Provided by The France Foundation

New Frontiers in the Treatment of DMD Across the Age Spectrum

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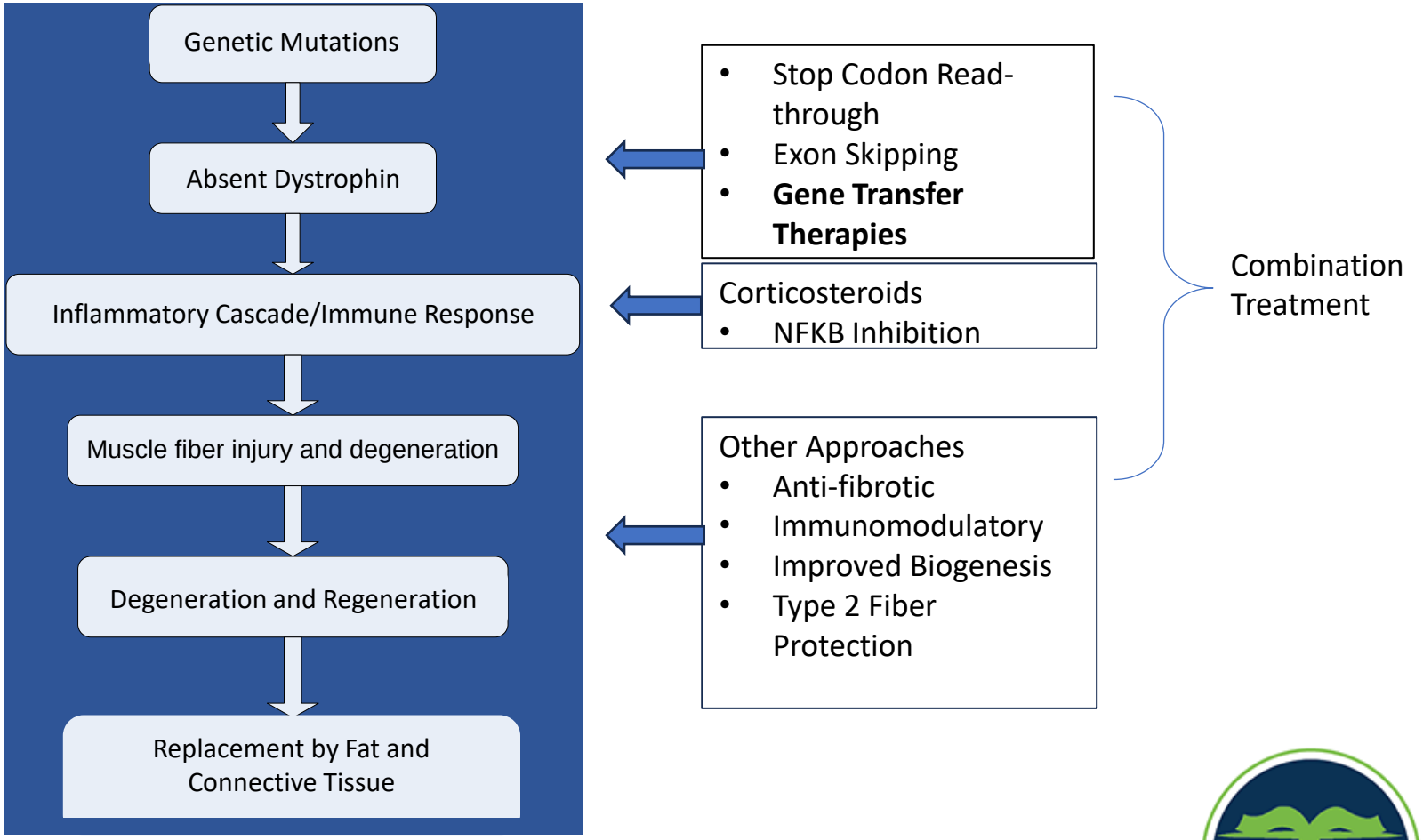
Learning Objectives

- Evaluate real-world, case-based scenarios for patients with DMD to help determine therapeutic candidacy across the age spectrum
- Assess the latest clinical trial data for DMD treatments to help inform clinical decision-making
- Describe best practices for ongoing monitoring of patients at various ages who are receiving treatment for DMD

DMD Toolbox

The DMD Toolbox: Individualizing Gene Therapy to Each Patient

- There has been a rapid expansion of the treatment paradigm for DMD over the past decade
- Approval of exon skipping therapies, gene therapy, and other supportive therapies have transformed patient outcomes



NIH: National Center for Advancing Translational Sciences. Accessed December 4, 2023. https://rarediseases.info.nih.gov/diseases/6291/duchenne-muscular-dystrophy; Yao S, et al. *Front Cell Dev Biol*. 2021;9:689533.

Considerations for Goals of Treatment as Applicable to Each Phase of DMD

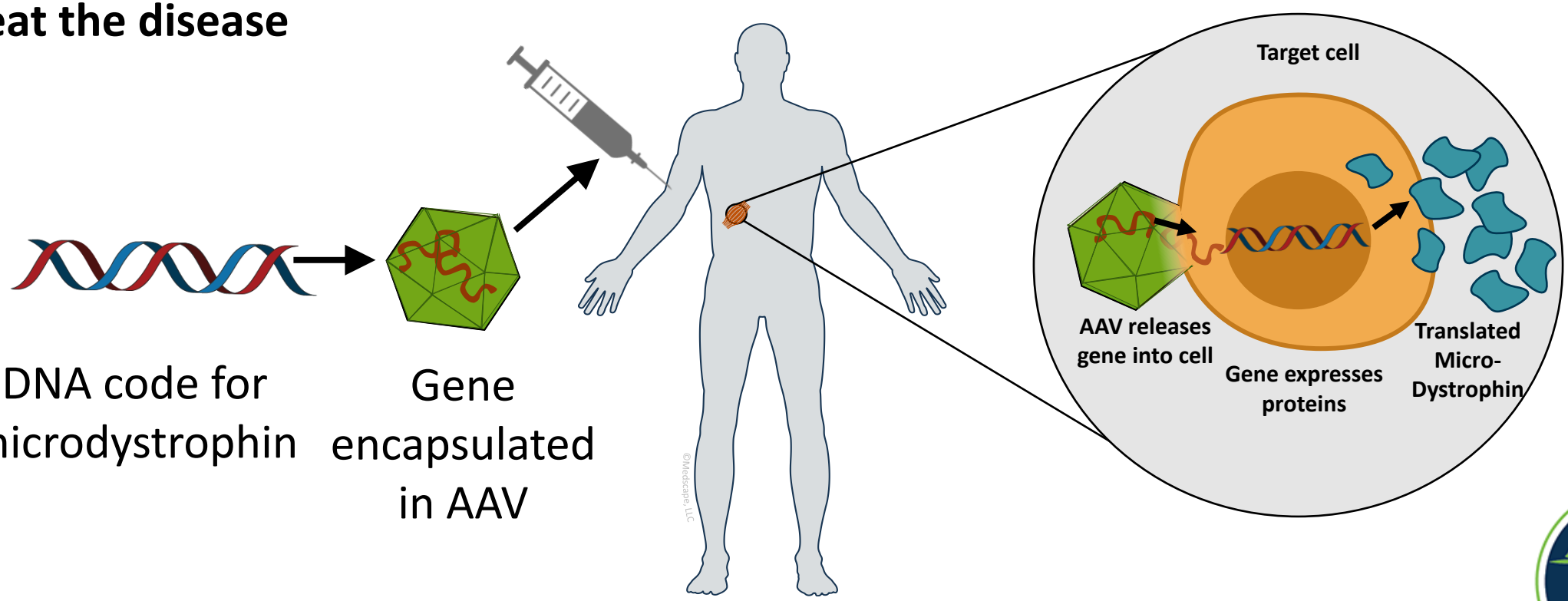
Phase	Motor	Respiratory	Cardiac
Ambulatory Phase (Early/Late)	Prevention of loss (or prolonged time before loss) of ambulation Maintenance of standing (weight bearing)	Avoidance of need (or prolonged time before need) for nocturnal NIV or assisted cough	Prevention of (or prolonged time before) reduction of cardiac function and cardiac fibrosis
Early Non-Ambulatory	Preservation of arm function (hands over head, hand to mouth)	Avoidance of need (or prolonged time before need) for nocturnal NIV or assisted cough	Prevention of (or prolonged time before) reduction of cardiac function and cardiac fibrosis
Late Non-Ambulatory	Preservation of hand function (propelling chair independently, utilizing computer/remote)	Avoidance of need (or prolonged time before need) for diurnal NIV or invasive ventilation	Maintenance of cardiac function, avoidance of progressive cardiac fibrosis

NIV, noninvasive ventilation

Schwartz CE, et al. *Orphanet J Rare Dis*. 2023;18(1):90; Birnkrant DJ, et al. *Lancet Neurol*. 2018;17(3):251-267.

Gene Transfer Therapy Mechanism of Action

The goal of gene therapy is to compensate for the dysfunctional gene with a microdystrophin transgene to treat the disease



Mendell JR, et al. *Mol Ther*. 2021;29(2):464-488.

Gene Therapies Under Investigation

Therapy	Status	Features	Key INCLUSION Criteria	Key EXCLUSION Criteria
GNT0004	Phase 1/2/3; EudraCT: 2020-002093-27	• Used AAV8 vector • Driven by a Spc5.11 promotor	• **Aged 6-10 years old** • **Ambulatory** • **Mutations in Exon 18+**	• **Cardiomyopathy** • **Requiring any respiratory assistance**
RGX-202	Phase 1/2; NCT05693142; AFFINITY DUCHENNE	• Uses a novel AAV8 vector • Includes an exon coding for β-spectrin	• **Aged 1-11 years old** • **Mutations in exon 18+** • **Ambulatory**	• **Received exon skipping within 6 months of study**
SGT-003	Phase 1/2; NCT06138639; INSPIRE DUCHENNE	• Uses a novel AAV vector • Includes a neuronal nitric oxide synthase binding domain	• **Aged 4- < 12 years old** • **Ambulatory**	• **Mutations in exons 1-11 or 42-45**
Delandistrogene moxeparvovec	FDA Approved	• MHCK7 promoter • rhAAV74 vector	• **Ages 4+ years old**	• **Mutations in Exons 8 and/or 9 of *DMD***

Patients with detectable AAV titers were excluded from these clinical trials

GNT0004 Phase 1/2/3 Data

Efficacy

- **CPK Reduction: 50%–87% decrease** (mean 74%) at 12 weeks, sustained up to 18 months
- **Motor Function: Stabilization or improvement observed 1–2 years post-treatment**; one patient reached the maximum score (34) at 12 and 18 months

Safety

- GNT0004 was **well tolerated** in all subjects receiving sirolimus and steroid prophylaxis*
- 5 AEs were reported, including an **event of immunological complications** and **4 mild events**

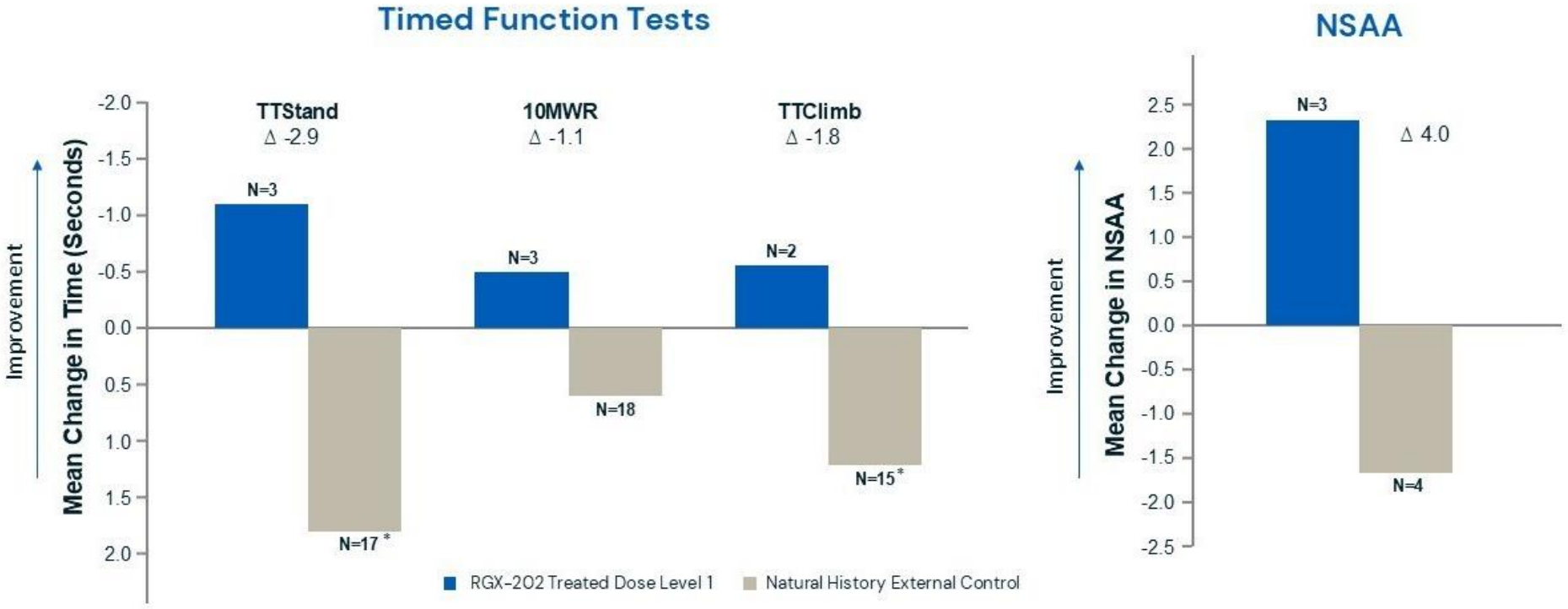
Overall, GNT0004 was well tolerated in 4 patients to date and longer follow-up data are being collected to assess long-term safety and clinical effectiveness

*Implemented after serious and unexpected suspected adverse reaction of immune-mediated myositis that occurred in 1st patient with dose 1

EU Clinical Trials Register. Accessed December 12, 2024. https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002093-27/FR; Laugel V, et al. *Neuromuscul Disord.* 2024;104441.281; https://www.neurologylive.com/view/gene-therapy-gnt0004-demonstrates-early-efficacy-safety-duchenne-muscular-dystrophy

RGX-202: AFFINITY DUCHENNE Data

Efficacy



Safety

As of November 1, 2024, RGX-202 was well tolerated with no serious adverse events; common AEs resolved as expected

EU Clinical Trials Register. Accessed December 12, 2024. https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002093-27/FR; https://www.prnewswire.com/news-releases/regenxbio-initiates-pivotal-phase-of-affinity-duchenne-trial-of-rgx-202-gene-therapy-and-reports-positive-functional-data-302307989.html

SGT-003: INSPIRE DUCHENNE Data

Efficacy

	Mean (N = 3)
Microdystrophin Expression % Normal (Western Blot)	110%
Microdystrophin Expression % Normal (Mass Spectrometry)	108%
% Dystrophin Positive Fibers (Immunofluorescence)	78%
Serum creatine kinase (CK) (IU/L)	-57%

Safety

- Adverse events (AEs) observed after SGT-003 treatment included nausea, vomiting, fever, and transient declines in platelets in some participants
- No serious adverse events or suspected unexpected serious adverse reactions were observed

EU Clinical Trials Register. Accessed December 12, 2024. https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002093-27/FR; https://www.sec.gov/Archives/edgar/data/1707502/000119312525028123/d913726d8k.htm

Delandistrogene Moxeparvovec Indications

2023: Ambulatory individuals 4 through 5 years of age with DMD with a confirmed mutation in the DMD gene

2024 Expansion: Ambulatory **and non-ambulatory** individuals **4 years of age and older** with DMD with a confirmed mutation in the DMD gene

Contraindications

Anti-AAVrh74 total binding antibody titers > 1:400

Active infections*

Mutations in Exons 8 and/or 9 of *DMD*

*Due to the increased risk of serious systemic immune response, gene therapy should be postponed in patients with infections until the infection has resolved

Mendell JR, et al. *Mol Ther*. 2021;29(2):464-488. ELEVIDYS (delandistrogene moxeparvovec) [Prescription insert]. Sarepta Pharmaceuticals. 2024.

Delandistrogene Moxeparvovec: EMBARK—Year 2 Data

EMBARK: Phase 3 Clinical Trial

Crossover-Treated Patients (n = 59) vs. EC

Functional Outcomes	LSM	P-Value
NSAA	**+2.34 points**	***P* < 0.0001**
TTR	-2.70 seconds (improvement)	*P* < 0.0001
10MWR	-1.07 seconds (improvement)	*P* = 0.0001

Part 1, Year 2 (n = 63) ELEVIDYS-Treated vs. EC

Functional Outcomes	LSM	P-Value
NSAA	**+2.88 points**	***P* = 0.0001**
TTR	-2.06 seconds (improvement)	*P* = 0.0033
10MWR	-1.36 seconds (improvement)	*P* = 0.0028

Safety data will be shared later in this presentation

EC = external control

Mendell JR, et al. *Nat Med*. Published online October 9, 2024; https://musculardystrophynews.com/news/motor-gains-elevidys-dmd-gene-therapy-evident-2nd-year/

Clinical Considerations for Selecting Gene Therapy

Are there biomarkers to predict which patients are going to respond to gene therapy?

Do you prescribe the approved gene therapy or enroll the patient in a clinical trial?

- Will redosing be possible?
- How long will it last?

Can you administer in patients who have received prior PMO therapy?

Can the patient tolerate pre- and post-infusion corticosteroid regimens?

Can the patient tolerate adverse events associated with the therapy?

Which product might be the best tolerated for a particular patient given its side effect profile?

Cope H, et al. *J Neuromuscul Dis*. 2024;11(5):1085-1093; Mendell JR, et al. *Pediatr Neurol*. 2024;153:11-18; Zaidman CM, et al. *J Neuromuscul Dis*. 2024;11(3):687-699.

Patient Case Review
Case 1

Patient Profiles: At-a-Glance

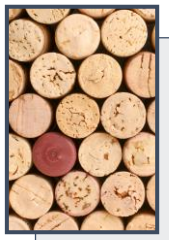
Patient Name	Age and Sex	Ambulatory (Y/N)	Genetic Diagnosis	Current/Previous Therapies	Labs
Ben	M, 16 years and 2 months	N	Deletion of exon 44	• Daily deflazacort • Exon 45 skipping treatment since age 9	• AAVRh74 antibodies = negative • CBC unremarkable • AST = 166 • ALT = 301 • GGT = 17 • CK = 7,895 • Troponin I = 0.03 (normal)
Jonathan	M, 5 years and 11 months	Y	Deletion of exon 52	• Daily deflazacort • Viltolarsen (previously eteplirsen)	• AAVRh74 antibodies = negative • AST = 875 • ALT = 953 • Bilirubin = normal • GGT = 13 • Troponin I = 0.30

AAVRh74 = adeno associated virus Rh74
ALT = alanine aminotransferase
AST = aspartate aminotransferase
CBC = complete blood count
CK = creatine kinase
GGT = gamma-glutyl transferase

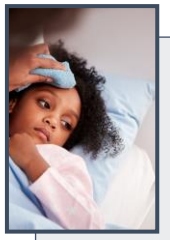
Patient and Caregiver Considerations for Selecting Gene Transfer Therapy

Access/financial

Unknown long-term effects

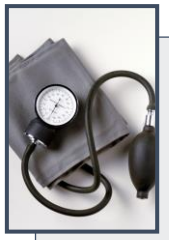


Variability in response



Adverse events

Psychosocial impact



Need for continuous monitoring

Need for additional therapy

National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Sciences Policy; Forum on Regenerative Medicine; Beachy SH, Alper J, Hackmann M, et al., editors. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559964/

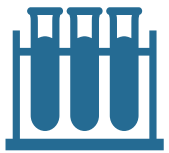
Patient Profile #1: “Ben”

- Ben is a 16-year-old male with a deletion in exon 44
- Diagnosed at age 6 when presenting with challenges ascending stairs and differences in his running compared to peers
- Started on deflazacort daily dosing at diagnosis
- Participated in clinical trial for and then continued commercial dosing of exon 45 skipping therapy
- Non-ambulatory at age 14
- Hopes gene transfer therapy will optimize arm/hand/torso strength and preserve lung function and cardiac function

Consensus Considerations for Assessing Patient Candidacy

Timing of the physical exam to determine candidacy

- A physical exam should be conducted one month prior to and again within 48 hours of the infusion



Timing of baseline lab collection

- Baseline labs should be collected twice prior to gene therapy infusion: at the evaluation appointment (~1 month prior) and again within one to three days of the procedure

Communication strategies

- Communication depends on the physician and institution, but patients/caregivers should be provided with contact options in case of questions or side effects

Zaidman CM, et al. *J Neuromuscul Dis*. 2024;11(3):687-699.

Pre-Infusion Considerations for Ben

Corticosteroids

- Discussed starting **additional prednisone a day before** infusion and continuing for **at least 60 days** and the need to **adjust dosing** if adverse effects occur
- Explored plans for continuing **corticosteroids after treatment**

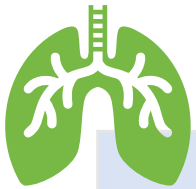
Strength/Mobility

- **PUL = 25**
- Discussed potential **impacts to strength** following gene transfer therapy
- Goal of **stability of strength** or **slowing decline**
- Reviewed that each person with DMD is an individual, and **results will be individual to that person**

Cardiology

- **EKG:** Normal sinus rhythm
- **Echo:** Ejection fraction 62%
- **Cardiac MRI:** Subtle small area of LGE, normal function
- **Medications:** Eplerenone and Enalapril
- Discussed potential **cardiac risks** associated with gene transfer therapy
- Reviewed safety data showing **no increased risk** with delandistrogene moxeparvovec
- Reviewed required post-infusion monitoring
- Emphasized starting at an appropriate cardiac baseline to **optimize tolerability** of systemic stressors

Pre-Infusion Considerations for Ben

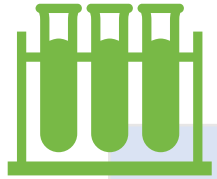


Pulmonary Status

- *FVC 98%; FEV1 100%*
- Discussed **considerations for airway protection** in the context of nausea/vomiting
- Discussed the potential for treatment to **maintain neuromuscular lung mechanics**

GI/Nutrition

- History of intermittent reflux: **Weight 42.5 kg**
- Discussed **considerations for nausea/vomiting** after delandistrogene moxeparvovec
  - Most common adverse effect
- Discussed consideration for some individuals to **add famotidine routinely** versus as needed in the context of increased corticosteroid dosing



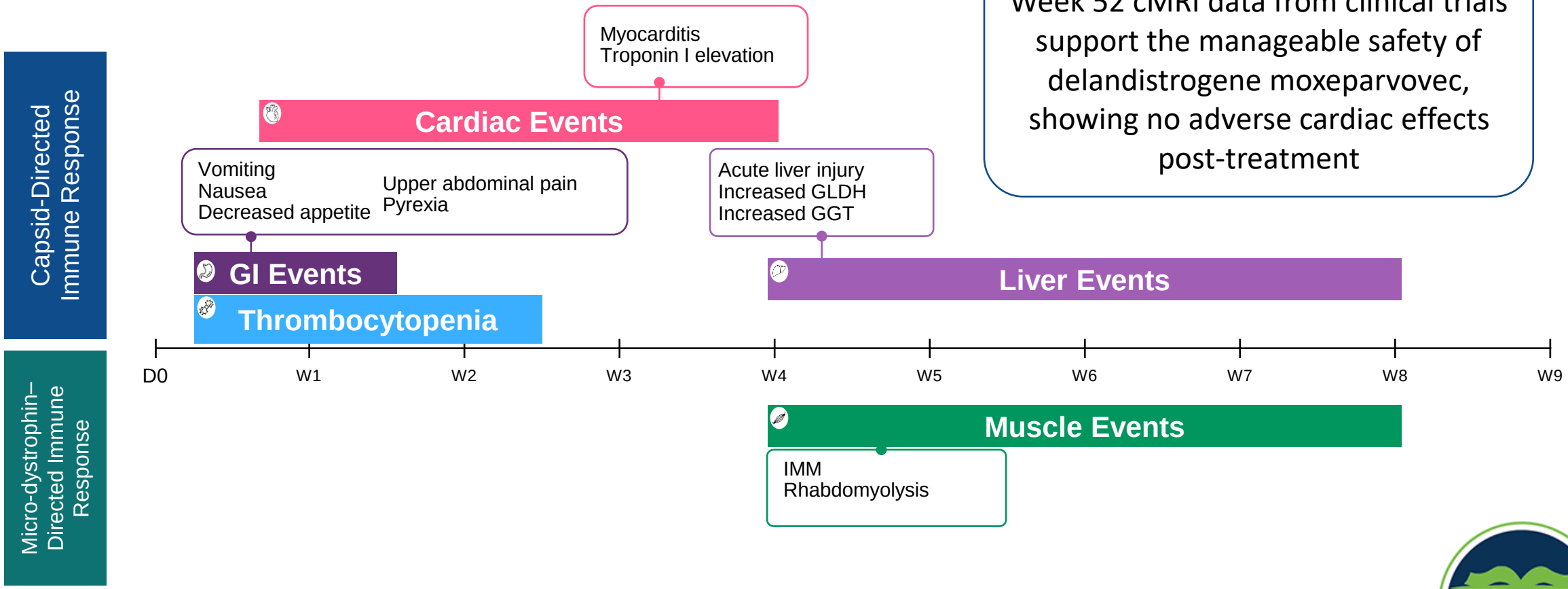
Baseline Labs

- AAV Rh74 antibodies = negative
- CBC unremarkable
- AST = 166
- ALT = 301
- GGT = 17
- CK = 7,895
- Troponin I = 0.03 (normal)

Would you infuse Ben with gene therapy? **Yes!**

Experience With Timing of Adverse Events in Clinical Trials

Week 52 cMRI data from clinical trials support the manageable safety of delandistrogene moxeparvovec, showing no adverse cardiac effects post-treatment



cMRI = cardiac magnetic resonance imaging

Crystal Proud, MD, et al. Presented at the 29th Annual Congress of the World Muscle Society; October 8-12, 2024; Prague, Czechia and virtual; Walter G, et al. *Neuromuscul Disord*. 2024;43:104441.299.

Ben Experienced an Infusion Reaction

- 8 minutes into infusion, patient experienced:
  - Flushing of the cheeks
  - Rash over chest, abdomen, some itching
  - Cough/wheeze
- Administered:
  - Diphenhydramine 50 mg IV x 1
  - Albuterol 5 mg inhaled
  - Famotidine 10 mg PO x 1
- Symptoms resolved shortly thereafter
- Infusion restarted at ¼ rate x 1 syringe, ½ rate x 1 syringe, ¾ rate x 1 syringe, and then returned to baseline infusion rate

Follow-Up and Long-Term Considerations for Ben

Labs remained reassuring during 12 weeks of lab monitoring

Steroids tapered per protocol

Some nausea/vomiting prompting initiation of ondansetron daily for 1 week (worse in the morning)

Some behavioral changes noted with additional prednisone, resolved with discontinuation

Corticosteroid considerations:

- Continue deflazacort
- Transition to a high dose weekend regimen
- Transition to vamorolone

Additional therapies:

- Return to exon skipping treatment versus discontinue
- Add givinostat
- Consider additional clinical trial opportunities

Patient Case Review
Case 2

Patient Profile #2: "Jonathan”

- Jonathan is a 5-year-old male with a deletion in exon 52
- Diagnosed with DMD via exome sequencing during infancy failure-to-thrive workup
  - Older brother later confirmed with DMD
- Currently taking deflazacort daily and viltolarsen
  - Previously treated with eteplirsen
- Ambulatory
- Behavioral concerns, possible autism but not formally diagnosed
- Mild hepatomegaly in infancy
- Hopes that this new medicine will help him keep up with his peers at recess and play on a soccer team

Pre-Infusion Considerations for Jonathan

Corticosteroids

- Discussed with parents **initiating prednisone 1 day prior to infusion and continuing up to 60 days after infusion**
- Explored plans for continuing **corticosteroids after treatment**

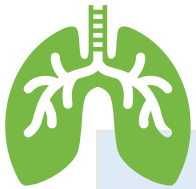
Strength/Mobility

- **NSAA = 20**
- Discussed with parents the potential **impacts to strength**
- Goal of maintaining ambulation and strength

Cardiology

- **Echo:** Normal
- **Medications:** None
- Discussed potential **cardiac risks** associated with gene transfer therapy
- Reviewed required post-infusion monitoring

Pre-Infusion Considerations for Jonathan

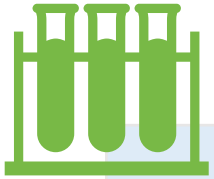


Pulmonary Status

- Discussed the potential for treatment to possibly **maintain neuromuscular lung mechanics**

GI/Nutrition

- Discussed **considerations for nausea/vomiting** after delandistrogene moxeparvovec
  - Most common adverse effect

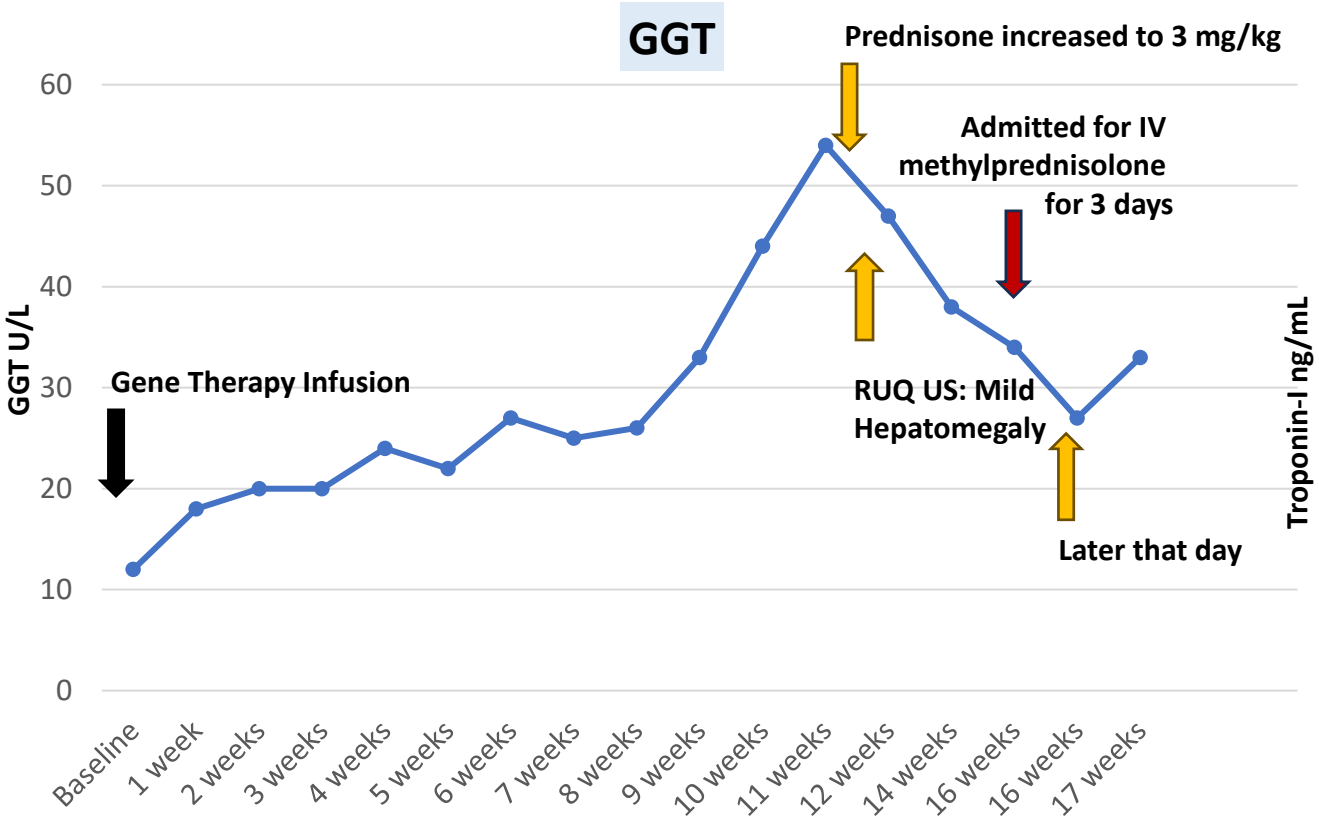


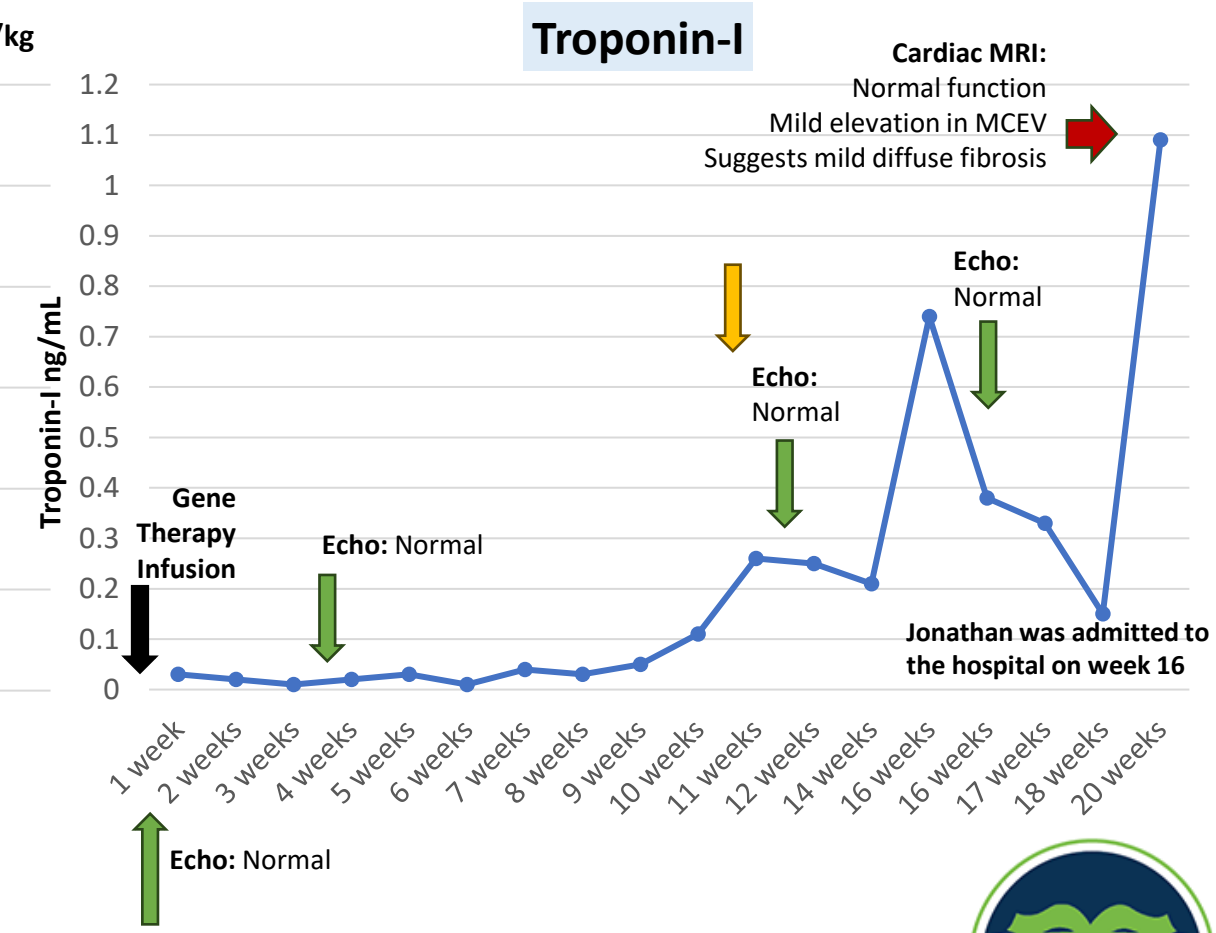
Baseline Labs

- AAVRh74 antibodies = negative
- CBC unremarkable
- AST = 876
- ALT = 953
- GGT = 13
- Troponin I = 0.03

Would you infuse Jonathan with gene therapy? **Yes!**

Jonathan Experienced an Increase in GGT and Troponin-I





Select Consensus Considerations for Managing Adverse Events

	Acute Liver Injury	Myocarditis	Immune-Mediated Myositis
Patient Presentation	• Acute liver injury is diagnosed/confirmed	• Suspected or confirmed myocarditis	• Physical signs of IMM (weakness, muscle pain/tenderness, and difficulty swallowing) that are progressive over days
Patient Monitoring	• Patient should be seen in person; assess need for hospitalization, based on laboratory and exam findings	• Patient should be seen for a physical exam; assess need for hospitalization based on laboratory and exam findings	• Patient should be seen urgently by the prescribing physician for physical assessment (including neuromuscular strength assessment) • Likely will require admission to the hospital for ongoing close observation
Laboratory Studies	• If not hospitalized, monitor closely, and repeat laboratory studies sooner than 1 week	• Monitor closely and repeat laboratory studies sooner than 1 week	• Monitor closely and repeat baseline laboratory studies sooner than 1 week
Additional Diagnostic and Laboratory Studies	• GGT, PT/INR	• Complement C3, complement C4, complement total CH50, CK-MB, CK, urinalysis, cystatin C, and CRP • Perform an echocardiogram and ECG; consider cardiac MRI	• ANA, CK, CRP, aldolase, ESR, myoglobin, cystatin C, urinalysis, and urine output • Echocardiogram, ECG, and swallow study may be performed
Medication and Treatment	• Increase oral corticosteroid dose to 2 mg/kg/day (max 120 mg/day)	• Increase corticosteroid to 2 mg/kg/day (max 120 mg/day) • Consider short-term pulse of IV methylprednisolone; also consider adding IVIg	• Increase steroid therapy to either 2 mg/kg/day (max 120 mg/day) or 3-day course of high-dose IV methylprednisolone
Consultation	• Consult with hepatologist as needed	• Consult with cardiologist	• Consult with appropriate specialists (consider rheumatology, immunology, and cardiology)

ANA, antinuclear antibodies; creatine kinase; CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; IVIg, intravenous immunoglobulin; MRI, magnetic resonance imaging; PT/INR, prothrombin time and international normalized ratio

Zaidman CM, et al. *J Neuromuscul Dis*. 2024;11(3):687-699.

Managing and Monitoring for Jonathan

Inpatient Course (8/7–8/10/24):

- **Treatment:** IV methylprednisolone for 3 days
- **Consultations:** Gene team, heart failure, and hepatology specialists consulted
- **Testing Results:**
  - Troponin levels decreased; echocardiogram was normal
  - Labs:
    - Hepatitis studies: Normal
    - Soluble IL-2 receptor (sIL-2r): Normal
    - Cytokine panel: IL-8 slightly elevated (likely due to processing)
    - Perforin/granzyme: Normal
    - Ceruloplasmin: 15 (reference range 18–37, not followed up)

- **Discharge Plan:**
  - Cardiac MRI to be performed
  - Steroids to be tapered if follow-up findings are reassuring

Long-Term Outcomes and Considerations for Jonathan

Motor Assessments:

NSAA Scores:

- 2/14/24: 20
- 6/12/24: 27
- 7/10/24: 27

Plan:

- **Steroid Tapering:**
- Prednisolone to be decreased by 2 mL weekly until reaching 5 mL daily (maximum dose: 45 mg = 15 mL = 3 mg/kg)

Cardiac Medication: Likely initiation for both the patient and their sibling

Additional Testing:

- Urine copper levels
- Ophthalmology evaluation (for Wilson's disease)

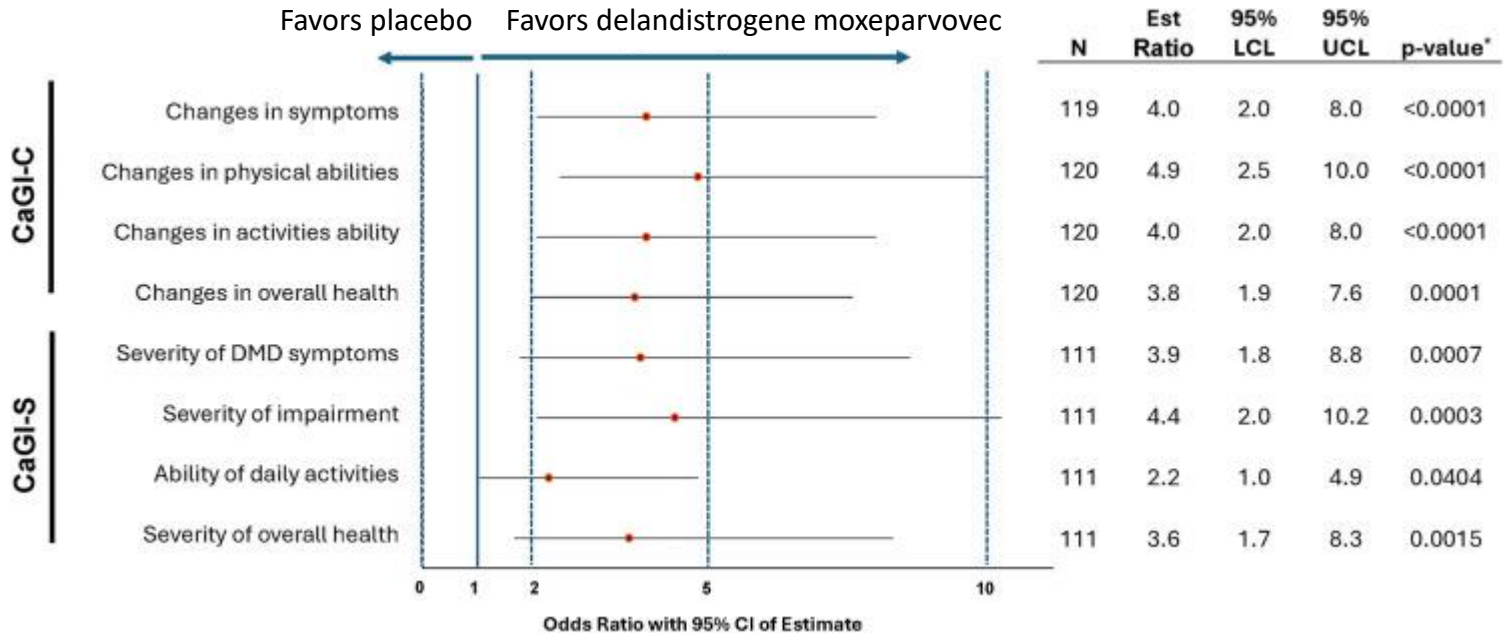
Genetic Re-Evaluation: Re-analysis of exome sequencing in progress

Therapeutic Considerations: Assess continuation of exon-skipping therapy

Comparing and Contrasting Patient Cases

Considerations for Caregivers: Results of a Caregiver Global Impression Study

- Caregivers of patients who received delandistrogene moxeparvovec were asked to rate the change from baseline to week 52 in:
  - DMD Symptoms
  - Physical ability
  - Ability to perform daily tasks
  - Overall health



	N	Est Ratio	95% LCL	95% UCL	p-value*
Changes in symptoms	119	4.0	2.0	8.0	<0.0001
Changes in physical abilities	120	4.9	2.5	10.0	<0.0001
Changes in activities ability	120	4.0	2.0	8.0	<0.0001
Changes in overall health	120	3.8	1.9	7.6	0.0001
Severity of DMD symptoms	111	3.9	1.8	8.8	0.0007
Severity of impairment	111	4.4	2.0	10.2	0.0003
Ability of daily activities	111	2.2	1.0	4.9	0.0404
Severity of overall health	111	3.6	1.7	8.3	0.0015

Caregiver-reported outcomes contribute to the overall evidence supporting the clinical benefits of delandistrogene moxeparvovec for patients with DMD

CaGI-C = caregiver global impression change; CaGI-S = caregiver global impression severity; LCL = lower control limit; UCL = upper control limit

McDonald CM, et al. *Neurol Ther*. 2025 Feb;14(1):211-225. doi: 10.1007/s40120-024-00685-8.

Key Takeaways

- Gene transfer therapy offers a promising treatment for DMD but requires a thorough evaluation of multiple organ systems before and after treatment
- Researchers are working on identifying the best practices for monitoring and managing patients with risk factors for complications
- Health care providers must establish a reliable system to monitor lab results and manage potential adverse events