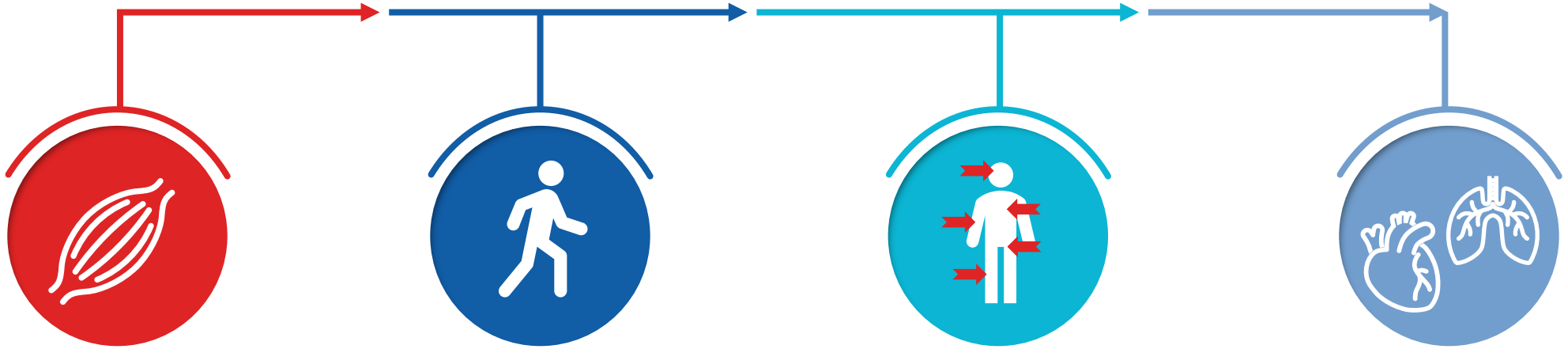
Dyne | Medical Central

Functional improvement: Moving beyond dystrophin in DMD

DMD is caused by dystrophin deficiency and manifests as a progressive multisystem disease, affecting muscle and the CNS

Greatly reduced or absent dystrophin protein expression[1]



Muscle weakness and gait abnormalities[2]

Progressive loss of upper and lower limb strength and function[2]

Multisystem involvement that affects skeletal, including pulmonary, smooth, and cardiac muscles and the CNS[3]

Cardiopulmonary failure as the leading cause of death[4]

CNS, central nervous system; DMD, Duchenne muscular dystrophy.

1. de Feraudy Y, et al. *Ann Neurol.* 2021;89:280–292; 2. Bushby K, et al. *Lancet Neurol.* 2010;9:77–93; 3. Ohlendieck K, Swandulla D. *Pflügers Arch.* 2022;473:1813–1839; 4. Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:251–267.

Therapeutic approaches in DMD have evolved from supportive care to targeted approaches

Supportive standard of care[1–3]

~1990s[2]

- Corticosteroid therapy[1,2]
- Multidisciplinary management[3,4]

Dystrophin-producing therapies[1,2]

2016*

Exon skipping therapy[2]

- RNA-level dystrophin restoration

Gene therapy[1]

- Micro-dystrophin protein replacement

HDAC inhibitors[1]

2024[1]

- Target inflammation, fibrosis, muscle degeneration[5]

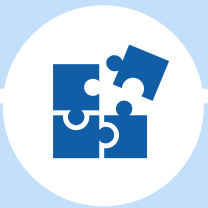
DMD, Duchenne muscular dystrophy; HDAC, histone deacetylase.
*The first exon skipping therapy was approved in 2016[2]; the first gene therapy was approved in 2023[1].

1. Komaki H. *Brain Dev*. 2025;47:104397; 2. D'Ambrosio ES, Mendell JR. *Neurotherapeutics*. 2023;20:1669–1681; 3. Bushby K, et al. *Lancet Neurol*. 2010;9:177–189; 4. Duan D, et al. *Nat Rev Dis Primers*. 2021;7:13; 5. Anjum AF, et al. *Curr Ther Res Clin Exp*. 2025;102:100787.

Despite progress, challenges remain with current treatments

Exon skipping and gene therapy

Dystrophin quantity and quality



- Low dystrophin expression levels[1]
  - <1% with approved exon 51 skipping therapy
- Micro-dystrophin functionality[1]
  - Shorter micro-dystrophin protein lacks key functional domains believed to support muscle health[2,3]

Effective distribution and durability of effect

- Limited delivery to muscle and the CNS[1,4]
- Modest clinical benefits with exon skipping[4]
- Unknown durability of effect with gene therapy[4]

All modalities

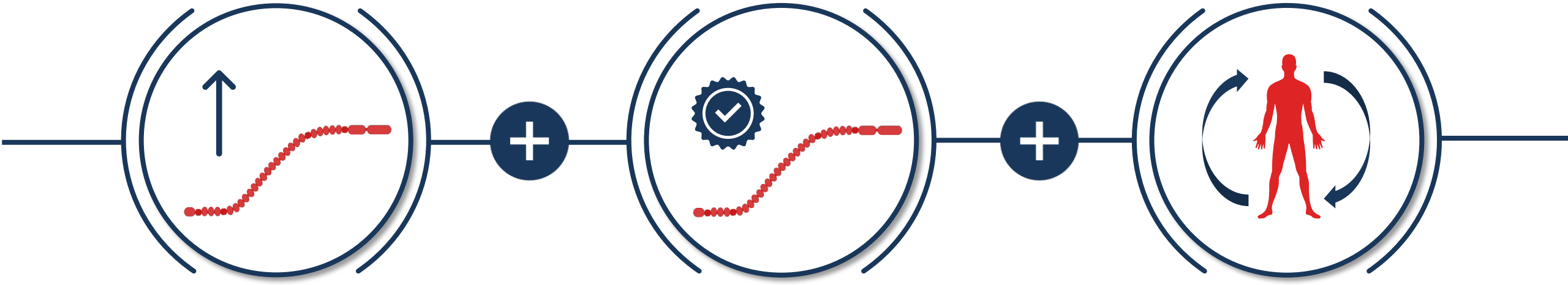
Treatment burden, safety, and access

- Access/clinical eligibility restrictions with gene therapy[4]
- Adverse events[1,5,6]
- Regular monitoring[5,7]
- Dosing
  - Inability to safely and effectively re-dose with gene therapy[1,8]
  - Frequent IV dosing with currently approved exon skipping therapy[8]

CNS, central nervous system; IV, intravenous.

1. Chwalenia K, et al. *J Muscle Res Cell Motil*. 2025;46:293–300; 2. Harper S, et al. *Hum Mol Genet*. 2002;11:1807–1815; 3. Davies KE, Guiraud S. *Mol Ther*. 2019;27:486–488; 4. Gonzalez Castillo Z, et al. *J Transl Genet Genom*. 2025;9:338–351; 5. Montagna C, et al. *Int J Mol Sci*. 2025;26(:6742; 6. D'Ambrosio ES, Mendell JR. *Neurotherapeutics*. 2023;20:1669–1681; 7. Das P, et al. *Pharmacology*. 2025;110:1–13; 8. Komaki H. *Brain Dev*. 2025;47:104397.

Functional improvement in DMD with dystrophin-producing approaches requires improvement in the quantity, quality, and distribution of dystrophin



Increased dystrophin production

Production of high-quality dystrophin

Broad and effective distribution of dystrophin-producing approaches to affected muscles and the CNS

Functional improvement

CNS, central nervous system; DMD, Duchenne muscular dystrophy.

Dystrophin quantity, quality, and distribution underlies functional improvement in DMD with dystrophin-producing approaches

Beyond dystrophin: functional improvement in practice

- Preserving motor function and retaining independence are important to individuals with DMD and caregivers[1]
- Dystrophin deficiency manifests in a multisystemic manner – individuals can experience CNS, GI, bladder, cardiac, and respiratory manifestations[2]

Dystrophin: quantity, quality, and distribution

- Increased dystrophin production
- Production of high-quality dystrophin
- Dystrophin-producing approaches require broad and effective distribution to affected muscle (skeletal, smooth, and cardiac) and the CNS

CNS, central nervous system; DMD, Duchenne muscular dystrophy; GI, gastrointestinal.

1. Gillman A, et al. *Front Neurol. 2025;*16:1509174; 2. Ohlendieck K, Swandulla D. *Pflügers Arch.* 2022;473:1813–1839.

How is meaningful change in functional improvement defined?

In clinical trials…

MCID
Minimal clinically important difference

The smallest difference that reflects a change that is meaningful for an individual and would impact their healthcare management[1]

May be measured as:

- **Velocity** e.g. in 10MWR, 4SC, TTR, SV95C[2,3]
- **Points/score** e.g. in PUL, NSAA[4,5]

By those affected by DMD…

ADLs
Activities of daily living

Ability to perform ADLs, maintain independence, and participate in hobbies[6]

In qualitative evaluation of meaningful change on functional assessments:*

- Patients interpret change by tasks[6]
- A single point may reflect real functional loss[6]

*The study utilized a non-interventional, descriptive, cross-sectional qualitative design consisting of 69 semi-structured interviews with individuals with DMD and their caregivers, as well as two interviews with neuromuscular expert physiotherapists. NSAA and PUL were used to measure motor performance in ambulatory and non-ambulatory individuals, respectively.

10MWR, 10-meter walk/run; 4SC, 4 stair climb; ADL, activities of daily living; MCID, minimal clinically important difference; NSAA, North Star Ambulatory Assessment; PUL, performance upper limb; SV95C, stride velocity 95th centile; TTR, time to rise.

1. Cook CE, et al. *J Man Manip Ther*. 2008;16:E82–83; 2. Duong T, et al. *J Neuromuscul Dis*. 2021;8:939–48; 3. EMA Qualification Opinion. July 2023. Accessed February 16, 2026. https://www.ema.europa.eu/en/documents/scientificguideline/qualification-opinion-stride-velocity-95th-centile-primary-endpoint-studies-ambulatory-duchenne-muscular-dystrophy-studies_en.pdf; 4. Naarding KJ, et al. *J Neuromuscul Dis*. 2022;9:555–569; 5. Ayyar Gupta V, et al. *PLoS One*. 2023;18:e0283669; 6. Gillman A, et al. *Front Neurol. 2025;*16:1509174.

Clinical measures can translate into meaningful outcomes for individuals with DMD

10MWR, 10-meter walk/run; 4SC, 4 stair climb; DMD, Duchenne muscular dystrophy; FVC%p, forced vital capacity percent predicted; LVEF, left ventricular ejection fraction; NSAA, North Star Ambulatory Assessment; PUL, performance upper limb; SV95C, stride velocity 95th centile; TTR, time to rise.

1. Arora H, et al. *Muscle Nerve*. 2018;58:631–638; 2. Servais L, et al. *Nat Med*. 2023;29:2391–2392; 3. McDonald CM, et al. *Lancet*. 2018;391:451–461; 4. Gillman A, et al. *Front Neurol*. 2025;16:1509174; 5. Lechner A, et al. *ERJ Open Res*. 2023;9:00176–2023; 6. Phillips MF, et al. *Am J Respir Crit Care Med*. 2001;164:2191–2194.

What are the treatment goals for individuals with DMD and their families?

Preserve daily function

- Maintain ability to walk, use arms and hands, and perform self-care[1,2]
- Delay loss of independence in school, work, and social life[1,2]
- Address under-recognized neurobehavioral symptoms that impact quality of life[3]

Protect vital organs

- Prevent or delay cardiomyopathy[4]
- Preserve breathing capacity[4]

Change the disease trajectory

- Delay irreversible milestones – loss of ambulation, need for ventilation, progressive heart and respiratory failure[1,4,5]

1. Brown V, et al. *J Patient Rep Outcomes*. 2023;7:129; 2. Gillman A, et al. *Front Neurol. 2025;*16:1509174; 3. Geuens S, et al. *J Neuromuscul Dis*. 2024;11:791–799; 4. Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:251–267;
5. Duan D, et al. *Nat Rev Dis Primers*. 2021;7:13.