Variability in Age at Loss of Ambulation by Genotype Among Boys With Duchenne Muscular Dystrophy (DMD)

Shelagh M. Szabo, MSc,[1] Katherine L. Gooch, PhD,[2] Alexis T. Mickle, MSc,[1] Anne Connolly, MD[3]

[1]Broadstreet HEOR, 203 – 303 Railway St, Vancouver BC Canada; [2]Sarepta Therapeutics, 215 First St, Cambridge MA 02142 USA;
[3]Nationwide Children's Hospital, Ohio State University, Columbus OH USA

BACKGROUND

- DMD is a rare X-linked disorder caused by mutations in the dystrophin (*DMD)* gene, a structural protein of muscle cells.[1]
- DMD patients present in early childhood with gait abnormalities and muscle weakness;[1,2,3] progressive muscle degeneration eventually leads to loss of ambulation (LOA) in the early teens, respiratory impairment, cardiomyopathy, and death in the second to third decade of life.[2,4,5]
- Deletions or duplications in the *dystrophin* gene that disrupt the open reading frame account for 70% of cases of DMD.[1,4,6]
- Antisense oligonucleotide-mediated exon skipping therapies aim to restore the disrupted DMD reading frame
  - Approximately 80% of DMD patients have genotypes theoretically amenable to exon skipping[6,7]
- There is evidence that the severity of clinical phenotypes – in particular, age at LOA - may vary by genotype, however, a synthesis of published data is lacking.[8-10]
- Such data are important for understanding disease progression and natural history by genotype.

OBJECTIVE

- To characterize age at LOA by genotype among patients with DMD.

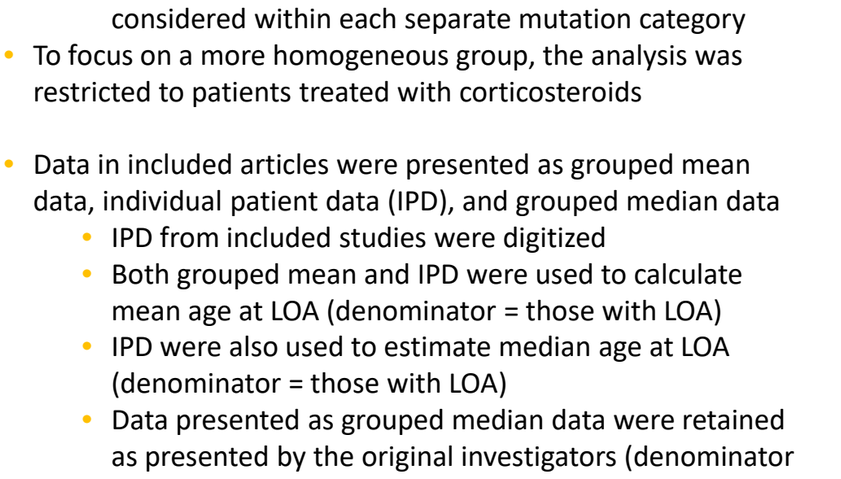
METHODS

- A systematic review was conducted using MEDLINE and EMBASE to identify articles describing the age at LOA among patients with DMD of known genotype.
  - The review was conducted according to PRISMA guidelines[11] and guided by study-specific PECOS criteria
    - Population: DMD patients treated with corticosteroids
    - Exposure/Comparators: Genotype
    - Outcomes: Mean, median age at LOA
    - Study designs: Observational and clinical studies
- Patient genotype was categorized according to amenability of mutations to potential exon skipping.
  - Mutations amenable to skipping multiple exons were considered within each separate mutation category
- To focus on a more homogeneous group, the analysis was restricted to patients treated with corticosteroids
- Data in included articles were presented as grouped mean data, individual patient data (IPD), and grouped median data
  - IPD from included studies were digitized
  - Both grouped mean and IPD were used to calculate mean age at LOA (denominator = those with LOA)
  - IPD were also used to estimate median age at LOA (denominator = those with LOA)
  - Data presented as grouped median data were retained as presented by the original investigators (denominator = those who had, and had not yet, experienced LOA)
  - Note, this resulted in different n's available by which to calculate mean and median estimates of age at LOA

RESULTS

- From 7,291 publications, 9 met inclusion criteria **(Figure 1).**

Figure 1. PRISMA diagram



RESULTS

- Five studies presented IPD,[5,12-14] and four presented grouped data (**Table 2**);[8-10,15] data were from a mix of large registries and individual clinical centers.
- Data were available from six studies to estimate mean age at LOA,[5,12-15] and from five of these studies to estimate median age at LOA.[5,12-14]
  - Mean (SD) age at LOA ranged from 10.2 (1.7) years among skip 53 patients (n=16), to 12.6 (3.2) years among skip 44 patients (n=13; **Figure 2**).
  - Median age at LOA ranged from 10.0 years among skip 53 patients (n=3) to 12.0 years among on skip 55 patient (**Figure 3**).
- Three studies reported median age at LOA (from samples where not everyone had experienced LOA; **Figure 4**)[8-10]
  - Estimates ranged from 12.0 (skip 51 amenable, n=106; exon 45 skip amenable, n=17) to 20 (n=74, exon 44 skip amenable) years.

Table 2. Study and patient characteristics

Citation	n	Follow-up (years)	Estimate type	Data/patient source	Genotype-specific n by outcome		
					Mean	Median	Grouped median
Bello 2016[8]	212	20	Group	CINRG	0	0	90
Goemans 2017[12]	12	3.4	Patient-level	NR	3*	3*	0
Kleopa 2006[13]	13	NR	Patient-level	CING	9	9	0
Koeks 2017[9]	5,345	NR	Group	TREAT-NMD DMD	0	0	355**
Seferian 2015[5]	53	2	Patient-level	4 centers in France	8	8	0
Servais 2015[14]	1,375	1	Patient-level	2 NH studies; UMD-DMD-Cochin database	3	3	0
van den Bergen 2014[15]	114	NR	Group	Dutch dystrophinopathy database	48	0	0
van Deutekom 2007[16]	4	0.08	Patient-level	NR	3	3	0
Wang 2018[10]	765	20**	Group	Duchenne Registry	0	0	429

CING = Cyprus Institute of Neurology and Genetics; CINRG = Cooperative International Neuromuscular Research Group; LOA = loss of ambulation; NH = natural history; NR = not reported; TREAT-NMD = Translational Research in Europe - Assessment & Treatment of Neuromuscular Diseases; UDP = United Dystrophinopathy Project
*3 of 3 included participants treated with drisapersen; **estimated; ***four genotypes groups estimated, 2 groups unable to estimate

Figure 2. Mean (SD) age at LOA, by exon skipping amenability

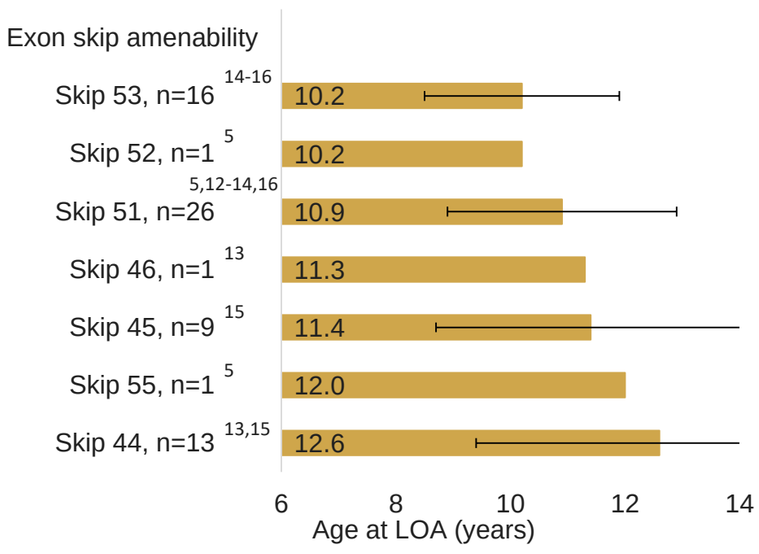


Figure 3. Median (min-max) age at LOA, by exon skipping amenability

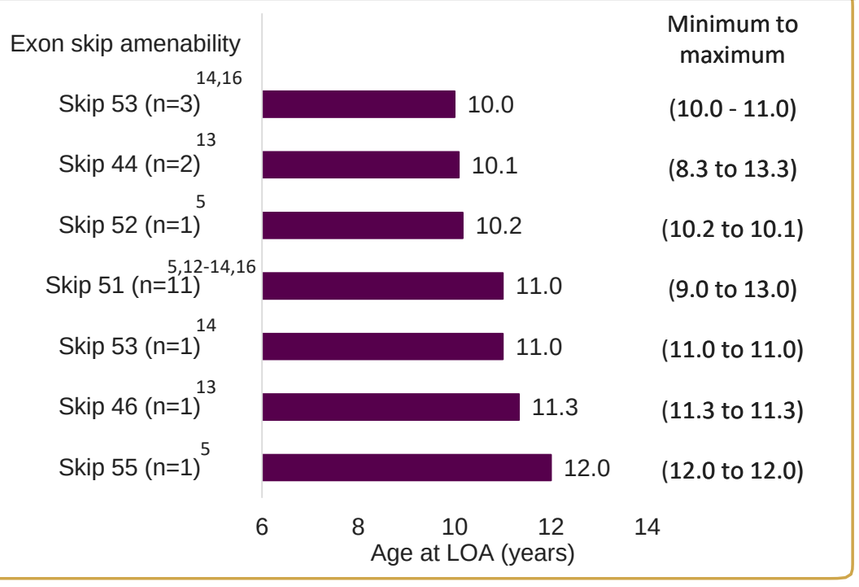
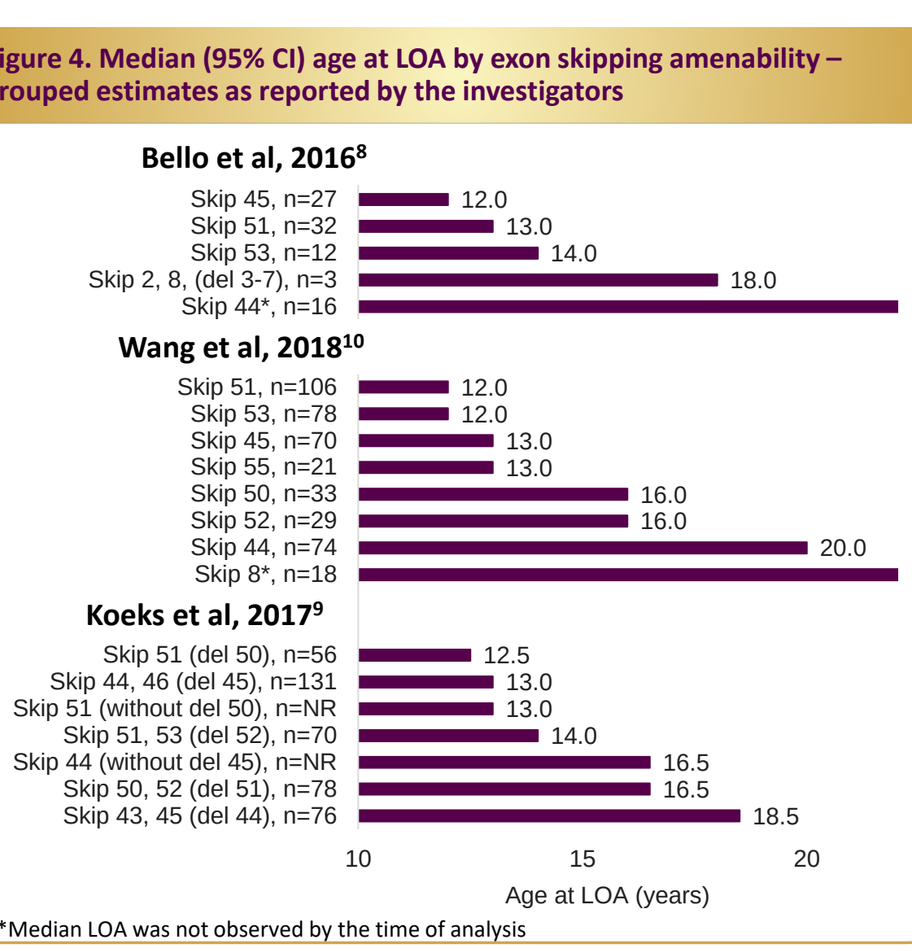


Figure 4. Median (95% CI) age at LOA by exon skipping amenability – grouped estimates as reported by the investigators



*Median LOA was not observed by the time of analysis

DISCUSSION AND CONCLUSIONS

- Those amenable to exon 52 and 53 skipping showed more severe phenotypes in age at LOA, compared to those amenable to exon 55 or 44 skipping.
  - These findings are consistent with published estimates from large registries.
- Estimates based on IPD were only available for patients who had lost ambulation.
  - These would represent lower bounds, compared to estimates from cohorts where not everyone had yet lost ambulation.
- Grouped median data were presented as reported, and not all patients had yet experienced LOA.
  - Estimate accuracy therefore depends on length of follow up and amount of censoring pre-LOA.
- While variability in age at LOA by DMD genotype was observed, caution is needed when comparing LOA from studies where designs differed.
- Furthermore, the natural history of certain genotypes is more fully characterized than for other genotypes.

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