Module 5
How is myotonic dystrophy type 1 (DM1) managed and monitored?

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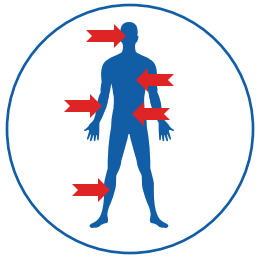
Module summary

In the absence of an approved disease-modifying treatment, management of DM1 focuses on symptom relief[1]

A range of interventions are used to treat the multi-systemic clinical manifestations of DM1[1–4]



A multi-disciplinary team is essential to support symptom management and reduce the risk of complications[5]

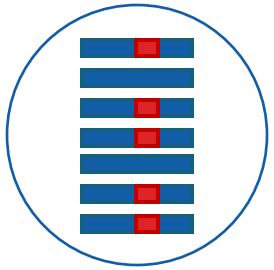
Personalized treatment is required for each individual[5]

Multiple measures are used to monitor multi-system functions in DM1[1,5–9]

Measures assess mobility, dexterity, cardiac and respiratory function, cognitive function, fatigue, GI symptoms, endocrine abnormalities, and patient-reported measures[1,5–9]

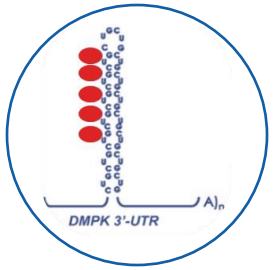
The Myotonic Dystrophy Health Index (MDHI) measures patient-reported disease burden in DM1[10,11]

Its 17 subscales assess the most impactful symptomatic themes, including mobility, fatigue, GI issues, breathing, and social satisfaction[10,11]



CASI quantifies RNA mis-splicing across a panel of 22 genes implicated in the pathophysiology of DM1[12–15]

CASI correlates with functional outcomes in individuals with DM1[12]



Several oligonucleotide-based technologies are in development for the treatment of DM1[16,17]

Approaches either degrade mutant DMPK RNA in the nucleus or DMPK RNA in the cytoplasm, prevent MBNL1 sequestration or upregulate MBNL[16,17]

DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase; GI, gastrointestinal; MBNL, muscleblind-like; miR-23b, microRNA 23b; RNA, ribonucleic acid.

1. Gutierrez Gutierrez G, et al. *Med Clin (Barc)*. 2020;153:82.e1–82.e17; 2. Kumar A, et al. *Austin J Genet Genomic Res*. 2015;2:1011; 3. McNally EM, et al. *J Am Heart Assoc*. 2020;9:e014006; 4. Ashizawa T, et al. *Neurol Clin Pract*. 2018;8:507–520; 5. Gutierrez Gutierrez G, et al. *Neurologia (Engl Ed)*. 2020;35:185–206; 6. Gagnon C, et al. *J Neuromuscul Dis*. 2018;5:523–537; 7. Kierkegaard M, et al. *J Rehabil Med*. 2018;50:269–277; 8. Mazzoli M et al. *Acta Myol*. 2020;39:109–120; 9. Hartog L, et al. *Front Neurol*. 2021;12:658532; 10. Heatwole C, et al. *Muscle Nerve*. 2016;53:183–190; 11. Sansone VA, et al. *Neuromuscular Disord*. 2017;27:1047–1053; 12. Provenzano M, et al. *J Clin Invest*. 2025;135:e185426; 13. Wang W. 2017. University of Rochester School of Medicine and Dentistry PhD thesis. Accessed July 7, 2025. http://hdl.handle.net/1802/32572; 14. López-Martínez A, et al. *Genes (Basel)*. 2020;11:1109; 15. Mikhail AI, et al. *Trends Mol Med*. 2023;29:512–529; 16. Pascual-Gilabert M, et al. *Drug Discov Today*. 2021;26:1765–1772; 17. Arechavala-Gomeza V, et al. *J Neuromuscul Dis*. 2025:22143602251324858.

What are the key management considerations after DM1 diagnosis?

Consensus-based care recommended evaluations following initial diagnosis of DM1 in children and adults[1–3]

	Evaluation in children	Evaluation in adults
Cardiovascular	ECG Cardiology consultation	ECG and Holter monitoring Echocardiogram
Respiratory	Pulmonary function tests	Pulmonary function tests
Neurologic	Baseline neurologic evaluation Screen for excessive daytime sleepiness	Baseline neurologic evaluation for strength, balance, sensation
Gastrointestinal	Clinical assessment for common symptoms (abdominal pain, constipation, fecal incontinence, diarrhea)	Clinical assessment for poor swallowing, pseudo-obstruction, diarrhea, and gallbladder dysfunction
Eyes	Ophthalmologic evaluation	Ophthalmologic evaluation
Endocrine	Fasting blood glucose and HbA1c determination	Fasting blood glucose and HbA1c determination Assessment for thyroid function
Surgery/ anesthesia		Evaluate for history of adverse reactions to drugs and anesthesia
Pregnancy		Obstetrics consultation
Other	Consultation with clinical geneticists and/or genetic counselor Developmental assessment	Consultation with clinical geneticists and/or genetic counselor Developmental assessment

In the absence of an approved disease-modifying treatment, management of DM1 focuses on symptom relief[4]

ECG, electrocardiogram; DM1, myotonic dystrophy type 1; HbA1c, hemoglobin A1c.

1. Ashizawa T, et al. *Neurol Clin Pract.* 2018;8:507–520; 2. Johnson NE, et al. *Neurol Clin Pract.* 2019;9:1–12; 3. Bird TD. Myotonic Dystrophy Type 1. 1999 Sep 17 [Updated 2021 Mar 25]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022; 4. Gutierrez Gutierrez G, et al. *Med Clin (Barc).* 2020;153:82.e1–82.e17.

What interventions are common in DM1 management?

Pharmacological interventions	Non-pharmacological interventions
Corticosteroids, procaine amide, phenytoin, carbamazepine, DHEAS, dexamethasone, mexiletine*, and nifedipine for myotonia[1–3]	Strength training/aerobic activity, physiotherapy, and occupational therapy to improve muscle and cardiorespiratory function[3]
Beta-adrenergic blockers, mineralocorticoid receptor antagonists, and either angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor neprilysin inhibitors[2]	Implantable cardioverter-defibrillators and pacemakers, as needed[1,3] Invasive electrophysiology testing if non-invasive testing indicates elevated risk for serious conduction block or arrhythmias[2]
Vaccinations for pneumonia/flu and antibiotics for respiratory infections[3,4]	Non-invasive nocturnal ventilatory support and physiotherapy[2,3]
Modafinil for EDS and low-dose pregabalin for myalgia[3,4]	Non-invasive nocturnal ventilatory support for EDS, speech therapy, and cognitive behavioral therapy[4]
Antibiotics, laxatives, loperamide, mexiletine, metoclopramide[4]	High-fiber diet, increased water intake, and supplements[4]
Ophthalmic lubricants for dry eye[4]	Surgical intervention and artificial lens implantation for cataract[1,3]
Troglitazone, statins, fibrates, and metformin[1,3]	Changes in diet and exercise to treat insulin resistance[2,4]

A range of pharmacologic and non-pharmacologic interventions are used to treat the multi-systemic clinical manifestations of DM1[3]

*Mexiletine should be prescribed with caution as proarrhythmic effects may be increased.[2]

DHEAS, dehydroepiandrosterone sulfate; DM1, myotonic dystrophy type 1; EDS, excessive daytime sleepiness.

1. Kumar A, et al. *Austin J Genet Genomic Res*. 2015;2:1011; 2. McNally EM, et al. *J Am Heart Assoc*. 2020;9:e014006; 3. Gutierrez Gutierrez G, et al. *Med Clin (Barc)*. 2020;153:82.e1–82.e17; 4. Ashizawa T, et al. *Neurol Clin Pract*. 2018;8:507–520.

Which specialists are involved in the care of individuals with DM1?

The multi-systemic nature of DM1 and variability in clinical manifestations means that a multidisciplinary team is essential, and personalized treatment and is required for each individual[1]

DM1, myotonic dystrophy type 1.

1. Gutierrez Gutierrez G, et al. *Neurologia (Engl Ed).* 2020;35:185–206; 2. Ashizawa T, et al. *Neurol Clin Pract.* 2018;8:507–520; 3. Bird TD. Myotonic Dystrophy Type 1. 1999 Sep 17 [Updated 2021 Mar 25]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022.

How is DM1 monitored? (1 of 2)

Function	Assessments	
Mobility and balance	6-minute walk test (6MWT)[1] 30-second chair-stand test (30s-CST)[1] Timed up and go (TUG)[2] Time to ascend/descend four stairs[3]	10-meter walk test (10MWT)[1] Berg balance scale (BBS)[2] Sit-to-stand test[4]
Muscle strength and manual dexterity[2]	Quantitative muscle testing (QMT) Handgrip strength (e.g. dynamometer) Manual muscle testing (MMT) (e.g. MRC)[5] Muscular impairment rating scale (MIRS)[5]	Pinch strength (e.g. B&L pinch gauge) Video hand opening time (vHOT)[6] Purdue pegboard test (PPT) Nine-hole peg test (9HPT)[1]
Cardiac[5]	Arterial blood gas analysis (EGAa) 24-hour electrocardiogram (ECG) Holter monitoring	Electrocardiogram (ECG) Trans-thoracic echocardiography (TTE)
Respiratory[7]	Forced vital capacity (FVC)[5,7] Forced expiratory volume in 1 sec (FEV1)[5,7] Maximal expiratory pressure (MEP)	Peak expiratory flow (PEF) Maximal inspiratory pressure (MIP) Respicheck questionnaire[8]
Cognitive function[9,10*]	Wechsler Adult Intelligence Scale (WAIS) Wechsler Intelligence Scale for Children (WISC) Wechsler Prescholar and Primary Scale Intelligence (WPPSI)	Rey's auditory verbal learning test (RAVLT) Rey's complex figure

Multiple measures are used to monitor multi-system functions in DM1

*There is currently no general consensus on the tests that can be performed to study the cognitive deficit in DM1.[9]
DM1, myotonic dystrophy type 1; MRC, Medical Research Council; Respicheck, respiratory symptom checklist

1. Gagnon C, et al. *J Neuromuscul Dis*. 2018;5:523–537; 2. Kierkegaard M, et al. *J Rehabil Med.* 2018;50:269–277; 3. Thornton CA, et al. *Lancet Neurol.* 2023;22:218–228; 4. Jimenez-Moreno AC, et al. *Ann Clin Transl Neurol.* 2019;6:1487–1497; 5. Mazzoli M et al. *Acta Myol*. 2020;39:109–120; 6. Puwanant A, et al. *Neurology*. 2012;78(Suppl 1); 7. Hartog L, et al. *Front Neurol*. 2021;12:658532;
8. De Mattia E, et al. *Neuromuscul Disord*. 2020;30:301–309; 9. Gutierrez Gutierrez G, et al. *Neurologia (Engl Ed)*. 2020;35:185–206; 10. Gutierrez Gutierrez G, et al. *Med Clin (Barc)* 2020;153:82.e1-82.e17.

How is DM1 monitored? (2 of 2)

Function	Assessments	
EDS, fatigue, apathy[1,2]	Fatigue and daytime sleepiness scale (FDSS) Apathy evaluation scale (AES) Fatigue severity scale (FSS) Daytime sleepiness scale (DSS)	Multiple sleep latency test (MSLT) Lille apathy rating scale (LARS) Epworth sleepiness scale (ESS)
Gastrointestinal[3–6]	Eating assessment tool-10 (EAT-10) Fibroendoscopy test Gastrointestinal patient-reported outcomes measurement information system (GI-PROMIS)*	Volume-viscosity swallow test (V-VST) Videofluoroscopy Gastrointestinal symptom rating scale (GSRS) Swallow-related quality of life (SWAL-QOL)
Endocrine[3,7]	Lipid panel assessments Hormone evaluation	Insulin resistance index (HOMA-IR)
Patient reported[1]	Myotonic dystrophy health index (MDHI) DM1-Activ[c] Assessment of life habits questionnaire (LIFE-H) Activity limitation (ACTIVLIM) questionnaire	QoL-gNMD Congenital and childhood MDHI (CCMDHI) 36-item short form survey (SF-36)

Multiple measures are used to monitor multi-system functions in DM1

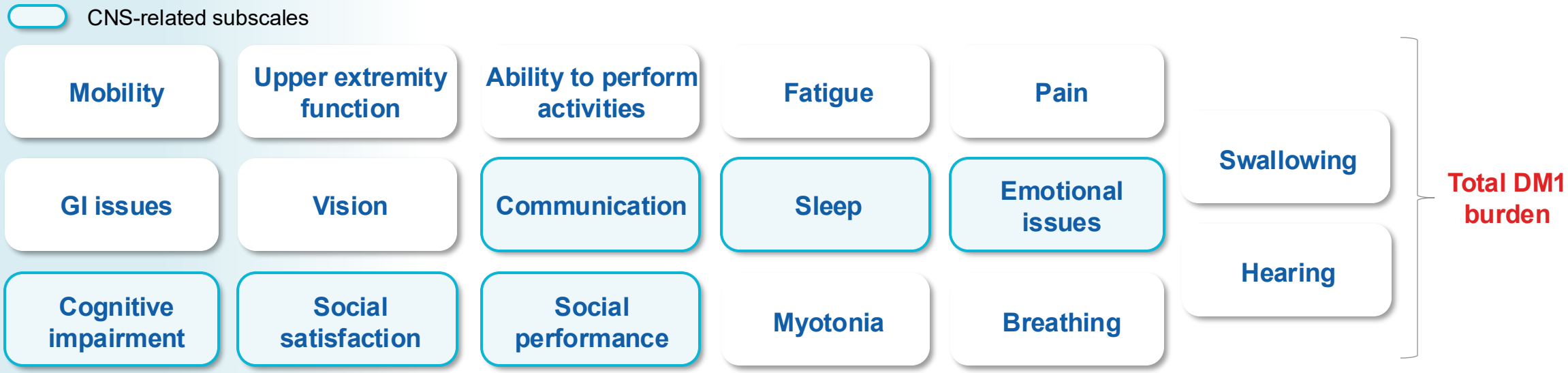
*Patient-reported outcome for use in people with GI symptoms. The scales are broadly applicable across populations, GI symptoms, GI diseases, and demographics and are not specific to DM1.[3]
DM1, myotonic dystrophy type 1; EDS, excessive daytime sleepiness; GI, gastrointestinal; gNMD, genetic neuromuscular disorder; QoL, quality of life.

1. Gagnon C, et al. *J Neuromuscul Dis*. 2018;5:523–537; 2. Laberge L, et al. *J Neurol Neurosurg Psychiatry*. 2005;76:1403–1405; 3. Gutierrez Gutierrez G, et al. *Neurologia (Engl Ed)*. 2020;35:185–206; 4. Spiegel BM, et al. *Am J Gastroenterol*. 2014;109:1804–1814; 5. Perna A, et al. *Front Neurol*. 2020;11:394; 6. Pilz W, et al. *Eur Arch Otorhinolaryngol*. 2020;277:2357–2362; 7. Mateus T, et al. *Int J Environ Res Public Health*. 2021;18:1794.

What does the Myotonic Dystrophy Health Index (MDHI) Measure?

- The MDHI is a validated tool that measures therapeutic response and disease burden in DM1 clinical trials, with the ability to differentiate disease severity[1,2]
- Its 17 subscales together measure total disease burden and separately assess the most impactful symptomatic themes identified by 278 individuals with DM1 (PRISM-1 study). Each subscale is scored from 0 to 100, where 0 represents no disease burden and 100 represents the maximum burden[1–3]

What do the 17 MDHI subscales measure?[1,2]



The Myotonic Dystrophy Health Index (MDHI) measures patient-reported disease burden in DM1, based on 17 scales[1,2]

CNS, central nervous system; DM1, myotonic dystrophy type; GI, gastrointestinal; MDHI, myotonic dystrophy health index.

1. Heatwole C, et al. *Muscle Nerve*. 2016;53:183–190; 2. Sansone VA, et al. *Neuromuscular Disord*. 2017;27:1047–1053; 3. Heatwole C, et al. *Neurology*. 2012;79:348–357.

What does CASI measure?

CASI quantifies RNA mis-splicing across a panel of 22 genes implicated in the pathophysiology of DM1[1–4]

Muscle weakness and/or altered contraction and relaxation[1,2]

RYR1 (calcium channel)
CACNA1S (calcium channel)
ATP2A1 (calcium pump)
CLCN1 (chloride channel)
DMD (muscle structure)
BIN1 (component of T-tubules)
SOS1 (cell cycle regulation)
OPA1 (mitochondrial dynamics)[3]

Aberrant mRNA splicing[1,2]

MBNL1 (alternative splicing)
MBNL2 (alternative splicing)

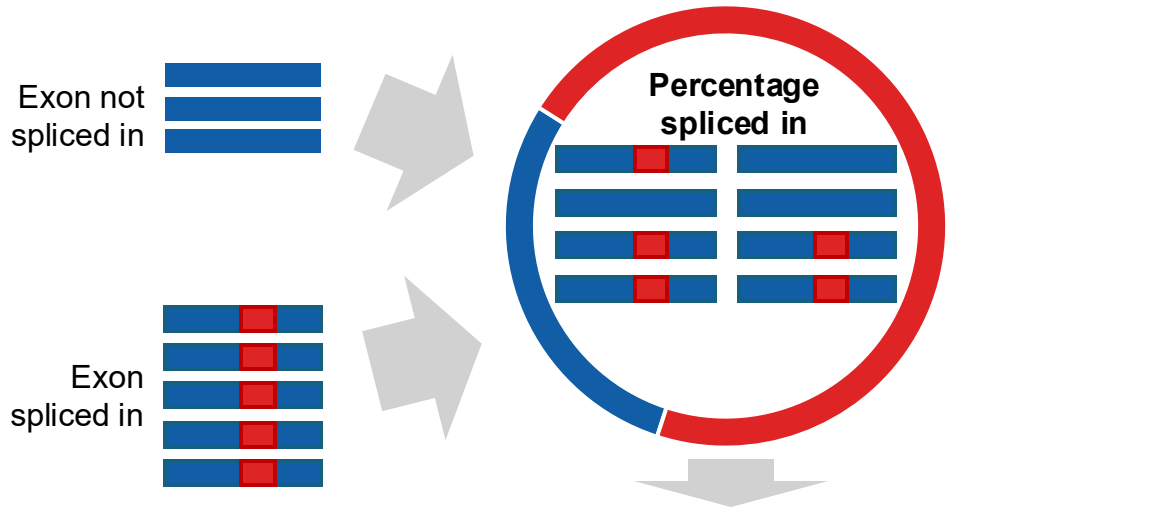
Insulin resistance[1,2]

INSR (glucose metabolism)

Undefined, regulated by MBNL[1,5]

VPS39 (vesicle fusion)
GOLGA4 (membrane trafficking)
KIF13A (motor protein)
CLASP1 (microtubule dynamics)
GFPT1 (glucose metabolism)[2]
CAMK2B (calcium signaling)
ANK2 (membrane targeting)
BEST3 (ion channel)
CCPG1 (GTPase regulation)
CAPZB (actin filament assembly)
NFIX (extracellular matrix component)[2]

Calculating CASI[4]



Normalize to standardized reference from healthy controls and average

CASI

0 Unaffected healthy control

Most affected DM1 individuals **1**

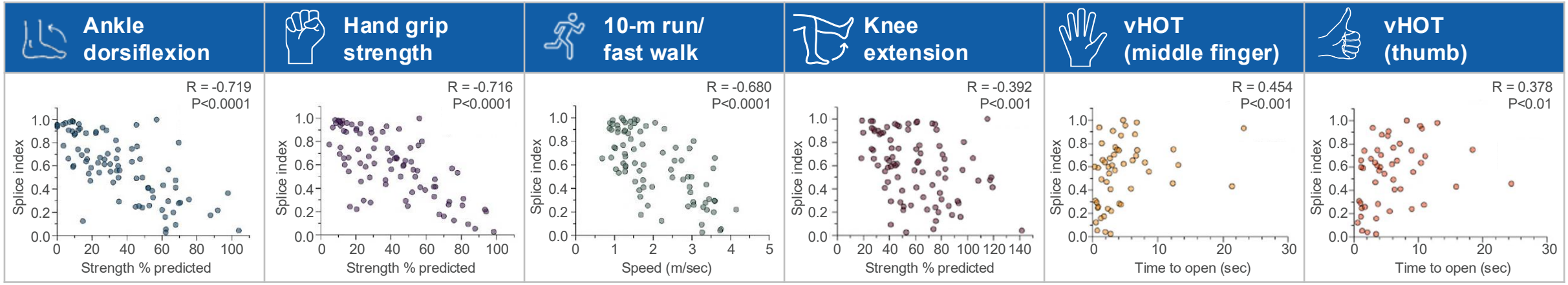
CASI measures therapeutic efficacy in DM1 by quantifying RNA splicing

CASI, composite alternative splicing index; DM1, myotonic dystrophy type 1; MBNL, muscleblind-like; mRNA, messenger ribonucleic acid.

1. Wang W. 2017. University of Rochester School of Medicine and Dentistry PhD thesis. Accessed February 19, 2025. http://hdl.handle.net/1802/32572; 2. López-Martínez A, et al. *Genes (Basel)*. 2020;11:1109; 3. Mikhail AI, et al. *Trends Mol Med*. 2023;29:512–529; 4. Provenzano M, et al. *J Clin Invest.* 2025;135:e185426;
5. Gene functions from AmiGO 2. Accessed February 19, 2025. https://amigo.geneontology.org/amigo.

Has mis-splicing been shown to correlate with clinical function in DM1?

- The mis-splicing of RNA has been shown to correlate with functional outcomes in several natural history studies of DM1 cohorts[1–4]
- In a study of 95 muscle biopsies taken from adults with DM1, composite SI score was shown to correlate with common clinical outcome measures for DM1:[3]



All correlations are reported as Pearson or Spearman r [95% CI] with two-tailed p-value.

CASI correlates with functional outcomes in individuals with DM1[3]

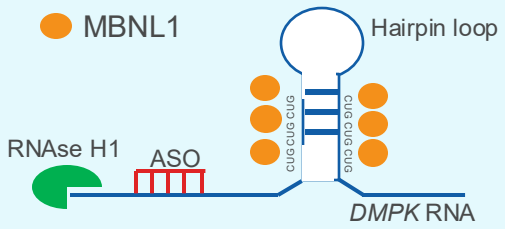
CASI, composite alternative splicing index; CI, confidence interval; DM1, myotonic dystrophy type 1; RNA, ribonucleic acid; SI, splice index; vHOT, visual hand opening time.

1. Nakamori M, et al. *Ann Neurol.* 2013;74:862–872; 2. Wang ET, et al. *Hum Mol Genet.* 2019;28:1312–1321; 3. Provenzano M, et al. *J Clin Invest.* 2025;135:e185426; 4. Hartman JM, et al. *Ann Clin Transl Neurol.* 2024;11:3175–3191.

What oligonucleotide-based approaches are in development as potential disease-modifying therapeutics for DM1?

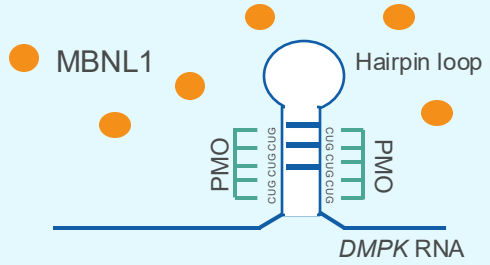
Oligonucleotide-based approaches employ different chemistries to target spliceopathy

Gapmer ASO[1,2]



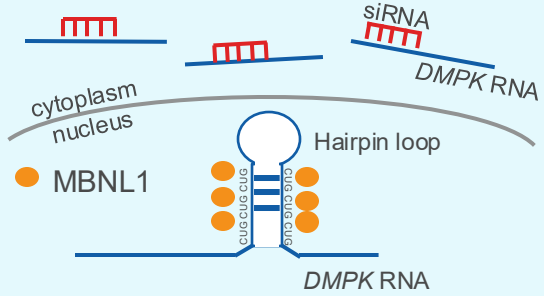
Mark *DMPK* RNA for RNAse H-mediated degradation and subsequent release of MBNL1

CUG-binding PMO[1,2]



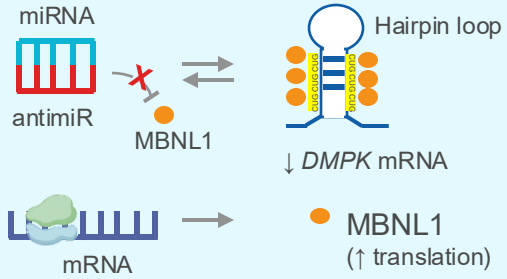
Displace MBNL1 by mechanism of steric hindrance

siRNA[1–3]



Function in the cytoplasm to degrade the cytoplasmic pool of *DMPK* RNA

antimiR oligonucleotide[1,4]



Inhibition of a target miRNA to upregulate MBNL proteins

Oligonucleotide delivery methods in development

- Antibody–oligonucleotide conjugates[1]
- Ligand-conjugated oligonucleotides[5]
- Cell-penetrating peptide–oligonucleotide conjugates[1]
- Adeno-associated virus (AAV)-delivered oligonucleotides[5]

Several oligonucleotide-based technologies are in development to either degrade mutant *DMPK* RNA in the nucleus or *DMPK* RNA in the cytoplasm, prevent MBNL1 sequestration or upregulate MBNL proteins, thereby correcting spliceopathy[1–4]

antimiR, antisense micro-RNA; ASO, antisense oligonucleotide; CUG, cytosine–uracil–guanine; DM1, myotonic dystrophy type 1; DMPK, dystrophia myotonica protein kinase; MBNL, muscleblind-like; miRNA, microRNA; mRNA, messenger RNA; PMO, phosphorodiamidate morpholino oligomer; siRNA, small interfering RNA.

1. Pascual-Gilabert M, et al. *Drug Discov Today.* 2021;26:1765–1772; 2. Arechavala-Gomeza V, et al. *J Neuromuscul Dis.* 2025:22143602251324858; 3. Ali Zaidi SS, et al. *J Nanobiotechnology*. 2023;21:381; 4. Cerro-Herreros E, et al. *Sci Adv.* 2024;10:eadn6525; 5. De Serres-Bérard T, et al. *Int J Mol Sci.* 2022;23:13359.