What’s New in Duchenne Muscular Dystrophy 2022
Slide Set Overview

- Review of Duchenne Muscular Dystrophy (DMD)
  - Clinical presentation, pathology
  - Diagnostic considerations
- Clinical management of DMD
  - Multidisciplinary approach to care
  - Current and emerging therapies
- DMD resources
Duchenne muscular dystrophy (DMD)

- DMD is a rare, progressive, X-linked recessive, muscular dystrophy, affecting predominantly males.
- DMD occurs in 1 in 5,000 male births and is the most common childhood-onset muscular dystrophy.¹,²
- DMD is caused by mutations in the *DMD* gene that result in absent or decreased dystrophin, a muscle membrane protein.²,³
- Dystrophin plays a key structural role in muscle fiber function and protects against damage during normal muscle contraction.

Clinical signs and symptoms\textsuperscript{1,2}

**Motor signs\textsuperscript{1,2}**
- Abnormal gait: waddling
- Frequent falls
- Difficulty climbing steps
- Difficulty getting up from the floor >2”
- Delayed walking
- Toe walking
- Lordosis
- Never able to jump or hop
- Abnormal running
- Enlarged calves

**Non-motor signs\textsuperscript{1,2}**
- Cognitive delay
- Learning deficits
- Attention deficits
- Language delay or difficulty

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DMD pathology: Genetics and reading frame theory

- Mutations that disrupt the reading frame (i.e. “out-of-frame” deletions) such as 48-50, lead to complete loss of dystrophin protein.

- Mutations that do not disrupt the reading-frame, allow for production of some dystrophin reduced in size/amount, resulting in a milder phenotype.

“Out-of-frame” mRNA

No dystrophin

Duan D, 2021.
DMD vs BMD: Differential diagnosis

- Dystrophinopathies share common pathology and symptoms along a spectrum, but symptoms are most severe among individuals with DMD.

**DMD**
- **More** severe
- **Earlier** onset (always before age 5)
- **Faster** progression
- Reading frame **disrupted**

**BMD**
- **Less** severe
- **Later** onset
- **Slower** progression
- Reading frame **preserved**

Images courtesy of E Ciafaloni
Example: Muscle biopsy and dystrophin staining

Normal

BMD

DMD

Normal

Mild BMD

Severe BMD

DMD

Images courtesy of E Ciafaloni
Stages of DMD Progression

**Stage**
- **Pre-symptomatic**
  - Can be diagnosed if elevated CK or family history
  - Possible developmental delay
  - No gait disturbance

**Symptoms**
- **Early ambulatory**
  - Gowers sign
  - Waddling gait
  - Unable to jump

- **Late ambulatory**
  - Labored gait
  - Losing ability to climb stairs
  - Losing ability to get up off the floor

- **Early non-ambulatory**
  - Able to self-propel
  - Able to maintain posture
  - Early scoliosis

- **Late non-ambulatory**
  - Upper limb function limited
  - Worsening scoliosis and postural maintenance becoming limited

Figure adapted from Birnkrant DJ, 2018
Diagnosis: Recommended tests

- **Elevated CK level** is a hallmark sign of DMD and always elevated from infancy.

- **Genetic testing** is confirmatory in >95% of DMD cases:
  - Muscle biopsy conducted **only** if genetic test is negative and can confirm DMD diagnosis based on absent dystrophin
  - Muscle biopsy rarely needed (<5%)

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**Figure adapted from Birnkrant DJ, 2018**

Birnkrant DJ, 2018.
Diagnostic delay in DMD

- An analysis of MD STARnet data indicates a ~2.5-year delay between symptom onset and DMD diagnosis
- Concerns often first noted at ~2 years of age
- First evaluation by a neuromuscular specialist is at ~4.5 years of age
- Definitive diagnosis is at ~5 years of age

Ciafaloni E, 2009

Table I. Timeline of diagnostic steps for patients with Duchenne dystrophy without family history of dystrophy (N = 156).

<table>
<thead>
<tr>
<th>Measure</th>
<th>n</th>
<th>Mean years of age ±SD</th>
<th>Range, years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Earliest sign or symptom noted</td>
<td>111</td>
<td>2.5 ± 1.4</td>
<td>0.2-6.1</td>
</tr>
<tr>
<td>First evaluation by health specialist</td>
<td>127</td>
<td>3.6 ± 1.7</td>
<td>0.2-8.0</td>
</tr>
<tr>
<td>First neurology/neuromuscular visit</td>
<td>131</td>
<td>4.6 ± 1.7</td>
<td>0.3-8.6</td>
</tr>
<tr>
<td>First CK test</td>
<td>151</td>
<td>4.7 ± 1.7</td>
<td>0.3-8.6</td>
</tr>
<tr>
<td>Age at definitive diagnosis</td>
<td>154</td>
<td>4.9 ± 1.7</td>
<td>0.3-8.8</td>
</tr>
</tbody>
</table>

Delay of ~2.5 years

Early CK testing can reduce delay in diagnosis
Common causes for diagnostic delay

• Non-universal screening of lab abnormalities at birth
  – Screening for CK/transaminase levels is not a universal standard
  – CK should be tested in any boy with early motor/developmental delay

• Subtle signs of early disease missed
  – Earliest signs are noted by parents and not trained professionals who may be more adept at recognizing subtle delays

• Cognitive delay/“autism” and DMD can be a comorbidity and may delay DMD diagnosis
Improving diagnosis

- **Early CK testing** in boys with developmental delay may help speed definitive diagnosis and enable earlier treatment.

- DMD is **not** currently included on the Recommended Uniform Screening Panel for genetic testing\(^1,2\)
  - Treatments may be most effective if initiated early in disease onset/prior to symptom onset.

- Efforts are underway by advocacy and government groups to implement newborn screening for DMD nationwide\(^3\)

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Ohio Duchenne Newborn Screening (DNBS) pilot study establishes success of a 2-tier approach to identify infants with DMD¹

- Dried blood spot first tested for elevated CK, then genetic testing

Pilot program initiated in NY state (a high birth-rate state)²

- First baby tested in Oct 2019
- Projected to screen up to 100K infants

FDA authorizes GSP Neonatal Creatinine Kinase-MM kit³

With ongoing success of pilot programs, DMD screening is likely to be adopted into state-based programs nationwide

Clinical Management of DMD
DMD care guidelines continue to evolve

• Care guidelines were updated in 2018 to align with the evolving DMD landscape\textsuperscript{1,2}
  – Prolonged survival associated with optimized multidisciplinary care has shifted care goals towards prevention, earlier identification, and treatment of predictable and modifiable complications
  – With patients surviving longer, more emphasis can be placed on quality of life, psychosocial management, and ensuring smooth care transitions across the lifespan
  – Therapeutic options continue to emerge

2010\textsuperscript{2}
Care considerations published

• Diagnostic advances
• New therapies
• Improved survival

2014-2018
Review and revision of care considerations

Emerging therapies

Multidisciplinary care has improved DMD outcomes

• A proactive and multidisciplinary approach has prolonged survival and improved outcomes in DMD\textsuperscript{1-3}
  – Prior to 1970, a patient with DMD could expect to live until their 20s\textsuperscript{3}
  – Those diagnosed after 1970 can expect to live into their 40s\textsuperscript{3}

• Requires coordination of specialists throughout the different stages of the disease\textsuperscript{1,2}

\textsuperscript{1} Bushby K, 2010. \textsuperscript{2} Birnkrant DJ, 2018. \textsuperscript{3} Duan D, 2021
Care recommendations (2018 update):

**Neuromuscular management**

- **Pre-symptomatic**
  - Lead multidisciplinary clinic, advise on new therapies, provide patient support/education/genetic counseling
  - Ensure immunizations complete
  - Discuss corticosteroids
  - Refer female carriers to cardiologist

- **Early Ambulatory**
  - Assess function, strength, movement to define disease stage (at least every 6 months)

- **Late Ambulatory**
  - Initiate and manage corticosteroids

- **Early non-ambulatory**

- **Late non-ambulatory**
  - Help navigate end-of-life care
Care recommendations (2018 update):

<table>
<thead>
<tr>
<th>Pre-symptomatic</th>
<th>Early Ambulatory</th>
<th>Late Ambulatory</th>
<th>Early non-ambulatory</th>
<th>Late non-ambulatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide multidisciplinary, standardized assessments (at least every 6 months)</td>
<td>Provide occupational, physical, speech therapy based on assessments and individualized to patient</td>
<td></td>
<td></td>
<td>Continue all prior measures</td>
</tr>
<tr>
<td>Prevent contractures, over-exertion, falls</td>
<td></td>
<td></td>
<td>Provide mobility-assistive devices, assist in pain management</td>
<td></td>
</tr>
<tr>
<td>Promote energy conservation, exercise, activity</td>
<td></td>
<td></td>
<td>Advocate for funding, access and self-actualization into adulthood</td>
<td></td>
</tr>
<tr>
<td>Provide orthoses, equipment, learning support</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Care recommendations (2018 update):

**Endocrine**

- **Pre-symptomatic**
  - Measure standing and non-standing growth (every 6 months)

- **Early Ambulatory**
  - Assess pubertal status starting by age 9 (every 6 months)
  - Provide family education and stress dose steroid prescription (if on corticosteroids)

- **Late Ambulatory**
  - Dietary assessment by registered dietician (every 6 months)
    - Initiate obesity-prevention strategies, monitor for over- or under-weight especially during critical transitions

- **Early non-ambulatory**
  - Assess serum vitamin D and calcium intake (yearly)

- **Late non-ambulatory**
  - Assess swallowing dysfunction, constipation, GERD, gastroparesis (every 6 months)
  - Discuss gastronomy tube (yearly)

**GI/ Nutrition**

- **Pre-symptomatic**
  - Measure standing and non-standing growth (every 6 months)

- **Early Ambulatory**
  - Assess pubertal status starting by age 9 (every 6 months)
  - Provide family education and stress dose steroid prescription (if on corticosteroids)

- **Late Ambulatory**
  - Dietary assessment by registered dietician (every 6 months)
    - Initiate obesity-prevention strategies, monitor for over- or under-weight especially during critical transitions

- **Early non-ambulatory**
  - Assess serum vitamin D and calcium intake (yearly)

- **Late non-ambulatory**
  - Assess swallowing dysfunction, constipation, GERD, gastroparesis (every 6 months)
  - Discuss gastronomy tube (yearly)
Care recommendations (2018 update):

- Ensure up-to-date immunizations: Pneumococcal, yearly influenza
- Early Ambulatory:
- Early non-ambulatory:
- Late non-ambulatory:

Proactive, regular monitoring of peak cough flow and FVC, early cough assist machine use, and nocturnal BiPap implementation is critical for optimal respiratory management.

Initiate use of lung volume recruitment
Begin assisted cough and nocturnal ventilation
Add daytime ventilation
Care recommendations (2018 update):

Pre-symptomatic:
Consult cardiologist
Assess electro- and echo-cardiogram or cardiac MRI

Early Ambulatory:
Assess cardiac function (yearly)
Start ACE inhibitors or angiotensin receptor blockers by age 10

Late Ambulatory:
Assess cardiac function yearly (more often if symptoms/ abnormal imaging)
Monitor for rhythm abnormalities

Early non-ambulatory:

Late non-ambulatory:
Use standard heart failure interventions with deteriorating function

Proactive cardiac care by age 10 is critical for optimal care
Care recommendations (2018 update):

### Bone Health

- **Pre-symptomatic**
  - Lateral spine x-rays: every 1-2 years if on corticosteroids, every 2-3 years if not
  - Refer to bone health expert at first sign of fracture

- **Early Ambulatory**
  - Assess range of motion (at least every 6 months)

- **Late Ambulatory**
  - Monitor for scoliosis (yearly)

- **Early non-ambulatory**
  - Refer for surgery on foot/ Achilles tendon to improve gait (select situations)

- **Late non-ambulatory**
  - Consider foot position for wheelchair; start intervention with posterior spinal fusion (select situations)

### Orthopedic

- Refer to orthopedic surgeon if needed (rare)
- Refer for surgery on foot/ Achilles tendon to improve gait (select situations)
Care recommendations (2018 update):

**Psychosocial**

- **Pre-symptomatic**
  - Discuss expectations for future/adulthood

- **Early Ambulatory**
  - Assess mental health of patient and family (every visit); provide ongoing support
  - Provide neuropsychological evaluations/interventions for learning, emotional, and behavioral problems

- **Late Ambulatory**
  - Assess educational needs, available resources and vocational support needs (adults)
  - Promote age-appropriate independence/social development

- **Early non-ambulatory**

- **Late non-ambulatory**

**Transition**

- **Pre-symptomatic**
  - Discuss expectations for future/adulthood

- **Early Ambulatory**
  - Assess transition-readiness by age 12

- **Late Ambulatory**
  - Start transition plan by age 13-14: Healthcare, education, employment, adult living
  - Monitor progress and enlist coordinator/social worker for guidance
  - Provide transition support and anticipate guidance on health changes

**Proactive, early planning is critical to successful care transition**
Key treatment strategies in DMD

Corticosteroid therapy (standard of care)\(^1,2\)

**Goal:** Reduce inflammation to increase muscle mass/ strength
- Exact mechanism of action unknown, but likely acts on several targets

Dystrophin-restoration strategies\(^3\)

**Goal:** Restore dystrophin by manipulating transcription/ translation activity or gene replacement\(^3\)
- Exon-skipping (anti-sense oligonucleotides)
- Nonsense mutation read-through
- Gene transfer (AAV-mediated delivery of micro/mini dystrophin)

Corticosteroid therapy

• Corticosteroids are recognized as the standard of care in DMD\textsuperscript{1-3}
  – Steroids are effective and associated with several benefits\textsuperscript{2}
• Guidelines recommend the use of prednisone or deflazacort
  – No consensus on which agent or regimen is best, but studies are ongoing

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Adverse events\textsuperscript{2,4,5}</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prolong ambulation (mean \textasciitilde 10 years)\textsuperscript{1,3}</td>
<td>• Weight gain</td>
</tr>
<tr>
<td>• Preserve upper limb and respiratory function\textsuperscript{1}</td>
<td>• Short stature</td>
</tr>
<tr>
<td>• Reduce the need for scoliosis surgery\textsuperscript{1,3}</td>
<td>• Skin marks</td>
</tr>
<tr>
<td>• Delay onset of cardiomyopathy\textsuperscript{2}</td>
<td>• Bone fragility</td>
</tr>
</tbody>
</table>

Corticosteroid therapy: Clinical trials

- Research is underway to help identify which corticosteroid regimens are most effective and may offer patients a more tolerable regimen/agent\(^1\sim6\)
- **Vamorolone** is being evaluated as a potentially safer alternative to currently available options\(^2\)

### Select Trials\(^6\)

<table>
<thead>
<tr>
<th>Topic</th>
<th>Select Trials</th>
</tr>
</thead>
</table>
| **Optimal regimens**      | • FOR-DMD: Finding the optimum regimen for DMD (NCT01603407)  
                           | • Weekend steroids and exercise (NCT04322357)            |
| **Vamorolone**            | • Vamorolone in boys with DMD (NCT03439670)             |
| **Combination therapy**   | • Pamrevlumab in combination with steroids (NCT04632940)  
                           | • Spironolactone vs prednisolone (NCT03777319)            |

For details, visit [clinicaltrials.gov](https://clinicaltrials.gov)

Dystrophin restoration: Exon-skipping

**Strategy:** Restore the reading frame of out-of-frame (ie, DMD) dystrophin transcripts to produce partially functional dystrophins (akin to BMD)

- Different exons are skipped based on mutation size and location (mutation-specific)

**Patient with DMD: Exon 48-50 out-of-frame**

1 2 3 4 5 6 7 8 9 10 11 12 13 14
15 16 17 18 19 20 21 22 23 24 25 26 27
28 29 30 31 32 33 34 35 36 37 38 39 40
41 42 43 44 45 46 47
51 52 53
54 55 56 57 58 59 60 61 62 63 64 65 66
67 68 69 70 71 72 73 74 75 76 77 78 79

Out-of-frame mRNA  DMD: No dystrophin

**Exon 51 skipping therapy**

Exon 46  Exon 47  ?  Exon 51  Exon 52  Exon 53
Exon 46  Exon 47  AON  Exon 52  Exon 53

In-frame mRNA  BMD-like dystrophin

Image courtesy of E Ciafoloni

Duan D, 2021
Dystrophin restoration: Exon-skipping

- Administered via **systemic IV** as an add-on to ongoing **oral** corticosteroid therapy
- **Four** exon-skipping therapies have been **FDA-approved**

<table>
<thead>
<tr>
<th>Exon</th>
<th>Population addressed</th>
<th>Agent</th>
<th>Status</th>
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<tbody>
<tr>
<td>45</td>
<td>8-9%</td>
<td>Casimersen (Amondys 45)</td>
<td>Approved</td>
</tr>
<tr>
<td>51</td>
<td>13-14%</td>
<td>Eteplirsen (Exondys 51)</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SRP-5051</td>
<td>Phase 2 ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suvodiresen (WVE-210201)</td>
<td>Phase 3 terminated (DYSTANCE 51)</td>
</tr>
<tr>
<td>53</td>
<td>7-10%</td>
<td>Golodirsen (Vyondys 53)</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Viltolarsen (Viltepso)</td>
<td>Approved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS-065</td>
<td>Phase 2 ongoing</td>
</tr>
</tbody>
</table>

Dystrophin restoration: Nonsense mutation-read through

**Strategy:** Force read-through of nonsense mutations to restore dystrophin

- A subset of individuals with DMD harbor *nonsense mutations* (vs *frameshifting* ones that are amenable to exon-skipping therapies)
  - In these mutations, a codon is substituted with a *stop* codon, which interrupts RNA translation and leads to a truncated, non-functional dystrophin

- Therapies that promote read-through may help the population of 11% of boys with DMD caused by nonsense mutations

- **No read-through therapies are approved in the US** for nonsense mutation-based DMD
  - Ataluren is approved for use in the EU

Dystrophin restoration: Gene transfer therapy

**Strategy:** Deliver a functional cDNA copy of dystrophin gene to muscle tissue

- Packaged and delivered to muscle tissue via an adeno-associated virus (administered as a one-time IV infusion)\(^1\)

- Delivering the dystrophin gene presents challenges due to its size\(^1\)
  - Dystrophin is one of the largest genes in the human genome (~11.4kb)
  - AAVs have a limited carrying capacity (~4.7kb)
  - Micro- or mini- dystrophin constructs have been developed to enable packaging and delivery

Image from Shieh 2018
1. Duan D, 2021. 2. Shieh PB, 2018
Gene transfer therapy: Micro- and mini-dystrophin agents in clinical trials

Dystrophin gene (Dp427)

AAVrh74 (SRP-9001; Nationwide/Sarepta)

AAV9 (SGT-001; Solid Biosciences)

AAV9 (PF-06939926; Pfizer)

Images from Shieh 2018
Clinical trial status: SRP-9001 (Sarepta)

- Phase 1 **ENDEAVOR** trial (NCT04626674) ongoing in boys with DMD (>4 years); enrolling via invitation only\(^1,2\)
- **Positive results in first 11 participants\(^2\)**
  - Treatment generally well-tolerated; 2 participants with SAEs (nausea/vomiting, elevated liver enzymes, resolved)
  - Robust micro-dystrophin expression at 3 months (~70% vs ~12% at baseline)
- Pivotal **EMBARK trial** will recruit up to 120 boys with DMD at 40 sites\(^3\)

**EMBARK Trial: Phase 3 trial enrolling in US**

- **N=120**
- **Key eligibility criteria**
  - Boys with DMD, 4-7 years
- **SRP-9001**
- **Placebo**

Clinical trial status: SGT-001(Solid Biosciences)

• Phase 1/2 trial is ongoing and recruiting\(^1\)
• **Positive results in first 6 participants**\(^2\)
  – Treatment generally well-tolerated; inflammatory SAE reported in 1 patient (resolved)
  – Increased micro-dystrophin at 3 months (up to ~17% of normal dystrophin); levels sustained or increased at 1-2 years
  – Decreased CK levels at 1-year post-treatment
  – Two additional patients have been dosed since data readout

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**Phase 1/2 IGNITE DMD Trial (NCT03368742): Recruiting**

**Key eligibility criteria**
- Boys with DMD, 4-17 yo
- ≥ 3 mo corticosteroid therapy
- AAV seronegative

**N=16**

**SGT-001 (Dose 1 or 2)**

**Placebo**

**Primary endpoint:**
- Micro-dystrophin protein change from baseline

**Primary completion: Dec 2023**

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Clinical trial status: PF-06939926 (Pfizer)

- Designated **Orphan Drug** status by FDA (May 2017)
- Phase 1 trial (NCT03362502) ongoing in boys with DMD (ambulatory, 5-10 years old)
- **Positive results in first 9 participants (1 year)**
  - Treatment generally well-tolerated
  - Sustained production of mini-dystrophin protein
  - Improved motor function based on NSAA score change (+3.5 points vs -4 points with placebo)
- Global CIFFREO **Phase 3 trial** is recruiting up to 99 boys with DMD

**Phase 3 CIFFREO Trial (NCT04281485): Recruiting**

- **Key eligibility criteria**
  - Boys with DMD, 4-8 yo
  - ≥ 3 mo corticosteroid therapy
  - AAV seronegative

- **Primary endpoint:**
  - NSAA change from baseline

- **Primary completion:** Jan 2023

### Additional strategies under investigation

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Agents</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibit myostatin (a muscle growth inhibitor)</td>
<td>Domogrozumab • Talditercept alfa</td>
<td>Clinical trials failed to demonstrate therapeutic effect(^2)</td>
</tr>
<tr>
<td>Improve mitochondrial function/ metabolism</td>
<td>Idebenone</td>
<td>Studies terminated due to lack of therapeutic effect(^2)</td>
</tr>
<tr>
<td>Reduce inflammation/ fibrosis and improve regeneration</td>
<td>Givinostat (HDAC inhibitor)</td>
<td>Phase 2/3 study ongoing(^3) (NCT03373968)</td>
</tr>
<tr>
<td>Reduce fibrosis</td>
<td>Pamrevlumab (anti-CTGF monoclonal antibody)</td>
<td>Phase 3 trial ongoing(^2,3) (NCT04371666)</td>
</tr>
<tr>
<td>Allogenic cardiosphere-derived cells</td>
<td>CAP-1002</td>
<td>Phase 2 extension ongoing(^3) (NCT02485938)</td>
</tr>
<tr>
<td>Modulate utrophin expression</td>
<td>AAV-based gene delivery (GALG2)</td>
<td>Phase 1/2 trial ongoing(^3) (NCT03333590)</td>
</tr>
</tbody>
</table>

CTGF, connective tissue growth factor
DMD resources: Clinicians

• DMD care recommendations

• NIH clinical trials database
  o [https://clinicaltrials.gov/](https://clinicaltrials.gov/)

• MDA Grand Round webinars:
  o [https://www.mda.org/meded/grand-rounds-webinars](https://www.mda.org/meded/grand-rounds-webinars)

• MDA Clinical Case studies (downloadable pdfs):
DMD resources: Free genetic testing

- **MDA/ Invitae Detect Muscular Dystrophy**
  - Free genetic testing for DMD
  - Remote saliva collection option (ship-to-home) option included
  - MDA-sponsored program: Visit MDA.org or call 1-833-ASK-MDA1

- **Decode Duchenne**
  - Free genetic testing (diagnostic and carrier) and counseling—US and CA only
  - [https://www.parentprojectmd.org/about-duchenne/decode-duchenne/](https://www.parentprojectmd.org/about-duchenne/decode-duchenne/)
DMD resources: Individuals and families

• MDA clinical trial finder tool: https://www.mda.org/research/clinical-trials

• MDA educational materials (downloadable pdfs):
  o Fact sheet, DMD emergency room card alert, DMD FAQ
  o https://www.mda.org/services/education-materials

• MDA Engage webinars (various topics)
  o https://www.mda.org/care/MDA-engage/disease-symposia
Enrolling observational studies

- Patients with DMD may be eligible to participate in ongoing registries or observational studies aimed at improving understanding of DMD

### Areas of observational research in DMD

<table>
<thead>
<tr>
<th>Research area</th>
<th>Select studies (US-based)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient registries</td>
<td>• The Duchenne Registry [<a href="https://www.duchenneregistry.org/">https://www.duchenneregistry.org/</a>]</td>
</tr>
<tr>
<td></td>
<td>• CureDuchenne Link™ [<a href="https://www.cureduchenne.org/cureduchenne-link/">https://www.cureduchenne.org/cureduchenne-link/</a>]</td>
</tr>
<tr>
<td>Wearable technology</td>
<td>Wearable technology to assess gait function [NCT04193085]</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>• Extracellular RNA biomarkers [NCT05016908]</td>
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<tr>
<td></td>
<td>• MRI and biomarkers [NCT01484678]</td>
</tr>
<tr>
<td></td>
<td>• Biomarker development for MDs [NCT05019625]</td>
</tr>
<tr>
<td>Newborn screening</td>
<td>Early check: Expanded screening for newborns [<a href="https://earlycheck.org/">https://earlycheck.org/</a>]</td>
</tr>
</tbody>
</table>

Additional information on clinical studies is available at [clinicaltrials.gov](https://clinicaltrials.gov)