



Module 5

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

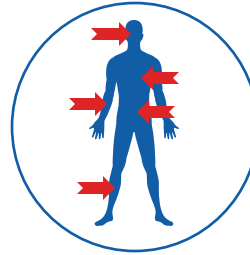


Module summary



In the absence of an approved disease-modifying treatment, management of DM1 focuses on symptom relief¹

A range of interventions are used to treat the multi-systemic clinical manifestations of DM1¹⁻⁴



A multi-disciplinary team is essential to support symptom management and reduce the risk of complications⁵

Personalized treatment is required for each individual⁵



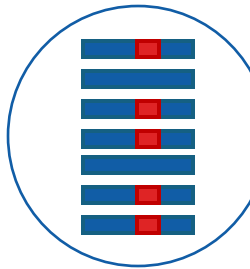
Multiple measures are used to monitor multi-system functions in DM1^{1,5-9}

Measures assess mobility, dexterity, cardiac and respiratory function, cognitive function, fatigue, GI symptoms, endocrine abnormalities, and patient-reported measures^{1,5-9}



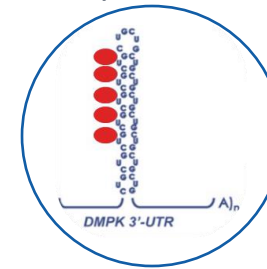
The Myotonic Dystrophy Health Index (MDHI) measures patient-reported disease burden in DM1^{10,11}

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 DM1¹²⁻¹⁵

CASI correlates with functional outcomes in individuals with DM1¹²



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, dystrophin myotonia 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-Gilbert M, et al. *Drug Discov Today*. 2021;26:1765–1772; 17. Arechavala-Gomez V, et al. *J Neuromuscul Dis*. 2025;22:143602251324858.

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 relief⁴

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 DM1³

*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 individual¹

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 Preschool 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

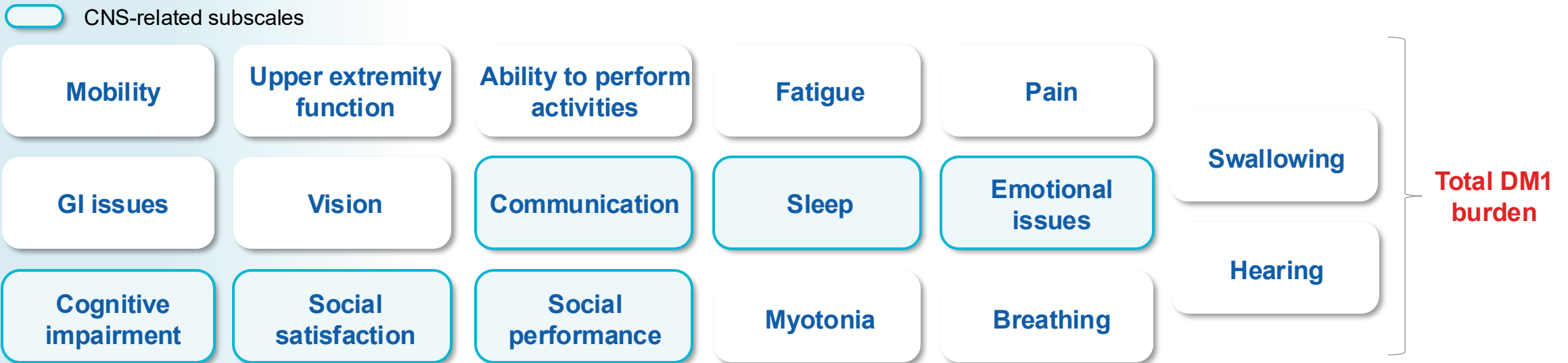
DM1, myotonic dystrophy type 1; EDS, excessive daytime sleepiness; GI, gastrointestinal; gNMD, genetic neuromuscular disorder; QoL, quality of life.

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}

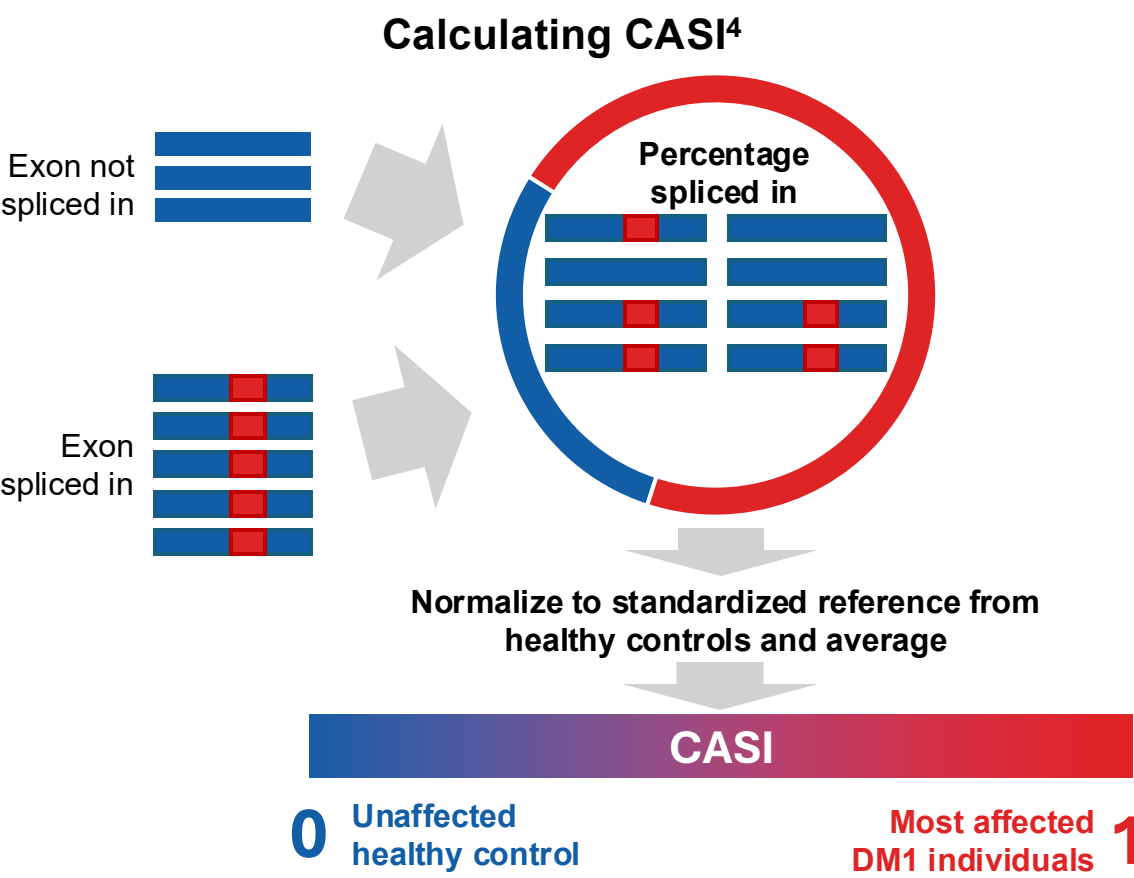


The Myotonic Dystrophy Health Index (MDHI) measures patient-reported disease burden in DM1, based on 17 scales^{1,2}

What does CASI measure?

CASI quantifies RNA mis-splicing across a panel of 22 genes implicated in the pathophysiology of DM1¹⁻⁴

Muscle weakness and/or altered contraction and relaxation ^{1,2}	Aberrant mRNA splicing ^{1,2}
<i>RYR1</i> (calcium channel) <i>CACNA1S</i> (calcium channel) <i>ATP2A1</i> (calcium pump) <i>CLCN1</i> (chloride channel) <i>DMD</i> (muscle structure) <i>BIN1</i> (component of T-tubules) <i>SOS1</i> (cell cycle regulation) <i>OPA1</i> (mitochondrial dynamics) ³	<i>MBNL1</i> (alternative splicing) <i>MBNL2</i> (alternative splicing)
Undefined, regulated by MBNL ^{1,5}	
<i>VPS39</i> (vesicle fusion) <i>GOLGA4</i> (membrane trafficking) <i>KIF13A</i> (motor protein) <i>CLASP1</i> (microtubule dynamics) <i>GFPT1</i> (glucose metabolism) ² <i>CAMK2B</i> (calcium signaling)	<i>ANK2</i> (membrane targeting) <i>BEST3</i> (ion channel) <i>CCPG1</i> (GTPase regulation) <i>CAPZB</i> (actin filament assembly) <i>NFIX</i> (extracellular matrix component) ²

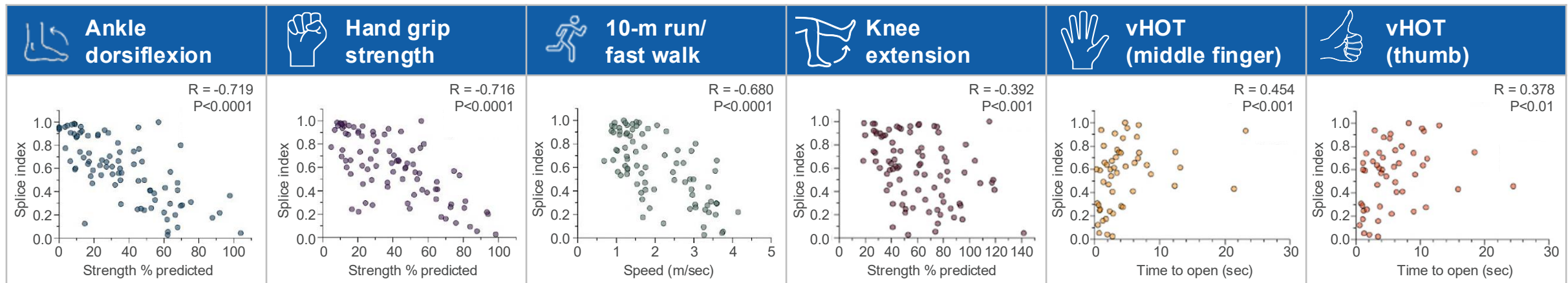


CASI measures therapeutic efficacy in DM1 by quantifying RNA splicing

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 DM1³

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

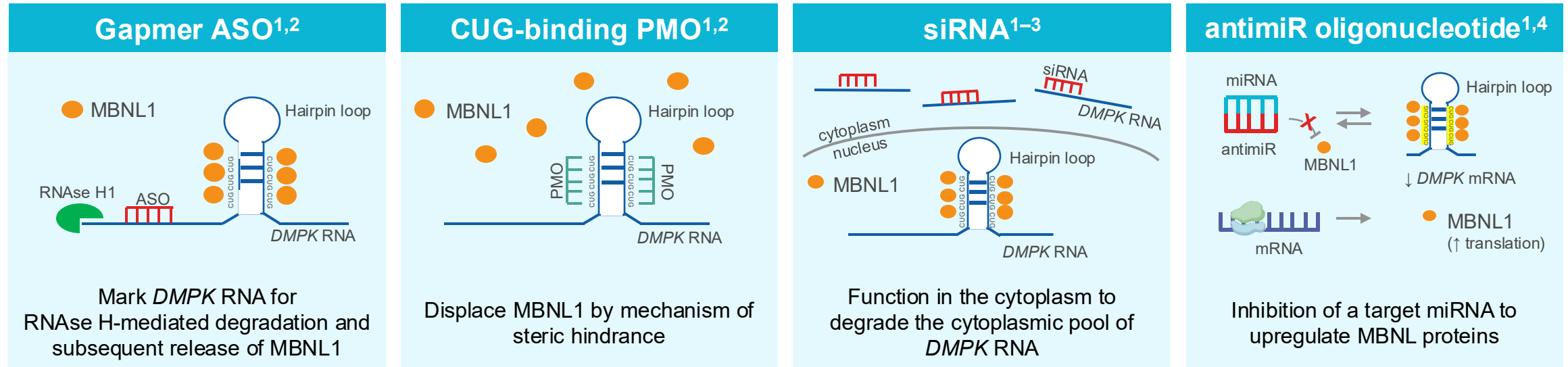
Images from Provenzano M, et al. *J Clin Invest.* 2025;e185426, licensed under a CC-BY 4.0 Creative Commons license.

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



Oligonucleotide delivery methods in development

- Antibody–oligonucleotide conjugates¹
- Ligand-conjugated oligonucleotides⁵
- Cell-penetrating peptide–oligonucleotide conjugates¹
- Adeno-associated virus (AAV)-delivered oligonucleotides⁵

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 spliceopathy¹⁻⁴

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-Gilbert M, et al. *Drug Discov Today*. 2021;26:1765–1772; 2. Arechavala-Gomez V, et al. *J Neuromuscul Dis*. 2025;22:143602251324858;

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.