

Duchenne Muscular Dystrophy Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful medical research in targeted program areas.

In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine was assembled to evaluate the CDMRP's two-tier review process and its coordination of research priorities with the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). As part of their final report,¹ the committee recommended that each CDMRP program "... develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future," and that these strategic plans "should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives."

In response to these recommendations, this document presents the current strategy for the CDMRP's Duchenne Muscular Dystrophy Research Program (DMDRP). The DMDRP Strategic Plan identifies the high-impact research goals most important to its stakeholders while providing a framework that is adaptable to changes in the medical research environment to address those goals. This plan has been formulated to provide greater clarity of the program's goals over time to the public and other stakeholders. Funding for the DMDRP is Congressionally appropriated on an annual basis; therefore, there is no guarantee of future funding. The DMDRP Strategic Plan will be reviewed during the program's annual Vision Setting meeting and updated as necessary.

DMDRP BACKGROUND AND OVERVIEW

Duchenne muscular dystrophy is an X-linked recessive disease and is the most common childhood form of muscular dystrophy, affecting approximately 1 out of every 5,000 male infants and about 20,000 babies worldwide each year. Duchenne mostly affects boys and reaches across all races and cultures. Duchenne is a severe, progressive disease that causes muscles to become weaker over time. Initially, Duchenne presents between ages 2 to 6, with loss of ambulation by age 12. Loss of upper arm use quickly follows in the teenage years, and muscle weaknesses progress to heart and respiratory failure, eventually leading to death before or during an individual's 30s. Improvements in care for Duchenne over the last 10+ years have resulted in delayed progression of the disease.

Duchenne is caused by nonsense or frameshift mutations in the dystrophin gene, resulting in loss of functional dystrophin protein. Dystrophin is an essential membrane-associated muscle protein in both skeletal and cardiac muscles. Dystrophin deficiency in the muscle cells of patients with Duchenne predisposes the muscles to contraction-induced damage due to membrane instability. Successive cycles of injury and repair lead to chronic inflammation, oxidative stress, and fibrosis, reducing the regenerative capacity of muscle and leading to progressive muscle wasting and weakness.

There is no cure for Duchenne. Currently, treatment is limited to managing the symptoms of the disease. Glucocorticosteroids are used to slow disease progression by facilitating the maintenance of muscle strength longer; however, they have serious side effects. Recently, the glucocorticosteroid, deflazacort, received marketing approval in the United States, with data supporting a potentially improved side-effect profile over prednisone. Cardiomyopathy is addressed with the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and/or beta blockers. Unfortunately, these treatments are only temporarily effective and, as previously noted, patients with Duchenne succumb to their disease due to heart and respiratory failure before or during their 30s.

VISION AND MISSION

The DMDRP was established in fiscal year 2011 (FY11), with a Congressional appropriation of \$4 million (M) to promote the understanding, diagnosis, and treatment of Duchenne. To address this guidance, the DMDRP has developed the following Vision and Mission statements:

DMDRP VISION: To preserve and improve the function and quality of life, and to extend the life span of all individuals with Duchenne

DMDRP MISSION: To better support discovery and development of therapeutics, devices, and other interventions, and to promote their rigorous clinical testing for the benefit of military beneficiaries and the general public

Since the program's inception, DMDRP has followed the Institute of Medicine's (IOM) recommendations² to the Department of Defense's (DoD) CDMRP on the peer review procedures to be used in evaluating an application's scientific merit and the preferred programmatic investment strategy for funds. A two-tier peer review system is used where the primary criterion for awarding grants is scientific excellence (first tier – peer review). Programmatic relevance is a secondary criterion (second tier – programmatic review) to ensure that awards are made to those excellent proposals that best meet the programmatic goals.

The IOM also recommended that consumers (disease survivors) should be included as members of the panel (termed the Programmatic Panel) conducting programmatic review. The DMDRP has adhered to this guidance, and consumers (people living with or family members of a person living with Duchenne) participate on the Programmatic Panel, as well as on peer review panels, as full voting members.

FUNDING HISTORY

Over its 8-year history, the DMDRP has received Congressional appropriations annually. **Figure 1** shows the program's funding from 2011 to 2018, totaling \$26.4M since its inception. During this time, the program has funded 29 awards* through a competitive peer review process targeted toward the program's vision. An additional four awards are anticipated for FY18.

RESEARCH PORTFOLIO

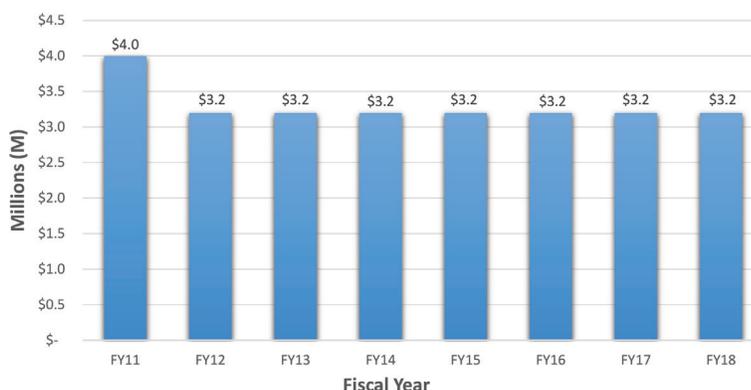
When the DMDRP was first established in FY11, the Programmatic Panel recommended focus areas to assist researchers in concentrating their projects around the program's priorities. Through the years, this framework has been generally followed. In FY15, however, the DMDRP introduced a new focus area on cardiopulmonary studies, which became cardiac studies in FY16. That same year, the biomarkers focus area was combined with the assessment of clinical trial tools and outcome measures focus area.

DMDRP FOCUS AREAS

- Cardiac studies, including identifying mechanisms of pathology and therapeutic interventions
- Clinical studies, novel interventions, and drug and biologic delivery technologies designed to improve clinical care and quality of life in areas such as:
 - Cognitive function
 - Endocrinology
 - Gastrointestinal issues
 - Immunology
 - Orthopaedics
 - Psychosocial issues
 - Pulmonology (including sleep-focused studies)
 - Skeletal muscle
- Assessment of clinical trial tools and outcome measures, such as:
 - Discovery and qualification of pharmacodynamic, prognostic, and predictive biomarkers
 - Patient-centered outcomes (e.g., quality of life, activities of daily living)
 - Novel clinical outcome assessment
 - Potential surrogate markers

* Negotiations of four awards for FY17 are underway and expected to be completed by September 30, 2018.

Figure 1. DMDRP Funding per Fiscal Year





- Extension or expansion of existing preclinical translational data in support of a specific therapeutic development path (including drug exposure, independent replication, and comparative studies)

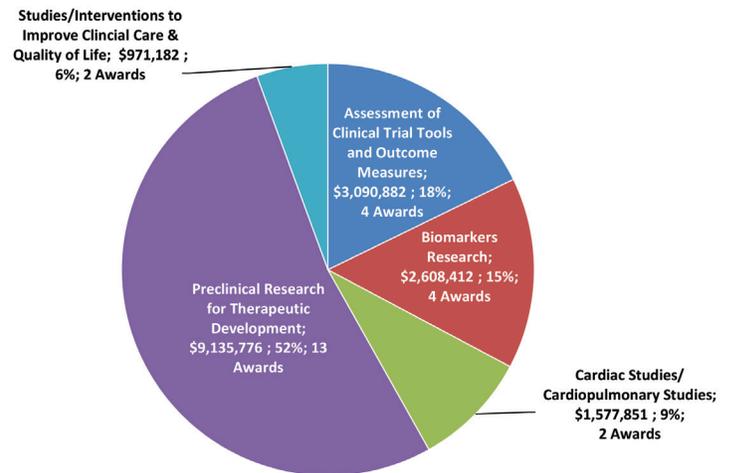
Figure 2 displays the DMDRP portfolio from FY11-FY16, based on the focus area the award is addressing, the percent investment, and the number of awards supported.

RESEARCH ACCOMPLISHMENTS

Over the years, the DMDRP has focused much of its research support on “translational type” projects in an effort to advance potential therapeutics to the clinic for testing in human subjects. The following DMDRP-funded projects have had their results translated to clinical trials:

- Studies demonstrating that the compound, VBP15 (renamed vamorolone), dissociated the harmful transactivation-induced side effects of glucocorticoid steroids from the beneficial transrepressive and anti-inflammatory effects that occur through inhibition of inflammatory factors. Vamorolone has since shown promising results as a potential replacement for glucocorticoids in a recently completed Phase 2a clinical trial in boys with Duchenne.
- Preclinical studies supporting vector optimization for GALGT2 gene therapy that led to approval of an investigational new drug application and recent opening of a Phase 1/2 gene therapy clinical trial in patients with Duchenne.
- Studies demonstrating that the combination of angiotensin-converting enzyme (ACE) inhibition and non-specific mineralocorticoid receptor antagonism resulted in significant improvement of dystrophic limb skeletal muscles, respiratory muscles, and the heart. A clinical trial has been opened based on these results (NCT02354352).
- Preclinical research evaluating the therapeutic efficacy of second-generation adeno-associated virus (AAV) vectors expressing micro-dystrophin in combination with variable AAV vector dosage that demonstrated long-term therapeutic benefit without adverse reactions. These studies provided the foundation for opening a clinical trial evaluating the safety, tolerability, and efficacy of micro-dystrophin gene transfer in adolescents and children with Duchenne (NCT03368742).

Figure 2. Dollars Invested per Focus Area (FY11-FY16)
Total Investment: \$17.4M



RESEARCH AND FUNDING ENVIRONMENT

The CDMRP is represented by a standing member of the Muscular Dystrophy Coordinating Committee (MDCC), as authorized by the Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001 (MD-CARE Act, P.L. 107-84). The MDCC coordinates muscular dystrophy activities across the NIH and other federal agencies, as well as muscular dystrophy patient organizations. As part of the MDCC’s mission, the committee is charged with developing an action plan for conducting and supporting research and education on muscular dystrophy through the national research institutes, which is periodically reviewed and revised. The first MDCC Action Plan was developed and approved in 2005. The 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. During the 10 years following the development of the 2005 MDCC Action Plan, significant progress has been made in several areas, but not all. Much of this progress came about through improved partnering among advocacy, academic, industry, and government stakeholders in the field. In 2015, the Action Plan was revisited and updated.

The recommendations put forth in the *2015 Action Plan for the Muscular Dystrophies* (2015 MDCC Action Plan; https://mdcc.nih.gov/Action_Plan) build on what has been learned during the previous decade. This includes a 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 develop biomarkers; improvement of the efficiency of preclinical and clinical vetting of candidate therapeutics in order to avoid failures in the 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. The DMDRP looks to the 2015 MDCC Action Plan as a resource when determining how it can best contribute and collaborate with other MDCC member organizations to help advance the DMDRP vision of preserving and improving the function and quality of life and extending the life span of all individuals with Duchenne.



RESEARCH FUNDING LANDSCAPE

In order to maximize the DMDRP's ability to fill gaps and leverage the findings of others in the Duchenne research field, each year the DMDRP analyzes: (1) the dollar investments and (2) the research portfolios of the major Duchenne research funding organizations. **Table 1** lists the Duchenne research funding investments from 2012-2016 for federal and several non-federal organizations.

The DMDRP is the third largest funder of Duchenne research after the NIH and Muscular Dystrophy Association (MDA). However, it should be noted that the DMDRP invests only in new awards, whereas the NIH invests about 20% of its funds in new awards and the remaining 80% in support for the out-years of existing, continuing awards.

Following the release of the 2015 MDCC Action Plan, MDCC member agencies and organizations began collecting information about their research funding activities related to the priority areas established in the plan. Information about muscular dystrophy research projects supported by the MDCC member organizations is shared among MDCC members and is publically available. The 2015 MDCC Action Plan has 81 objectives that can be summarized in five priority areas:

- Understanding causes
- Screening and diagnosis
- Developing treatments
- Preparing for clinical trials
- Providing care, management, and access to services

Figure 3 compares the Duchenne project portfolios for funding organizations that are MDCC members based on the five priority areas of the 2015 MDCC Action Plan.

As the largest funder in Duchenne research, the NIH has invested in all priority areas, with Developing or Improving Treatments (42%) as the highest funding priority, followed by Understanding Causes (39%); Clinical Trial Readiness (14%); Providing Care, Management, and Access to Services (2.8%); and Screening and Diagnosis (0.6%). The two major patient organizations, the MDA and Parent Project Muscular Dystrophy (PPMD), also have invested in almost all priority areas. The MDA's two largest investments were in Understanding Causes (47%) and Developing or Improving Treatments (44%); less than 10% was invested in the remaining three priority areas. PPMD's largest investment is in Developing or Improving Treatments (70%), followed by Understanding Causes (16%), Clinical Trial Readiness (9%), and Screening and Diagnosis (5%).

The DMDRP has invested a majority of its funding in Developing or Improving Treatments (71%) and Clinical Trial Readiness (26%). These are the two priority areas where the DMDRP believes it can make its greatest impact for the Duchenne research field and patient communities, particularly considering the limited research funding available from government and non-government organizations across the entire muscular dystrophy field. The resources required to produce a novel therapy/treatment are significant, and relying on only one organization to carry out this task is unrealistic; therefore, a considerable level of cooperation is required among all stakeholders in the field.

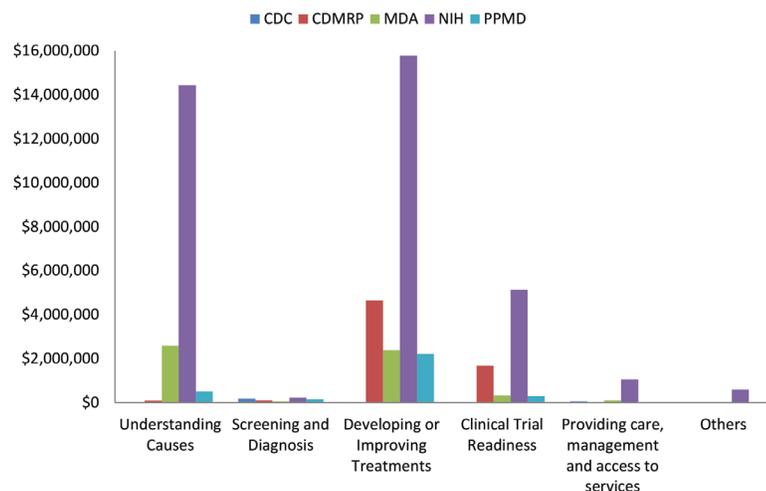
Today's medical research environment is dynamic. New research data sets are being created and made available to researchers at an ever-faster rate, and new technologies are emerging that will enable research that is impossible today. Funding for research comes from a variety of sources through a variety of programs. Many are funded by the government through the NIH, Centers for Disease

Table 1. Duchenne Research Funding Investments (2012-2016)

Funding Organization	Dollars Invested
CDC	\$10,466,939
CDMRP DMDRP	\$13,854,190
CureDuchenne	\$8,246,635
FDA	\$1,098,393
MDA	\$39,152,105
NIH (all awards)	\$162,947,854
NIH (new awards)	\$31,170,523
PPMD	\$11,220,680

CDC = Centers for Disease Control and Prevention; FDA = Food and Drug Administration; MDA = Muscular Dystrophy Association; PPMD = Parent Project Muscular Dystrophy.

Figure 3. Amounts Invested by MDCC Organizations per Research Priority Areas (Open Awards as of 2016)





Control and Prevention, CDMRP and other DoD organizations, and various non-government organizations focused on disease-specific areas. The DMDRP must fit within this environment and effectively respond to changes in it to maximize the value and impact of DMDRP-funded research.

STRATEGIC DIRECTION

The DMDRP considered a broad range of unanswered research questions that are potentially critical to treating Duchenne patients, improving their quality of life, and developing a cure. Many of the research questions evaluated are covered by the 2015 MDCC Action Plan (https://mdcc.nih.gov/Action_Plan). The DMDRP recognizes that it plays a critical role in funding Duchenne research by strategically directing its efforts in the following areas:

- Support discovery and development of therapeutics, devices, and other interventions
- Accelerate promising therapeutic ideas into clinical applications
- Advance basic research on the effect of Duchenne on the heart, bone, central nervous system (CNS), and gastrointestinal system
- Support the training of new researchers, particularly physician researchers, to facilitate their pursuit of careers in Duchenne research

STRATEGIC GOALS/PRIORITIES

The DMDRP has established four priorities/goals around which it will build its funding efforts; however, the program enables investigators to propose their best ideas and is interested in furthering high-impact, innovative Duchenne research. The DMDRP does not define which specific projects or products will be funded. The overarching strategic priorities for the DMDRP are listed below, and the program will focus on specific areas to help address each of these priorities:

- Support research on bone, cardiac, CNS, and/or gastrointestinal tract studies, including identifying mechanisms of pathology and therapeutic interventions
 - Prevention and treatment of cardiomyopathy
 - Understanding the effects of restoring dystrophin on the heart, bone, endocrine, CNS, and/or gastrointestinal system
- Support research on translational and clinical studies, novel interventions, and drug and biologic delivery technologies designed to improve care and quality of life
 - Development of assistive devices (e.g., wearables, upper-arm robotics)
 - Immunology and understanding the role inflammation plays in the disease process, both in advancing or mitigating the pathology and how it may interfere with various types of therapeutic strategies
 - Development of alternative delivery systems of macromolecules and particles to muscle
 - Cognitive function
 - Endocrinology
 - Gastrointestinal issues
 - Orthopaedics
 - Psychosocial issues
 - Pulmonology (including sleep-focused studies)
- Support research on assessment of outcome measures and other clinical trial tools
 - Discovery and validation of pharmacodynamic, prognostic, and predictive biomarkers
 - Biomarkers essential for making go/no go decisions for therapeutic development
 - Development of novel clinical outcome assessment tools
 - Development of patient-centered outcome measures
 - Identification and assessment of potential surrogate markers
 - Conducting secondary data analysis to assist in clinical research tool validation and/or understanding the natural history of the disease
- Extension or expansion of existing preclinical translational data in support of a specific therapeutic development path
 - Optimizing delivery to target tissue
 - Drug exposure
 - Independent replication of preclinical data



INVESTMENT STRATEGY

Looking forward to the next 3 to 5 years, the DMDRP has developed an investment strategy that will allow it to solicit the type of research that will facilitate accomplishing its strategic goals. After each fiscal year, the program will evaluate whether the award mechanism supporting the strategic investment is working well or needs to be improved or discontinued.

The following award mechanisms will be used:

- Researcher Development
 - Career Development Award
 - Optional Nested Resident or Medical Student Traineeship (offered with the Investigator-Initiated Research Award)
 - Optional Interdisciplinary Collaborator (offered with the Investigator-Initiated Research Award)
- Clinical and Translational
 - Investigator-Initiated Research Award

MEASURING PROGRESS

As shown below, the DMDRP will measure its near-term success based on its successful investments in those areas that are important to its investment strategy. Longer-term success may be evaluated based on how contributions have advanced the field of research by following the scientific findings and therapies linked to DMDRP-funded projects.

- Near-Term Progress (3-5 years)
 - Investments in each strategic priority/goal
 - Encouraging more research in strategic priorities that are understudied
 - Contributions to advancing the research field, including publications, patent applications, patents, drug approvals, and clinical trials, which will vary based on the stage of the research project
- Medium- to Longer-Term Progress (6+ years)
 - Proportion of funded investigators receiving additional awards from other sources to continue successful research
 - Increase in the number of new investigators who establish their careers as Duchenne researchers and their contributions to the Duchenne research field (tracking criteria here will include faculty appointments, publications, and awards of new research grants)
 - Funded areas leading to clinical research studies or clinical trials
 - Tracking of contributions to advancing the research field, including publications, patent applications, patents, drug approvals, clinical trials, commercialization of treatments, devices, and changes in standard of care

REFERENCES

1. *Evaluation of the Congressionally Directed Medical Research Programs Review Process*. 2016. The National Academies of Sciences, Engineering, and Medicine. The National Academies Press. Washington, DC.
2. *Strategies for Managing the Breast Cancer Program: A Report to the U.S. Army Medical Research and Development Command*. 1993. Institute of Medicine. The National Academies Press. Washington, DC.