Newborn Screening for Duchenne Muscular Dystrophy: Phase 3 Update

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Duchenne Muscular Dystrophy (DMD)

- Severe and progressive neuromuscular disorder
- Belongs to a group of inherited conditions characterized by progressive muscle weakening
- Can impact other systems (e.g., intellectual disability)
- X-linked condition
  - Some female carriers are symptomatic
- Incidence:
  - ~ 17-30 per 100,000 liveborn male births
  - < 1 per million liveborn female births

Becker Muscular Dystrophy (BMD)

- Also caused by mutations in the gene for dystrophin
- Unlike DMD, which has absence or near absence of functioning dystrophin, BMD has reduction of functioning dystrophin, leading to later onset and less severe involvement
- Incidence: <8 per 100,000 liveborn male births

Clinical Course: DMD

Signs and Symptoms	Age	Summary
Delayed walking, falling, difficulty running and climbing stairs. Muscles, especially calf, pelvis, thigh appear bulkier than normal	~1-3 years	---
DMD Diagnosis	~5 years	---
Continued muscle weakening, Loss of ambulation (LOA), wheelchair bound	~9-14 years	Up to 30% patients - LOA by age 10 years Up to 90% patients – LOA by age 15 years
Comorbidities with LOA Scoliosis (spinal curvature) Orthopedic problems (uneven shoulders, hips)	Teens, after LOA	Mean age at scoliosis onset was approximately 14 years.
Respiratory/breathing problems, increase in severity, life threatening	Late teens – 20s	Ventilatory support began from 15 to 18 years, Up to 50% of patients required ventilation by 20 years of age.
Cardiomyopathy symptoms and signs (enlarged heart chambers, thinning heart walls, increased heart and muscle damage)	Late teens – 20s	70% had evidence of cardiomyopathy by 15 years Almost 100% had cardiomyopathy by 20 years of age.
Death	20s – 30s	Up to 16% died by age 20 years; Among those surviving to adulthood, up to 60% died by age 30 years.

Szabo, S.M., Salhany, R.M., Deighton, A. *et al.* The clinical course of Duchenne muscular dystrophy in the corticosteroid treatment era: a systematic literature review. *Orphanet J Rare Dis* 16, 237 (2021).

Update on Activities

Activities

- TEP Call 1: October 27, 2023
- TEP Call 2: March 28, 2024
- Additional key informant interviews
  - Institute for Clinical and Economic Review regarding a 2019 report on the effectiveness and value of deflazacort, eteplirsen, and golodirsen
  - Kevin Flanigan, MD, Nationwide Children's Hospital, an expert in DMD, focusing on genotype-phenotype prediction
  - Catharine Riley, PhD, and Natalie Street, MS, Centers for Disease Control and Prevention, regarding MD STARnet
  - Hadley Smith, PhD, and Kurt Christensen, PhD, Harvard Medical School, about a model for assessing the potential impact of DMD newborn screening
- Literature Review - ongoing

Activities

- Public Health System Impact Assessment
  - Webinar held on January 17, 2024
  - Factsheet and survey sent to 53 public health programs afterwards
  - By March 22, 2024, 39 of 53 (74%) programs responded
  - Quantitative survey results focus on the 36 with no DMD screening activity
  - Interviews with two planning to implement screening (MN, NY)
- Decision-Analytic Modeling
  - Forthcoming

Update on DMD Screening Activity

Screening Update

- States planning to begin DMD newborn screening in 2024
  - Ohio, to begin April 22, 2024
  - Minnesota
  - New York
- In addition, legislation introduced in Arizona and Illinois for DMD newborn screening

Screening Implementation

- Ohio
  - First-tier: CK-MM testing, with subsequent testing by primary care clinicians
- New York plans….
  - First-tier: CK-MM, interpretation will adjust for age at collection and incorporate a CLIR tool
  - Second-tier: Repeat CK-MM unless above a high cutoff value
  - Referral to a specialist for diagnostic evaluation, including genetic testing
- Minnesota plans…
  - First-tier: CK-MM testing
  - Second-tier: Genetic testing, contracted to an outside laboratory

Survey Results

- Top challenges to implementing DMD screening
  - Availability of staff to report and track infants
  - Increasing the NBS fee
  - Molecular testing

Readiness

- Nearly half reported that it would take 2 to 3 years to implement DMD newborn screening after they have the authority to screen
- Many programs would need to purchase additional instrumentation

Framework: Potential Outcomes of Diagnosis through Newborn Screening Compared With Usual Case Detection

Framework: Benefits to the Affected Child Explored

- Direct health benefits
  - Improved quality of life
  - Longer length of life
- Functional improvements leading to benefit
  - Motor status and ability to ambulate
  - Cardiac status
  - Pulmonary status
  - Neurodevelopment

Framework: Benefits to the Family Explored

- Avoiding the diagnostic odyssey
- Avoiding ineffective therapy
- Earlier options for potentially effective pharmacologic and non-pharmacologic treatment
- Ability to prepare for the future
- Diagnosing other family members
- Reproductive decision making

Additional Benefits Explored

- Improved health status before eligibility for gene therapy or other novel therapies
- Earlier access to treatment trials
- Health equity

Framework: Harms Explored

- Prognostic odyssey
- Patients in waiting
- Limited information to inform decision making related to treatment options
- System barriers, including poor access to care
- Adverse effects of earlier treatment
- Treatment with AAV gene therapy might lead to ineligibility for future gene therapies
- Exposure to ineffective therapy

Industry Guidance from the FDA for DMD Drug Treatment

- In 2018, the FDA released ”Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment, Guidance for Industry” (https://www.fda.gov/media/92233/download)
  - Partnership between FDA, industry, and the DMD community
  - “Patients most severely affected by the disease, along with their caregivers, can provide insight into the outcomes that are most appropriate to designate as primary endpoints, how these outcomes might be assessed, and the meaningfulness of treatment effects when considered in the context of the overall disease.”
- Updated draft guidance published in 2024 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10977441/pdf/jnd-11-jnd230219.pdf)

Brief Overview of Pharmacologic Treatments

General Overview of Pharmacologic Treatment

- No curative treatments
- Corticosteroids
  - Standard of care treatment
  - Reduces muscle inflammation to slow damage, but does not reverse damage

Antisense oligonucleotides – exon-skipping therapies

  - Genotype specific exon-skipping therapies
  - Goal to increase dystrophin expression similar, making DMD more like BMD

- Gene therapy
  - Microdystrophin expression

Drug	FDA approval	Indication	Dosing
Corticosteroids			
Prednisone	n/a	No clear consensus on age of initiation	Variable
Deflazacort	2017	≥ 2 years old	Daily oral
Vamorolone	2023	≥ 2 years old	Daily oral
Exon-skipping antisense oligonucleotides			
Eteplirsen	2016*	Amenable to skipping exon 51, age not specified	Weekly IV
Golodirsen	2019*	Amenable to skipping exon 53, age not specified	Weekly IV
Vitolarsen	2020*	Amenable to skipping exon 53, age not specified	Weekly IV
Casimersen	2021*	Amenable to skipping exon 45, age not specified	Weekly IV
Adeno-associated viral vector Gene replacement			
Delandistrogene moxeparovec	2023*	4- to 5-year-old ambulatory patients	Single IV

*Accelerated approval based on surrogate endpoints

Key Studies of Potential Outcomes from DMD Newborn Screening

Sibling Reports

Sibling Reports

- Can provide insight into the benefit of presymptomatic treatment
  - Siblings typically have similar biology and environment
  - Can fill gaps when cases are often not picked up by screening and when there are insufficient treatment trials
- To provide evidence about impact of earlier detection compared with usual case detection, reports should include
  - Diagnosis or phenotype of each sibling
  - Description of therapeutic interventions
  - Standardized outcome measures when the siblings are the same chronologic ages
  - Information to support generalizability of the findings

Sibling Reports

- No peer-reviewed publications, only meeting abstracts
- None presented standardized outcome measures at similar chronologic ages, so unable to interpret the impact of earlier treatment based on these meeting abstracts

Sibling Reports

- Three brothers with deletion of exons 45-50 treated with eteplirsen at 108 months, 79 months, and 24 months of age
- Lacks clear information on outcomes at the same chronologic ages, so unable to interpret the impact of earlier treatment

Ramos-Platt L and Darazi M. Clinical outcomes: a case series study of 3 brothers with deletion of exons 45-50. 2020 SEHA International Conference.

Sibling Reports

- Two sets of siblings with information submitted by certified Duchenne Care Centers from a total of 6 sibling sets, non-standardized outcome assessment
  - Sets excluded because they represented an error (no siblings) or not helpful in understanding early treatment
- First Set:
  - Diagnosed at 7 years, corticosteroids started at 8 years, loss of ambulation at age 14 years
  - Diagnosed at 5 months, corticosteroids started at 5 years, at 7 years runs with rest, inability to jump, does not use motility aids
- Second Set:
  - Diagnosed at 3 years, eteplirsen started at 3 years, corticosteroids started at 4 years, vitolarsen started at 6 years, at 6 years has age-appropriate gait
  - Diagnosed at 4 months, eteplirsen started at 10 months, corticosteroids at 4 years, vitolarsen started at 4 years, at 4 years has age-appropriate gait but does have cognitive deficits
- Lacks clear information on outcomes at the same chronologic ages, so unable to interpret the impact of earlier treatment

Armstrong N, Nagaraj CB, Paterno A, Brandsema JF. Sibling case reports in DMD: Benefits of early diagnosis and treatment. 2024 MDA Clinical & Scientific Conference.

Sibling Reports

- 17 sibling pairs from 24 potential sibling pairs
- Younger siblings diagnosed on average 2.7 years earlier and started corticosteroids 0.8 years earlier
- “Visual inspection of the [North Star Ambulatory Assessment] score shows that after 8 years old, the younger siblings consistently scored higher values.”
- No data on the scores or on outcomes at the same chronologic ages, so unable to interpret the impact of earlier treatment

Rye C, Main M, Muntoni F. Comparison of functional abilities in siblings with Duchenne muscular dystrophy. 2020 GOSH Conference.

Early Corticosteroid Treatment

Twice-Weekly Corticosteroids in Young Children

- Prospective study of twice-weekly corticosteroids compared with an untreated natural history comparison group followed for 1 year
- Primary Outcome: Bayley-III gross motor scaled score
  - sitting, standing, locomotion, and balance
  - Higher scores better, mean = 10, standard deviation 3

Connolly AM, Zaidman CM, Golumbek PT, et al. Twice-weekly glucocorticosteroids in infants and young boys with Duchenne muscular dystrophy. *Muscle Nerve*. 2019;59:650-657.

Twice-Weekly Corticosteroids in Young Children

- Baseline Characteristics
  - Prospective Cohort (n=23)
    - Age: 1.5 ± 0.7 years
    - Bayley III Gross Motor Scale Score: 4.2 ± 2.5
  - Natural History Comparison Group (n=12)
    - Age: 1.5 ±0.8 years
    - Bayley III Gross Motor Scale Score: 6.6 ± 1.6

Connolly AM, Zaidman CM, Golumbek PT, et al. Twice-weekly glucocorticosteroids in infants and young boys with Duchenne muscular dystrophy. *Muscle Nerve*. 2019;59:650-657.

Twice-Weekly Corticosteroids in Young Children

- Bayley III Gross Motor Outcomes after 12 months of treatment
  - No statistically significant improvement from baseline in the treated group (4.2 to 4.8; p=0.28)
  - The natural history comparison group declined by 1.3 points 12 months after baseline (p-value not reported).
  - The difference after 12 months between the treated group and the natural history comparison group was statistically significantly different (p=0.03), driven by those in the treatment group who had a low motor score (≤3; 8 of the 23 subjects) at baseline.
  - No effect of age at baseline on treatment outcomes; disease progression appears to be a more important predictor of benefit

Connolly AM, Zaidman CM, Golumbek PT, et al. Twice-weekly glucocorticosteroids in infants and young boys with Duchenne muscular dystrophy. *Muscle Nerve*. 2019;59:650-657.

Earlier Diagnosis and Corticosteroid Initiation

- Meeting abstract
- Males with DMD from The Duchenne Registry born in 2000 or later
- Outcome: Subset of Pediatric Outcomes Data Collection Instrument (PODCI)
  - Caregiver or participant report
  - Cumulative score for 8 items related to lower limb functioning
  - Range of score from 8-32, with lower scores better
- Outcome: age at full-time wheelchair use for subjects ≥ 14 years (n=188)
- Comparisons
  - Early diagnosis: (< 1 year (n=77)) to average age of diagnosis (4-5 years (n=393))
  - Early corticosteroid treatment: (2-3 years (n=142)) to average corticosteroid treatment (5-7 years (n=593))

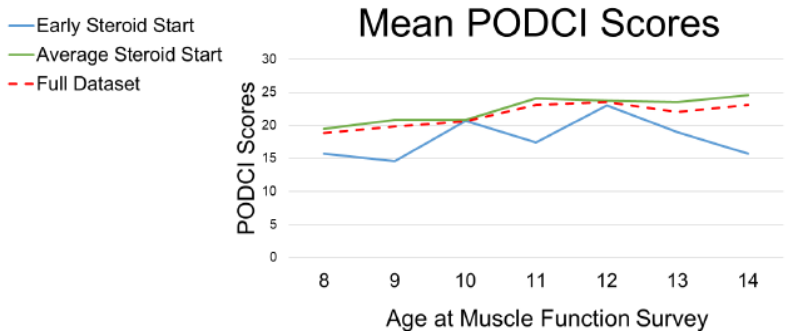
Armstrong N, Martin A, Dasgupta S. Early diagnosis and early corticosteroid initiation: potential benefits in Duchenne muscular dystrophy. 2023 Annual Congress of the World Muscle Society.

Earlier Diagnosis and Corticosteroid Initiation

- Age at steroid initiation
  - Early diagnosis (<1 year): 4.2 years
  - Typical diagnosis (4-5 years): 5.2 years
- Average age of wheelchair use (no statistical analysis)
  - Early treatment (2-3 years): 12.9 years
  - Typical treatment (5-7 years): 12.0 years
- No statistical testing related to these findings
- Variability between early diagnosis and early treatment not explored in the abstract

Armstrong N, Martin A, Dasgupta S. Early diagnosis and early corticosteroid initiation: potential benefits in Duchenne muscular dystrophy. 2023 Annual Congress of the World Muscle Society.

Earlier Diagnosis and Corticosteroid Initiation



- Scores at 9 and 11 years were lower (P<0.05) for early treatment, with mean scores ”consistently lower at all ages” (no P-value provided).
- Limitations
  - Some, but not all, contributed multiple PODCI scores. The number at each age is not provided and repeated individual measures not considered in the analysis. Assessment is not necessarily longitudinal.
  - No sample size provided at each age. Fewer than 5 PODCI scores for subjects ≥ 12 years
  - Not stratified based on what led to diagnosis
  - Not stratified by baseline disease involvement
  - Dosing regimen, adherence, drug adverse effects, or withdrawal of treatment not considered
  - No assessment of other therapies

Armstrong N, Martin A, Dasgupta S. Early diagnosis and early corticosteroid initiation: potential benefits in Duchenne muscular dystrophy. 2023 Annual Congress of the World Muscle Society.

Earlier Exon-Skipping Treatment

Earlier Exon-Skipping Therapy

- Subjects from the manufacturer's patient support program (n=579)
  - Dates of eteplirsen initiation and discontinuation
  - Date of death or last date known to be alive
  - Related clinical trials participation
- Compared to natural history studies, digitizing survival curves (5 studies, n=1,321)

Iff J, Done N, Tuttle E, et al. Survival among patients receiving eteplirsen for up to 8 years for the treatment of Duchenne muscular dystrophy and contextualization with natural history controls. *Muscle Nerv*. 2024; Online ahead of print.

Earlier Exon-Skipping Therapy

- Eteplirsen-treated subjects
  - Average age of eteplirsen initiation: 11.9 years (range: 1-35 years)
    - Information about age not further stratified
  - Average duration of eteplirsen exposure: 3.7 years (± 1.9 years)
  - Median survival: 32.8 years (5% risk of death during follow-up), compared with median survival in the natural history group of 27.4 years (range: 23.7-34.5 years)
  - Compared with natural history controls, lower hazard of death (0.34 (95% CI: 0.23-0.50))

Iff J, Done N, Tuttle E, et al. Survival among patients receiving eteplirsen for up to 8 years for the treatment of Duchenne muscular dystrophy and contextualization with natural history controls. *Muscle Nerv*. 2024; Online ahead of print.

Earlier Exon-Skipping Therapy

- Effectiveness in improving survival was reported to be better with earlier age at initiation
- Potential threats to validity are not addressed in the analysis
  - No stratification by earlier age of initiation vs. later age of initiation
  - Other potential confounders, such as what led to diagnosis, and other therapies, and health status at diagnosis and over time is not included in the analysis

Iff J, Done N, Tuttle E, et al. Survival among patients receiving eteplirsen for up to 8 years for the treatment of Duchenne muscular dystrophy and contextualization with natural history controls. *Muscle Nerv*. 2024; Online ahead of print.

Earlier Exon-Skipping Therapy

- Meeting abstract
- Subjects reported by clinicians who began an exon-skipping therapy before 3 years of age, treated for at least 1 year, and had an outcome measure
- Five subjects:

1. Diagnosed at 4 months, began exon-skipping therapy at 10 months, corticosteroids at 3 years
2. Diagnosed prenatally, began exon-skipping therapy at 14 months
3. Diagnosed at 2 months, began exon-skipping therapy at 7 months
4. Diagnosed at 34 months, began exon-skipping therapy at 35 months, corticosteroids at 59 months
5. Diagnosed at 5 months, began exon-skipping therapy at 10 months, corticosteroids at 4 years

- Standardized outcomes not reported, but the abstract notes that “Gross motor delays were common, with only Patients 3 and 5…meeting typical milestones including walking at 15 months…”
- Unable to determine the impact of early diagnosis

Armstrong N, Hamid OA, Lakhotia A. Exon skipping therapies in Duchenne muscular dystrophy: a case series of children who initiated before 3 years of age. 2024 MDA Conference.

Gene Therapy

Gene Therapy

- FDA approved for 4- and 5-year-old children
- Early detection could facilitate timely access
- No studies about the degree to which early detection led to improved access or better outcomes for gene therapy.

Parent Perspectives

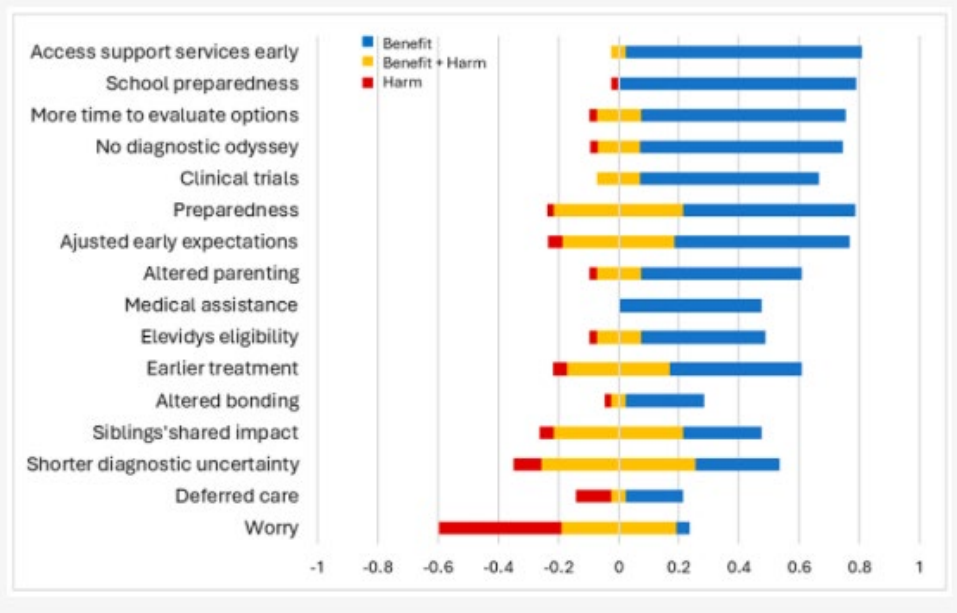
Parent Perspectives

- Subjects
  - Parents or guardians of at least two living children with DMD in the United States identified in The Duchenne Registry (n=45) completed a web-based survey conducted in partnership with Parent Project Muscular Dystrophy
- Survey
  - Lived experience about early diagnosis as “Benefits”, “Harms”, ”Neither a benefit nor a harm”, “Both a benefit and a harm”, or “Did not experience.”
  - Scores standardized from benefits (+1) to harm (-1), with 0 implying both
- Sibling characteristics
  - Average age of diagnosis of the older sibling was 4.3 years and 2.6 years for the younger sibling
  - At the time of the survey, mean age of the older sibling was 13.6 years and the younger sibling was 10.8 years
  - By age 10 years, 62.9% of the older and 38.7% had loss of ambulation

Bhattacharyya O, Campoamor NB, Armstrong N, et al. Assessing the benefits and harms associated with early diagnosis from the perspective of parents with multiple children diagnosed with Duchenne muscular dystrophy. *Int J Neonatal Screen.* 2024; 10:32.

Parent Perspectives

- Perceived benefits and harms



- Overall mean: 0.39
- No statistically significant trend in positive experiences based on the age of diagnosis of the younger sibling.

Bhattacharyya O, Campoamor NB, Armstrong N, et al. Assessing the benefits and harms associated with early diagnosis from the perspective of parents with multiple children diagnosed with Duchenne muscular dystrophy. *Int J Neonatal Screen.* 2024; 10:32.

Parent Perspectives

- Limitations
  - Overall participation rate not provided
  - No formal qualitative analysis of open-ended questions
  - No formal mixed-methods assessment, linking diagnosis, treatment, and patient/family level outcomes

Bhattacharyya O, Campoamor NB, Armstrong N, et al. Assessing the benefits and harms associated with early diagnosis from the perspective of parents with multiple children diagnosed with Duchenne muscular dystrophy. *Int J Neonatal Screen.* 2024; 10:32.

Summary

Status of DMD Newborn Screening Evidence Review

- Newborn screening for elevated CK-MM can identify infants with DMD
  - Can also identify other dystrophinopathies, including Becker muscular dystrophy
  - Molecular analysis can help predict phenotype
  - States that are implementing DMD newborn screening can help fill in evidence gaps
- Important evidence gaps around the benefits and harms of identification through newborn screening compared with usual case identification
  - Limited information from sibling studies, none of which have appeared in the peer-reviewed literature

Next Steps

- Completing
  - systematic evidence review, including peer-reviewed reports and grey literature that meets our inclusion criteria
    - Unlikely to find additional evidence related to benefits of identification from newborn screening compared with usual case identification
  - The decision-analytic model, reflecting the data that we have
  - The public health system impact assessment

Questions