Changes in RNA Splicing as a Surrogate Endpoint for Myotonic Dystrophy Type 1 (DM1) Clinical Trials

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An overview of how a key driver of disease can predict functional improvement in DM1

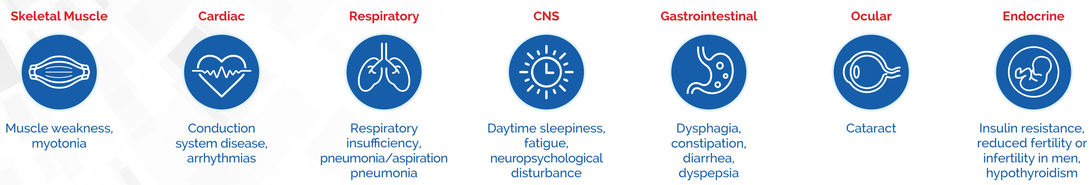
Measuring changes in gene splicing may accelerate DM1 research[1]

In this study, the authors reviewed evidence related to the use of splicing change in DM1 as a surrogate endpoint in clinical trials. A surrogate endpoint is a biomarker or physical sign that is used in trials to predict clinically meaningful benefit as measured by functional endpoints.

Given that DM1 can progress slowly, a surrogate endpoint may help researchers learn more quickly if a potential new therapy for DM1 is working in the clinical trial setting.

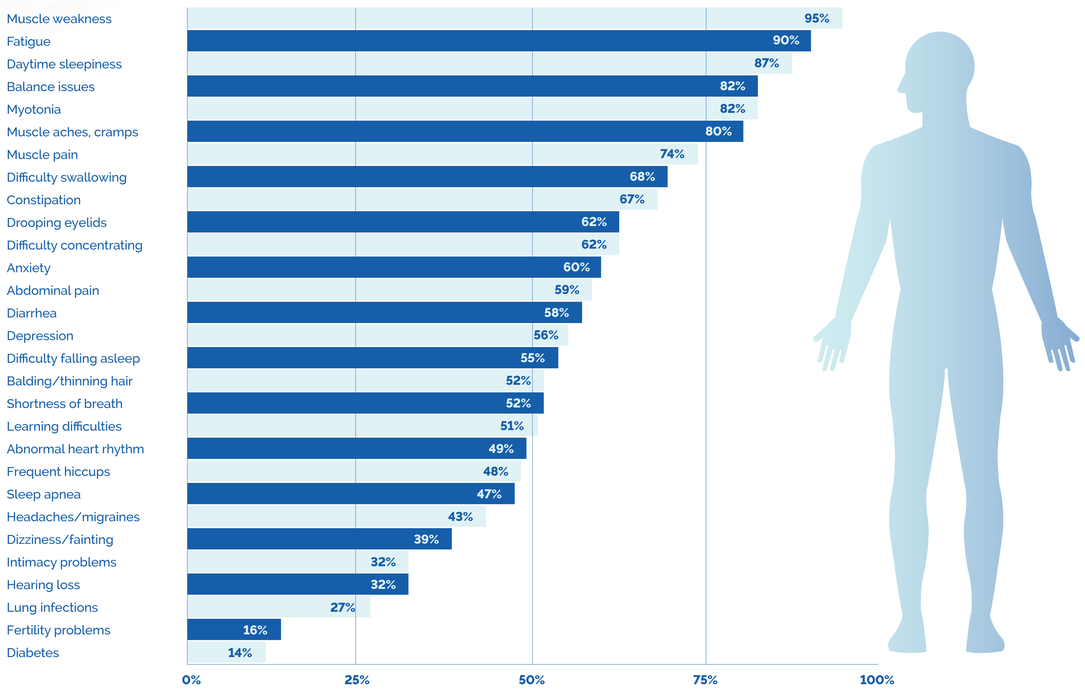
DM1 affects different people differently, but all people living with DM1 have mis-splicing in common[1,2]

- DM1 may affect many organs and systems in the body
- The specific symptoms—and their severity—may vary greatly from person to person
- These differences in symptoms can make it hard to compare how different people respond to treatment in a clinical study
- The inability of the body to correctly splice (or cut) RNA—which contains instructions for making proteins—is the hallmark of DM1, shared by all people living with the disease
- Mis-splicing occurs in many different cell types, which contributes to the diversity of symptoms in DM1



Symptom prevalence[3]

The percentage of respondents who reported that they experience a particular symptom is shown below:



The composite alternative splicing index (CASI) measures RNA splicing[1,2]

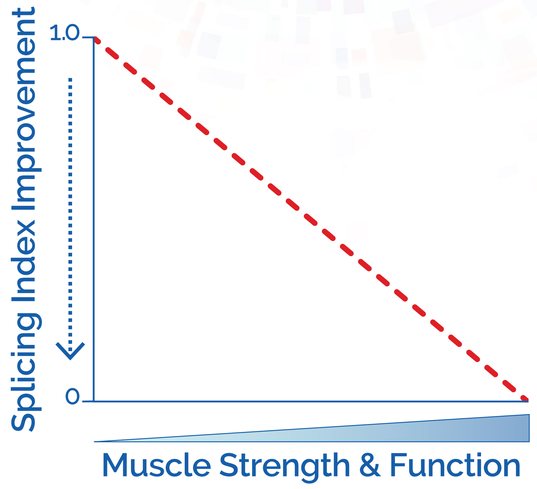
- The CASI looks at the number of RNA splicing abnormalities in 22 different genes representing a number of tissues affected by DM1
- The CASI can be used to evaluate how well a potential medicine works by measuring the number of mis-spliced events before and after treatment
- CASI is a robust, reliable, and sensitive biomarker for DM1 that has been shown to be correlated to functional outcomes and may help predict future function

CASI SCORE
22 Genes Tested

A **biomarker** is a measurable characteristic in your body that has many roles in helping to understand disorders and diseases. Biomarkers can be used to help predict how your condition might respond to treatment.

How the CASI score is correlated to muscle performance[2]

Lower splicing index indicates more accurate splicing, and correlates with higher muscle strength and function.



Stay connected to the emerging science in DM1.

References: 1. Data on file. Waltham, MA: Dyne Therapeutics; 2025. **2.** Provenzano M, Ikegami K, Bates K, et al. The Splice Index as a prognostic biomarker of strength and function in myotonic dystrophy type 1. *J Clin Invest*. 2025;135(4):e185426. **3.** The Christopher Project. *Report to the Myotonic Dystrophy Community*. The Christopher Project; 2019.

Disclosures

AN, IIH, and SR are employees of Dyne and may hold stock in the company. JAB serves on the Scientific Advisory Committee and Board for the Myotonic Dystrophy Foundation, has consulted or currently consults for D.E. Shaw Research, Dyne Therapeutics, Entrada Therapeutics, Juvena Therapeutics, Kate Therapeutics, Syros Pharmaceuticals, Wayfinder Biosciences and received research funding from Agios Pharmaceuticals, BioMarin Pharmaceuticals, PepGen, Syros Pharmaceuticals and Vertex Pharmaceuticals and has received licensing royalties from the University of Florida. JAB and NEJ are co-founders and have financial interest in Repeat RNA Therapeutics Inc. NEJ has received grant funding from NINDS (R01NS104010, U01NS124974), NCATS (R21TR003184), CDC (U01DD001242) and the FDA (7R01FD006071). He receives royalties from the CCMDHI and the CMTHI, research funds from Novartis, Takeda, PepGen, Sanofi Genzyme, Dyne, Vertex Pharmaceuticals, Fulcrum Therapeutics, AskBio, ML Bio, and Sarepta, and has provided consultation for Arthex, Angle Therapeutics, Juvena, Rgenta, PepGen, AMO Pharma, Takeda, Design, Dyne, AskBio, Avidity, and Vertex Pharmaceuticals.

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At Dyne, we are committed to listening to and learning from the communities we serve, including individuals and families living with DM1.