

# Neuromuscular Diseases Caused by Repeat Expansions and Opportunity for Non-Invasive Biomarkers

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## Abstract

Microsatellite repeat expansion diseases represent a major class of inherited neuromuscular and neurological disorders in which pathogenic RNA contributes to devastating multisystem dysfunction. Among these, myotonic dystrophy types 1 and 2 (DM1 & DM2) are leading examples for the molecular mechanism in which toxic repeat RNAs sequester RNA-binding proteins leading to disruption of alternative splicing across a broad set of transcripts. The resulting “spliceopathy” correlates with clinical severity and affects a multitude of tissue systems, including muscle, heart, and the central nervous system. While the molecular mechanisms are well established for DM and many repeat expansion diseases, clinically relevant biomarkers remain a critical barrier to proper and timing diagnosis, monitoring disease progression, and evaluating emerging therapeutics in preclinical and clinical settings.

Invasive muscle biopsies are currently used in the DM field to determine splicing changes across a panel of disease-relevant splicing events. However, in DM1, quantifiable mis-splicing events are also detectable in peripheral blood mononuclear cells and plasma-derived RNA, offering promising non-invasive biomarker candidates. The sensitivity of splicing biomarkers to therapeutic intervention, such as antisense oligonucleotides and small molecules that modulate RNA–protein interactions or reduce toxic repeat RNAs, positions these markers as powerful pharmacodynamic readouts. Extending these findings into other non-invasive biofluids, such as urine, buccal and saliva, has tremendous potential to advance preclinical and clinical therapeutic development

The broader implications for non-invasive biomarkers extend beyond DM, as other repeat expansion disorders, including amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD), Huntington’s disease, and spinocerebellar ataxias, exhibit RNA dysregulation, aberrant splicing, or altered RNA-binding protein activity. Biofluid-based splicing signatures couple to transcriptomic analysis have the potential to enable cross-disease biomarker platforms. Such cross-disease markers would significantly

enhance differential diagnosis, permit assessment of pathway-specific engagement, and support precision medicine strategies across neuromuscular and neurodegenerative conditions.

Overall, RNA splicing biomarkers derived from non-invasive biofluids represent a rapidly advancing frontier with significant translational potential. In myotonic dystrophy, they offer a mechanistically grounded, reproducible, and clinically relevant means to track the molecular effects of repeat expansion toxicity. Ultimately this current work on DM may provide a biomarker framework for a broader array of repeat-associated disorders.