc.), and evaluate immune system effects (interaction with neutralizing antibodies and elicitation of T and B cell responses to vector). For types of muscular dystrophy where the models exist and are sufficiently available, cardiorespiratory muscle delivery studies will benefit from canine and porcine models. Approaches to optimize delivery should include dose escalation studies, assessment of routes of vector infusion and recirculation, and development of methods to avoid liver gene transfer. Immunological studies will benefit from evaluation of non-human primates, as they more closely model the human immune system. Finally, it is critical that animal studies draw upon results from ongoing human clinical trials, which will almost all use a single vector serotype.

Clinical gene therapy trials for several genetic disorders have identified dose-dependent immune responses as a significant issue that can limit the efficiency of gene transfer, especially for systemic delivery methods that require high doses. Cellular (T-cell) immune responses have been observed against both vector and transgene. Neutralizing antibodies can be a barrier either to direct vector delivery or vector re-administration. Each of these issues needs to be

better characterized in appropriate animal models and in ongoing clinical trials. Methods to limit the consequences of cellular immune responses against vectors should focus on both short-term immune suppression and vector de-targeting of non-muscle and immune effector cells. Immunological recognition of transgene products needs to be studied in more detail to ascertain the significance of and methods to address this problem. Such methods can focus on the development of tolerizing or reverse vaccination strategies, the use of surrogate gene products that are not immunologically foreign to patients, and the use of regulatory cassettes to drive gene expression that are more tissue-specific. Increased study of neutralizing antibodies and other serum factors that limit gene transfer should be performed with the goal of overcoming these barriers in initial clinical trials and allowing for repeat vector administration possibly years after an initial treatment. Research topics here include the study of methods to remove neutralizing factors from blood, improving methods to block neutralization of vectors while in serum, developing libraries of vectors that could be rotated in their use either in different subsets of patients or in the same patient over time and possibly the development of synthetic blood replacements for use during vector infusion.

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5. Evaluate the safety and efficacy of agents that promote stop codon read-through or exon skipping using cell or animal models of muscular dystrophy

The decisions to advance a novel drug into clinical trials and the design of these trials must be based upon a clear understanding of the short- and long-term safety and efficacy of the drug in animal models. Significant progress has been made in developing agents that induce stop codon read-through or exon skipping for DMD. These efforts have progressed well into clinical development in DMD. However, it is likely that therapeutic effects can be improved by finding agents with better potency or enhanced delivery—these efforts may be aided by a better understanding of, at a structural level, how these drugs work. In the case of agents that modulate RNA splicing or promote stop codon read-through, the preclinical evaluation will need to include specific components that are tailored to the therapeutic approach. For example, it is important to determine the impact on natural termination codons or nonsense-mediated RNA decay for drugs that promote stop codon read-through or, in the case of exon skipping, the expression level and functional capability of the intended protein. Additional improvements of oligonucleotide chemistry and delivery technology are needed for antisense drugs that induce exon skipping. As new agents are developed, comparisons against the first-in-class drugs will be required, using optimal regimens and state-of-the-art testing for each candidate.

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6. Develop novel agents to improve efficacy of current gene repair strategies or to facilitate new strategies

Gene repair strategies are a promising approach for correcting mutations that lead to neuromuscular disorders and must be optimized to address both muscle cells and myogenic progenitors if they are to achieve their potential. Genome-editing strategies are being explored in conjunction with stem cell therapies and also for direct gene repair in vivo. For some types of muscular dystrophy, rather than restoring gene expression, there may be value in repair technology to silence gene expression through editing. Important next steps include the pursuit of technologies to improve efficiency of repair, while minimizing off-target genomic

modifications. A current major limitation to the use of repair strategies in the muscular dystrophies is getting the methods to work in non-dividing myofibers and myocytes, as well as in muscle satellite cells. Several technical advances have been made over the past five years that raise the hope of correct targeting once the modification machinery is within a cell, but serious limitations remain on how to get the machinery to the right cells and how to make it work in non-dividing cells. Current methods that show promise are: (1) using single-stranded AAV vectors to elicit homologous recombination at either the mutant locus or at a genetic locus leading to therapeutic levels of gene expression and (2) using gene editing strategies that work at the nucleotide level to either repair a mutant gene or to upregulate expression of a therapeutic gene. Considerable advances have been made for this latter strategy using TALEN vectors to target specific sequences in a cell. More recently, the CRISPR/Cas9 systems are showing even greater efficiency and possibly fewer off-target effects, while being simpler to implement.

Although genomic editing is a promising new approach there are a number of technical challenges that need to be overcome. An appropriate delivery system for getting the genomic editing components to the intended target cells remains a significant hurdle. The AAV delivery system has proven to be safe and effective but the large size of the gene editing nucleases (TALEN and Cas9) limits their efficient expression. Further research is needed into alternative, non-viral gene delivery methods, including injection of naked DNA or RNA and nanoparticles containing nucleic acids. Scale-up remains another challenge due to the significant increase in body size between animal models and humans, necessitating more efficient genome editing in target tissues. Finally, the safety of the gene editing systems needs to be determined, especially for high-dose and long-term use. These new gene editing strategies hold promise and may warrant further exploration with a focus on applications to muscle. Development of novel alternative approaches to gene repair should also be pursued. The major successes of each of these systems to date have been in dividing cells, either in culture or in vivo. Refinements of the repair methodology to allow production of modified genes in muscle without elicitation of an immune response and development of approaches that are applicable to non-dividing cells represent major requirements before a therapeutic can be advanced for the muscular dystrophies.

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7. Evaluate the safety and efficacy of targeted gene silencing as a therapeutic strategy for muscular dystrophy

The technology for targeted gene silencing continues to mature and has been successfully applied in preclinical models for dominantly inherited forms of muscular dystrophy. Current methods for targeted gene silencing employ antisense oligonucleotides, small interfering RNAs, and gene therapy vectors for expression of antisense RNA or short hairpin RNAs. All of these methods have been adapted to achieve post-transcriptional silencing in mouse models. Further, antisense oligonucleotide-mediated RNase H degradation of a toxic mutant gene product has advanced into clinical trials for DM. Transcriptional silencing is also feasible with small molecules or oligonucleotides. While initial efforts to harness targeted gene silencing have shown impressive phenotypic correction in cell and mouse models of muscular dystrophy, more work is needed to refine the approach and optimize the chemical design of agents. In particular, methods to deliver antisense or short interfering RNAs to striated and smooth muscle need to be improved and optimal targeting sequences need to be selected—thus far, there are no

algorithms to facilitate sequence selection, and optimization has required walk-throughs of targeted regions. Substantial remaining challenges include tissue delivery and issues arising from oligonucleotide pharmacology that includes very long tissue half-life. Central nervous system bioavailability of oligonucleotide agents is needed in DM, as well as other types of muscular dystrophy with central nervous system phenotypes. Exploration of small molecule approaches to obtain transcriptional silencing may represent a next generation approach to these challenges.

For autosomal dominant disorders, therapeutic development programs must also determine whether knocking down expression of the wild-type allele will have deleterious effects. If so, strategies to obtain allele-specific knockdown, or the coupling of knockdown with gene therapy to restore expression of the wild-type allele, will need to be developed. While the gene silencing strategy was initially applied to dominantly inherited muscular dystrophies, there is also potential for application to recessive diseases, by targeting substrate pathways or modifier genes.

Improving the process of therapy development:

8. Identify new strategies to implement translational research projects for muscular dystrophy

Translational research in muscular dystrophy has undergone a paradigm shift, particularly with changes in the industry environment, the role of foundations, funding models (venture capital and venture philanthropy), and increased flexibility at U.S. and European regulatory agencies. As a consequence, the expectations for level of evidence/rationale are higher for what will move forward in the drug development pipeline for any type of muscular dystrophy (data rigor is essential; see http://www.ninds.nih.gov/funding/transparency_in_reporting_guidance.pdf). To be effective, all partners in advocacy, academia, industry, and government have to collaborate in the design of therapy development programs and need to ensure that: (1) clinical outcomes are considered at program launch (i.e., preclinical programs are dependent upon well-defined goals as described in a target product profile) and (2) the critical questions are asked and sufficient data obtained such that the answers are clear at each stage of the development of drugs and biologics for the muscular dystrophies. Decision making as to what candidate therapeutics go forward to clinical trials must be strongly evidenced-based; independent milestone-driven vetting of candidates at multiple stages may play an important role in reducing the number of late-stage clinical trial failures [the Translational Research in Europe—Assessment and Treatment of Neuromuscular
Diseases (TREAT-NMD) Advisory Committee on Therapeutics is one independent means of vetting translational programs in the muscular dystrophies].

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9. Facilitate research (discovery, validation, and dissemination) of the biochemical pathways involved in muscular dystrophy

It is unlikely that all key, or even the best therapy discovery targets have been identified for muscular dystrophy. Thus, it remains critical to identify the biochemical and regulatory pathways that contribute to the disease pathophysiology in each muscular dystrophy. Although

the primary cause of muscle damage might be known in many of the muscular dystrophies, the pathways that might modify the damage, or have additional less well characterized contributions to disease, need to be carefully studied. In addition, for some muscular dystrophies, the major pathways causing pathology remain to be determined. Identifying the components of causative pathways and disease modifying pathways will be critical for target identification and validation in therapeutic development.

In addition to extending discovery-oriented research on biochemical pathways in the muscular dystrophies, facilitation of studies by collaborative teams of biochemists, molecular geneticists, and bioinformaticians are encouraged in order to develop public resources that assemble all domain knowledge of biochemical pathways in the muscular dystrophies. The emphasis should be on characterization of key pathway components, with particular attention to muscle-specific members of ubiquitous pathways.

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10. Encourage the development of target-directed and phenotypic assays suitable for screening or validation of compounds to identify therapeutic candidates for the muscular dystrophies

The increased knowledge of the pathophysiology of the muscular dystrophies provides the basis to develop target-directed and phenotypic screens to identify compounds for therapeutic development. In vitro assays for target engagement, cellular assays of target-activity modulation or phenotypic assays, and model organism assays for in vivo validation or screening are all critical for successful identification and development of therapies for muscular dystrophies. Across the types of muscular dystrophy, a range of strategies, from specific reporter assays to phenotypic screens in model organisms (fly, zebrafish) have emerged; some of these have transitioned to use in high-throughput screens in industry or NIH Molecular Libraries screening center settings. Careful attention to validating the biological relevance of the targets, or phenotypic readouts, and the specificity of the assays will be necessary to assure meaningful results.

An important point in this process is to develop screening assays that have maximal predictive power for clinical efficacy, meet rigorous industry standards, and that are transportable for performance in public or private facilities. Early consultation with experts is critical in ensuring that the properties of assays developed in academic labs are sufficiently robust to facilitate rapid transition into screening centers for hit identification and optimization. Other important considerations will include expanded access of the research community to high-quality screening technology, including RNAi and CRISPR screens, improvements in the efficiency of post-screening validation and follow-up, chemical optimization, and methods for dissemination of screening results that do not conflict with subsequent industry partnerships.

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11. Develop the animal models, assays, and tools necessary for preclinical translational research projects that focus upon rapidly moving the accumulated mechanistic knowledge into clinical trials

There has been a rapid expansion in animal models for muscular dystrophy. Small animal models for various types of muscular dystrophy are widely available and are highly useful for target development and validation as well as early phase preclinical testing. Advantages of the

small animal models include relatively easy genetic manipulation, shorter lifespan, cost and speed. The major drawback of the small animal models is that they may not always faithfully replicate all aspects of disease; this has been well described for the mdx model of DMD. Moreover, modeling cardiac complications of the muscular dystrophies in mouse may prove problematic for therapeutic testing, due to both species differences in cardiac function (e.g., heart rate) and the endpoint measures available for mice. Few labs have the expertise and equipment needed for measuring respiratory outcome measures in mice and other animal models, despite the significance of pulmonary and respiratory complications in disease progression and morbidity for the dystrophies. There is a need to expand the capabilities of labs and core facilities to collect standardized data on cardiac and pulmonary/respiratory function in animal models.

Larger animal models offer advantages for preclinical testing, especially when aspects of the disease are not present in the small animal model. Moreover, larger animal models are most useful when the pathway or the target that is being tested does not substantially impact the mouse models. In contrast, larger animal models are costly, phenotypic variation must be factored into appropriately powering studies, and there is limited availability of both the animals and expertise in handling and evaluation. Because of these concerns, larger animal models should be judiciously used in preclinical testing; the landscape of genetically relevant animal models beyond those currently available may indeed change with the application of CRISPR technology. Overall, the decision to use canine or other larger animal models for preclinical testing should be based on risk/benefit analysis, available safety data, and data from nonhuman primates and healthy human volunteers.

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12. Establish standardized endpoints for preclinical trials in mouse and dog models, and ensure that facilities are available that enable testing of drugs and other therapeutic approaches

The design and conduct of preclinical studies has come under scrutiny across many disciplines in recent years, with focus on reproducibility or lack thereof. Preclinical models of muscular dystrophy are no exception. Progress has been made through TREAT-NMD to recommend standard evaluations of the mdx mouse, and these guidelines are helpful for other animal models. While these guidelines may not apply to all evaluations of the mdx or other models of disease, they provide a highly useful starting point. One caveat of such guidelines is that they can be very helpful as long as they are flexible and allow for differing opinions as to the best way to evaluate a therapeutic intervention. Cardiopulmonary endpoint measures for small animal models were identified by the working group as a particular need for the community. As other model organisms have emerged as potential screens for therapeutics in muscular dystrophy, it is important to address the development of standardized endpoints for these models.

Efforts going forward should focus on good preclinical practices (see http://www.ninds.nih.gov/funding/transparency_in_reporting_guidance.pdf) with sufficiently powered, unbiased treatment and control groups. Studies should be conducted in a blinded fashion and analysis should include all relevant data points. Presentation and publication of data should reference whether these practices were followed, and display of data should be as informative as possible regarding the range of outcomes observed. Analysis of responses in each sex should also be considered.

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13. Develop preclinical strategies for selecting, testing and prioritizing combination therapies.

Clinical care for muscular dystrophy patients is likely to involve combinations of drug/biologics and/or other treatments. Some combinations may act in different ways on the same target or on different targets in the same therapeutic pathway for additive or synergistic effects. Other combinations may address different symptoms by engaging targets in different pathways. Testing and optimizing combinations of therapies through clinical trials using approved monotherapies could require exponentially larger numbers of patients, depending on the number of candidate therapies to be tested.

Preclinical studies are needed to test combinations of candidate therapeutics in cell and animal model systems. Well-designed preclinical studies may contribute to an understanding of which therapeutics may work well together, are there overlapping toxicities, and what dose ratios, sequences and timing may contribute to therapeutic effects. Studies in animal models may not accurately predict the therapy combinations that will work best in dystrophy patients. But combining the results of studies using carefully selected animal models, with results from studies in patient cells will help to prioritize combination therapies for testing in clinical trials.

CLINICAL THERAPY DEVELOPMENT FOR THE MUSCULAR DYSTROPHIES

The focus of the Clinical Therapy Development for the Muscular Dystrophies Working Group was on the identification of high priority objectives that address both the types and design of clinical trials, but also ensuring adequate readiness for clinical trials in the muscular dystrophies. Clinical trials often focus on drugs or biologics, but trial interventions may be devices, exercise programs, health services approaches etc. For some types of muscular dystrophies, multiple clinical trials have already been conducted using targeted agents developed through academic-biotech/pharmaceutical firm interactions. For other types of muscular dystrophy, the key issues lie in clinical trial readiness, so that, as therapeutic candidates emerge, stakeholders have the ability to adequately test them. In keeping with the optimization of candidate therapeutics in preclinical studies, through an emphasis on rigorous design and transparency in data reporting, clinical trials launched in the muscular dystrophy field should have adequate scientific rationale to go forward. Researchers are encouraged to publish both positive and negative data, and the Journal of Negative Results in Biomedicine contributes to this goal of transparency in research reporting. In addition, patients and their families are encouraged to be included throughout the development process. FDA recently released draft guidances that address important regulatory considerations relevant to the development of therapies for the dystrophies (Rare Diseases: Common Issues in Drug Development Guidance for Industry and Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry).

Optimizing available therapies:

1. **Optimize the use of corticosteroids as a treatment for DMD**

   Since the Clinical Investigation of Duchenne Dystrophy (CIDD) studies first documented their effectiveness in randomized, controlled trials, the use of corticosteroids in DMD has received exhaustive examination. However, most of the important clinical questions related to steroid use in DMD have not yet been answered, including: (1) the choice of the optimal agent (i.e., prednisone vs. deflazacort) and dosing regimen (at least 29 different regimens have been used); (2) the long-term benefit of steroids in this population, even in the non-ambulatory patients; and (3) the issue of whether early treatment (i.e., at < 3 years of age) is more effective than the more commonly used later initiation (i.e., at age 4-7). The first of these questions is being addressed in the FOR-DMD study (ClinicalTrials.gov ID NCT01603407), which is evaluating the optimal agent and dosing regimen in a double-blind, parallel-group design analysis in 300 DMD boys. In regards to the second question, increasing anecdotal and retrospective evidence suggests that there is long-term benefit to steroid treatment in terms of ambulation, function, quality of life, scoliosis, and (probably) cardiac function. There remains some controversy and discrepancies in human and animal studies concerning the effects of corticosteroids on cardiac function, but the FOR-DMD study is also addressing this issue. Studies also are underway to explore issues with early initiation of corticosteroid treatment in muscular dystrophy.

   The potential applicability of corticosteroids in most other types of muscular dystrophy is largely anecdotal and has not been systematically evaluated [e.g., clinical trials in FSHD and LGMD2B (dysferlinopathy) failed to show efficacy, while efficacy is being studied in LGMD2I].

   Risk/benefit evaluation is needed for corticosteroid use in non-ambulatory and older patients. Since many of the novel treatment approaches under development continue to focus on ambulatory patients, opportunities to study steroids in non-ambulatory and older patient

populations may remain. There also is substantial need for evidence-based guidance on corticosteroid dose adjustment for body weight.

Several other clinical issues related to steroid use in DMD have been incompletely studied, including (but not limited to) the effects of long-term corticosteroids on bone health (including fracture risk), puberty, growth, personality, and cognitive function; the interaction of corticosteroids with other treatments (e.g., lisinopril and beta blockers used to manage cardiomyopathies); and the possible value of combination therapy of corticosteroids with other agents. However, a detailed prospective study of these issues may not be feasible. In many respects, steroid use in DMD has been generally accepted, so if the FOR-DMD study is successful, addressing these other questions may be of relatively low yield.

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2. Determine the mechanism of action of the corticosteroids in muscular dystrophy in order to develop new, potentially more efficacious agents

The mechanism by which corticosteroids improve strength and delay loss of ambulation in DMD remains unknown. Knowledge of the mechanism of action of corticosteroids may yield insights into their potential value in other muscular dystrophies, particularly since the mechanism of action may vary with either the targeted muscle or type of muscular dystrophy or both. Likewise, elucidation of the mechanism of action may inform corticosteroid use in cardiopulmonary complications, an area that has received study, but still remains an open question.

Various mechanistic hypotheses have linked the efficacy of corticosteroids in DMD to anti-inflammatory or immunosuppressive activity, up- or down-regulation of modifier genes, alterations of calcium metabolism, alterations of nitric oxide metabolism, membrane stabilization, calcineurin-NFAT cell signaling pathways, expression of dystrophin-associated proteins, actions on integrin or laminins, and/or non-myofiber effects on dendritic cells, fibroblasts, and/or other cell lines. Recent studies suggest a role for corticosteroids in correcting for asynchronous tissue regeneration.

Determining the mechanism of action of corticosteroids in DMD is important, especially since their side effect profile is not inconsequential and steroids, by nature, are catabolic and can cause weakness. The ideal outcome would be mechanistic knowledge supportive of the identification of small molecule compounds that might have equal or greater efficacy than corticosteroids, but with fewer side effects. Efforts in this direction have already identified dissociative steroids (e.g., VBP15)—drugs optimized for their anti-inflammatory activity, while minimizing the glucocorticoid receptor engagement activity thought to underlie the side effects of the drug class. Clinical trials are being planned to test a drug with this mechanism of action.

Corticosteroids are standard of care for DMD, and thus represent baseline treatment underlying most clinical trials of novel agents. There is a substantial gap in understanding the potential interactions of steroid treatment with small molecule and biologic-based therapies. A recent gene therapy study suggested just such an interaction; in that study, the frequency of dystrophin-specific T cells was observed to be lower in patients treated with deflazacort compared to prednisone. Understanding the mechanism of action of corticosteroids in the muscular dystrophies will support studies of drug-drug and drug-biologic interactions of many

agents under development that likely will be administered under a baseline of corticosteroid therapy.

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3. **Examine the efficacy of existing immune-modulating and anti-fibrotic drugs for treatment of muscular dystrophy**

   Validation and targeting of pathogenic pathways that are downstream of the primary genetic defects in muscular dystrophy remains an important goal for the field, particularly since drugs targeting these pathways may have efficacy in multiple types of muscular dystrophy. New chemical entities targeting downstream pathways are either in or close to entering clinical evaluation for muscular dystrophy indications. Clinical trials of new or repurposed immune-modulating or anti-fibrotic agents should have an appropriate level of preclinical evidence of efficacy and safety in order to establish clear rationale for moving forward. Then, carefully planned, harmonized, and well-controlled clinical studies may ascertain whether such drugs have a role in different forms of muscular dystrophy or not. A potential path forward has been addressed by the International Rare Diseases Research Consortium (IRDiRC), and reports may provide important guidance.

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4. **Evaluate the efficacy of existing therapies for myotonic dystrophy symptoms affecting disease burden.**

   Symptoms that affect disease burden in myotonic dystrophy patients include pain, daytime sleepiness, diminished cognition and follow through, muscle and central fatigue, loss of strength, myotonia, and gastrointestinal disorders. Studies have demonstrated efficacy of mexiletine, a drug used to treat cardiac arrhythmias, for myotonia in myotonic dystrophy patients. Other existing drugs may hold promise for the treatment of symptoms affecting the brain, muscle, gut, and other organs. Anecdotal data may be available, which could help to prioritize candidate treatments for clinical trials.

Cell and gene therapy/editing:

5. **Improve the efficiency of gene therapy delivery in the muscular dystrophies, while minimizing the immune response to both gene product and delivery vehicle in patients**

   Considerable progress has been made over the last decade in improving efficiency of gene delivery in animal models. Multiple new AAV serotypes have been developed in order to achieve greater affinity for skeletal muscle and less affinity for other organs (e.g., liver). One current difficulty for this therapeutic modality is the length of time required to develop a clinical program and obtain regulatory approval—as a consequence, clinical trials may evaluate vectors that may not be the current state of the art. As technological advances in vector development are likely to continue, if not escalate, a strategy to facilitate more efficient entry into clinical trials is needed.

   In addition to challenges associated with targeting vectors to specific cells or tissues (i.e., vector tropism), host immune response to vector and/or gene product has emerged as a major cause

of suboptimal efficiency in gene therapy for muscular dystrophy. Various approaches to reduce the immune response, from stringent vector purification to alternative engineering of the vector capsid to immune modulation of the host, have resulted in some progress, but optimization of gene therapy approaches and clinical trial strategies remains a clear need. Several gene therapy development programs are following a clinical trial path where exposure is gradually increased in subsequent trials; initial trials have used intramuscular delivery, then have moved to isolated limb delivery, and subsequently will evaluate whole body delivery. While this staged approach is necessary for safety, there is hope that cross-lessons can be learned and that testing of each new vector in a muscular dystrophy will soon be able to forego the staged delivery approach.

A recent workshop co-sponsored by the Muscular Dystrophy Association (MDA) and National Institute for Neurological Disorders and Stroke (NINDS) emphasized the need to focus on issues of: (1) what constitutes adequate rationale in order to move a gene therapy product into clinical trial; (2) fostering a better understanding of regulatory climate; and (3) drawing attention to intellectual property issues that will ultimately impact marketing (summary can be found here). Gene therapy clinical trials should be designed with knowledge of prior and other ongoing trials, to ensure that they complement them by asking questions that advance the field (e.g., new serotype, alternate delivery mechanism, different immune system status, etc.), as opposed to simply repeating the same experiment using a different gene.

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6. Evaluate the safety and efficacy of gene repair, stop codon readthrough, upregulation of compensating genes and exon skipping agents through additional translational studies and clinical trials

Gene modification strategies have drawn considerable attention for DMD and have potential applicability for other types of muscular dystrophy. The strong engagement of regulators of this therapeutic strategy, in both the U.S. and Europe, will inform therapy development across the muscular dystrophies.

A stop codon readthrough drug (Translarna) completed a Phase III clinical trial and has received conditional marketing authorization in Europe. Development of next generation approaches to readthrough drugs is an important goal. Breakthrough designation and other expedited programs may have a significant impact on therapy development for the muscular dystrophies; leading to the need for additional innovative approaches to collect clinical data. Given this regulatory path, there is a need for specialized registries and other infrastructure to support long-term post-marketing studies, to ensure thorough evaluation of safety and efficacy and to inform next generation chemistries.

There is significant interest in strategies to upregulate or overexpress normal genes to compensate for loss of function of another gene. For example, increasing the expression of utrophin, which has similar sequence and function as dystrophin, may help compensate for the loss of dystrophin expression in DMD. A candidate drug to increase utrophin expression (SMT C1100) is in early stage clinical testing. Biglycan, an extracellular matrix protein, is in preclinical development to harness its ability to increase utrophin expression and stabilize the muscle membrane in the absence of dystrophin. Viral vector gene delivery is another way to increase utrophin expression, and this may eliminate concerns of immune responses to modified dystrophin gene products. In addition to their potential as single therapies, the overexpression

of compensating genes may have potential in combination with approaches to repair or replace the primary gene defect. Increasing the expression of compensating genes for other dystrophies warrants further study.

Exon skipping also represents a clinically advanced gene repair strategy in DMD, but each oligonucleotide developed for this purpose is mutation specific and thus applicable to only a subset of patients. Thus far, the two exon skipping agents that have progressed to clinical evaluation are targeted to patients where reading frame can be restored by skipping exon 51 (Eteplirsen and Drisapersen). At least for the near future, oligonucleotide drugs for each subsequent exon will require a complete regulatory package. While stakeholders have raised issues of possible platform approval for exon skipping (i.e., that subsequent oligonucleotides targeted to additional exons could be approved based on the safety of backbone chemistry and on demonstrated safety and efficacy of one or more specific oligonucleotide sequences), regulatory issues in this area are unresolved and it currently is hard to see a clear path forward for the very rare exons.

Improved efficacy of oligonucleotide drugs may be obtained through further optimization of backbone chemistry, or development of small molecule drug co-treatment paradigms, that enhance their target exposure and thereby increase efficacy. Specifically, improvements in oligonucleotide backbone chemistry may increase cell penetrance and thereby enhance exon skipping efficiency. Data from preclinical studies suggest that adjunct small molecule approaches also may improve the effect of the primary exon skipping agent (e.g., recent data on dantrolene) and thus it is worthwhile to further develop screening platforms for the various exon skipping oligonucleotides currently in clinical development. Clinical trials for combination therapy approaches, using small molecule drugs to enhance the activity of oligonucleotide drugs, will be challenging, but may represent an important path forward.

Improving the processes and resources for patient care:

7. **Improve treatment for systemic consequences in muscular dystrophy patients: developing guidelines based on evidence and/or current practice standard of care and continually updating guidelines for multi-disciplinary aspects of these diseases**

   The systemic consequences of the muscular dystrophies are heterogeneous, and improvements in their clinical assessment and treatment can be better addressed through development and dissemination of evidence-based practice guidelines. To this end, Care Considerations were developed for DMD through a partnership of the CDC (utilizing the RAND Appropriateness Method, 2009) with healthcare professionals, university researchers, patient advocacy groups, and other governmental agencies—these guidelines were published in 2010 (Bushby et al., 2010a; Bushby et al., 2010b) and patient/family-appropriate versions have been issued by patient advocacy groups. An update of the DMD recommendations, to reflect the latest information from healthcare professionals who treat these patients and to account for increasing numbers of adults living with muscular dystrophy, was launched in 2013. CDC also is collaborating with the American Academy of Neurology (AAN) to extend this process and develop treatment and care guidelines for DM, LGMD, FSHD, and CMD. The AAN will develop guidelines using evidence from existing medical studies and expert opinion and will disseminate

the guidelines. The first of these new guidelines, for diagnosis and treatment of LGMD, was released in Fall 2014 with subsequent guidelines for CMD and FSHD released in Spring and Summer 2015. Given the rapidly moving progress in the muscular dystrophies, it will be important to revisit the care guidelines every three to five years.

Care considerations for the muscular dystrophies are addressing the multi-faceted nature of these diseases (skeletal muscle, central nervous system, heart, bone, respiration, psychosocial, rehabilitation, etc.). Less attention has been given to life management issues (e.g., palliative care, hospice, end-of-life care) and to unique needs of people living with muscular dystrophy who need routine primary care (e.g., cancer and other health screenings, vaccinations, nutrition and weight management). Development of medical multi-disciplinary teams represents the best means to implement care considerations, but may not be available at many of the sites where dystrophy patients receive their care. Implicit in best practices for clinical management of muscular dystrophy patients is determination of assessment modality, timing, and frequency of assessments and defining the criteria for intervention, based on those assessments.

Adequately measuring the adoption of care guidelines is a difficult task, but important to establishing a baseline practice upon which clinical intervention trials will have fewer variables to consider. Patient advocacy groups could be a critical partner in this task. In the case of rural and other underserved populations, telemedicine networks may be an important way to meet care standards. On the physician-patient level, attention needs to be given to improving both "measure adherence," the physician's implementation of care considerations, and "measure compliance," on the part of the patient. The patient advocacy groups can play a major role in increasing both adherence and compliance with care guidelines. Evaluation/accountability for adherence to care standards (a "clinics of excellence" model) has been established in other diseases (e.g., cystic fibrosis) and this model should be, and indeed is (e.g., Parent Project Muscular Dystrophy (PPMD) clinic certification program), considered for the muscular dystrophies.

The need for cardiopulmonary care considerations has been particularly acute, in part because of the considerable diversity in cardiopulmonary phenotypes across various types of muscular dystrophy. Although there is data available for the cardiac and pulmonary consequences of most types of muscular dystrophy, efforts toward establishing clinical care guidelines must address a moving target, as the standard of care inevitably changes with new means to diagnose and treat patients. Since many of the candidate therapeutics currently under development address only skeletal muscle, any consequent improvements in patient activity/mobility may exacerbate cardiopulmonary manifestations, if they are not concurrently addressed.

The evolution of diagnostic tools and interventions for the systemic manifestations of muscular dystrophies is an iterative process that should be ongoing for the foreseeable future. Often, there is little data to guide development of particular care consideration items. Thus, long-term surveillance registries, using Common Data Elements (CDE) and other collection standards, should be the norm in providing opportunities to revisit recommendations to ensure that they are evidence-based and optimize care. The changes in systemic phenotypes, as the standard of care advances in the muscular dystrophies, should be assessed via randomized clinical trials and observational studies. For example, in some of the less common LGMDs, the pathophysiology of cardiomyopathy and pulmonary involvement may have both similarities and differences from those in the more common muscular dystrophies—the lack of this knowledge is a substantial

barrier to improved care and therapy development. These disorders will need to be studied in a smaller format as dictated by their lower incidence, increasing the difficulty in arriving at best practices. By contrast, other forms of muscular dystrophy have a very different involvement of the cardiac and pulmonary systems. For example, DM exhibits cardiac and pulmonary pathophysiology that may be different from other dystrophies, requiring other approaches to clinical research and care. Emerging treatments that address the molecular defect in DM have the potential to change manifestations of this multi-system disease at multiple levels and will have to be understood and subsequently accounted for in the care guidelines.

Taken together, improvement of treatment paradigms for systemic manifestations of the muscular dystrophies will require the development and dissemination of guidelines for care. Coordination of care across multiple clinical departments and facilities is also a challenge. The Affordable Care Act provides reimbursement to accountable care organization for health information technology to enhance quality of care and preventing illness. This must be an evolving process, dictated by a deepening knowledge of the pathophysiology, the development of increasingly sensitive diagnostic approaches, and an understanding of the effects of emerging therapies. Dissemination of care guidelines is a critical component to ensure that best practices are applied at all clinics. Finally, standardization of care provides a consistent baseline upon which to evaluate interventions, and thus will be critical to the efficient and effective conduct of clinical trials.

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8. Improve treatment for cardiac consequences in muscular dystrophy patients: establishing evidence for use of FDA-approved agents and advancing new and more targeted therapies to treat the hearts of dystrophy patients.

Cardiac care for patients with muscular dystrophies varies markedly and is often based on insufficient evidence. Improved understanding of the role of standard heart failure management agents—including angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and diuretics—is needed. The use of such agents in combination and the identity of the optimal combinations need to be better defined. The use of ACE inhibitors or angiotensin receptor blockade is established practice for cardiac complications in some types of muscular dystrophy. Currently available data on the value of corticosteroids is inconclusive, and additional insights are needed as to whether their use negatively impacts other standard heart failure treatments. The use of beta blockers remains inconsistent and requires more definitive evidence–whether via trials or open label database/consortium analyses. More efforts and/or clinical trials to determine how and when to best use this treatment are needed—workshop participants acknowledged the difficulty in conducting appropriate placebo controlled trials of repurposed drugs in muscular dystrophy. As new drugs are developed to improve contractility of the heart, such as novel agents that target the cardiomyocyte contractile apparatus, the therapy options for muscular dystrophy may well expand. At present, drugs that affect cardiac muscle contraction and would be prudent in this population are extremely limited, and more work is needed in this area.

Consensus guidelines are needed to encompass the type and timing of early interventions for cardiac symptoms of the muscular dystrophies, as well as to make available more advanced management options. Once developed, these options should be readily available to neuromuscular disorder clinics and to patients and their families via websites for health care

provider/patient-based education. For DMD, many topics related to current standard of care and major gaps in knowledge were discussed at a workshop convened by NHLBI in collaboration with Parent Project Muscular Dystrophy in July of 2014. A report from this workshop summarizing contemporary cardiac issues in DMD was published and can be found here.

A critical area of need is identifying when and how to best evaluate for the presence and progression of cardiac disease in muscular dystrophy patients. Many different modes of imaging and other analyses are used in small studies, and this has added variance and confusion as to what parameters are best used to initiate therapy and/or predict risk. Establishing baseline data on cardiac structure/function is important. Currently, the tools used in young children with muscular dystrophy are frequently based upon clinical instinct, rather than driven by consensus guidelines. Each of the cardiac outcome measures used has its own variability and limitations, including cardiac MRI, echocardiography, or computerized tomography. The demonstrated sensitivity of cardiac MRI over echocardiography in evaluation of ejection fraction and other parameters of cardiac function may allow for the powering of studies with considerably smaller cohorts, and thus make MRI a better tool for conduct of clinical trials in the muscular dystrophies. In the development of therapies, optimization of tools to detect the earliest signs of cardiac fibrotic changes may provide opportunities for earlier intervention, rather than delaying interventions until systolic function changes have been detected. Overall, a better understanding is needed as to which cardiac parameters are most effective to use for clinical care and follow-up, and provide quantitative values for these parameters to guide therapeutic development and treatment.

Although there are guidelines for the use of internal defibrillators in the adult cardiomyopathy population, there currently is insufficient information to guide practice in pediatric muscular dystrophy patients. Cardiomyopathy patients with left ventricular ejection fraction of less than 30-35% percent are receiving implanted cardiac defibrillators. Alternative options for pediatric muscular dystrophy patients include external defibrillators. Even in the adult population of DM patients where cardiac manifestations include arrhythmias/conduction system abnormalities; there is a real question as to when implanted defibrillators are appropriate.

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9. Improve treatment for respiratory and pulmonary consequences of muscular dystrophies and address sleep disturbances.

There is a concern that the respiratory and pulmonary consequences of the muscular dystrophies have received insufficient attention, both from research and clinical practice perspectives. These consequences include ineffective cough, nocturnal hypoventilation, sleep disordered breathing and ultimately daytime respiratory failure. Such consequences are prevalent in DMD, congenital and other muscular dystrophies. Care guidelines for respiratory management in DMD have been published, and may provide a good starting point in developing strategies for other dystrophies. Interventions include volume recruitment training, cough assist devices, ventilators and tracheostomy tubes. Care strategies should strive to monitor hypercapnia, maintain respiratory function and use of minimally invasive interventions. Surgical anesthesia presents special risks to dystrophy patients. There is a need for additional training for pulmonologists and anesthesiologist in caring for dystrophy patients and to promote their participation in coordinated and comprehensive clinical care teams. Additional training for staff

in sleep centers to improve their knowledge for conducting testing on dystrophy patients is also needed.

Clinical outcome assessments for respiratory function, including forced vital capacity and peak expiratory flow, are available, and further use may strengthen clinical trial design. Additional studies are needed to validate respiratory outcome assessments for use in certain populations of dystrophy patients. Preclinical use of respiratory outcomes in animal models requires specialized equipment and training that few labs have. Existing core facilities that perform physiological testing on dystrophy animal models should consider adding services for evaluating respiratory function, if not currently available.

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10. Monitor, coordinate, and communicate the rehabilitation and educational assessment activities of the various Federal agencies, voluntary, and patient advocacy groups to identify clinical research needs and improve clinical outcomes

Given the complex multi-systemic effects of muscular dystrophies, and the evolving course of their natural histories and clinical management approaches, there is an ongoing need to identify high priority medical and rehabilitation requirements of patients with the different forms of muscular dystrophy. Such studies represent a prerequisite to determining the additional resources and infrastructure required for optimal patient management and treatment. Partnering among Federal, academic and voluntary organization stakeholders is needed to promote innovation that emphasizes activities of daily living in clinical studies and trials. There also is a clear need to understand and optimize how different aspects of clinical care can best work together in coordinated management of what are multi-systemic diseases.

The expanding number of patient registries, prospective studies using existing and new patient databases, and patient reported outcomes of care for associated medical problems (e.g. PROMIS network) can be used to define clinical needs. Necessary additional resources and infrastructure can be identified through partnerships with large patient populations, such as clinics and networks sponsored by the MDA or other patient organizations, as well as through clinical investigations of muscular dystrophies currently funded by Federal and non-Federal stakeholders. Patients, health care providers, social services, health care economists, government agencies, and private industry, as well as academic biomedical researchers, are groups that should be encouraged to partner on such studies. Standardization of data collected and compatible computer networking are needed to accomplish these goals.

Training and research opportunities and mechanisms to partner with various Federal Government and non-governmental groups should be explored as strategies to facilitate studies that define the natural history and determine optimal treatments for the highest priority medical and functional problems associated with each type of muscular dystrophy. Defining approaches to address clinical problems that occur at specific stages of each of the muscular dystrophies will be a necessary part of achieving this goal. Standardization of clinical information tracked for each form of muscular dystrophy and how it is stored by muscular dystrophy centers will greatly facilitate these efforts.

Improving the process of therapy development:

11. Evaluate the endpoints needed for clinical trials in the muscular dystrophies

Note: this objective strongly relates to biomarker objectives in the Diagnosis, Screening, and Biomarker section of the Action Plan—research needs associated with molecular, biochemical, and imaging biomarkers with potential applications as outcome measures are primarily reviewed in that section.

The clinical endpoints necessary for early phase clinical trials are primarily safety-related, and these are fairly standard and generally accepted. By contrast, the efficacy outcome measures for various muscular dystrophies, and for various stages of disease, continue to be evaluated in order to provide both initial indications of efficacy and proof of concept for both early and later phase clinical trials. Endpoint measures for therapeutic registration trials must be sufficiently robust, but also feasible for trials of one year or less in duration—this is a tall order for the slowly progressive muscular dystrophies, but their importance cannot be overstated. TREAT-NMD has established a Registry of Outcome Measures (http://www.researchrom.com/), which serves as an important information source for the muscular dystrophy field.

Potentially valuable endpoint measures emerge from careful natural history studies, where the longitudinal behavior (magnitude and temporal properties of change) of the measure is determined. To date, natural history studies have evaluated measures of ambulation (e.g., 6-minute walk test) and upper extremity function in multiple types of muscular dystrophy, as well as at various stages of disease. There is a need for improved outcome measures of muscle function over a longer period of disease progression, so that patients who lose ambulation can remain in clinical trials. Measures of respiratory and cardiac function are important because of their close relationship to patient survival. Longitudinal studies of imaging biomarkers and other measures are underway for a few types of dystrophies. Valid clinical trial design depends upon meaningful assessment tools. Rasch analyses (determinations of the fit between data and model) are recognized as an important tool in assessment of the reliability of clinical trial outcome measures. In the muscular dystrophy field, a few groups have completed Rasch analysis of a limited number of outcome measures, but much more effort is needed in this area, including increasing the involvement of statisticians in both outcome measure assessment and clinical trial design.

Development of clinical outcome measures that are independent of external variables, such as motivation, is an important goal. To this end, imaging biomarkers for muscle quality (rather than quantity) continue to be explored, with the ultimate intent of validating them as registration trial endpoints. A recent study demonstrated the capability of muscle MRI/MRS to detect the therapeutic effects of corticosteroid treatment in DMD. Additional work is necessary to achieve qualification for such non-invasive measures of muscle quality (e.g., muscle fibrosis, fat infiltration) for use in clinical trials.

In terms of bioethical issues, the regulatory approach to pediatric patients in early phase clinical trials has been well defined. Each child must have the potential to benefit from a trial in which there is more than minimal risk. In practice, this often means that either there is no placebo group or there is an extension trial in which participants who are randomized to placebo are crossed over to treatment group. An important step has recently been taken to evaluate risk-benefit considerations in DMD. The availability of information about family attitudes toward risk

versus benefit of a particular intervention has drawn attention from regulatory authorities and thus these analyses may prove important to approval of drug and biologic therapies. Additionally, bioethical issues likely will still be encountered for clinical trials in types of muscular dystrophy where central nervous system delivery is required in pediatric subjects. It is considered ethical for adults to participate in more than minimal risk studies, if the disease population has the potential to benefit.

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12. Improve understanding of disease burden, quality of life, cognitive, and central nervous system function for the muscular dystrophies through continued development and use of standardized instruments. I

Instruments have been advanced for the measurement of disease burden and quality of life in the muscular dystrophies—accurate information is important for evaluation of the effectiveness of intervention programs and novel therapeutics. Various quality of life tools have been used in assessments of individuals with muscular dystrophy. There is a continued need to assess the availability of existing data, measures and databases and identify gaps in an effort to develop comprehensive resources, extend research capabilities and promote common data elements across the muscular dystrophies. The development of muscular dystrophy type-specific patient-reported outcome measures that include quality of life assessments (e.g., such as those developed for DM and FSHD) would represent an important advance for clinical studies and trials and further effort on their development is warranted.

The status of tools for cognitive and neuropsychological assessments for patients with muscular dystrophies was viewed as quite limited and warrants additional research focus. While some instruments have been developed, a systemic assessment of the value of these instruments for the muscular dystrophy field has not yet been undertaken and could lead to improvements in tools for clinical studies and trials.

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13. Better establish readiness for clinical trials in all types of muscular dystrophy and initiate clinical trials

For most of the rare muscular dystrophies, there have not yet been any clinical trials. Even in more common muscular dystrophies (e.g., DM and FSHD), acquisition and sharing of natural history data could be improved and there have been few clinical trials in recent years. To drive clinical trials in these diseases, it is important to focus on establishing natural history and consequent design and validation of outcome measures to support trials of a feasible duration. Clinical trials utilizing targets and treatment modalities that may, at most, have a mild impact on disease are still beneficial in mobilizing the community and gaining experience with disease-specific outcome measures and trial design. Moreover, evidence of trial readiness and clinical trial expertise and experience within the community serving the rarer types of muscular dystrophy would help to attract industry interest and the development of novel, targeted therapeutics. Also, dialogue around regulatory issues that may be specific to the particular type of muscular dystrophy, and discussion of reimbursement, are essential tasks best addressed early in therapy development programs for rare muscular dystrophies. While obtaining support for clinical trial readiness activities is often difficult, the muscular dystrophy field is encouraged to explore options such as those available through the NIH Rare Disease Clinical Research Network initiative, which is designed to fund clinical trial readiness and early stage clinical trials.

14. **Be rigorous and systematic about the de-risking process of drugs and biologics that are advanced into clinical trials**

Many clinical trials fail. Among the avoidable failures are those trials that are initiated without sufficient preclinical rationale to support clinical testing. Preclinical studies should be designed and conducted rigorously in order to adequately de-risk the drugs and biologics that are moved into clinical testing in muscular dystrophy patients. The NIH is developing new policies around rigorous design of preclinical studies and a consortium of scientific journals has developed policies where transparency of reporting of methodology and data is expected of submitted manuscripts. The TREAT-NMD Translational Advisory Committee on Therapeutics (http://www.treat-nmd.eu/resources/tact/introduction/) model is also a way to address this concern. This committee independently evaluates the status of therapy development candidates (from robustness of preclinical data to medicinal chemistry plans to clinical trial design to regulatory issues), with their evaluations used in corporate and/or funding agency go/no go decision making. A lesson from the experiences in therapy development in the muscular dystrophy field is that interactions between the academic and industry communities are essential in de-risking the candidate therapeutics that are taken into clinical trials and increasing the likelihood of trial success.

Researchers are also encouraged to publish significant negative findings that are of value to the research enterprise. Such publications will increase transparency in scientific reporting, reduce efforts spent on "dead ends" and will provide publications needed for career advance of students and fellows involved in the research. The Journal of Negative Results in Biomedicine was created for these purposes.

LIVING WITH MUSCULAR DYSTROPHY

The Living with Muscular Dystrophy Working Group focused on the considerable change that has taken place in the last decade. The 2005 MDCC Action Plan emphasized research objectives that largely were the purview of academic investigators supported by a limited number of Federal agencies and patient advocacy groups. In its current iteration, the Living with Muscular Dystrophy Working Group identified high-priority objectives that were more patient-centric and will require a broader range of stakeholders to address. In addition, as therapies targeted to the skeletal muscle and cardiac consequences of the muscular dystrophies have been emphasized in preclinical and clinical development, assessing and managing the multi-system consequences and impacts on patient well-being of this disease class have become a priority and are emphasized in this document. Finally, it was universally recognized that as treatments for some childhood onset muscular dystrophies lengthen life, resources will be needed to help individuals transition from pediatric care to adult providers.

Quality of life and burden of disease measures:

1. **Identify and evaluate the quality of life and burden of disease measurement tools that are currently available**

   Considerable progress has been made toward the goal of having effective quality of life and burden of disease measurement tools for use in clinical studies and trials for the muscular dystrophies. There now are several web-based catalogs that list measurement tools (e.g., a TREAT-NMD database (http://www.researchrom.com/masterlist#i) and NIH PROMIS network's Assessment Center (http://www.nihpromis.org/software/assessmentcenter). The TREAT-NMD site lists tools by domains, languages, age group, and references, but does not specifically address their sensitivity, reliability, validity, or psychometric properties, and the list of outcome measures is not comprehensive. While the PROMIS Assessment Center identifies instruments that were designed to measure specific domains in the general public, these outcome measures are not specific for the muscular dystrophies and, in most instances, were not created or validated for use in muscular dystrophy populations. There is a clear need for additional work to disseminate information about the availability and qualification of burden of disease measurement tools.

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2. **Develop disease-specific quality of life and burden of disease measures where gaps in existing measures are found**

   There are few properly validated disease-specific (patient-reported) instruments available for individual types of muscular dystrophy. The FDA has approved and encouraged the use of such measures for drug labeling purposes—their development may facilitate approval of therapeutics and thereby increase the attractiveness of muscular dystrophy indications to the pharmaceutical industry. Although some outcome measures of this type have been initially developed using sound psychometric principles, fewer have undergone the necessary rigor to definitively demonstrate and document their covered domains, age range, sensitivity, reliability, validity, and psychometric properties. Some generic and semi-generic patient-reported outcome measures exist; however, while useful to compare populations with different diseases, they may have lower precision, poorer responsiveness, decreased relevance, higher ceiling effects, and decreased sensitivity compared to disease-specific instruments when used in therapeutic trials.

While substantial work has been done to validate disease-specific outcomes in several dystrophies (e.g., DM types 1 and 2, childhood-onset and juvenile DM type 1, and FSHD), there continues to be a considerable need to create and validate instruments for other select muscular dystrophy populations in preparation for clinical trials. The burdens of adult onset dystrophies can be quite different from those of children, and improvements in instruments are needed to effectively measure the burden experienced by each patient. Since the efficacy of interventions targeted to early onset muscular dystrophies likely will be optimized by treating the youngest patients, measures that evaluate quality of life in pre-verbal children and infants will also be important. Subsequent efforts to develop and validate disease-specific quality of life and burden of disease measures should also address caregiver burdens to help identify useful interventions for this population.

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3. Assess the cognitive, neuropsychological, and neurobehavioral profiles that most impact quality of life of people living with various forms of muscular dystrophy and identify interventions and supports to positively impact quality of life

Several forms of muscular dystrophy include specific neuropsychological and neurobehavioral profiles as components of the disease. The specific neurologic impairments are, however, variable and include mild to severe developmental disabilities, learning disorders, difficulty coping with disease, stress/depression, executive function impairment, and problems with behavior, interpersonal relationships, and community participation. These impairments are quite different for adult onset dystrophies compared to infant or childhood onset. The degree to which cognitive impairments may be progressive in specific forms of muscular dystrophy is variable and is an area of investigation that has not be widely explored; yet, the cognitive, neuropsychological and neurobehavioral symptoms of muscular dystrophy are sometimes reported as those with the most significant impact on quality of life. Thus, there is a research need for formal assessments of the cognitive, neuropsychological, and neurobehavioral profiles that most impact quality of life of people living with various forms of muscular dystrophy, as well as a systematic identification of interventions and supports to positively impact quality of life of these individuals.

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4. Advance research into reproductive health issues in the muscular dystrophies

There is a need to expand research and education on reproductive and sexual health, and document the importance of these issues to patients and family members. Studies should assess what is currently known related to sexuality, quality of life, fertility, genetics, and parenthood, how these issues impact relationships, and where gaps in knowledge may exist.

The scarcity of support, services, and resources for individuals living with muscular dystrophy who choose to bear children must be addressed. Opportunities for outreach and care include a broad range of issues from genetic counselling, support and management during pregnancy and other aspects of obstetric care, to systemic support of cardiac, pulmonary, GI/GU health throughout pregnancy, delivery, and beyond.

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5. **Conduct studies to determine the economic impact of the muscular dystrophies on patients, families and society.**

   Better understanding of the economic impact of the muscular dystrophies on patients and families, and costs to state and federal governments and to society can inform policy decisions with the potential to improve patients' care and quality of life. Economic analyses should take into account disease incidence and prevalence, medical care utilization and expenditures, costs of social and educational services, costs of transportation, care coordination, home and vehicle modifications, and the lost income and productivity of patients and family caregivers as well as employers. Establishing effective data collection methods and analyzing economic impact of the dystrophies in a comprehensive manner will facilitate decision making in allocating resources for patient care and providing access to programs that can improve quality of life and benefit society. In this area, the MDA completed a preliminary study of the costs associated with DMD and DM, and TREAT-NMD has reported on the cost of illness and economic burden in DMD. A thorough understanding of the economic burden of the muscular dystrophies at a national level will also facilitate a discussion of investment opportunities for the Federal government and for private corporations regarding research and treatment.

Prioritizing and facilitating clinical trials:

6. **Determine the sensitivity of clinical endpoints to changes in disease severity and the magnitude of changes in endpoints which are clinically meaningful to patients and family members**

   While development and validation of endpoints to measure therapeutic benefit in clinical trials is an important goal for each of the muscular dystrophies, the concern here is whether there is a correspondence or a discrepancy between how clinicians interpret meaningful change and how families and affected individuals interpret meaningful change. Regulatory agencies have increasingly moved in the direction that approval of therapies requires attaining an endpoint regarded, by the subject, as of clinical benefit (e.g., impact on activities of daily living). Attainment of this goal requires involvement of people with muscular dystrophy and patient advocacy groups in clinical trial design. Another approach is the development of a patient-powered portal network that allows for self-reporting of symptoms and changes over time, and of fluctuations in symptomatology and how it impacts daily functioning. Finally, regulatory agencies are now taking into account risk versus benefit considerations of people with muscular dystrophy. Such analyses have been piloted in DMD by Parent Project Muscular Dystrophy (PPMD) and could provide important contributions for other types of muscular dystrophy.

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7. **Develop standardized data collection approaches nationally using clinically meaningful, readily obtainable parameters; develop a minimum data set for national data gathering efforts; complete and maintain Common Data Elements (CDEs) for muscular dystrophies across life span**

   The standardization of data collection approaches across clinical studies and clinical trials in the muscular dystrophies is essential to data interpretability and comparability (meta-analysis). The community should take advantage of every opportunity to share information to gain knowledge

of disease progress (e.g., aggregation of phenotypic data from study participants who were assigned to a placebo control group).

The NINDS CDE project (http://www.commondataelements.ninds.nih.gov/) has taken an important step in the standardization of data collection by developing CDEs for DMD/BMD, CMD, and FSHD, as well as for DM. In implementing its new registry system, the MDA is adopting the NINDS CDEs. To take full advantage of CDEs, their use needs to be harmonized within and across individual physician records, clinical studies and trials, and registries, as this would allow for improved linkage of disparate databases, registries, and clinical study/trial efforts. Achievement of this goal likely will require steps to both standardize collection and an ability to extract data directly from electronic medical records. Supporters of muscular dystrophy research can help facilitate the widespread use of CDEs by encouraging applicants to use CDEs whenever possible. It is also important to note that the FDA has expressed a desire for all data submissions to be submitted in the Clinical Data Interchange Standards Consortium format, or CDISC. While CDEs provide a list of features to measure, CDISC standards help define how those measurements should be recorded. The standardization of both of these elements is likely to expedite the comparison of data sets and the entire regulatory review process in general.

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8. Determine the benefits and risks of varied exercise approaches in the muscular dystrophies and develop scientifically based recommendations concerning optimal exercise, physical activity, and recreation; examine nutrition both in relationship to exercise, and as an independent variable in improving the lives of those living with muscular dystrophy

Questions as to the potential beneficial/detrimental value of exercise (and, where recommended, the parameters of exercise) are among the most common inquiries received by patient advocacy groups in the muscular dystrophy arena. There continues to be an ongoing flux of studies evaluating exercise in muscular dystrophy populations. These studies include, but are certainly not limited to: group exercise training in DM1, physiotherapy in LGMD, physical training in DMD, a rehabilitation program in DM1, aerobic exercise in FSHD, an endurance program in BMD, and aerobic training in DM1. Strenuous exercise is known to cause transient muscle damage and increased serum creatine kinase levels in healthy people, and may accelerate muscle degeneration in dystrophies. Studies of exercise regimens designed for dystrophy patients have either been positive (demonstrating the usefulness of exercise), or non-conclusive (usually due to limitations in study design). There have been no rigorously conducted studies that have suggested that appropriately designed exercise programs are detrimental to patients. Additional, rigorously designed and conducted studies are needed so that recommendations for a safe and effective protocol can be made. Studies outside of the muscular dystrophy field have universally shown the benefit of exercise. One clear research hurdle involves not only finding the optimal exercise for muscular dystrophy patients, but also finding factors that encourage patient participation. There remains a substantial gap in knowledge of the value and recommended type/intensity of exercise that is recommended for individuals living with muscular dystrophy. The exercise question remains an important one and the answer may differ from one type of muscular dystrophy to another.

A correlate to recommendations on exercise is another set of unresolved questions about diet and performance supplements/drugs. These variables collectively influence metabolic activities

of persons living with muscular dystrophy and, in turn, may determine the course of cardiac and other chronic conditions. In addition to the need to address these questions directly in the affected population, additional preclinical studies may yield additional insights into the interaction of diet and exercise in the muscular dystrophies. Finally, the background nutritional and exercise programs of patients participating in clinical trials may directly influence intervention efficacy and thus should be studied and accounted for in clinical trials.

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9. Assess the prevalence of secondary conditions in muscular dystrophy using existing longitudinal data collection efforts; assess the effectiveness of clinical management approaches to prevent and treat secondary conditions

Several registries now exist for one or more types of muscular dystrophy (e.g., MD STARnet, MDA's Clinical Neuromuscular Disease Registry, Duchenne Connect, the National Registry for Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy, the Congenital Muscle Disease International Registry, etc.). There is now considerable ability to identify and characterize unique complications that may be either disease-specific or pan-muscular dystrophy. Conceptually, the muscular dystrophy field may be better served by thinking of these not just in terms of isolated secondary conditions, but rather expanding the phenotypic spectrum of the muscular dystrophies in integrated management of the diseases. In identification, characterization, and multi-disciplinary management of such secondary consequences, the extensive longitudinal databases being collected in registries could have considerable value.

In addition, there are substantial variations in the clinical management of secondary conditions, between centers and even within an individual center. This can largely be attributed to gaps in dissemination of care guidelines where they exist, or the lack of evidence-based care guidelines for many secondary conditions. The problem needs to be addressed through rigorous, prospective, multicenter studies to generate practice guidelines to prevent and manage secondary conditions and to ensure dissemination of the guidelines.

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10. Newborn screening and infant identification: a need for a national outreach, care, information, and support delivery model

As infants and babies affected by muscular dystrophies are identified earlier (and pre-symptomatically), the ability to streamline referral processes and outreach services becomes critical, not to mention the future possibility of starting treatment earlier. It also will be important to establish infrastructure to capture these data (e.g., national level registry). While a few state pilots have successfully demonstrated the capacity to initiate integrated services for newborn screening in one form of muscular dystrophy, efforts must ensure that this model is reproducible across the nation, within a variety of state health systems and birthing center models, and through innovative collaborations across the muscular dystrophy patient organizations and expert neuromuscular care centers. In particular, a delivery model for national outreach will be necessary if wide-spread newborn screening is to be feasible and successful. The Duchenne newborn screening pilot done in Ohio provides important lessons for future activities, in that it was a very intentional model of coordinated information delivery and family support services across the birthing centers, the community pediatricians, and the community

support resources. As efforts include multiple types of muscular dystrophy, delivery of information and support services must be carefully tailored to the specific type of muscular dystrophy.

Lifestyle, education, and employment issues:

11. Using novel partnerships and research approaches, identify strategies to improve patient integration into educational systems and employment

Information is readily available to school systems to support the education of children with muscular dystrophy in the least restrictive environments. In particular, the MDA offers "A Teacher's Guide to Neuromuscular Disease," "Education Matters" is offered by PPMD, and the FSH Society has childhood education resources. These organizations, in partnership with the families they serve, should continue to work to push these resources out to school systems and the educators and administrators that comprise them. Good educational tools concerning the rights and responsibilities of students with muscular dystrophy and their families are available through patient advocacy organizations, and in the public domain. Patient advocacy organizations, in partnership with independent living centers, should continue their work to empower families through availability of this type of information and self-advocacy training.

A systemic program to assess the effectiveness of the No Child Left Behind Act (NCLB), the Individuals with Disabilities Education Act (IDEA), and other education programs as they relate to muscular dystrophy patients remains a research need.

Progress has been made in educational integration into college. Indeed, the MDA's Transitions Survey indicates that adults with pediatric onset neuromuscular diseases are more likely to be college educated than the general population. However, because vocational rehabilitation agencies are often reluctant to sponsor graduate education, and graduate education is now frequently required for employment opportunities that pay the type of salaries that would allow people with muscular dystrophy to address their independent living needs, access to graduate education must be expanded for people with muscular dystrophy. Although students with muscular dystrophy are doing well in terms of participation in college, they did not fare nearly as well when compared to their peers with other disabilities. Research is also needed to help inform and address employment disparities.

There has been some improvement in collaboration between school systems and state vocational rehabilitation systems in promoting successful transitions from high school to college or employment. However, more work must be done to create synergy between student 504 Plans and Individualized Education Programs (required by the IDEA) and the Individualized Plans for Employment (required by the Rehabilitation Act) especially as they relate to the needs of dystrophy patients. The Department of Labor has several resources that may be helpful for the muscular dystrophy community within the Office of Disability Employment Policy. One additional note is that efforts should be made to avoid the reinforcement of stereotypical vocations for individuals with muscular dystrophy.

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12. Empowering autonomy, independent living, and employment through exploration of alternate resource models for men and women living with muscular dystrophy

Men and women with pediatric-onset muscular dystrophies are now living decades into adulthood and outliving their parents. While this is a remarkable achievement, it creates new challenges to ensure that patients continue to receive comprehensive clinical care in their transition to adulthood, and they do not encounter unnecessary obstacles in their education and integration into employment and society. Individuals living with adult-onset dystrophies experience the loss of abilities, progressive functional limitations or other factors that affect quality of life including pain and withdrawal from social interactions.

The Americans with Disabilities Act and IDEA allow for access to educational systems and public facilities, however federal resources that support employment and independent living are tied to poverty (rather than disability). This can create obstacles to independent living, and acquiring or maintaining gainful employment for adults with muscular dystrophy. Changes in policies are needed to improve the circumstances for adults with dystrophies and avoid a crisis. Too often, adults with dystrophies are living with family members or in nursing care/institutional living, which can contribute to lives of dependence and isolation. There often is considerable burden of disease for family caregivers, including providing for long-term care and funding for in-home personal care assistants).

There is a substantial need to explore independent living issues, including accessible housing, personal care attendant funding reimbursement, and support to enable independence and employment, accessible transport and mobility, benefit navigation, tax issues, and more. Research into innovative devices that support independent living is an important part of the answer. Tracking the costs of the current model and savings through improvements would provide important data for health economic research to demonstrate return on investment in promising programs that empower men and women to be/remain employed (tax payers) if they choose, rather than the current benefit model tied to poverty and institutionalization. Addressing the problem must involve efforts of a broad cross-section of Federal Agencies that are already engaged outside of the muscular dystrophies. Services such as personal care attendants are currently lost when an income threshold is reached, thereby creating a disincentive to work for people with disabilities. Patient advocacy partners have been working to change this paradigm in partnership with the DoEd, Department of Labor, Centers for Medicare and Medicaid Services, and the SSA and have held two federal summits to begin to address the problem. The MDCC provides an important forum to discuss this system and explore more fiscally beneficial models that promote 'independence' from the system.

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13. Address mental health needs and opportunities for improving social connectedness throughout the life-span of individuals and their family members

Understanding of the potentially unique psychiatric and psychological issues that are endemic to people with chronic progressive conditions represents a substantial gap, and research effort and intervention development represent unmet needs for people living with muscular dystrophies. Mental health services are reportedly under-utilized across muscular dystrophy patient communities and seldom do even more advanced, multi-disciplinary neuromuscular clinical teams include regular services from specialized mental health providers. Throughout the life-

span, family members often report elevated levels of stress, anxiety, depression, worry, isolation, and fear. While connections to other patient community members are beneficial, formalized assessments of the availability of interventions from trained mental health professionals may improve quality of life and overall satisfaction. With these considerations in mind, progress towards this objective should be measured using quality of life, social satisfaction, and social isolation indices. Research efforts should be initiated to formally evaluate mental health needs within the muscular dystrophy community, both for individuals living with muscular dystrophy as well as their families. Efforts should also be made to increase outreach in this area and promote the use of existing mental health services for all individuals with muscular dystrophy as well as their caregivers and families.

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14. Create a national formalized assessment of vocational outcomes for adults living with muscular dystrophies transitioning to, or remaining in the workforce as a basis to identify strategies to improve vocational outcomes

Vocational Rehabilitation services facilitate the transition from school or training programs to work and community living for youth and adults with significant disabilities. As men and women with muscular dystrophies complete vocational trainings, college, and graduate school and seek to enter the workforce, there is a need to systematically support and track that transition through federal partnerships. Individual with adult-onset dystrophies experience obstacles to their remaining in the workforce as their disease progresses. Partnerships with community, professional, and governmental entities are needed to improve outcomes and to engage in activities such as piloted navigation of benefits/resources, rehabilitation support for workplace accommodations, and tracking of workplace integration. The data collected through such a national formalized assessment could provide the basis for calculating the return on investment for education, training, benefits retention, employee productivity and job accommodations. This would inform public policy decisions related to adults with significant disabilities entering or remaining in the workforce.

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15. Educate and empower people with muscular dystrophy in self-management strategies and educate their family members and primary care providers to promote and reinforce these strategies.

Patients that take an active role in the management of their condition can decrease the burden and experience better outcomes. Self-management includes an awareness of the course of the disease, participating in decisions regarding treatment options, and maintaining compliance with treatment regimens. Patients should also learn about exercise, nutrition and dietary supplements, and share this knowledge with family members and care providers. Enhanced independence and social interactions can improve mental health. Self-management will also facilitate transition to adulthood and independent living.

INFRASTRUCTURE FOR THE MUSCULAR DYSTROPHIES

The 2015 MDCC Action Plan for the Muscular Dystrophies process did not engage a Working Group to address infrastructure needs. Instead, cross-cutting objectives in the infrastructure arena emerged during the discussions of the other five Working Groups and have been assembled here.

Facilitating mechanistic and preclinical studies:

1. **Establish additional mouse and large animal models to facilitate advances in understanding disease mechanisms, to develop candidate therapeutics, and to identify and characterize disease modifying genes**

   Development of new and improved mouse models that better replicate the mechanisms of human muscular dystrophies may allow investigators to better characterize those mechanisms and increase the likelihood that therapy development would translate successfully from mice to clinical trials. In addition to mice, canine and newer porcine models in development for some muscular dystrophy types can provide an important bridge from mouse studies to human trials. Adequate access to appropriate models and the availability of optimized standard operating procedures (SOPs) remains a limitation for some research on the dystrophies.

   Progress has also been made in developing and publicizing SOPs for testing disease related outcomes in DMD and CMD animal models (see SOPs for Animal Models maintained by TREAT-NMD for DMD and CMD). However, these resources are not available for all forms of dystrophy or all important outcomes. SOPs for outcome measures must also be updated as new testing technologies become available.

   In addition to SOPs for testing phenotypes and outcomes in mouse models, there are also needs for SOPs for assays that probe mechanisms of the disease. For example, there need to be optimized methods for testing whether apoptosis or inflammation contribute significantly to the pathology in the mouse model. This could streamline the steps between establishing a novel dystrophy mouse model and selecting candidate therapeutics to test in clinical trials, if dystrophies are grouped according to common pathophysiology, therapeutic targets or modifier genes.

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2. **Establish invertebrate, other vertebrate, and alternative model systems to study pathogenetic mechanisms of gene/RNA/protein defects that cause muscular dystrophies in human**

   Much progress has been made in relationship to this objective. Perhaps the most impressive area of growth has been the identification/generation and characterization of zebrafish models of muscular dystrophies. Models, both transient (usually morpholino based) and germline mutants (usually through ENU mutagenesis but more recently using gene editing technologies), have emerged for nearly all muscular dystrophy subtypes. Furthermore, the fish models have enabled new insights into the pathogenesis of muscular dystrophy, and have provided a novel platform for drug discovery. Both targeted treatment studies as well as non-biased drug screens have been performed on zebrafish models of muscular dystrophy, and particularly on models of dystrophinopathies. There has also been further development and study on invertebrate models. Most notably, there have been interesting studies using the *C. elegans* model of DMD

and fly models of DM1 and sarcoglycanopathies. These have served as unique adjuncts to mammalian and cell culture studies.

Moving forward, there is a need to establish additional zebrafish models (particularly knockouts and those with specific point mutations) for screening, as well as to more actively utilize both new and existing models for drug discovery. Also, more intensive work using flies and worms, and linking those studies with zebrafish in a drug development pipeline, would be of great help. As with other animal model studies, the quality of the data will be enhanced and the research will proceed more efficiently if SOPs for outcome measures and infrastructure for the sharing and quality control of models are developed and widely utilized by the research community.

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3. Facilitate studies of human disease mechanisms and the translation of discoveries of pathogenic mechanism from animal models to human by increasing the availability of well characterized, high quality tissues/cells/serum and clinical data from muscular dystrophy patients

There is a need for easy access to anonymized patient data and samples to test hypotheses of disease mechanisms and to determine whether mechanisms identified in animal models of muscular dystrophy also contribute to dystrophy in human patients. Researchers face obstacles in obtaining appropriate biospecimens from dystrophy patients. Repositories of patient samples are being developed for DMD/BMD, DM and FSHD, with support from public and private organizations. But, better integration of these samples and data and greater awareness of their availability in the research community would make access easier and increase utilization. Repositories do not exist for many of the other rarer forms of muscular dystrophy.

Further study of affected tissues such as cardiac and diaphragm muscle (or retina in the case of FSHD) is limited by the availability of scarce tissue samples. Through advances in adult heart failure therapy, there has been increased availability of myocardial tissue (generally available from heart transplantation, but also from heart biopsy). Patient-derived tissue for the study of muscular dystrophy-related cardiac disease has been extremely rare, and, as a result, the understanding of the molecular biology and histology of cardiac involvement remains rudimentary. While heart transplantation is not likely to be a treatment modality and left ventricular assist device samples also remain limited, studies that couple myocardial biopsy samples with blood samples for molecular and genetic analyses could shed light on this poorly understood aspect of muscular dystrophies. The ethical issues associated with myocardial biopsy are significant, but biopsies are being obtained in adult patients with other forms of heart disease in order to advance research and aid in the development and testing of new therapies.

Creating a more coordinated, national system for the collection, storage and distribution of tissue samples from muscular dystrophy patients for research is plausible, but will require active cooperation from interested muscle pathologists at sites where archived muscle biopsies are stored. There are a number of private labs that are not participating in research and their pathology groups are not interested in storing materials long term. Institutions interested in archiving biopsies should be identified so that biopsies from such labs can be transferred for storage and distribution. Filling requests from researchers requires a careful, hands-on approach from a muscle pathologist, so additional support for these activities would be necessary.

Also, banking and distribution of samples from animal models, especially dogs, can accelerate progress and make research more cost effective.

A central repository is not necessarily the only way to fill the need for increased availability of patient samples. As an alternative to a centrally located repository, the availability of a consolidated inventory linking repositories to registry data, and including global patient identifiers, and CDEs for samples that are housed at various institutions could also benefit researchers. This objective will need extensive informatics development and staff/IT support to make it available to the scientific community. Researchers who collect and distribute samples require support to fulfill their responsibilities in respecting the well-established quality criteria for sample collections and filling requests in a timely manner.

Even though the need for patient muscle biopsies for diagnostic purposes is decreasing, there continues to be the need for samples in research projects to validate findings from animal studies, identify biomarkers and validate assays. Currently, there are academic institutions that maintain collections of specimens and the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center at the University of Iowa has a core facility that shares its specimens with researchers across the nation.

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4. **Define the most efficient mechanisms to generate skeletal and cardiac muscle stem cells, as well as other relevant cell types, from embryonic and induced pluripotent cells; create iPS and ES cell lines from various forms of muscular dystrophy and different mutations, and make them available to the wider research community.**

Evolving methods to efficiently convert embryonic stem (ES) cells and induced pluripotent stem (iPS) cells to cardiac muscle, neurons, or other cell types are providing valuable disease models for mechanistic studies and advancing preclinical therapy development in the muscular dystrophies. Programming pluripotent cells to skeletal muscle stem cells has proven to be more difficult. However, some notable progress has been made in demonstrating feasibility and providing guidance for future studies to increase efficiency, reliability, and specificity. ES and iPS cell-derived skeletal muscle cells, as well as cardiac muscle cells, neurons, and other relevant cell types, have several potential uses as therapy development tools or modalities, that include: drug screens, gene correction and genetic modifications, in vitro or in vivo systems for therapy assessment, and, ultimately, can be evaluated for therapeutic transplantation. SOPs for the use of such cell lines including quality control measures would enhance the reproducibility of findings. There should also be a mechanism in place for sharing these samples and making them available to the research community. As described in the cell and genetic therapy section, further research is also needed to determine optimal delivery and engraftment methods of these cells once they are derived.

Ex vivo organotypic cultures, such as in vitro reconstituted skeletal or cardiac muscle, also represent an application for muscle stem cells that should be evaluated as models for mechanistic studies and drug discovery and development applications.

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5. **Create a mechanism to maintain mouse models of muscular dystrophy at approved vendors in a live or cryopreserved state, available for easy and rapid importation into academic colonies**

   Significant progress has been made in providing access to dystrophy mouse models (Muscular Dystrophy Mouse Model Resource at the Jackson Laboratory). Continued effort and support is needed to maintain central repositories, establish quality control measures and provide timely and cost effective access of researchers to the growing number of mouse models important for progress in this field. Many academic institutions have moved to housing animals in specific pathogen-free facilities; this approach has, at least partially, improved the capacity for inter-institutional transfer. Limitations on maintaining adequate numbers of mice for preclinical studies are still present, and these lead to lengthy delays and increased cost. As an alternative to the need for researchers to bring mouse models into their lab, with required periods of quarantine or re-derivation, it would be useful to have central facilities that house the mice and assist researchers to conduct experiments.

Facilitate clinical trial readiness:

12. **Explore the benefits of harmonization of the existing clinical trial networks that conduct research on the muscular dystrophies**

    Fragmentation in how clinical trials are designed and sites are selected is detrimental to the evaluation of candidate therapeutics in the muscular dystrophies. In current practice, clinical trials are inefficient in utilization of existing infrastructure (accessing different registries and natural history data sets, unnecessarily duplicating site certification and training, etc.). Working group members viewed the relative lack of input of muscular dystrophy-experienced trialists into clinical trial design and conduct as problematic for many industry-sponsored trials.

    Although there are existing clinical trial networks dedicated to neuromuscular disease (e.g., Cooperative International Neuromuscular Research group (CINRG; http://www.cinrgresearch.org/, Muscle Study Group (MSG; http://www.urmc.rochester.edu/neurology/muscle-study-group/), and TREAT-NMD (http://www.treat-nmd.eu/)), and an NIH-sponsored network (NeuroNEXT) that will consider neuromuscular disease trials, to date these academic-based networks: (1) have very different structures and, as a consequence, have not harmonized efforts in trial readiness and design and (2) have not been the primary loci for industry-sponsored clinical trials in muscular dystrophy. Such harmonization is essential in pooling expertise and experience to ensure an underlying standard of care for trial participants, utilization of best practices in, and standardization of, trial design and endpoints, use of CDEs, and comparability across trials and transparency in access to clinical trial outcomes. Moreover, investigators working in muscular dystrophies that have now accumulated considerable experience in clinical trials need to help inform the design and conduct of clinical trials in those types of muscular dystrophy where candidate therapeutics are just starting to move into clinical testing. The NINDS has developed CDEs for many of the muscular dystrophies (see http://www.commondataelements.ninds.nih.gov/#page=Default); utilization of these CDEs is important for comparability/meta-analysis of clinical study and trial data. Likewise, cooperation among the muscular dystrophy community can facilitate pooling of clinical trial placebo group data, thereby adding to understanding of disease natural history.

Administrative and regulatory processes are another area that could benefit from harmonization. The use of central Institutional Review Boards (IRB) for example can have a significant role in accelerating the launch of a trial, and the NIH is already taking steps to promote the use of central IRBs in multi-site clinical trials with the NeuroNEXT Network serving as a leader in this area.

Other disease communities have better addressed the goal of harmonizing efforts to improve the quality of clinical trials across an entire disease area—a notable example is the Parkinson Study Group (http://www.parkinson-study-group.org/), which has established as the largest and most experienced network of credentialed centers in the field, one that provides comprehensive services and flexibility, and has established a track record of rigor and transparency in > 40 completed studies. The existing clinical trial networks in muscular dystrophy should explore the Parkinson Study Group model for lessons learned, particularly to increase partnering across networks and with industry to ensure optimal design and conduct of each clinical trial.

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6. Support and foster cross-communication among neuromuscular registries and consider strategies to harmonize registries across neuromuscular disorders

Registries that collect detailed and moderated clinical information can be used for research, for instance, to describe a patient population, follow a population over time, obtain natural history data, and perform genotype/phenotype correlations. Other registries are less comprehensive and serve as a contact point to recruit patients for research projects including clinical trials. The purpose of the registry should be clear, along with who has access to the data and how the data will be used. Prior to initiating a new registry, consideration should be given to what national or international registries are already actively collecting data and how the new registry will interact or compliment others. While multiple registries are important for validation purposes in multiple cohorts, too many registries recruiting from the some patient population dilutes the value of all of them.

The value of registries for research purposes is dependent on the type of information that is gathered and the quality control processes that have been put in place. A distinction should be made between self-reported registries and curated registries. Searchable disease-specific registries that provide comprehensive data linking genomic/proteomic data to clinical data and biological specimens/biorepositories are particularly valuable. These may be used for biomarker development, genetic modifier (e.g., osteopontin, LTBP4) identification, and mutation-specific drug screening. Additionally, steps should be taken to link patient information across registries to enhance knowledge and ensure that the same participant is not represented duplicated in different databases. This can also save time as data will not have to be entered into multiple databases. Through the use of improved synchronization, these databases become further tools for longitudinal tracking of healthcare and accountability in outcomes. The use of national electronic health records in countries that have them can enhance this effort. Consideration should be given to the use of a single federated system that allows data to be followed from source to source. The development of interfaces that allow the direct transfer of data, and related changes to integrate information technology platforms, are needed to improve research and clinical care.

The fragmentation in assembling robust phenotypic data on people with muscular dystrophy still represents a barrier to clinical trial readiness and appropriately powered clinical trials. The largest registries (and even the largest countries) may not have sufficient numbers of affected patients to provide for clinical trial readiness activities and rigorous assessment of the large number of evolving novel candidate therapies. TREAT-NMD has established a successful model for harmonization of national patient registries, but current data availability across the muscular dystrophies is still far from ideal. The muscular dystrophy field needs to build on current efforts in this area in order to develop a system to support registry development/integration for trial readiness across the types of muscular dystrophy. The path forward includes combining efforts of patient advocacy groups to develop and link registries into a federated system to facilitate international aggregation of data and improved access to investigators and industry.

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7. Address the issues of setting up multinational trials especially in the academic arena relating to trial set up and administrative burden

The experience of the muscular dystrophy community in organizing multinational trials has shown that this is a daunting task for both academic- and industry-driven clinical trials. For example, the FOR-DMD trial had to engage regulators in several countries and approximately 140 separate protocol reviews were necessary before the trial was launched. Since multinational trials are essential for rare diseases, efforts should be undertaken to facilitate multinational funding, master trial agreements, and harmonization of regulatory approvals.

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8. Prioritize the development of therapies that may be applicable across the various types of muscular dystrophy

Given the substantial barriers to developing therapeutics that will target the primary disease mechanism (e.g., mutated gene and/or its immediate consequences) for each type of muscular dystrophy, investigators should consider pursuing therapy development strategies targeted at common mechanisms of mutations or common pathways of disease pathophysiology. It is also unlikely that therapies targeted at primary disease mechanisms will provide a singular solution to any one muscular dystrophy. Emphasis on downstream pathways may yield therapies that are applicable to multiple types of muscular dystrophies, either as standalone drugs and biologics or as agents for combination therapy strategies in the muscular dystrophies.

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9. Continue to provide high quality mentoring and support for training and career development for researchers new to the muscular dystrophies and throughout their careers.

Well-trained and highly motivated researchers constitute a great resource for the muscular dystrophy field. To maintain momentum and even accelerate progress toward effective therapies and reduced burden for all of the muscular dystrophies, the need for new investigators and experienced researchers new to the field has never been greater. Researchers are needed in basic, translational and clinical research for each of the dystrophies. Even when specializing in one of these approaches, researchers bring greater strength to their teams when they have training and awareness of the other approaches. As more candidate therapeutics are

developed for testing in clinical trials, there is a greater need for physician/scientists capable of leading and contributing to those trials. Academic institutions and professional societies should continue to expand the attention to neuromuscular conditions in neurology training programs and provide practicing physicians with up-to-date information on the care of dystrophy patients (as demonstrated by the recent AAN guidelines on FSHD, CMD and LGMD). The NIH, other federal agencies and advocacy groups provide opportunities for support of researchers at various career stages. Increased awareness and education on the dystrophies at the undergraduate and medical school levels may lead to more trainees choosing careers in dystrophy research. Stable support for senior researchers will allow them time to provide quality mentoring to their students and fellows.

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10. Develop and propose revised International Classification of Disease (ICD) codes for the muscular dystrophies

The current ICD codes are too broad, in that they do not allow for identification of most types of dystrophies. While there is a specific code for DM, ICDs are lacking for all other types of muscular dystrophy. The scope of the problem is exemplified in the efforts of the CDC MD STARnet, where labor-intensive abstraction of medical records has been necessary to describe the epidemiology of various types of muscular dystrophy, and, as a consequence, has limited these studies to a manageable number of states. This lack of specification in medical records inhibits health services research utilizing electronic medical records, Medicare, Medicaid, health insurance claims data, and other administrative records. ICD codes that accurately identify the major types of muscular dystrophy would help facilitate both clinical and epidemiologic research. More specific codes will help describe the epidemiology of the muscular dystrophies, the costs and cost drivers of health care for these patients, and the geographic distribution of various types of muscular dystrophy. Improving the ICD codes is a timely goal for the muscular dystrophy field, as the use of electronic medical records becomes more widespread.

The establishment of new ICD codes is a substantial undertaking and will require partnership between the clinical and public health communities to develop codes that can be effectively applied at a clinic level. There is a large European effort lead by Orphanet to redefine clinical codes for all rare diseases. All types of muscular dystrophy for which the genetic mutation has been identified now have an Orphanet code (searchable at: http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN); these codes could provide the basis for revision of the ICD system. The Orphanet program is linked into a World Health Organization effort focused on preparation of the ICD-11 (projected for 2017-18). A single, international coding system for the muscular dystrophies is essential for interoperability of registries and other clinical studies and trial infrastructure.

ABBREVIATIONS

ACL	Administration for Community Living
BMD	Becker Muscular Dystrophy
CDC	Centers for Disease Control and Prevention
CDE	Common Data Elements
CMD	Congenital Muscular Dystrophy
DM/DM1	Myotonic Dystrophy/Myotonic Dystrophy type 1
DMD	Duchenne Muscular Dystrophy
DMDRP	Duchenne Muscular Dystrophy Research Program
DoD	Department of Defense
DoEd	Department of Education
ECM	Extracellular Matrix
FDA	Food and Drug Administration
FSH or FSHD	Facioscapulohumeral Muscular Dystrophy
HRSA	Health Resources and Services Administration
ICD	International Classification of Disease
IDEA	Individuals with Disabilities Education Act
LGMD	Limb-Girdle Muscular Dystrophy
MD-CARE Act	Muscular Dystrophy Community Assistance, Research, and Education Amendments
MD STARnet	Muscular Dystrophy Surveillance Tracking and Research Network
MDA	Muscular Dystrophy Association
MDCC	Muscular Dystrophy Coordinating Committee
MRI	Magnetic Resonance Imaging
NCLB	No Child Left Behind Act
NIH	National Institutes of Health
NHLBI	National Heart, Lung, and Blood Institute
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NINDS	National Institute of Neurological Disorders and Stroke
NO/NOS/nNOS	Nitric Oxide/Nitric Oxide Synthase/neuronal Nitric Oxide Synthase

OPMD	Oculopharyngeal Muscular Dystrophy
PPMD	Parent Project Muscular Dystrophy
PROMIS	NIH Patient Reported Outcomes Measurement Information System
SOPs	Standard Operating Procedures
SSA	Social Security Administration
TREAT-NMD	Translational Research in Europe-Assessment and Treatment of Neuromuscular Diseases