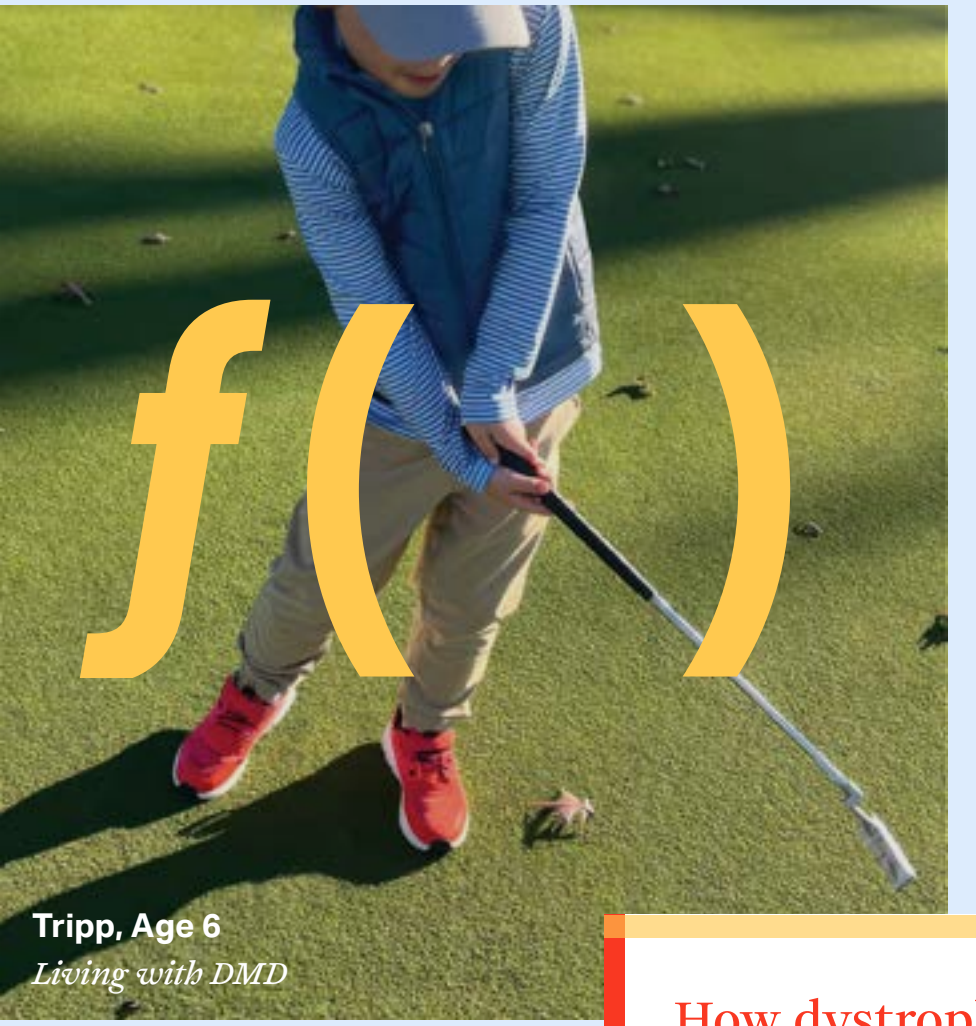

Tripp, Age 6
Living with DMD

The Duchenne Functional Improvement Equation

How dystrophin **quantity** ⊕ **quality** ⊕ **distribution** ⊜ **functional improvement** in DMD

Learn about a new equation for dystrophin production that could drive **meaningful functional outcomes** in Duchenne muscular dystrophy (DMD).

Dyne® THERAPEUTICS

Understanding the foundational components of dystrophin that are critical to DMD pathophysiology

DMD is a progressive, multisystem disease with a definitive root cause: little to no functional dystrophin[1–3]

Dystrophin is an essential structural protein found in all muscles of the human body, including skeletal, cardiac, and smooth muscle.[4-6,*]

- It is a key component of a large, multiprotein assembly known as the dystrophin-associated protein complex (DAPC), localized to the sarcolemma, the membrane that surrounds the muscle cell[7,8]
- The DAPC stabilizes the sarcolemma and provides resilience during muscle contraction, allowing dystrophin to provide shock absorption[7,9]
- Dystrophin links the intracellular actin cytoskeleton to the extracellular matrix through the DAPC, creating a structural scaffold across the sarcolemma[9,10]

*The structural and protective role of dystrophin and the DAPC in muscle has been extensively studied in striated muscle (skeletal and cardiac muscle).Its precise role in smooth muscle is not as well understood.[4-6]

The absence of functional dystrophin disrupts muscle integrity[9,11]

- In DMD, there is little to no expression of full-length dystrophin across all types of muscle and other tissues[2,3,12,13]
- This results in sarcolemmal fragility and increased permeability everywhere that functional dystrophin is very low or absent, leading to calcium dysregulation and free radical formation[9]
- The end result is muscle damage and degeneration, where damaged muscle cells are replaced by fat and fibrotic tissue that disrupts function in systems throughout the body[1,9,11,13]

Specific domains within dystrophin interact with various cytoskeletal components for the protein to function appropriately[9,14–16]

The domains each play distinct structural roles that work in concert to stabilize the sarcolemma

N-TERMINAL DOMAIN

Anchors dystrophin to the cytoskeleton and contractile apparatus

CYSTEINE-RICH DOMAIN

Facilitates binding to the sarcolemma, the membrane that surrounds the muscle cell

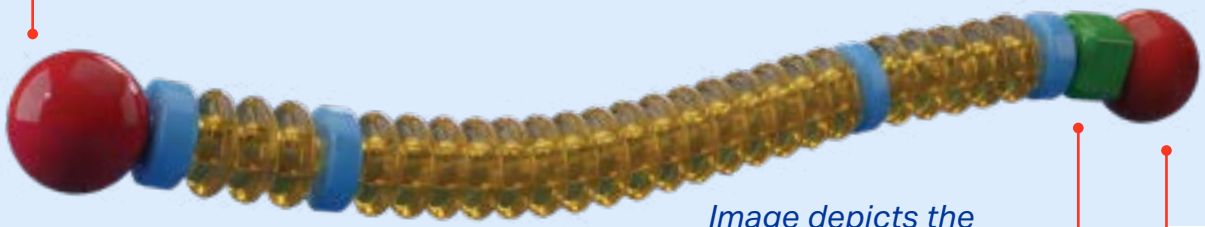

Image depicts the dystrophin protein

C-TERMINAL DOMAIN

Mediates sarcolemma localization via the binding of dystrophin-associated proteins

CENTRAL ROD DOMAIN

Provides elasticity and flexibility via hinge regions and spectrin-like repeats, acting like a molecular shock absorber and helping protect the sarcolemma from damage

Meaningful functional improvement in DMD requires **simultaneously** achieving 3 key components of dystrophin[9,11,17-19]

Functional improvement for those living with DMD requires dystrophin produced in suitable quantities, with sufficient quality, and distributed to the muscle cells most impacted by the disease.

Quantity
+
Quality
+
Distribution

Functional improvement

f Advances in the understanding of DMD and research into dystrophin quantity, quality, and distribution are essential in a disease for which there remains an unmet need despite treatment availability[7,11,20-23]

Quantity

Increased dystrophin expression in DMD is associated with improved muscle biology, which may enhance structural muscle support and reduce muscle cell damage[24-29]

Preclinical and observational clinical studies have shown an association between higher dystrophin levels and delayed loss of ambulation and slower disease progression.[24-29]

In studies comparing dystrophin levels and clinical phenotype, patients with very **low levels of dystrophin were associated with more severe disease**; those with higher levels had moderate or mild disease[25,27,28]

Studies suggest that even low levels of residual dystrophin may provide functional benefit[2,10,25,30,31]

Quality

For dystrophin to function properly, key domains critical to sarcolemmal stability and shock absorption must be expressed[9,10,32-35]

Dystrophin restoration that is as close as possible to **naturally occurring dystrophin** is more likely to provide functional benefit and protect muscles.[9,10,32-35]

Certain domains of dystrophin are critical. For example, the central actin-binding domain, ABD2, helps protect muscle from contraction-induced injury by bringing together the sarcolemma and actin filaments[9,14,36]

Distribution

For meaningful functional improvement in DMD, dystrophin restoration needs to occur across all muscle types, and dystrophin should be appropriately distributed *within* muscle cells[2,9-11,13,17,18,37,38]

Skeletal, cardiac, and smooth muscles have different structures and functions, but all express dystrophin; its role in sarcolemmal integrity has been most directly demonstrated in skeletal and cardiac muscle[9,18,39]

Skeletal muscle is composed of lengthy, multinucleated cells where it is thought that individual nuclei regulate the cytoplasmic area proximal to each one; these units are described as myonuclear domains (MNDs). Dystrophin restoration that does not extend beyond certain MNDs could still make the cell vulnerable to contraction-induced damage[6,38,40-42]

Cardiac muscle is continuously active, and therefore has a different contractile phenotype compared to skeletal muscle. Cardiac muscle is less tolerant of heterogeneous dystrophin expression and lacks the regenerative capacity present in skeletal muscle[9,39,40,43-46]

Smooth muscle is widely distributed in the body, including the gastrointestinal (GI) tract and vasculature. Smooth muscle cells are organized and function differently based on tissue type, and it is believed that the role of dystrophin also varies; however, this has not been well studied[2,39,47-49]

Advancements have been made that target the underlying cause of the disease, not just the symptoms[10,11]

Existing dystrophin-producing approaches have helped to establish awareness of the individual elements of dystrophin that are important for muscle function.

EXON SKIPPING

- Exon skipping therapy uses an antisense oligonucleotide that binds pre-mRNA to alter the cell's machinery and bypass a specific exon during the splicing process to restore the production of dystrophin[21,50]
- It was the first approach that proved functional, near full-length dystrophin could be generated[2,10,50,51]
- Because of the method of delivery, the therapy may not reach all the muscle cells impacted by DMD[10,50,52]

GENE THERAPY

- Gene therapy involves packaging the micro-dystrophin transgene into an adeno-associated virus (AAV) vector that is targeted to muscle cells[11]
- The gene stays as a stable episome of the cell to produce robust expression of micro-dystrophin[16,53,54]
- Gene therapy is given once and may not be re-dosed. As the body naturally grows, new muscle cells impacted by DMD may not receive the medicine[7,9,15]

f Achieving all 3 components of dystrophin simultaneously remains one of the most persistent and defining challenges in DMD therapeutic development[9,11,17–19]

Ongoing research is critical in the continued pursuit of functional improvement

Despite treatment availability, individuals with DMD continue to experience functional decline, underscoring the complexity of fully restoring dystrophin's role in muscle protection. Ongoing scientific advancements are attempting to overcome the challenge of addressing all 3 components of dystrophin in the functional improvement equation.[11,20-23]

A deeper understanding of these 3 components provides a clinically relevant framework for aligning treatment goals on functional outcomes. This supports an emphasis on functional improvement in areas that matter most to individuals living with DMD.

Treatment goals must be anchored to functional outcomes that are important to individuals living with DMD

PRESERVING DAILY FUNCTION[55-60]

- Maintaining ambulation
- Inhibiting the loss of upper limb function
- Supporting independence with activities of daily living

PROTECTING VITAL ORGANS[1,58]

- Preventing or delaying cardiomyopathy
- Conserving respiratory capacity
- Addressing issues related to GI dysfunction

f Ongoing dialogue with your patients can help ensure that clinical goals, patient expectations, and functional outcomes align

It's time to shift expectations for function in DMD

The Duchenne Functional Improvement Equation

Current drug development is increasingly focused on simultaneously achieving sufficient dystrophin quantity, quality, and distribution—striving towards the shared goals that could reflect meaningful functional improvement to the DMD community.[9,11,17-19]

Sign up now

Keep up with the *latest advances* in DMD science

> **We need to understand dystrophin in a much more nuanced way. We really need to understand all 3 of these aspects. And then importantly, how those 3 aspects translate to benefit for a patient.**

Erika Finanger, MD, MS
Pediatric Neurologist and Neuromuscular Specialist

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