Expert Consensus on Dystrophin and Creatine Kinase as Predictors of Clinical Benefit in Duchenne Muscular Dystrophy: a RAND/UCLA Modified Delphi Panel

Edward Smith[1]; Lindsay Alfano[2]; John Brandsema[3]; Tina Duong[4]; Katherine Mathews[5]; Leigh Maria Ramos-Platt[6]; Aravindhan Veerapandiyan[7]; Brenda Wong[8]; Craig Zaidman[9]; Justin Weiss[10]; Irina Yermilov[10]

[1] Rare Disease Research, Hillsborough, NC; [2] Nationwide Children's Hospital, Columbus, OH; [3] Children's Hospital of Philadelphia, Philadelphia, PA; [4] Stanford University, Stanford, CA; [5] Iowa Carver School of Medicine, Iowa City, IA; [6] Children's Hospital Los Angeles, Los Angeles, CA; [7] Arkansas Children's Hospital, Little Rock, AR; [8] UMass Memorial Health, Worcester, MA; [9] Washington University in St. Louis, St. Louis, MO; [10] ADVI Health, Washington, D.C.

Background

- Duchenne muscular dystrophy is characterized by reduced dystrophin protein leading to muscle destruction and progressive motor and cardiopulmonary dysfunction.[1-6]
- Dystrophin restoration remains a central therapeutic goal, while creatine kinase (CK)–which has traditionally been considered unreliable for monitoring disease progression or therapeutic response–may be informative in the context of therapies that restore functional dystrophin.[4,7-12]
- However, data quantitatively linking changes in dystrophin and CK levels to long-term outcomes remain limited.
- **We aimed to develop consensus on how changes in these biomarkers in patients on exon-skipping therapies may be associated with functional and clinical outcomes.**

Methods

- We used a double-blinded RAND/UCLA modified Delphi method with nine US panelists (seven pediatric neurologists and two physical therapists).
- The panel reviewed and rated 376 hypothetical patient scenarios across disease stages (early/late ambulatory, early/late non-ambulatory) with specified dystrophin and CK levels 3 months after exon-skipping initiation.
- Scenarios varied by several clinical characteristics (**Table 1**).
- Panelists rated anticipated impacts on motor, cardiac, and pulmonary outcomes at 3 years on a 1-9 scale before and after a virtual meeting. Confidence was scored from 1 to 9.
- Disagreement was defined as >2 panelists rating a scenario on the extremes of the scale (1-3 and 7-9).

Results

- Panelists disagreed on <1% of scenario ratings following the meeting, compared with 34% prior.
- There was panel consensus that larger biomarker changes at 3 months (≥21% dystrophin and a >75% reduction in CK) in earlier disease stages are more likely to be associated with favorable motor outcomes at 3 years (**Figure 1**).
- There was consensus that larger biomarker changes at 3 months in ambulatory patients are likely to be associated with favorable pulmonary outcomes after 3 years (**Figure 2**).
- There was consensus that 7-21% dystrophin and a >25% decrease in CK levels are moderately likely to be associated with favorable cardiac outcomes after 3 years (**Figure 3**).

Figure 1. Anticipated future motor function outcomes by change in dystrophin and CK levels

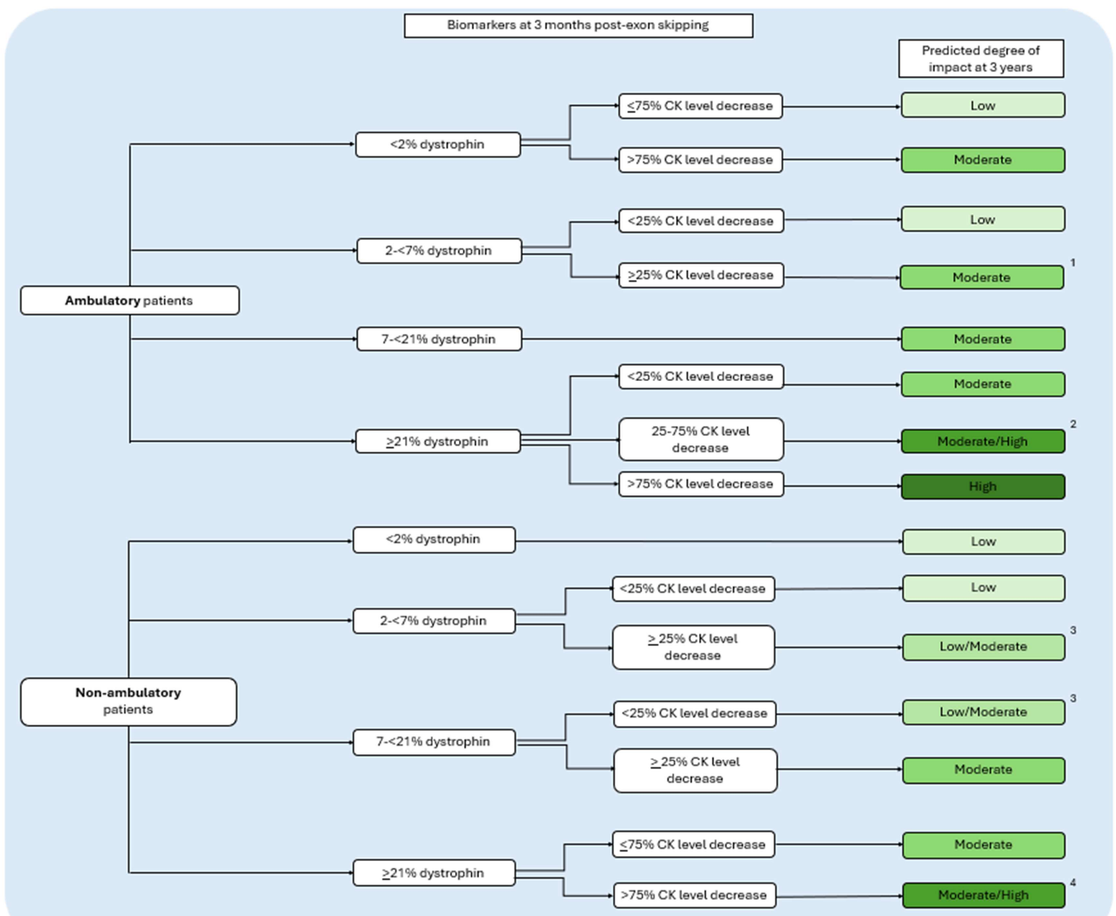


Figure 1: [1]In late ambulatory patients, a 75% decline in CK levels was anticipated to have a high degree of impact. [2]High anticipated degree of impact for early ambulatory patients; moderate anticipated degree of impact for late ambulatory patients. [3]Moderate anticipated degree of impact for early non-ambulatory patients; low anticipated degree of impact for late non-ambulatory patients. [4]High anticipated degree of impact for early non-ambulatory patients; moderate anticipated degree of impact for late non-ambulatory patients.

Table 1. Clinical characteristics

Core elements included in patient scenarios	Categories	Definitions/Measures
Percent dystrophin expression	<2%	% of the level present in healthy controls, as measured by Western blot, 3 months after initiation of exon-skipping medication. This measure assumes patients have genetically confirmed DMD and no or very low levels of dystrophin at baseline (<1%).
	2-<7%	
	7-<21%	
	≥21%	
Percent decrease in CK levels	<25%	As measured through a serum CK (or CPK test), 3 months after initiation of exon-skipping medication.
	25-75%	
	>75%	
Clinical and functional changes [a]	Motor function	E.g., measured by NSAA, PUL, 6MWT, 10MWRT, TRF, 4SC, or as subjectively evaluated at an office visit.
	Pulmonary outcomes	E.g., measured by FVC, PEF, MIP and MEP, or SNIP.
	Cardiac outcomes	E.g., measured by LVEF, cardiac troponins (e.g., hs-TnI), NT-proBNP or BNP, or cardiac MRI.
Disease stage	Early ambulatory	Delayed motor milestones; Gowers' sign; difficulty running, jumping, or climbing stairs.
	Late ambulatory	Long-distance walking fatigue; progressive loss of walking ability; frequent falls; calf muscle hypertrophy.
	Early non-ambulatory	Loss of independent ambulation; begin using a wheelchair; retain good upper limb function.
	Late non-ambulatory	Loss of arm function; development of scoliosis; respiratory muscle weakness; onset of cardiac complications; often needs BiPAP/CPAP.

4SC = Four-Stair Climb, 6MWT = 6-Minute Walk Test, 10MWRT = 10-Meter Walk Run Test, BiPAP = bilevel positive airway pressure, BNP = B-type Natriuretic Peptide, CK = creatine kinase, CPAP = continuous positive airway pressure, CPK = creatine phosphokinase, FVC = Forced Vital Capacity, LVEF = Left Ventricular Ejection Fraction, hs-TnI = High-Sensitivity Troponin I, MEP = Maximal Expiratory Pressure, MIP = Maximal Inspiratory Pressure, MRI = Magnetic Resonance Imaging, NSAA = North Star Ambulatory Assessment, NT-proBNP = N-terminal pro-B-type Natriuretic Peptide, PEF = Peak Expiratory Flow, PUL = Performance of the Upper Limb, SNIP = Sniff Nasal Inspiratory Pressure, TRF = Timed Rise from Floor.
[a] Degree of impact refers to the extent to which an increase in dystrophin and a decrease in CK levels predict changes in the patient's motor abilities and cardiac and pulmonary function, compared to the expected natural history of disease. A rating of 1-3 corresponds to no impact (per natural history of disease), a rating of 4-6 corresponds to some impact (slowed progression of disease), a rating of 7 corresponds to moderately high impact (progression halted), and a rating of 8-9 corresponds to high impact (improvement).

Figure 2. Anticipated future pulmonary function outcomes by change in dystrophin and CK levels

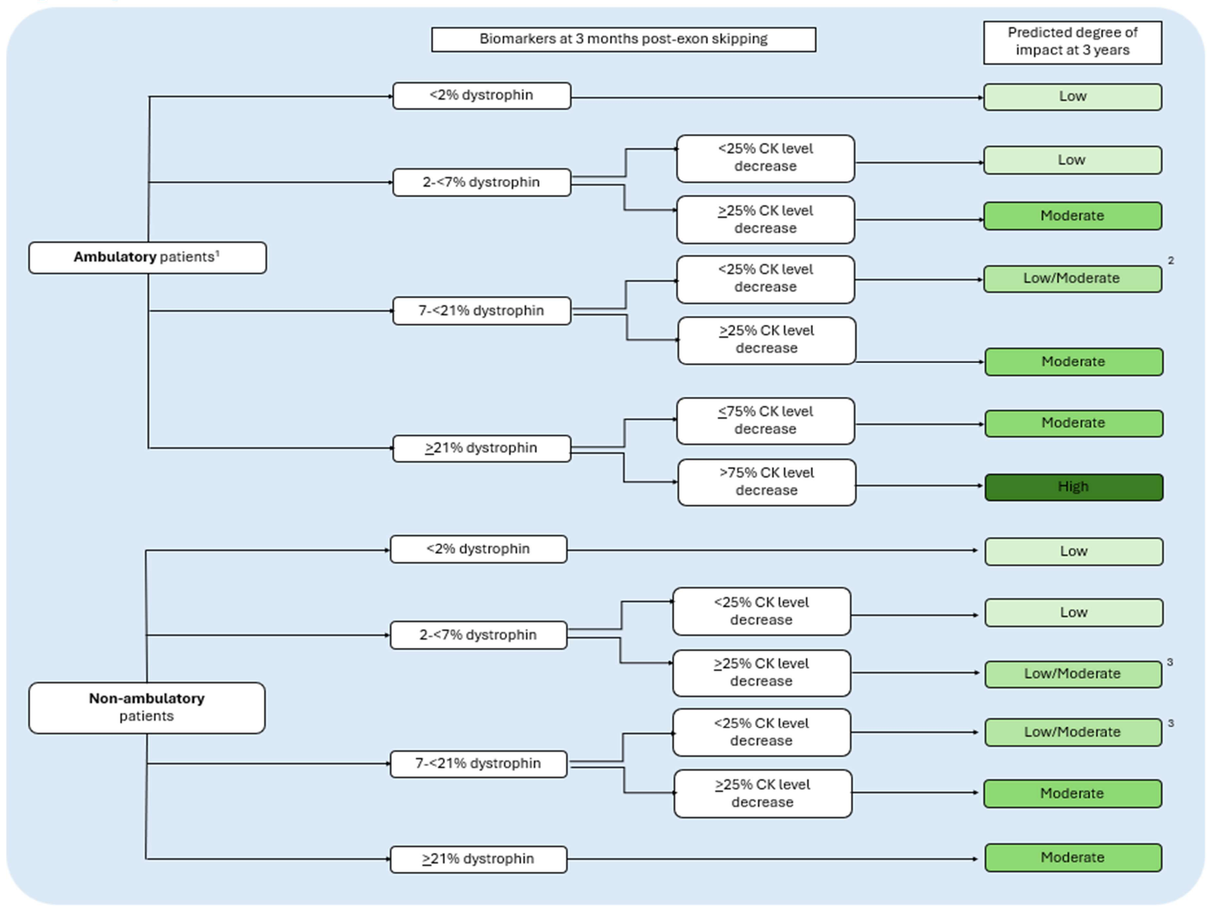
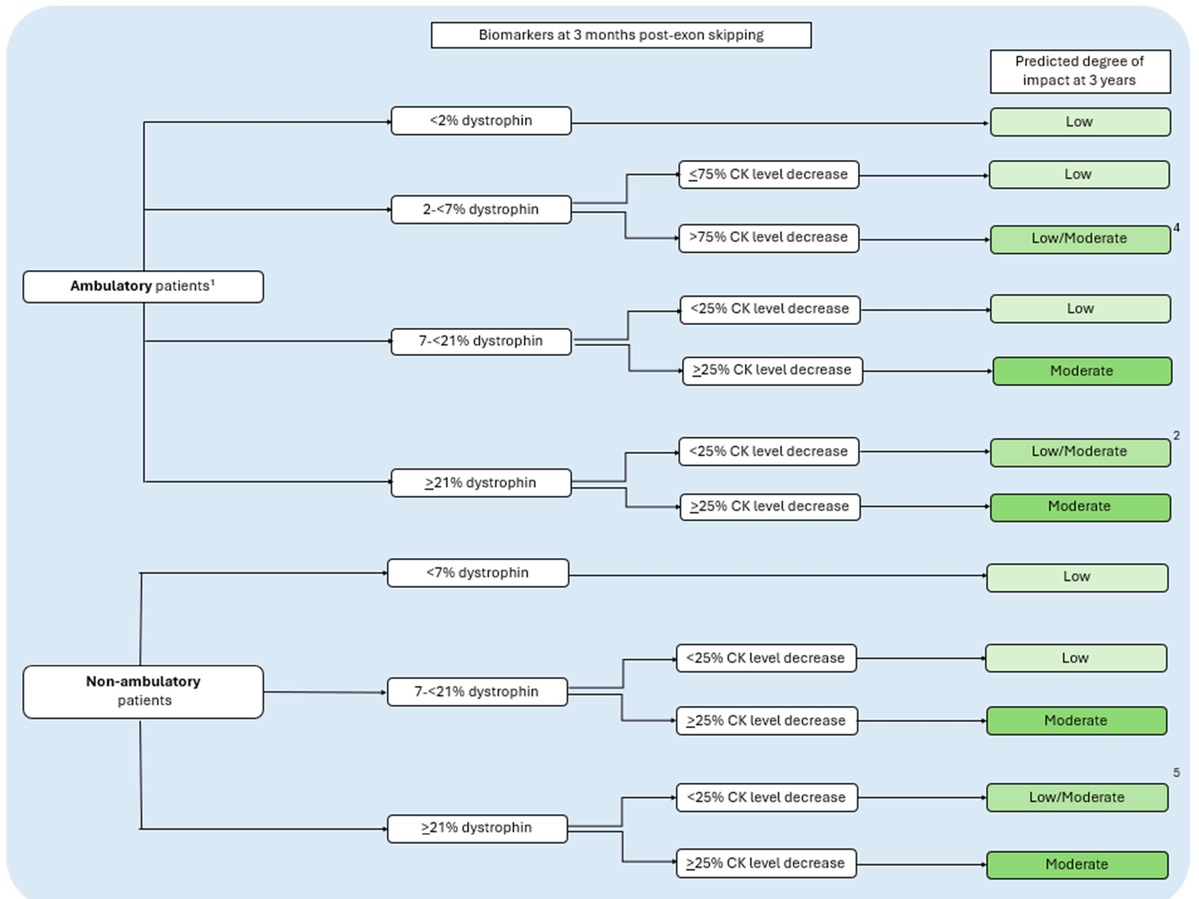


Figure 3. Anticipated future cardiac function outcomes by change in dystrophin and CK levels



Figures 2 & 3: [1]In the early ambulatory stage, pulmonary function was assumed to be stable, with no measurable decline; thus, any anticipated future impact reflected the panel's belief that early biomarker changes were predictive of an altered disease trajectory.
[2]Low anticipated degree of impact for early ambulatory patients; moderate anticipated degree of impact for late ambulatory patients.
[3]Moderate anticipated degree of impact for early non-ambulatory patients; low anticipated degree of impact for late non-ambulatory patients.
[4]Low anticipated degree of impact for late ambulatory patients; moderate anticipated degree of impact for early ambulatory patients.
[5]Low anticipated degree of impact for late non-ambulatory patients; moderate anticipated degree of impact for early non-ambulatory patients.

Key Expert Consensus Takeaways

- Based on this panel's opinion, **favorable clinical outcomes are anticipated to occur** with larger CK reductions during earlier disease stages.
- **Meaningful biomarker changes** are expected to most strongly influence motor and pulmonary function, with smaller and less certain effects on cardiac outcomes.
- **Dystrophin and CK levels are relevant** as early biomarkers of treatment benefits in patients receiving exon-skipping therapies.

References

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