2026 Myotonic Dystrophy Type 2 (DM2) Landscape Assessment



Table of Contents

Acknowledgments 3

DM2 Landscape Assessment: Community Summary 3

Executive Summary 4

The 2026 DM2 Landscape Assessment 6

Where We Are Today: A Literature Review of the State of DM2 Research 7

DM Research Funding: A Lever for Field-Building 9

Active US National Institutes of Health (NIH) Funded Projects 10

US Department of Defense (DoD) Funding 11

Muscular Dystrophy Association (MDA) Funding 11

Myotonic Dystrophy Foundation (MDF) Active Funding as an Historic Accelerator 12

Animal Models of DM2 14

Mouse Models 15

Zebrafish Animal Models 18

Drosophila Animal Models 19

Cell Culture Systems 20

Natural History Studies 21

Drug Development Progress 25

Community Engagement, Clinical Care, and Care Guidelines 26

Insights from Scientific and Clinical Expert Interviews 28

Clinical Heterogeneity and Multisystem Burden 28

Natural History, Trial Readiness, and Outcome Development 28

Diagnostic Modernization and Clinical Recognition 29

Biomarkers, Mechanisms, and Standardized Protocols 29

Cross-cutting Themes Across Expert Interviews 30

Summary and Conclusions: A Call to Action for DM2 31

APPENDIX 34

A. The 2019 DM2 Landscape Assessment 34

B. MDF Funded Projects 35

C. Key Opinion Leaders Interview Approach 36

D. NIH Funding: Historic and Project Specific 38

Acknowledgments

The development of this resource was led by Andy Rohrwasser, PhD, MBA, with support from Sofia Olmos, PhD; Nadine Ann Skinner, PhD, MPA; and Tanya Stevenson, EdD, MPH.

MDF gratefully acknowledges Benedikt Schoser, MD, for his valuable suggestions and Charles Thornton, MD, and Andrew Berglund, PhD, for their thorough and insightful review.

DM2 Landscape Assessment: Community Summary

For the Community:

People living with myotonic dystrophy type 2 (DM2) face a wide range of symptoms that can affect mobility, pain, fatigue, thinking, sleep, heart and breathing health, work, family life, and independence. Yet the research and treatment-development landscape for DM2 have not kept pace with this burden.

This assessment looks across the DM2 field to ask a practical question: **what would it take to accelerate progress?** The answer is not one single project or one single therapy. DM2 needs stronger foundations: better natural history data, improved diagnostic tools, disease models that can support research and drug development, meaningful outcome measures, and a larger community of investigators focused on the disease.

The good news is that the path forward is becoming clearer. DM2 is not limited by lack of importance or lack of therapeutic potential. It is limited by barriers that can be addressed through coordinated investment and leadership. MDF has already begun supporting this work through DM2-focused funding, community engagement, care resources, and early research infrastructure. The next step is to scale these efforts and bring more partners into the field.

DM2 is an investable, actionable, and urgent disease area. With focused effort, the field can move from scattered progress toward a more coordinated path to clinical trials and, ultimately, better treatments for people living with DM2.

Executive Summary

Myotonic dystrophy type 2 (DM2) is a multisystem repeat-expansion disorder and a high-opportunity area for targeted research investment. Although DM2 imposes substantial multisystem burden on patients and families, its research and therapeutic-development ecosystem remain earlier in its translational trajectory than myotonic dystrophy type 1 (DM1). This gap is not a measure of underdevelopment, it defines a timely opportunity: foundational investments made now could have disproportionate impact by shaping the research agenda, attracting new investigators, strengthening clinical readiness, de-risking therapeutic development, and accelerating progress toward effective treatments.

To identify the highest-leverage opportunities for accelerating progress in DM2, MDF conducted a comprehensive Landscape Assessment across the research, clinical, translational, and therapeutic-development continuum. The assessment builds on MDF's 2019 DM2 Landscape Assessment and integrates peer-reviewed literature trends, research funding patterns, disease-model availability, natural history and clinical evidence, diagnostic and care resources, therapeutic pipeline activity, and semi-structured interviews with leading scientific and clinical experts.

The analysis shows that DM2 progress is not limited by lack of need, relevance, or therapeutic potential, but by identifiable and addressable barriers. These include limited natural history data, insufficient disease-relevant model systems, incomplete diagnostic reach, a small investigator base, and an early therapeutic pipeline. Publication and funding trends further reflect this gap: DM2 publication volumes remain substantially lower than DM1 and have plateaued for more than a decade, while research funding remains heavily weighted toward DM1. In addition, no validated DM2 mouse model is currently available to broadly support mechanistic or drug-development studies, and no advanced repeat-targeted therapeutic strategy is currently available for DM2. These barriers are substantial, but actionable; together, they define the roadmap for investment.

The central conclusion of this assessment is that DM2 is undercapitalized relative to its opportunity. The field has an engaged patient community, emerging clinical and scientific tools, active foundational research, and increasing recognition of the barriers that must be addressed. Experience in DM1 demonstrates that progress accelerates when foundational biology, natural history infrastructure, disease models, endpoint development, patient engagement, and therapeutic-development efforts begin to align. DM2 now requires a similarly coordinated investment strategy.

Five strategic priorities emerge. First, the field needs a large, well-designed DM2 natural history study that spans age groups and disease severity; captures muscle, cardiac, respiratory, metabolic, sleep, cognitive, and other central nervous system manifestations; and integrates clinic-based and at-home assessments with patient-reported outcomes, imaging, molecular biomarkers, and trial-relevant endpoints. Second, DM2 requires sustained investment in disease-relevant model systems and pathomolecular research, including splicing, RNA toxicity, CNBP biology, RAN translation, modifier pathways, and immune response signaling pathways. Third, diagnostic strategies must improve through broader clinical recognition, more systematic electrophysiologic evaluation, and modern repeat-expansion methods, including long-read sequencing where conventional genetic

testing is negative or inconclusive. Fourth, the investigator base and collaborative infrastructure must grow through targeted grants, early-career support, expert convening, standardized protocols, conference visibility, and cross-disciplinary engagement. Fifth, therapeutic-development efforts should be diversified, supporting both near-term symptomatic, functional, regenerative, or downstream approaches and longer-term repeat-targeted or disease-modifying strategies.

Expert interviews reinforce and sharpen this roadmap. Across interviews, experts emphasized that DM2 requires a disease-specific framework rather than the direct transfer of DM1 assumptions. Priorities included better characterization of the broad and heterogeneous multisystem phenotype; severity grading and clinically meaningful subgroups; longitudinal assessment across age groups; diagnostic modernization; biomarker validation; and deeper investigation of splicing, RNA toxicity, CNBP biology, and immune response pathways. Views differed on how much interventional work can proceed before a comprehensive natural history platform is established, but there was broad and majority agreement that coordinated natural history, diagnostic, biomarker, endpoint, and mechanism-development efforts are essential to strengthen clinical-trial readiness.

MDF has already begun to build this foundation through prioritized DM2 funding, expanded community engagement, care-resource development, support for emerging investigators, and investment in model-system and clinical research. These efforts demonstrate that targeted action can shift the trajectory of the field. However, foundation support alone cannot build a fully trial-ready ecosystem. Larger federal, philanthropic, academic, and industry investments will be needed to scale the work, validate tools, generate longitudinal evidence, and reduce therapeutic-development risk.

The opportunity now is to move from fragmented progress to coordinated acceleration. DM2 should not be viewed primarily as a neglected or secondary area within myotonic dystrophy research. It should be treated as an investable, actionable, and strategically important disease area where well-placed resources could generate outsized returns for patients, researchers, funders, and therapeutic developers.

The priority is clear: build the foundations, expand the field, and accelerate the path toward effective treatments for people living with DM2.

The 2026 DM2 Landscape Assessment

To identify the highest-leverage opportunities for accelerating progress in DM2, MDF conducted a comprehensive landscape assessment across the research, clinical, translational, and therapeutic-development continuum. The goal was not only to document current gaps, but to define where targeted investment and coordinated action could most effectively strengthen the field.

This assessment builds on MDF's 2019 DM2 Landscape Assessment (Appendix A) and evaluates progress since that time. It also examines where important needs remain unresolved and where new opportunities have emerged. Comparisons to DM1 are included where useful, not to frame DM2 as lagging behind, but to illustrate what sustained investment, coordinated infrastructure, and therapeutic-development focus can make possible in a related repeat-expansion disorder.

The 2026 assessment integrated multiple data sources, including:

1. Peer-reviewed literature available through PubMed and the National Library of Medicine;
2. Publicly available research funding data from the National Institute of Health (NIH), US Department of Defense (DoD)/Congressionally Directed Medical Research Program (CDMRP)/Peer Reviewed Medical Research Program (PRMRP), Muscular Dystrophy Association (MDA), and Myotonic Dystrophy Foundation (MDF);
3. ClinicalTrials.gov entries for interventional and observational studies;
4. Public disclosures from biotechnology and pharmaceutical companies with active or emerging DM2 programs;
5. Information on available disease models, cell systems, diagnostics, care resources, and natural history studies; and
6. Semi-structured interviews with leading clinical and scientific experts in DM2 and related areas of myotonic dystrophy research.

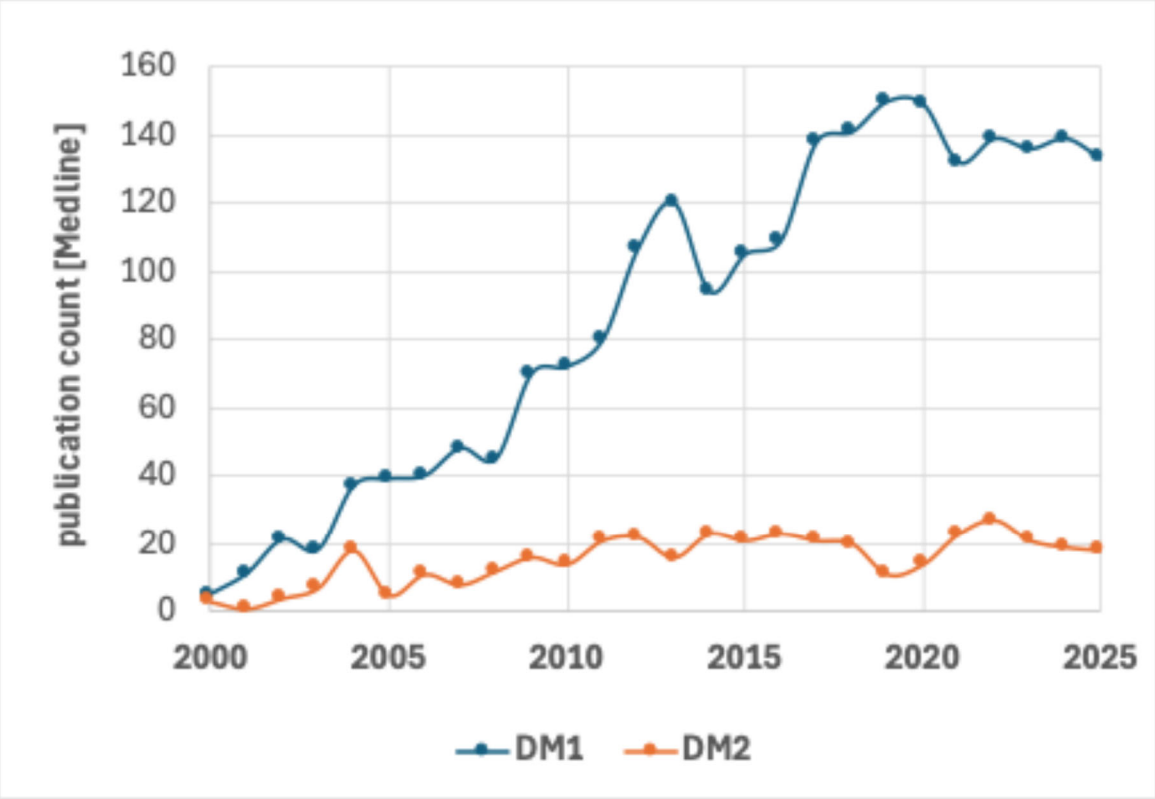
Together, these data sources provide a broad view of the current DM2 landscape and identify the areas where focused investment could have the greatest impact. The assessment highlights five recurring priorities: building a stronger natural history and clinical evidence base; developing disease-relevant model systems; improving diagnostics and patient identification; expanding investigator and funder engagement; and strengthening the foundations for therapeutic development.

These priorities form the organizing framework for the sections that follow. Each section summarizes the current state of the field, identifies key barriers, and translates those findings into actionable opportunities for MDF, funders, investigators, industry partners, clinicians, and the DM2 community.

Where We Are Today: A Literature Review of the State of DM2 Research

Peer-reviewed publication activity provides one useful indicator of scientific momentum, field maturity, and translational readiness. In rare genetic diseases, research activity often progresses from early disease description and gene discovery to mechanistic studies, natural history research, endpoint development, and ultimately therapeutic intervention. Assessing the DM2 literature through this lens helps clarify where the field stands today and where targeted investment could most effectively accelerate progress.

Analysis of peer-reviewed publications indexed in PubMed between 2000 and 2025 shows that DM2 research has generated a meaningful but comparatively small body of literature. Using the search terms "Myotonic Dystrophy Type 2" and "Myotonic Dystrophy Type 1," we identified 359 publications focused on DM2 compared with 2,021 publications focused on DM1. Annual DM2 publication output has remained relatively stable since approximately 2010, while DM1 publication activity expanded substantially over a longer period before plateauing after 2020. One factor contributing to this difference is of course the later identification of the DM2 gene (1994) and its disease-causing expansion (2001). It is also notable that the mid-growth phase of DM1 publication output around 2014 coincided with the first interventional study targeting the toxic repeat, the Biogen/Ionis program (2014).

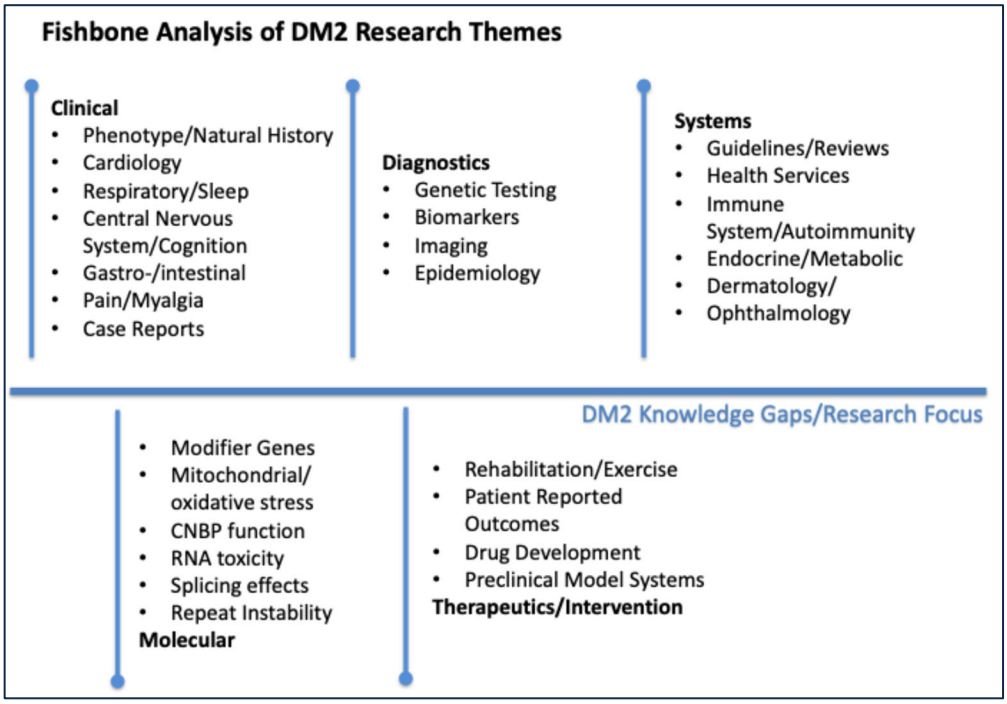


Rather than viewing this difference only as evidence of underdevelopment, it should be understood as an indicator of opportunity. DM2 has not yet benefited from the same scale of sustained investment, investigator density, natural history infrastructure, endpoint development, and

therapeutic-development focus that helped accelerate DM1. As a result, well-coordinated investments in DM2 could have substantial leverage by expanding the knowledge base, attracting new investigators, and strengthening the foundation for future clinical trials.

To further characterize the DM2 literature, we used Medical Subject Headings (MeSH), the National Library of Medicine's controlled vocabulary for indexing PubMed articles, to categorize publications without imposing predefined assumptions. This keyword and MeSH-based analysis suggest that DM2 research remains concentrated in clinical descriptions, molecular mechanisms, case reports, guidelines, and reviews. By contrast, fewer publications address organ-system-specific disease impact, translational model systems, biomarker development, or therapeutic and preclinical development. This distribution highlights a clear set of priorities for the next phase of DM2 research: deeper mechanistic investigation, better characterization of multisystem disease burden, stronger natural history data, and translational tools that can support therapeutic discovery and clinical readiness.

A complementary fishbone analysis grouped publications into clinical, diagnostic, systems, molecular, and therapeutics categories. This framework reinforced the same conclusion: the DM2 literature has established important foundations, but key areas needed for translational acceleration remain comparatively thin. In particular, the limited depth of work in organ-system disease biology, model systems, biomarkers, and therapeutics points to specific areas where targeted investment could help move the field from description toward intervention.



Temporal trends in the literature also suggest that the field is beginning to shift from descriptive and diagnostic work toward more translational questions. Early DM2 publications focused heavily on phenotype definition, gene discovery, diagnostic criteria, and case series. Subsequent work expanded into RNA toxicity, CNBP biology, repeat instability, imaging, biomarkers, registries,

and clinical characterization. More recent studies increasingly address multisystem burden, patient-reported outcomes, endpoint development, and early therapeutic strategies.

Temporal & Contextual Shifts in DM2 Research

Early 2000s: Descriptive & Diagnostic:

- Initial clinical phenotype descriptions (PROMM)
- Gene discovery: CNBP CCTG expansions
- Early diagnostic guidelines and case series

2010s: Mechanistic Insights & Imaging:

- RNA toxicity, CNBP biology, repeat instability mechanisms
- Natural history studies and registry initiation
- Growing focus on MRI/biomarker development

2020s: Multisystem & Translational Focus:

- Cardiac, CNS, pain, cognition, and endocrine complications explored
- Cross-cohort registries, epidemiology, and cost-of-care studies
- Emerging preclinical therapeutic strategies (RNA-targeting, small molecules)
- Integration of patient-reported outcomes and trial readiness frameworks

Current Trends: Toward Clinical Trials:

- Consolidated guidelines, international collaboration
- Biomarker qualification (imaging, digital endpoints, PROs)
- First translational therapies advancing into testing phases

Although overall publication output has remained relatively steady, the content of the literature suggests that DM2 is not static; rather, it is moving toward a stage where coordinated field-building investments could meaningfully accelerate clinical and therapeutic progress.

Overall, the literature review shows that DM2 remains earlier in its translational development trajectory than DM1, but also that the field has reached a point where its next priorities are increasingly clear. The opportunity now is to convert a growing but fragmented knowledge base into a coordinated research agenda focused on natural history, diagnostics, disease models, patient-centered outcomes, and therapeutic development. Because publication activity is closely linked to research funding, the next section examines whether current funding patterns are sufficient to support the coordinated investment needed to move DM2 toward trial readiness.

DM Research Funding: A Lever for Field-Building

Research funding is one of the most important drivers of scientific progress, publication output, investigator recruitment, infrastructure development, and therapeutic readiness. In DM2, where the research ecosystem remains relatively small, funding does more than support individual projects; it catalyzes building the field itself. Targeted funding can attract new investigators, generate preliminary data for larger grants, create shared tools and resources, and signal to academic and industry stakeholders that DM2 is an investable area for discovery and therapeutic development.

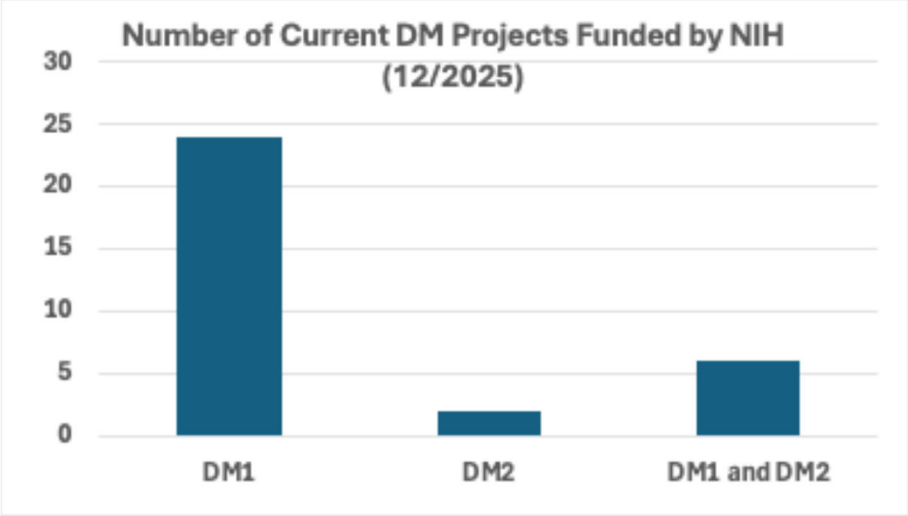
To assess the current funding landscape, we analyzed major U.S.-based funding mechanisms supporting myotonic dystrophy research, including the National Institutes of Health (NIH), the U.S. Department of Defense Congressionally Directed Medical Research Programs and Peer Reviewed Medical Research Program (DoD/CDMRP/PRMRP), the Muscular Dystrophy Association (MDA), and the Myotonic Dystrophy Foundation (MDF). Because these mechanisms differ substantially in award size, duration, and scope, this assessment emphasizes the number and distribution of funded projects rather than direct dollar-for-dollar comparisons.

Across these funding sources, DM research funding remains heavily weighted toward DM1. This pattern is not unexpected: DM1 has a larger research community, a longer history of mechanistic investigation, more mature natural history infrastructure, and a more advanced therapeutic-development ecosystem. These factors reduce perceived scientific and development risks, making DM1 projects more competitive for funding and more attractive for industry engagement. However, this same dynamic also creates a self-reinforcing cycle: greater investment produces more data, stronger tools, more publications, and more investigators, which in turn further increases the fundability and translational readiness of the field.

For DM2, the opportunity is to deliberately interrupt the opposite cycle. Limited funding has contributed to a smaller publication base, fewer investigators, less mature model systems, limited natural history data, and a less developed therapeutic pipeline. Yet these are precisely the areas where targeted investment could have disproportionate impact. Strategic funding in DM2 can generate the foundational evidence and infrastructure needed to increase competitiveness for larger federal awards, attract new academic laboratories, and de-risk future therapeutic development.

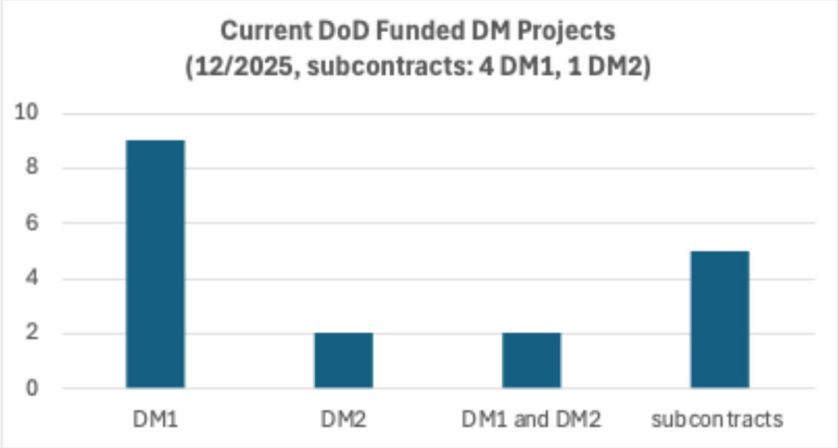
Active US National Institutes of Health (NIH) Funded Projects

NIH funding remains the largest and most influential source of biomedical research support in the United States (Appendix D). Current NIH project-level funding shows a substantial imbalance, with approximately 12 times more active DM1 projects than DM2 projects. This imbalance reflects the greater maturity and scale of the DM1 field, but it also highlights the opportunity for targeted DM2 investments to expand the investigator base and generate the preliminary data needed for future NIH competitiveness.



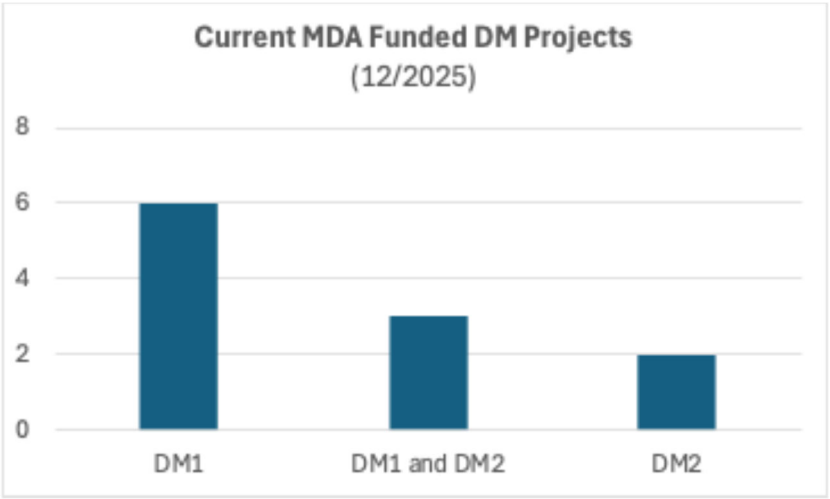
US Department of Defense (DoD) Funding

The DoD/CDMRP/PRMRP has also become an important source of support for myotonic dystrophy research. In 2024, the PRMRP provided more than $6 million for DM research. However, as with NIH funding, support has been predominantly focused on DM1, with no DM2-specific project funded in 2023 and only one joint DM1/DM2 project funded in 2022. This pattern underscores the need for more DM2-focused applications, stronger preliminary data, and clearer alignment between DM2 research priorities and available federal funding mechanisms.



Muscular Dystrophy Association (MDA) Funding

MDA funding provides another important component of the neuromuscular research ecosystem. Although MDA awards are smaller in scale than NIH or DoD mechanisms, they can serve as critical steppingstones toward larger federal grants by supporting early-stage projects, investigator development, and preliminary data generation. Current MDA-funded DM2 projects include LEOPARD-DM2, focused on establishing DM2-specific clinically meaningful outcome measures, and a project led by Matthew Disney, PhD, targeting the RNA repeat expansion that causes DM2.



However, MDA is not awarding new grants in 2026 as part of its current evaluation and strategic planning process, further narrowing near-term funding opportunities for emerging DM2 research.

The following DM2 projects are currently being funded by the MDA:

- LEOPARD-DM2: A project establishing DM2 specific clinically meaningful outcome measure.
  Grantee: Chad Heatwole MD, University of Rochester
  Funded: 1/1/2026 - 12/31/2028
- Targeting the RNA Repeat Expansion that Causes Myotonic Dystrophy Type 2
  Grantee: Matthew Disney, PhD; University of Florida
  Funded: 9/1/2023 - 8/31/2026

Projects with multiple disease focus include:

- The mechanism, synergies, and therapeutic horizon of quercetin in DM and C9-ALS 05,
  Grantee: Subodh Mishra, MDA Development Grant
  Funded: May 2025

Myotonic Dystrophy Foundation (MDF) Active Funding as an Historic Accelerator

MDF has played a catalytic role in addressing the DM2 funding gap by directing early research support toward areas where foundation investment can have outsized influence. Since issuing its first DM2-specific grant in 2016, MDF has invested approximately $1.18 million in DM2 research across Research Fellowship awards, Pilot Grants, and Early Career Scholar support (Appendix B). These investments have supported investigator development, preliminary data generation, model-system development, biomarker exploration, genotype–phenotype research, repeat-expansion prevalence studies, and patient-centered clinical research.

The catalyst role is particularly important because DM2 remains early in its translational trajectory. In emerging and undercapitalized fields, early foundation funding often does more than support individual projects; it helps build the field itself. MDF awards enable investigators to test new hypotheses, generate feasibility data, establish research tools, publish early findings, and compete for larger federal or philanthropic grants. They also create entry points for trainees and early-career scientists, helping expand the future investigator pipeline in a disease area where research capacity remains limited.

The Research Fellowship Program has been an especially important mechanism for sustaining DM2-focused investigator development. As MDF's longest-running research funding mechanism, the program accounts for a substantial portion of MDF's DM2 research support. Beginning in 2022, in alignment with MDF's strategic prioritization of DM2, the program has supported at least one DM2-focused Research Fellow each year. This sustained commitment has helped keep DM2 visible to emerging investigators and has provided structured support for early-career researchers developing expertise in the disease.

The longer-term value of this approach is illustrated by the trajectory of Lukasz Sznajder, PhD, MDF's first DM2-focused Research Fellow. Early MDF support contributed to his development as an independent investigator, and he is now expanding his DM research agenda in his own lab at the University of Nevada, Las Vegas. His subsequent recognition by MDA with the inaugural Research Momentum Award in 2026 further illustrates how early, disease-specific foundation support can help catalyze broader investigator success and increase visibility for DM research[1].

More recently, MDF's Pilot Grant Program has become an important tool for broadening the DM2 research portfolio. Launched in 2024, the program has attracted substantial DM2 interest, with 44 percent of awards directed specifically to DM2 research. One of four MDF Pilot Grants in 2024 focused on DM2, followed by three of five Pilot Grants in 2025. This response suggests that when targeted funding opportunities are available, investigators are ready to bring forward DM2-relevant ideas. The Pilot Grant mechanism is therefore well suited to a field where much of the work remains emerging and where relatively small investments can help generate the preliminary data needed for larger follow-on funding.

MDF has also used its funding strategy to address specific knowledge gaps identified as barriers to progress. For example, to address the need for better repeat-expansion prevalence data, MDF directly engaged Arianna Tucci, MD, PhD, at Queen Mary University of London to explore expansion frequencies at the CNBP locus. This engagement led to a successful 2025 Pilot Grant application and has generated needed prevalence data for the field. This example illustrates a key function of foundation funding: identifying high-priority gaps, connecting investigators to field needs, and using targeted support to move strategically important questions forward.

Collectively, MDF-funded DM2 projects span several of the field's highest-priority areas, including model-system development, therapeutic hypothesis testing, biomarker development, exercise and clinical intervention research, genotype–phenotype characterization, and repeat-expansion biology. This breadth reflects a deliberate field-building strategy. Rather than concentrating only on one therapeutic modality or research domain, MDF has used its funding portfolio to support multiple foundational pillars needed for future therapeutic readiness.

At the same time, MDF's role must be understood within the broader funding ecosystem. Foundation grants are essential for stimulating new work, supporting early-career scientists, and generating preliminary data, but they are not sufficient on their own to build and sustain a robust DM2 research pipeline. Larger federal, philanthropic, and industry investments will be needed to advance comprehensive natural history studies, validate disease-relevant models, develop trial-ready endpoints, and support therapeutic proof-of-concept studies.

Taken together, the funding analysis reinforces a central conclusion of this landscape assessment: **DM2 is not simply underfunded; it is undercapitalized relative to its opportunity.** The field has clearly defined needs, an engaged patient community, emerging scientific momentum, and identifiable barriers that targeted funding could help address. What is needed now is not only more

[1] https://www.mda.org/press-releases/2026/muscular-dystrophy-association-announces-lukasz-sznajder-phd-msc-to-receive-inaugural-mda-research

funding, but strategically sequenced investment that builds the foundations required for sustained progress.

Priority funding areas include large-scale natural history studies, disease-relevant model systems, diagnostic innovation, endpoint and biomarker development, investigator recruitment, and therapeutic proof-of-concept studies. These areas are mutually reinforcing: natural history data can support endpoint development and trial readiness; improved diagnostics can expand patient identification and research participation; validated model systems can enable mechanistic studies and therapeutic testing; and targeted investigator support can expand the scientific community needed to sustain progress.

Moving forward, the most effective funding strategy will likely combine foundation support with larger federal, philanthropic, and industry mechanisms. MDF and partner organizations can play a key convening role by defining priority areas, supporting early-stage projects, helping investigators generate preliminary data, and encouraging coordinated applications to NIH, DoD, MDA, and other funders. In this way, targeted funding can become a multiplier: strengthening the scientific base, attracting new investigators, increasing competitiveness for larger grants, and improving the conditions for industry engagement and therapeutic development.

One of the clearest areas where coordinated funding could have immediate strategic value is disease-relevant model-system development. The absence of validated DM2 models remains a major bottleneck for mechanistic research and therapeutic development, making model development a high-priority investment opportunity for the next phase of DM2 research.

Animal Models of DM2

Disease-relevant model systems are essential for advancing mechanistic understanding, testing therapeutic hypotheses, and de-risking drug development. In many genetic diseases, animal and cellular models provide the bridge between molecular biology and clinical translation by allowing investigators to study disease mechanisms, evaluate biomarkers, test candidate therapies, and generate preclinical proof-of-concept data before moving into human studies.

For DM2, model-system development represents one of the most important and actionable opportunities to accelerate the field. Because DM2 is a complex repeat-expansion disorder with multisystem involvement, no single model system is likely to capture the full biology of the disease. Instead, progress will require a complementary model ecosystem that includes mammalian models, non-mammalian animal systems, and patient-derived cellular platforms. Each system can answer different questions: mouse models can support tissue-level and in vivo therapeutic studies; zebrafish and Drosophila can enable scalable genetic and drug-screening approaches; and cell-based systems, including iPSC-derived models, can support controlled studies of repeat biology, RNA toxicity, splicing, RAN translation, and therapeutic modulation.

The following sections therefore review the current state of DM2 model development across mouse, zebrafish, Drosophila, and cell-culture systems. Together, these model platforms represent a critical translational toolkit. Although no validated DM2 mouse model is currently available to

broadly support therapeutic development, ongoing work across multiple systems provides important starting points. Coordinated investment in complementary models could substantially strengthen DM2 biology, support biomarker and endpoint development, enable preclinical testing, and improve the conditions for future industry engagement.

Mouse Models

Mouse models remain a particularly important component of the DM2 translational toolkit because they can support in vivo studies of tissue pathology, disease progression, biomarker development, pharmacology, safety, and therapeutic proof-of-concept. In successful rare-disease drug-development programs, disease-relevant mouse models often provide a critical bridge between

Mouse Models	Description	Status
HSALR-DM2, Thornton lab	Similar model and strategy to the successful DM1 system	Work in progress: Initial characterization did not show "DM"-like phenotype in animals. No publications to date.
Swanson lab	CRISPR-Cas9 mediated integration of DM2 repeats in in endogenous DM2 intron 1 of CNBP	Work in progress: Study ongoing, but the animals do not show "DM"-like phenotype.
Bacterial artificial chromosome (BAC) transgenic, Ranum lab	BAC transgenic based integration of CNBP with expanded repeat, current stage: multiple lines, clonal expansion	Work in progress: No publications to date.
Krahe lab	(CCTG)121 expansion in intron 1 of the human skeletal actin gene (DM2HSATG)	Investigator retired: Based on similar approaches, simple CCTG overexpression likely does not result in significant phenotypic changes. No publications.
CNBP KO mouse, Timchenko lab	Gene knockout[2,3]; Lethal, LOF dominating gain-of-function effects seen in DM1	Published. CNBP KO causes late skeletal muscle atrophy while the reduction of CNBP affects the Central Nervous System (reduction in total brain volume and grey matter).

[2] Jennings K, Lindquist D, Poonia A, Schoser B, Schneider-Gold C. The role of CNBP in brain atrophy and its targeting in myotonic dystrophy type 2. Hum Mol Genet. 2025 Mar 7;34(6):512-522. doi: 10.1093/hmg/ddaf002. PMID: 39807631; PMCID: PMC12167764.
[3] Wei C, Stock L, Schneider-Gold C, Sommer C, Timchenko NA, Timchenko L. Reduction of Cellular Nucleic Acid Binding Protein Encoded by a Myotonic Dystrophy Type 2 Gene Causes Muscle Atrophy. Mol Cell Biol. 2018 Jun 28;38(14): e00649-17. doi: 10.1128/MCB.00649-17. PMID: 29735719; PMCID: PMC6024164.

molecular hypotheses and human trials by allowing investigators to test whether candidate interventions modify disease biology in a living system.

For DM2, however, mouse-model development has proven more challenging than initially anticipated. Several approaches have attempted to adapt strategies that were successful in DM1, including repeat overexpression systems and targeted integration of expanded repeats. To date, these efforts have not produced a broadly validated model that reliably recapitulates key DM2 molecular, tissue, and functional features that can be used with confidence for drug-development studies. This does not mean that model development has failed; rather, it suggests that DM2 biology may require more tailored and complementary modeling strategies than those used for DM1.

The current state of DM2 mouse models should therefore be viewed as both a bottleneck and an opportunity. A validated mouse model would substantially strengthen mechanistic research, enable pharmacologic testing, support biomarker development, and increase confidence among funders and industry partners. At the same time, the difficulty of generating such models underscores the need for coordinated investment, transparent sharing of positive and negative findings, and support for multiple parallel approaches. These may include transgenic, knock-in, bacterial artificial chromosome (BAC)-transgenic, and humanized strategies designed to capture different aspects of CNBP repeat-expansion biology.

The following section summarizes the major DM2 mouse-model approaches attempted or in development, including their rationale, current status, and implications for future investment. Together, these efforts show that mouse-model development remains one of the highest-priority opportunities for accelerating DM2 therapeutic readiness.

For this landscape assessment, projects focusing on generating models were reviewed based on:

- Review of publications available in PubMed and the assessment of whether studies were concluded and shared with the scientific community through peer-review publication.
- Inclusion in the MDF Research Landscape Assessment (2023).
- Interviews, when possible, with the principal investigator leading the respective project.
- Interviews with academic and clinical experts collaborating or working on similar projects.

In 2016, MDF funded Dr. Lukasz Sznajder, then a postdoctoral scholar in Dr. Maurice Swanson's laboratory at the University of Florida, to support development of a CNBP-CCTG repeat knock-in mouse model. During the project, the Swanson laboratory generated animals carrying approximately 150–480 CCTG repeats; however, these mice did not show typical DM-like features, including muscle pathology or splicing alterations (key opinion leader interviews, 2025). Characterization of this model remains ongoing, and detailed findings have not yet been published.

In parallel, the Thornton laboratory at the University of Rochester developed a transgenic model containing approximately 1,000 CCTG repeats inserted into intron 3 of the ACTB gene, using a strategy conceptually modeled on prior DM1 systems. This model also has not recapitulated DM2-relevant splicing changes or disease-specific muscle pathology to date. Although not yet

comprehensively characterized, Dr. Charles Thornton has made the model available for further study by collaborating laboratories, including groups at the University of Florida.

Together, these early efforts suggest that DM2 biology may not be adequately modeled by directly adapting strategies that were successful in DM1. While MBNL-mediated splicing disruption plays a central role in DM1, DM2 may involve a broader and more complex set of disease mechanisms, including additional RNA-binding proteins (RBPs) such as members of the RBFOX family, as well as potentially non-splicing-mediated pathways, as well as loss-of-function effects of CNBP itself. These findings support the need for continued investment in multiple, complementary DM2 model-development strategies.

Systematic work by Mackenzie Davenport and Maurice Swanson[4], further highlights these differences, including muscle involvement patterns, relative RBP contributions, and histopathology differences between DM1 and DM2. The research focused on alternative splicing and its contributions to disease progression, a process regulated through a network of *cis*-regulatory sequence elements and *trans*-acting RBP. The work examined MBNL and RNA binding fox-1 homolog (RBFOX) proteins, which regulate fetal to adult splicing transitions critical for normal muscle, heart, and central nervous system development. They showed that rather than a simple relationship between the organization of RBP binding sites and a specific splicing outcome. Instead, complex interaction networks govern both splicing inclusion and exclusion events influenced by RNA-binding protein gradients.

The cause of the disparities in how muscles are affected within each disease and between DM2 and DM1 remains unknown. More broadly, it remains unclear if current DM mouse models recapitulate these differences.

The MDF has also funded the development of the BAC transgenic mouse model in the Ranum lab at the University of Florida, led by Laura Ranum, PhD, through historic and current doctoral and postdoctoral fellowships. This mouse model uses bacterial artificial chromosome (BAC) approaches. While this model is not yet characterized in terms of its potential specific or non-specific transgene effects, the MDF is currently funding a doctoral project identifying effects using a backcross strategy. While the approach remains risky and uncertain, especially considering species-specific differences between humans and mice, Dr. Ranum's strategy recapitulates the genetic or "DNA" environment of the human disease rather than relying on a limited repeat approach, that, while successful in DM1, may not translate to DM2.

Considering repeat associated non-AUG (RAN) mediated translation, which has been shown to have clear mechanistic and exclusive disease mediating contributions in an increasing number of repeat expansion diseases, it is important to emphasize that the current efforts of transgenic animal model development are hypothesis-driven. As such, their outcomes and utility are never a forgone conclusion. Each model is designed to test an underlying null-hypothesis, and in this capacity, it may or may not yield definitive mechanistic information about the relevance or applicability regarding the underlying human disease. The current state of animal models also highlights the

[4] Davenport ML, Fong A, Montoya-Vazquez G, de Moura MFA, Bubenik JL, Swanson MS. Differential pathology and susceptibility to MBNL loss across muscles in myotonic dystrophy mouse models. JCI Insight. 2025 Aug 14;10(18): e195836. doi: 10.1172/jci.insight.195836. PMID: 40811031; PMCID: PMC12487862.

significant need to complement current studies and build a comprehensive knowledge base that captures all mechanistic distributions (splicing (MBNL mediated versus other factors), RAN translation, etc.). Such a framework is needed to test the relative contributions of these mechanisms to both the muscular and non-muscular disease elements in humans.

At present, no validated DM2 mouse model is available that can reliably support, de-risk, or enable broad drug-development studies. This remains one of the most important bottlenecks in the field. Model development is further complicated by the biology of CNBP itself: complete loss of function appears developmentally lethal or severely compromising, while partial loss-of-function models produce neuroanatomical effects but do not reproduce the alternative-splicing features typically associated with myotonic dystrophy.

Among current efforts, Dr. Ranum's BAC-transgenic DM2 mouse model represents the most active and potentially promising approach. Because this strategy preserves more of the human CNBP genomic context, it may offer advantages over simpler repeat-insertion or overexpression systems. However, additional characterization is needed to determine whether the model recapitulates disease-relevant molecular, tissue-level, and functional features. This includes evaluation of transgene insertion effects, repeat stability, generational changes, and the extent to which any observed phenotype reflects DM2-relevant biology.

Overall, the mouse-model landscape underscores both the challenge and the opportunity in DM2 research. Developing a useful DM2 mouse model is inherently uncertain, but it is also one of the highest-leverage investments the field can make. Progress will likely require multiple well-funded, complementary approaches, transparent sharing of positive and negative findings, and clear communication with funders and donors that model development is a high-risk but essential step toward therapeutic readiness. A validated DM2 mouse model would substantially strengthen mechanistic research, enable preclinical therapeutic testing, and improve the conditions for future industry engagement.

Zebrafish Animal Models

Zebrafish models provide a vertebrate, genetically tractable, and high-throughput platform for studying disease pathophysiology, functional outcomes, and potential therapeutic interventions. For DM2, zebrafish systems could offer value as scalable models for testing repeat-associated toxicity, identifying modifier pathways, and screening candidate interventions. MDF has previously supported potentially catalytic projects using zebrafish model systems in myotonic dystrophy. Although promising, these efforts have not yet led to sustained follow-on funding or peer-reviewed publications reporting major new findings.

To assess the current state of the field, we reviewed peer-reviewed publications indexed in Medline through the National Library of Medicine in December 2025. Searches were performed using the terms "myotonic dystrophy" and "zebrafish," with "Danio rerio" used as a validation term. A second search added the term "type 2" to identify publications with specific relevance to DM2.

Of the 13 publications generated by the search, only four publications were associated with the term “type 2”. One of the publications from the Berglund lab, deLorimier et al. 2014 study “Modifications to toxic CUG RNAs induce structural stability, rescue mis-splicing in a myotonic dystrophy cell model and reduce toxicity in a myotonic dystrophy zebrafish model” in *Nucleic Acids Research* focused on DM1 repeats and showed the potential of applicability of the model for DM2.[5] While studies exploring zebrafish are in progress (e.g. mbnl deletion systems), a “universal” zebrafish model available for drug screening studies is not available today.

Drosophila Animal Models

Like zebrafish, *Drosophila melanogaster* (“Drosophila,” also known as the common fruit fly) models offer a rapid, genetically tractable, and cost-effective platform for studying disease mechanisms, identifying modifier pathways, and screening potential therapeutic targets. For DM2, Drosophila systems could be particularly useful for investigating repeat-associated toxicity, RNA-mediated mechanisms, and genetic modifiers that may contribute to disease biology.

The 2019 DM2 Landscape Assessment highlighted several promising Drosophila-based efforts and collaborations. However, these efforts have not resulted in sustained model-system development, major follow-on studies, or broadly adopted tools for DM2 therapeutic discovery. As with zebrafish, this suggests that Drosophila models remain a potentially valuable but underdeveloped component of the DM2 translational toolkit.

Using the same methodology, utilizing peer reviewed publications as an indicator of progress, we performed a Medline search (December 2025) using the search terms "myotonic dystrophy" AND “drosophila” AND "type 2". The nine publications included proof-of-concept studies, molecular investigations of the differing disease mechanisms between DM2 and DM1, and a review outlining how Drosophila can be effectively used as a tractable animal model to identify novel gene modifiers of the pathogenic pathway and discover potential new drugs.[6]

Interestingly, Dr. Wen Huang at Central South University in Changsha, Hunan, China, is utilizing the Drosophila system for DM2 drug screening studies, identifying affected pathways and generating testable hypotheses.[7]

Overall, Drosophila models should be viewed as a complementary discovery platform rather than a stand-alone translational solution for DM2. While they are unlikely to fully recapitulate the multisystem features of human disease, they can provide scalable and efficient tools for studying repeat toxicity, identifying genetic modifiers, and prioritizing pathways for further investigation. Strategic investment in Drosophila models, particularly when integrated with mouse, zebrafish,

5 deLorimier E, Coonrod LA, Copperman J, Taber A, Reister EE, Sharma K, Todd PK, Guenza MG, Berglund JA. Modifications to toxic CUG RNAs induce structural stability, rescue mis-splicing in a myotonic dystrophy cell model and reduce toxicity in a myotonic dystrophy zebrafish model. Nucleic Acids Res. 2014 Nov 10;42(20):12768-78. doi: 10.1093/nar/gku941. Epub 2014 Oct 10. PMID: 25303993; PMCID: PMC4227782.

6 Coni S, Falconio FA, Marzullo M, Munafò M, Zuliani B, Mosti F, Fatica A, Ianniello Z, Bordone R, Macone A, Agostinelli E, Perna A, Matkovic T, Sigrist S, Silvestri G, Canettieri G, Ciapponi L. Translational control of polyamine metabolism by CNBP is required for Drosophila locomotor function. Elife. 2021 Sep 14;10: e69269. doi: 10.7554/eLife.69269. PMID: 34517941; PMCID: PMC8439652.

7 Zhu Y, Xiao S, Guan X, Deng H, Ai L, Fan K, Xue J, Li G, Bi X, Xiao Q, Huang Y, Jiang L, Huang W, Jin P, Duan R. Modulating CCTG repeat expansion toxicity in DM2 Drosophila model through TDP1 inhibition. EMBO Mol Med. 2025 May;17(5):967-992.

and patient-derived cellular systems, could strengthen the broader DM2 model ecosystem and accelerate early therapeutic discovery.

Cell Culture Systems

Advances in induced pluripotent stem cell (iPSC) technology provide important opportunities for DM2 research and therapeutic discovery. iPSCs are generated by reprogramming blood or skin cells into an undifferentiated, pluripotent state, after which they can be directed into multiple cell types, including disease-relevant muscle, cardiac, or neural lineages.[8] For DM, these systems offer a controlled experimental platform to study repeat biology, RNA toxicity, splicing abnormalities, RAN translation, cellular stress pathways, and potential therapeutic modulation.

Cell-based systems are especially valuable in DM2 because validated animal models remain limited. Patient-derived iPSC lines can preserve disease-relevant genetic context and allow investigators to test specific molecular hypotheses in human cells. They can also support early therapeutic screening, biomarker discovery, and comparison of disease mechanisms across cell types. Progress establishing and utilizing patient-derived DM2 cell lines has been limited. However, recent studies demonstrate feasibility and utility for drug screening of such systems.[9] While iPSC-based regenerative therapies for muscle disease remain largely preclinical and face important barriers—including uncertain in vivo differentiation, tumorigenicity risk, and epigenetic abnormalities—their immediate value for DM2 lies in research and drug discovery rather than direct cell-replacement therapy.

As part of MDF's 2025 research strategy, MDF supported the development of patient-derived iPSC resources for myotonic dystrophy. A 2016 grant to RUCDR Infinite Biologics and Rutgers University ultimately generated 21 iPSC lines from seven subjects with DM2 or DM1. These resources remain currently available to academic and commercial researchers through the NINDS Human Cell and Data Repository (https://stemcells.nindsgenetics.org/). Repository use data indicate that the lines received more than 150 requests between 2019 and 2025, with most requests involving DM1-derived lines (85% vs 15% for DM2 lines). DM2 line requests peaked in 2022, and overall use data suggest substantial industry interest, with industry users accounting for approximately 70% of all requests.

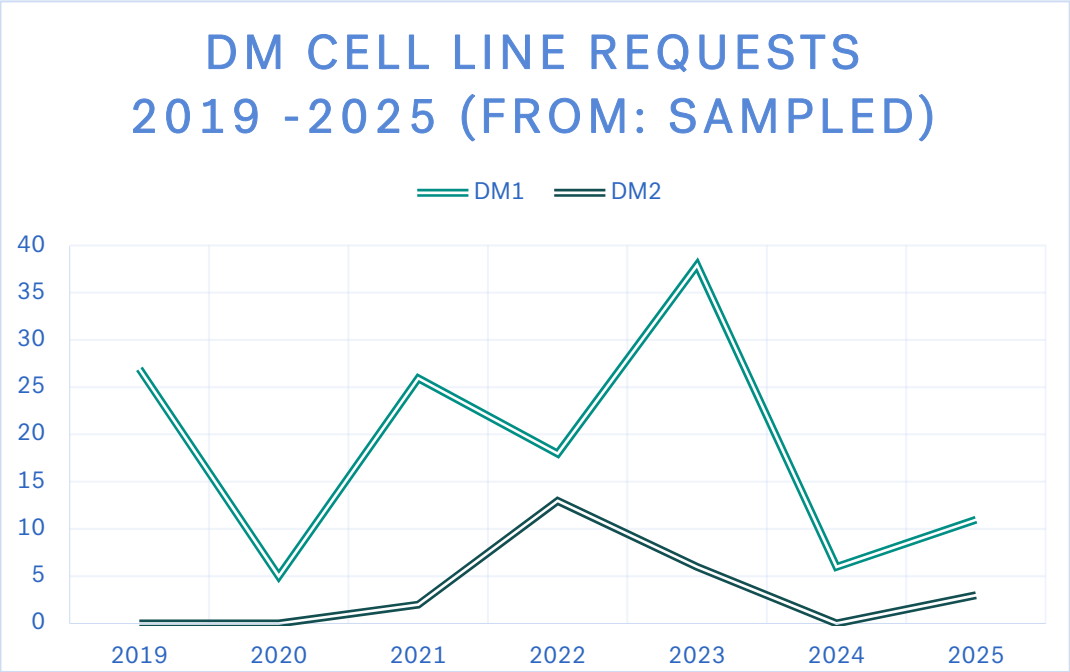
These patterns are informative. The strong use of DM1 lines demonstrates that well-curated patient-derived cell resources can support a broader research and development ecosystem. The more limited use of DM2 lines suggests that similar momentum has not yet fully materialized for DM2, likely reflecting the smaller investigator base, more limited therapeutic pipeline, and fewer

[8] https://www.waisman.wisc.edu/stem-cell-research-program/ipsc/#:~:text=iPSC%20Highlights%20&%20Timeline-,About%20iPSC,to%20three%20months%20to%20complete.

[9] Jenquin JR, O'Brien AP, Poukalov K, Lu Y, Frias JA, Shorrock HK, Richardson JI, Mazdiyasni H, Yang H, Huigens RW 3rd, Boykin D, Ranum LPW, Cleary JD, Wang ET, Berglund JA. Molecular characterization of myotonic dystrophy fibroblast cell lines for use in small molecule screening. iScience. 2022 Apr 4;25(5):104198. doi: 10.1016/j.isci.2022.104198. PMID: 35479399; PMCID: PMC9035709.

active translational programs. However, the existence of these lines represents an important starting point. With targeted promotion, integration into funded research programs, and pairing with mechanistic and therapeutic-development priorities, DM2 iPSC resources could become a more active component of the DM2 model ecosystem. Similar, progress with patient derived DM2 cell lines is underway with manuscripts in preparation (Berglund, personal communication, 2026).

Overall, patient-derived cellular systems should be viewed as a strategic complement to animal models. They are unlikely to replace the need for validated in vivo systems, but they can help bridge current model gaps by enabling human-cell-based studies of disease mechanisms, therapeutic modulation, and biomarker discovery. Expanded use and further development of DM2 cellular models could strengthen the translational toolkit, support early therapeutic discovery, and help generate preliminary data needed for larger model-system and drug-development efforts.



Natural History Studies

Natural history studies are one of the most important foundations for therapeutic development in rare diseases. They define how a disease progresses over time, identify clinically meaningful changes, clarify variability across patient subgroups, and support the selection and validation of outcome measures for clinical trials. For DM2, a comprehensive natural history effort represents one of the highest-leverage opportunities to move the field toward trial readiness.

In drug development, natural history data serve several essential functions. They help determine which symptoms and organ systems should be prioritized, how quickly measurable changes occur, which patient populations are most appropriate for specific interventions, and what magnitude of change may be clinically meaningful. These data can also reduce development risk by helping

sponsors design feasible trials, select endpoints, estimate sample sizes, and interpret treatment effects against a well-characterized disease trajectory.

At present, DM2 lacks a large, sufficiently powered natural history study comparable to the major efforts that have helped advance DM1 trial readiness. This gap is a major barrier, but also a clear and actionable opportunity. A coordinated DM2 natural history study could define disease progression, characterize multisystem involvement, identify clinical subtypes, validate patient-centered outcomes, and provide the evidence base needed for future regulatory and therapeutic-development planning.

As a technical note, while interventional studies must be disclosed on clinicaltrials.gov, such requirements are not applicable for all non-interventional, observational studies, such as natural history studies, making this assessment less precise.[10] While there has not been a similar study to the large DM1 natural history study (END-DM1)[11] establishing comprehensive longitudinal evidence in DM2, several smaller or more targeted studies have contributed important insights. ASCEND-DM, which was designed to assess clinical endpoints and biomarkers in DM1 and DM2, was terminated after the principal investigator left NIH. COMEDY-2 evaluated clinical outcome measures in DM2 and helped show that some measures, including walking, strength, and pain assessments, may be informative while also reinforcing the need for DM2-specific validated tools. Additional studies are now examining exercise, brain structure, clinical endpoints, and disease progression, but these efforts remain narrower in scope than what is needed for a field-wide natural history platform.

- ASCEND-DM (Assessing Clinical Endpoints and Biomarkers in Myotonic Dystrophy Type-1 and Type 2): ClinicalTrials.gov ID NCT03867435, sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) with information provided by the NIH Clinical Center. The study was last updated on November 4, 2021, and was terminated when the principal investigator left the NIH.

- COMEDY-2 (Clinical Outcome Measures in Myotonic Dystrophy Type 2): ClinicalTrials.gov ID NCT03603171, sponsored by LMU Klinikum. The study was last updated on February 20, 2020.

The COMEDY-2 study aimed to identify measures of DM2 progression for clinical trials, focusing on patient-reported outcomes (PROs) and clinical tests for symptoms including muscle weakness, pain (myalgia), and myotonia (muscle stiffness/locking). Key findings of the study showed that while some general measures, such as the six meter walking test (6MWT), the Handheld Myometry/Dynamometry (HHD) for strength[12], and the McGill Pain Questionnaire (MPQ) for

[10] (https://clinicaltrials.gov/policy/fdaaa-801-final-rule)
[11] Mul K, Eichinger K, Hung M, Sansone VA, Gagnon C, Subramony S, Roxburgh RH, Hamel J, Statland JM, Elsheikh B, Turner C, Sampson J, Ragole T, Matthews E, Schoser B, Swenson A, Laverty C, Shieh P, Greene EP, Takahashi M, Wicklund M, Dekdebrun J, Raymond J, DeSpain E, Thornton CA, Johnson NE; Myotonic Dystrophy Clinical Research Network. Establishing biomarkers and clinical endpoints in myotonic dystrophy type 1 (END-DM1): Protocol of an international natural history study. PLoS One. 2025 Dec 11;20(12): e0331163.
[12] https://www.apta.org/patient-care/evidence-based-practice-resources/test-measures/hand-held-myometrydynamometry-#:~:text=What%20it%20measures:,muscle%20group%2C%20or%20individual%20muscle.

pain[13], show promise, DM2 needs its own validated tools. This led to support for the development of disease-specific measures, including the Myotonic Dystrophy Type 2 Health Index (MD2HI), to capture its unique and diverse symptoms.[14] MD2HI constitutes one of the first validated DM2-specific assessment tools to capture patient experiences.

The following smaller studies are currently underway with goals to investigate specific organ impact and their respective contributions to disease impact and burden. These include:

- Investigating Exercise in Myotonic Dystrophy Type 2 (DM2): ClinicalTrials.gov ID NCT06716931, sponsored by Massachusetts General Hospital with information provided by Paloma Gonzalez Perez, MD, PhD. The study was last updated on September 29, 2025 (personal communication).

- Brain Structure and Clinical Endpoints in Myotonic Dystrophy Type 2 (BraCE-DM2): ClinicalTrials.gov ID NCT05854433, sponsored by Wake Forest University Health Sciences with information provided by the same institution. The study was last updated on July 11, 2025.

- STOPP-DM2 (not disclosed on clinicaltrials.gov), investigating pathogenesis and disease progression in DM2, sponsored by the University of Rochester, Rochester NY and funded by the NIH. Studies have been ongoing; results will be presented at IDMC-15 (oral presentation).

The MDF also participated in an international registry analysis coordinated by the TREAT-NMD Global registry network[15] to consolidate and analyze DM2 registry data. Using harmonized data from multiple national registries, including the Myotonic Dystrophy Family Registry (MDFR), the study assembled a cohort of ~1,700 individuals**.** This represents one of the largest DM2 datasets reported to date. The analysis provides important insights into demographics, age of onset, and disease burden.[16] Key findings include:

- **Adult-onset predominance**, with a median age in the early 50s, but with a meaningful minority reporting symptom onset before age 20.
- **Moderate functional impact overall**, with most individuals being ambulatory, though approximately **1 in 5 require walking aids**.
- **Multisystem involvement that is less frequently present than in DM1** but presents through cardiac device use and respiratory support in a minority of patients.

[13] Moshourab R, Palada V, Grunwald S, Grieben U, Lewin GR, Spuler S. A Molecular Signature of Myalgia in Myotonic Dystrophy 2. EBioMedicine. 2016 May; 7:205-11. doi: 10.1016/j.ebiom.2016.03.017. Epub 2016 Mar 14. PMID: 27322473; PMCID: PMC4909324.
[14] Montagnese F, Rastelli E, Khizanishvili N, Massa R, Stahl K, Schoser B. Validation of Motor Outcome Measures in Myotonic Dystrophy Type 2. Front Neurol. 2020 Apr 21; 11:306. doi: 10.3389/fneur.2020.00306. PMID: 32373059; PMCID: PMC7186332.
[15] Peric S, Ivanovic V, Ashley EJ, Esparis B, Campbell C, Wenninger S, Monckton D, Marini-Bettolo C, Walker H, Voháňka S, Cumming K, Łusakowska A, Hodgkinson V, Cosyns M, Rodrigues M, Yiu E, Mazanec R, Stevenson T, Kostera-Pruszczyk A, Korngut L, Jagut M, Schoser B, Forbes R, Poll A, Roxburgh R. International collaboration to improve knowledge on myotonic dystrophy type 2. J Neuromuscul Dis. 2024 Nov;11(6):1229-1237. doi: 10.1177/22143602241290353. Epub 2024 Dec 8. PMID: 39973464.
[16] Peric S, Ivanovic V, Ashley EJ, Esparis B, Campbell C, Wenninger S, Monckton D, Marini-Bettolo C, Walker H, Voháňka S, Cumming K, Łusakowska A, Hodgkinson V, Cosyns M, Rodrigues M, Yiu E, Mazanec R, Stevenson T, Kostera-Pruszczyk A, Korngut L, Jagut M, Schoser B, Forbes R, Poll A, Roxburgh R. International collaboration to improve knowledge on myotonic dystrophy type 2. J Neuromuscul Dis. 2024 Nov;11(6):1229-1237. doi: 10.1177/22143602241290353. Epub 2024 Dec 8. PMID: 39973464.

- **Substantial underdiagnosis and under-representation** of DM2 across countries, with wide variability in registry participation and data completeness.

However, this international analysis also highlighted persistent limitations in data completeness, registry participation, and systematic capture of DM2-relevant features such as pain, fatigue, myotonia severity, progression metrics, and patient-centered outcomes.

While some experts in the field make a compelling argument that natural history studies per se are not needed to engage in or initiate drug development *today*, literature and survey data suggest a clear next step: DM2 needs a coordinated, longitudinal natural history initiative designed specifically around trial readiness and patient relevance. Such a study should capture the full multisystem burden of DM2, including muscle weakness, pain, myotonia, fatigue, cognitive symptoms, cardiac and respiratory involvement, endocrine and metabolic features, functional limitations, and quality-of-life impact. It should also integrate genetic and molecular data, including repeat size, repeat structure, haplotype information, and modifier loci, where feasible. This would allow the field to examine whether distinct clinical trajectories exist and whether genetic or molecular features can refine patient stratification.

A strong DM2 natural history study should be designed from the outset with endpoint development and trial readiness in mind. This requires integrating clinician-reported outcomes, performance-based assessments, biomarkers, imaging measures, digital tools, and patient-reported outcomes into a coherent framework for measuring disease progression. Because pain, fatigue, gastrointestinal disruption, myotonia, functional variability, and daily-life impact are central to the lived experience of DM2, patient-centered measures should be embedded as core components of the study design rather than treated as secondary considerations.

Importantly, natural history research would also support standardized assessment protocols, strengthen clinical site readiness, support registry harmonization, improve patient identification, generate biospecimen and data resources, and provide a shared foundation for academic and industry studies. It could also help align clinicians, researchers, regulators, funders, industry partners, and the patient community around a common evidence base.

Overall, the natural history landscape reinforces the central opportunity in DM2: the field has enough clinical experience and emerging tools to define what is needed, but still lacks the coordinated longitudinal evidence required for therapeutic readiness. A large, well-designed natural history study would be one of the most important investments the field could make. It would help convert fragmented clinical observations into a structured development pathway and provide the foundation for endpoint validation, trial design, regulatory engagement, and future disease-modifying therapies.

Drug Development Progress

Clinical drug-development activity is one of the clearest indicators that a disease field is moving toward therapeutic translation. For DM2, the current therapeutic pipeline remains limited, but it also signals an important shift: the field is beginning to move from disease characterization toward early therapeutic exploration.[17] This creates an opportunity to align emerging drug-development interest with the foundational investments needed to make DM2 a more attractive and actionable area for future and much expanded therapy development.

As of June 2026, three publicly disclosed development programs include DM2. Lupin Neurosciences is investigating mexiletine in DM1 and DM2; ARTHEx Biotech has reported mechanistic data supporting miR-23b modulation with potential relevance to both DM1 and DM2; and GrittGene Therapeutics has disclosed a DM2-focused program targeting muscle-regeneration mechanisms. These programs reflect growing recognition that DM2 is therapeutically relevant, but they also illustrate the early stage of the field. Current programs largely target symptoms or downstream disease mechanisms rather than the causal CCTG repeat expansion itself. Dr. Schoser is leading a funding consortium and proposal (EREDRA; European Rare Diseases Research Alliance) proposing first in human studies in collaboration with Arthex performing ASO targeted DM2 trials with 4 EU clinical sites (personal communication August 2026).

This distinction is important because it frames two complementary paths for DM2 therapeutic development. One path focuses on symptomatic, compensatory, or downstream mechanisms, including pain, myotonia, fatigue, muscle function, regeneration, and quality of life. These approaches may provide meaningful benefit for individuals living with DM2, particularly while disease-modifying therapies remain unavailable. While such focus should not be dismissed simply as not being causal; however, they will equally require rigorous clinical evaluation, appropriate outcome measures, and regulatory-grade evidence to demonstrate meaningful benefit.

The second path is more directly disease-modifying: targeting the repeat expansion or its toxic molecular consequences. If the expanded CCTG repeat is indeed the central disease-causing mechanism in DM2, then many downstream features of the disease—including RNA toxicity, RNA-binding protein disruption, splicing abnormalities, RAN translation, cellular stress pathways, and tissue dysfunction—may ultimately arise from the biological effects of the repeat expansion itself. Under this model, therapies that silence, degrade, block, excise, or otherwise neutralize the pathogenic repeat transcript could potentially improve multiple aspects of disease biology simultaneously.

This repeat-centered therapeutic rationale is important because it offers a more optimistic and potentially transformative view of DM2 drug development. If repeat-derived toxicity is the dominant upstream driver, DM2 may also not require separate therapies for each downstream mechanism or organ system. Instead, a causal intervention could, in principle, reverse molecular pathology and improve clinical manifestations across multiple domains. Experience in DM1 supports the plausibility of this approach, as several advanced therapeutic strategies are designed to target toxic repeat RNA or its downstream molecular effects. While DM2 differs from DM1 in

[17] https://myotonic.org/resources/drug-development-pipeline/

important biological and clinical ways, the shared repeat-expansion framework provides a compelling rationale for pursuing analogous causal strategies in DM2.

At the same time, this therapeutic hypothesis together with the also extreme symptom heterogeneity increases the importance of foundational investment rather than reducing it. Repeat-targeted approaches will require model systems capable of demonstrating target engagement, reversal of molecular pathology, and tissue-level benefit. They will also require natural history data, patient stratification strategies, biomarkers, and trial-ready endpoints to determine whether molecular correction translates into meaningful clinical improvement. Improved diagnostics and repeat characterization will be essential for identifying appropriate participants, understanding genotype–phenotype relationships, and selecting patient populations most likely to benefit.

The current DM2 pipeline therefore should not be interpreted simply as evidence of limited progress. Rather, it identifies where the field must invest to unlock therapeutic development. The presence of even a small number of active programs shows that DM2 is therapeutically actionable, while the absence of repeat-targeted clinical programs highlights a major opportunity. Strategic investment in disease-relevant model systems, natural history studies, biomarker development, diagnostic strategies, patient identification, and clinically meaningful outcome measures could help convert early therapeutic interest into a more robust and diversified pipeline.

Overall, DM2 drug development is at an early but actionable stage. Symptomatic, downstream, and regenerative approaches may offer meaningful near-term benefit, while repeat-targeted strategies represent a potentially transformative disease-modifying path. The key challenge is to build the experimental, clinical, and regulatory infrastructure needed to test both approaches rigorously. By reducing uncertainty around disease biology, patient identification, endpoints, and preclinical testing, the field can improve the conditions for academic innovation, industry engagement, and future clinical trials.

Because therapeutic development depends not only on scientific and clinical tools but also on patient identification, clinical care infrastructure, and community engagement, the next section examines the current state of DM2 clinical care, diagnostics, and care-resource development.

Community Engagement, Clinical Care, and Care Guidelines

Progress in DM2 therapeutic development depends not only on scientific discovery, but also on strong community engagement, accurate diagnosis, informed clinical care, and research-ready patient identification. For a multisystem disorder such as DM2, clinical and community infrastructure are essential components of field-building. They improve awareness, support earlier recognition, strengthen patient participation in research, and help ensure that future trials are grounded in symptoms and outcomes that matter to individuals living with the disease.

During MDF's 2021–2024 Strategic Plan period, MDF made a focused commitment to elevating DM2 visibility and strengthening DM2-specific care and engagement resources. This included the intentional integration of DM2-specific data-capture strategies, targeted community outreach,

expanded DM2 educational content through the Digital Academy and community care resources, a DM2 community listening session, and increased frequency of DM2-specific support groups for both individuals living with DM2 and caregivers. These efforts have helped create a stronger platform for community engagement and future research participation.

MDF also expanded DM2 representation within its scientific and community programming. The establishment of a DM2 panel of experts and the strategic expansion of DM2-specific tracks at MDF International Conferences have increased visibility for DM2 research, and created dedicated space for scientific dialogue. These activities are important because they help signal DM2 as a strategic priority, attract investigator attention, and create opportunities for interaction among patients, clinicians, researchers, and potential therapeutic developers.

Improving access to knowledgeable clinical care is another key element of DM2 field-building. MDF has identified and expanded DM2-engaged healthcare providers within the Find-a-Doctor Map and related clinical resources. MDF has also developed the first-ever DM2 Toolkit to better reflect the lived experience and clinical nuances of DM2, with release expected in 2026. These resources can help patients and families navigate care, support clinicians who may see only a small number of DM2 patients and improve consistency in disease recognition and management.

Up-to-date clinical guidance is also equally essential. The GeneReviews chapter on DM2 was updated in 2025[18] and provides current, clinically actionable information on diagnosis, management, and genetic counseling. This resource complements MDF's 2019 Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type 2[19], which remain an important disease-specific care reference and have been translated into multiple languages. Together, these resources provide a foundation for improving clinical care while the field works toward disease-modifying therapies.

Despite these advances, important opportunities remain. DM2 is still under-recognized, and many individuals may first present outside of neuromuscular clinics, including in cardiology, ophthalmology, endocrinology, pain, rheumatology, rehabilitation, or primary care settings. Broader clinician education is therefore needed to improve diagnostic suspicion, increase appropriate genetic testing, and reduce delays in diagnosis. Better awareness across specialties would also strengthen future research readiness by improving case identification and connecting more individuals with DM2 to registries, natural history studies, and clinical trials.

Diagnostic improvement is especially important. Incorporating repeat-expansion testing more consistently into neuromuscular disease panels and diagnostic workflows could increase recognition of both DM2 and DM1. In addition, deeper characterization of repeat size, repeat structure, haplotypes, and potential modifier loci may help refine genotype–phenotype understanding, support patient stratification, and improve the design of future natural history and interventional studies.

[18] https://www.ncbi.nlm.nih.gov/books/NBK1466/

[19] Schoser B, Montagnese F, Bassez G, Fossati B, Gamez J, Heatwole C, Hilbert J, Kornblum C, Kostera-Pruszczyk A, Krahe R, Lusakowska A, Meola G, Moxley R 3rd, Thornton C, Udd B, Formaker P; Myotonic Dystrophy Foundation. Consensus-based care recommendations for adults with myotonic dystrophy type 2. Neurol Clin Pract. 2019 Aug;9(4):343-353.

Overall, MDF's community engagement, clinical care, and care-guideline activities represent an important foundation for the next phase of DM2 research and therapeutic readiness. These efforts improve visibility, support patients today, strengthen clinician awareness, and create the infrastructure needed for future research participation. The opportunity now is to connect these care and engagement resources more directly with natural history studies, diagnostic innovation, endpoint development, and therapeutic-development planning.

These care and engagement efforts are also reflected in scientific and clinical expert interviews. The next section synthesizes recurring priorities and areas of differing emphasis relevant to accelerating DM2 research, clinical readiness, and therapeutic development.

Insights from Scientific and Clinical Expert Interviews

Perspectives from scientific and clinical experts provide important context for interpreting the data presented in this landscape assessment. While publication, funding, model-system, natural history, and pipeline analyses identify measurable gaps, expert interviews help clarify how those gaps affect day-to-day research, clinical care, and therapeutic-development decisions. The purpose of these interviews was not to establish formal consensus, but to identify recurring themes, strategic priorities, and barriers that may be limiting progress. Findings are synthesized thematically and without individual attribution to preserve confidentiality and avoid linking differing viewpoints to participants. The interview approach is summarized in Appendix C.

Clinical Heterogeneity and Multisystem Burden

Experts described DM2 as a broad, heterogeneous multisystem disorder whose presentation can overlap with aging and frequently evolving from stiffness toward weakness. The muscular phenotype is not always the dominant source of burden. Fatigue, daytime sleepiness, cognitive and other central nervous system manifestations, autoimmune disease, metabolic complications, cardiac disease, and cancer may be equally important for clinical characterization and research planning. Cardiac complications may emerge later in the disease course but can be serious and may contribute to premature mortality; metabolic differences, including obesity and diabetes, and the reported cancer association warrant more systematic study.

Because of the wide clinical spectrum, experts recommended grading patients by clinical severity and prospectively defining mild, moderate, and severe cohorts across all age groups. Potential clinically meaningful subgroups, including channelopathy-like and bulky-muscle or Parkinsonian-like phenotypes, should be tested rather than assumed. These proposed categories illustrate why DM2 should not be treated as a uniform population in natural history studies or future trials.

Natural History, Trial Readiness, and Outcome Development

Experts broadly agreed that DM2 needs a coordinated longitudinal initiative designed to generate and validate outcome measures for therapeutic development. Views differed on sequencing: some

emphasized that emerging endpoints could support focused interventional studies now, while most experts placed comprehensive natural history and protocol standardization ahead of large efficacy trials. A shared platform should span age groups and severity levels and incorporate splicing and other molecular measures, central nervous system and cognitive assessments, sleep and fatigue measures, cardiac and metabolic characterization, patient-reported outcomes, and field or at-home assessments. Isolated, n-of-1 approaches were not viewed as sufficient to define generalizable disease trajectories or trial endpoints.

Diagnostic Modernization and Clinical Recognition

Experts identified diagnostic modernization as a major priority, including greater use of long-read sequencing to resolve DM2 repeat expansions when conventional testing is negative, ambiguous, or discordant with the phenotype. Elevated creatine kinase, myalgia, and early-onset cataracts were highlighted as a clinical pattern that should raise suspicion for DM2 in middle-aged adults. Electromyography should sample proximal muscles in both upper and lower limbs rather than rely on a single muscle, and unusually severe myotonia should prompt consideration of broader muscle gene panels, including chloride- and sodium-channel disorders.

Unresolved genetic questions include the clinical meaning of gray-zone repeats, the adequacy of current anticipation models, the possibility of congenital or very early-onset DM2, and whether the repeat expansion is necessary but not sufficient, with secondary variants such as DNA-repair modifiers influencing phenotype. Better characterization of repeat structure, somatic instability, modifier loci, and genotype-phenotype relationships could improve diagnosis, patient stratification, and therapeutic planning.

Biomarkers, Mechanisms, and Standardized Protocols

High-priority pathomolecular research areas include splicing, RNA toxicity, CNBP-related biology, immune or interferon signaling, and possible relationships among somatic repeat expansion, tissue injury, and cancer risk. Experts also recommended incorporating brain MRI and neuropsychological assessment to characterize cognitive and central nervous system changes. Muscle carnosine measured by magnetic resonance spectroscopy was identified as a promising cross-sectional marker based on preliminary data, while emphasizing that imaging and molecular biomarkers must be validated within longitudinal studies rather than only in cross-sectional case-control comparisons.

Experts recommended a multicenter natural history effort involving experienced centers with substantial DM2 cohorts and a multidisciplinary task force or roundtable to establish a standardized protocol. The framework should address clinical severity and myopathy subgroups, cognitive and neuropsychological testing, muscle and brain imaging, electrophysiology, functional and patient-reported outcomes, and longitudinal biomarker collection. A high-visibility, field-defining initiative could help reposition DM2 as a consequential multisystem disease, while credible community leadership could strengthen patient, investigator, funder, and industry engagement.

Cross-cutting Themes Across Expert Interviews

Across interviews, experts consistently emphasized that DM2 remains a scientifically compelling but underdeveloped field. Basic science experts highlighted the need for greater mechanistic clarity, stronger model systems, and more rigorous foundational research. Several noted that DM2 biology may involve multiple interacting mechanisms, including deleterious effects of CNBP disruption, RNA toxicity, RNA-binding protein dysregulation, altered splicing, bidirectional transcription, RAN translation, immune signaling, and downstream cellular stress pathways. This complexity supports broader therapeutic thinking rather than reliance on a single presumed mechanism or modality.

At the same time, experts also emphasized that the repeat expansion remains a central and therapeutically important target. If the expanded CCTG repeat is the primary upstream driver of disease, then therapies that reduce, silence, degrade, excise, or otherwise neutralize repeat-derived toxicity could have broad disease-modifying potential. This view reinforces the importance of developing experimental systems capable of testing repeat-targeted strategies and linking molecular correction to tissue-level and clinical benefit.

A major recurring theme was the need for validated disease models. Experts emphasized that the absence of a DM2 mouse model that replicates important disease features or hallmarks remains one of the most significant barriers to mechanistic investigation and preclinical therapeutic testing. However, they also recognized that model development in DM2 is inherently challenging and may require several complementary approaches. Rather than expecting one model to capture the full disease spectrum, the field may need a coordinated model ecosystem that includes mouse models, patient-derived cellular systems, iPSC-derived platforms, zebrafish, Drosophila, and other experimental tools.

Clinical experts similarly emphasized the need for stronger natural history data. Views differed on the scope of interventional work that can proceed before a full natural history platform is established: some experts noted that meaningful endpoints and assessment tools are emerging and can support focused studies, while others cautioned that progression, patient subgroups, and outcome trajectories remain insufficiently defined for large efficacy trials. Across these perspectives, there was broad agreement that a large, well-designed natural history study would be transformative. Such a study could clarify progression, define clinical subtypes and severity strata, validate clinic-based and at-home outcomes, and provide a foundation for trial design and regulatory engagement.

Improved diagnostics were also identified as a major opportunity. Experts noted that DM2 remains under-recognized and that many patients may first present outside neuromuscular clinics, including through cardiology, ophthalmology, endocrinology, pain, rehabilitation, rheumatology, or primary care pathways. Broader clinician education, improved access to repeat-expansion testing, and more consistent inclusion of DM2 in neuromuscular diagnostic workflows could improve patient identification, shorten diagnostic delays, and strengthen research readiness.

Several experts also emphasized the importance of genetic characterization beyond diagnosis alone. Better understanding of repeat size, repeat structure, haplotypes, modifier loci, and potential

genotype–phenotype relationships could improve patient stratification, clarify clinical variability, and support future therapeutic-development strategies. These data would be particularly valuable if repeat-targeted approaches advance, because patient selection and molecular characterization may become central to trial design.

Therapeutic strategy was another area of active discussion. Experts recognized the importance of disease-modifying approaches, including repeat-targeted or RNA-directed therapies, but also emphasized that symptomatic and functional interventions should not be overlooked. In the absence of approved disease-modifying therapies, interventions addressing pain, fatigue, myotonia, exercise tolerance, function, and quality of life may provide meaningful benefit to individuals living with DM2. However, such approaches still require rigorous clinical testing and outcome measures that capture clinically meaningful change.

Overall, the interviews reinforced the central conclusion of this assessment: DM2 is a high-opportunity field where targeted investment could have disproportionate impact. Experts identified a consistent set of priorities, including increased research funding, validated model systems, comprehensive natural history studies, improved diagnostics, stronger endpoint development, broader investigator recruitment, and greater clinical education. These priorities are not isolated needs; they are interconnected components of a field-building strategy. Progress in one area can accelerate progress in others, creating the conditions for a more trial-ready and therapeutically actionable DM2 ecosystem.

Summary and Conclusions: A Call to Action for DM2

DM2 is a high-opportunity field where targeted investment could have disproportionate impact. This landscape assessment shows that the field is not defined by a lack of need, lack of relevance, or lack of therapeutic potential. Rather, DM2 is constrained by a set of identifiable and addressable barriers: limited natural history data, insufficient model systems, incomplete diagnostic reach, a small investigator base, and a therapeutic pipeline that remains early in development. These barriers are substantial, but they are not insurmountable. They define the roadmap for action.

The central conclusion of this assessment is that DM2 is undercapitalized relative to its opportunity. The disease imposes meaningful multisystem burden, the patient community is engaged, and the research field has begun to generate the tools and insights needed for translational progress. However, the current level of investment remains insufficient to convert this momentum into a robust therapeutic-development ecosystem. The experience in DM1 demonstrates that progress accelerates when foundational biology, natural history infrastructure, model systems, clinical endpoints, patient engagement, and industry participation begin to align. DM2 now requires the same deliberate coordination.

Expert interviews reinforce and sharpen this roadmap. Across interviews, experts argued that DM2 requires a disease-specific framework, longitudinal studies spanning age and severity, clinically meaningful stratification, validated biomarkers and outcome measures, and a coordinated protocol

rather than isolated projects. Areas of emphasis included the full multisystem phenotype - including central nervous system, sleep and fatigue, autoimmune, metabolic, cardiac, and cancer-related features - as well as diagnostic modernization and deeper mechanism research involving long-read sequencing, systematic proximal-muscle electrophysiology, splicing, RNA toxicity, CNBP biology, and immune or interferon pathways. Although views differed on how much interventional work can proceed before comprehensive natural history data are available, the combined perspectives support a multidisciplinary task force linking natural history, diagnostics, mechanism, biomarker validation, endpoint development, and trial readiness.

The next phase of DM2 progress should focus on five strategic priorities.

1. The field needs a large, well-designed natural history study that includes all age groups and severity levels; captures muscle, cardiac, respiratory, metabolic, sleep, cognitive, and other central nervous system manifestations; evaluates potential clinical subgroups; and integrates clinic-based and at-home assessments, genetic and molecular variation, patient experience, biomarkers, and trial-relevant outcomes.
2. DM2 requires sustained investment in disease-relevant model systems and pathomolecular research. Mouse models, patient-derived cellular platforms, and complementary non-mammalian systems should be developed alongside studies of splicing, RNA toxicity, CNBP biology, RAN translation, modifier pathways, and immune or interferon signaling.
3. Diagnostic strategies must improve so that individuals with DM2 are identified earlier, characterized more completely, and connected to care, registries, and research opportunities. Priorities include broader clinician recognition, systematic proximal-muscle electromyography, access to modern repeat-expansion testing such as long-read sequencing, and deeper characterization of repeat structure and modifier loci.
4. The field must expand its investigator base and collaborative infrastructure through targeted grants, early-career support, conference visibility, strategic publications, and a multidisciplinary expert convening to standardize natural history, biomarker, imaging, electrophysiologic, cognitive, and patient-centered assessment protocols.
5. Therapeutic-development efforts should be diversified, supporting both near-term symptomatic or functional interventions and longer-term repeat-targeted or disease-modifying strategies.

MDF has already begun to build this foundation through prioritized DM2 research funding, expanded community engagement, care-resource development, support for emerging investigators, and investment in model-system and clinical research. The next high-leverage step is to convene clinical, scientific, imaging, diagnostic, biomarker, regulatory, and patient experts around a standardized DM2 research protocol and to strengthen public visibility through credible community leadership. In its role of reducing barriers MDF also supports and collaborates with international efforts. MDF will support and participate in the ENMC workshop “Reboot DM2” proposed and led by Dr. Schoser (2027). These efforts demonstrate that targeted action can shift the trajectory of the field. But foundation support alone cannot build a fully trial-ready ecosystem. Larger federal, philanthropic, academic, and industry investments are needed to scale the work,

validate tools, generate longitudinal evidence, and de-risk therapeutic development. MDF will support such efforts (e.g. Horizon Europe[20]; PI Dr. Schoser).

The opportunity now is to move from fragmented progress to coordinated acceleration. DM2 should be treated as an investable, actionable, and strategically important disease area where well-placed resources could generate outsized returns for patients, researchers, funders, and therapeutic developers. With focused investment and coordinated leadership, DM2 can move toward a more trial-ready and therapeutically actionable future. The field has enough evidence to define the gaps, enough experience from DM1 to understand what infrastructure is needed, and enough community urgency to justify action now. The priority is clear: build the foundations, expand the field, and accelerate the path toward effective treatments for people living with DM2.

[20] https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe_en; 2027

APPENDIX

A. The 2019 DM2 Landscape Assessment

The 2019 DM2 Landscape Assessment (MDF website, myotonic.org) identified several key areas for research investment and focus, summarized here:

1. Longitudinal DM2 single and multi-site studies to drive disease understanding, and clinical trial outcome measures and design.
2. Research into modifier genes and their potential role in DM2 disease progression.
3. Exploration of DM2 CNS symptoms and mechanisms behind "brain fog" reported by many DM2 patients.
4. Research into DM2 repeat size and penetrance, including collecting data from more patients with “small” DM2 expansions and known repeat tract structure to better estimate penetrance and provide for better genetic counseling for DM2 patients.
5. Research examining age and sex differences in DM2.
6. Cancer and DM2 to explore earlier study results suggesting that cancer should be considered in the overall pathogenesis of disease manifestation in DM2 patients.
7. Studies of cellular nucleic acid-binding protein (CNBP) as a transcription regulators: Such studies may determine whether CNBP acts as a transcription regulator required for activating the innate immune response. Such studies may lead to the identification of specific binding motifs present in the promoter region of inflammatory cytokines that induce activity of the CNBP gene.
8. Overexpression of rbFOX1: rbFOX1 has been identified as a possible molecular mechanism in DM2. More studies looking at its overexpression may lead to a greater understanding of the role it plays in releasing MBNL1 from sequestration within CCUG RNA foci and muscle atrophy.
9. Publication and availability of animal models and cell lines.

B. MDF Funded Projects

Grant Program	Cycle	Researcher(s)	Project Title	Total Award Amount	Lead Institution
Research Fellow	2016	Lukasz Sznajder	DM2: Mouse models, pathomechanism and therapy	$102,500	U. of Florida
Research Fellow	2017	Kaalak Reddy	Pre-clinical investigations of small molecule-mediated targeting of toxic RNA production in DM2	$102,500	U. of Florida
Research Fellow	2018	Kiruphagaran Thangaraju	Molecular characterization of RNA and RAN protein effects in DM2	$105,000	U. of Florida
Research Fellow	2020	Jana Jenquin	Improving the activity of diamidines for potential therapeutic use for patients with DM1 & DM2	$105,000	U. of Florida
Research Fellow	2020	Raphael Benhamou	Targeting the RNA that Causes DM2 for Degradation with Small Molecules	$105,000	Scripps Research Institute
Research Fellow	2022	Avery Engelbrecht	Characterization of a Novel BAC Transgenic Mouse Model for DM2	$55,000	U. of Florida
Research Fellow	2023	Jiss Maria Louis	Determining the therapeutic efficacy of natural compounds in DM2	$105,000	RNA Institute
Research Fellow	2024	Diana Madrid Fuentes	Validating Muscle MRI as a Biomarker of Disease Status in DM2	$55,000	Wake Forest U. Health Sciences
Pilot Grant	2024	Paloma Gonzalez Perez	Investigating Benefits of a Physical Therapist-Guided Exercise Program in DM2	$50,000	Massachusetts General Hospital
Early Career Scholar	2024	Lukasz Sznajder	Probing Expanded RNA Species and Their Role in DM2	$190,000	U. of Nevada, Las Vegas
Pilot Grant	2025	Stephanie Tome	Redefining the Genotype-Phenotype Paradigm in DM2	$50,000	Sorbonne Université
Pilot Grant	2025	Arianna Tucci	DM2: Using genomics to understand frequency and expressivity of the disease	$50,000	Queen Mary U. of London
Pilot Grant	2025	Juan Manuel Fernandez	Biomimetic Muscle Models for in vitro functional analysis and drug assessment in DM2 (BMM-2)	$50,000	Institute for Bioengineering of Catalonia
Research Fellow	2026	Hannah Golliher	Characterization of a DM2 BAC transgenic mouse model	$55,000	U. of Florida
			Total Funding:	**$1,180,000**	

C. Key Opinion Leaders Interview Approach

Semi-structured interviews were conducted with clinical and scientific experts spanning neurology, molecular biology, clinical outcomes, diagnostics, model systems, and therapeutic development. The interviews were intended to identify recurring themes, strategic priorities, barriers, and areas of differing emphasis rather than to establish formal consensus.

Interviewed Key Opinion Leaders

Participant names and affiliations were not reported in the assessment. Interview findings are synthesized thematically and without individual attribution to preserve confidentiality and prevent viewpoints from being linked to identifiable participants.

Andrew Berglund, PhD, Director of the RNA Institute and an Empire Professor of Innovation in the Biological Sciences at the University at Albany, MDF Board Member and Chair of the MDF Scientific Advisory Committee

Araya Puwanant, MD, Associate Professor, Neurology at Wake Forest University School of Medicine

Benedikt Schoser, MD, Department of Neurology, Friedrich-Baur-Institute, LMU Clinics, Munich, Germany

Chad Heatwole, MD, MS-CI, Professor of Neurology and the Director of the Center for Health and Technology at the University of Rochester Medical Center

Charles Thornton, MD, Professor of Neurology at the University of Rochester, MDF Board Member and member of the MDF Scientific Advisory Committee

Giovanni Meola, MD, PhD, Department of Neurorehabilitation Sciences, Casa di Cura Igea, Milan, Italy; Department of Biomedical Sciences for Health, University of Milan, Milan, Italy

Johanna Hamel, MD, Associate Professor of Neurology, Pathology and Laboratory Medicine at the University of Rochester

Laura Ranum, PhD, Professor of Molecular Genetics and Microbiology and Director of the Center for Neurogenetics at the University of Florida, Member of the MDF Scientific Advisory Committee

Maurice Swanson, PhD, Professor and Associate Program Director at the University of Florida

Nicholas Johnson, MD, MSci, FAAN, Associate Professor of Neurology and Human and Molecular Genetics and Vice Chair of Research in Neurology at Virginia Commonwealth University, Member of the MDF Scientific Advisory Committee

Paloma Gonzalez-Perez, MD, PhD, Assistant Professor of Neurology at Harvard University, Massachusetts General Hospital

D. NIH Funding: Historic and Project Specific

Historic Funding (https://report.nih.gov/funding/categorical-spending#/, increased funding in 2021 is the result of misclassification)

