

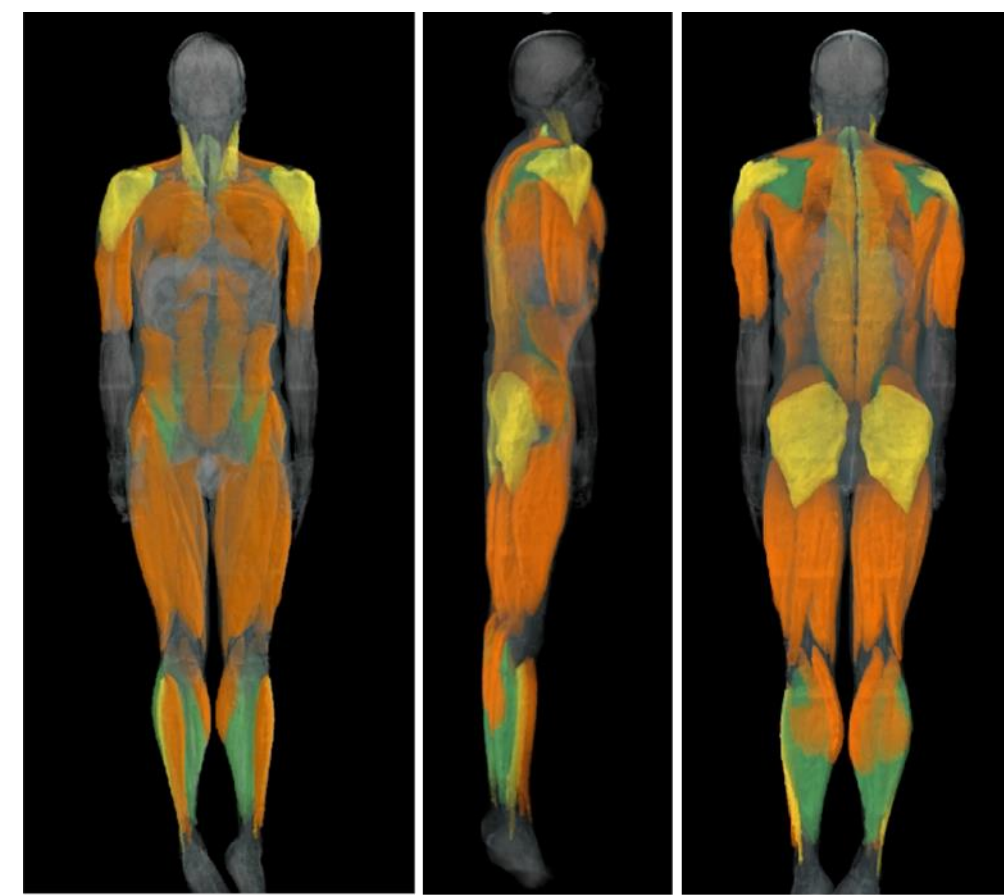
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Background

- One of the most common muscular dystrophies
- Estimated prevalence in US between 16,500 and 22,000
- Autosomal Dominant
- Onset usually around 15-30 years old
- Clinical Presentation
 - Slowly progressive
 - Asymmetric muscle weakness
 - Affects face, arms, legs and trunk
 - Variable progression
 - Inconsistent severity

Reported Muscle Involvement in FSHD

- No fat replacement
- Small fat replacement
- High fat replacement



Muscles affected by the disease are seen in all parts of the body

Objective

Develop a whole-body MR imaging protocol and analysis algorithms to volumetrically measure fat replacement of skeletal muscle in FSHD feasible to use in multi-site clinical trials

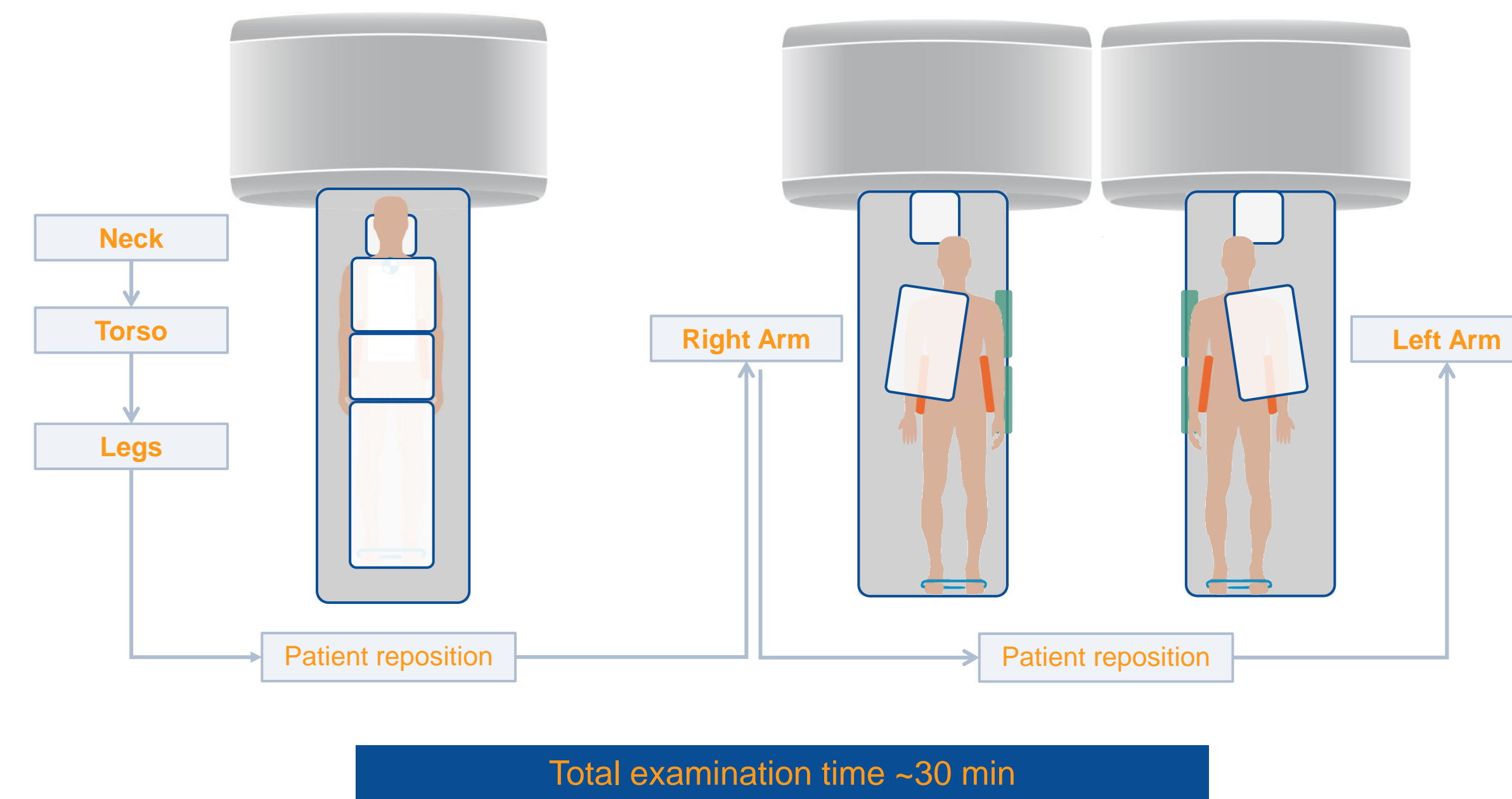
Methods

- 17 patients were scanned twice, 4-12 weeks apart
- Patients were scanned using the AMRA FSHD-protocol including whole-body T1-weighted Dixon images
- Images were processed using AMRA[®] Researcher, which includes:
 - Image calibration
 - Automatic segmentation of muscles
 - Manual quality control of segmentations
 - Quantification of muscle biomarkers

Muscles studied

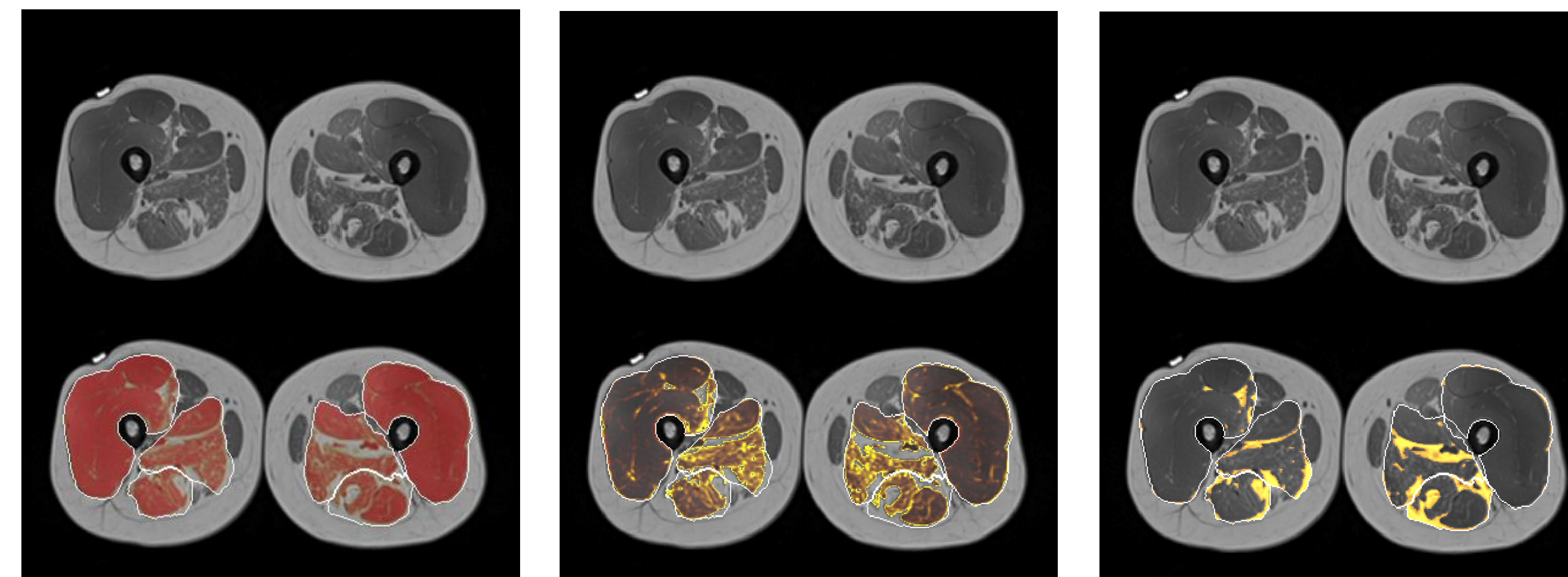
Neck	Torso
<ul style="list-style-type: none"> Supraspinatus Infraspinatus Subscapularis Teres Minor 	<ul style="list-style-type: none"> Pectoralis Major Rhomboides Latissimus Dorsi & Teres Major Trapezius Serratus Anterior Paraspinal (C3-Sacrum)
Legs	Arm
<ul style="list-style-type: none"> Quadriceps Hamstrings Adductors Tibialis Anterior Gastrocnemius Medialis 	<ul style="list-style-type: none"> Deltoid Biceps Brachii Triceps Brachii

Imaging Protocol



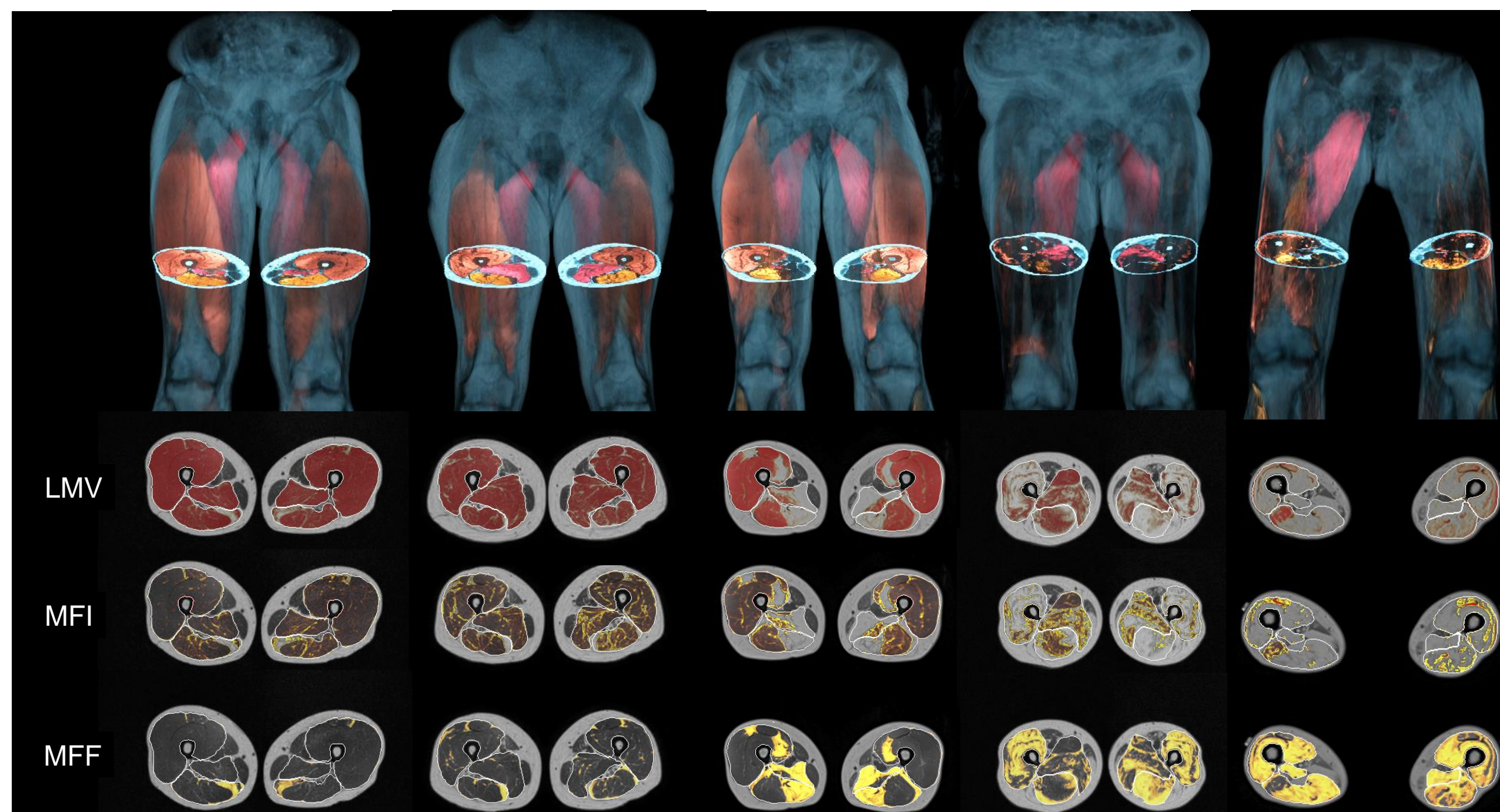
MRI Measurement

- A. Lean Muscle Volume (LMV)
- B. Muscle Fat Infiltration (MFI)
- C. Muscle Fat Fraction (MFF)



(A) Amount of functional muscle tissue, measured by completely removing all fat within the muscle fascia – Measures functional tissue & insensitive to segmentation performance. (B) Diffuse fat infiltration, measured as relative amount of fat within the muscle tissue. Insensitive to segmentation performance, Indicator of muscle quality, specifically sensitive to early muscle fat replacement. MFI does not capture late phase of muscle fat replacement. (C) Relative amount of fat within the muscle fascia. Known MRI biomarker in neuromuscular disorders associated with weakness and disability. Can be quantified if fat replacement <60%. Sensitive to segmentation performance if measuring change.

Segmentation Across FSHD Patients With Increasing Severity of Disability



Results - Baseline Characteristics

N	17
Male (%)	71
D4Z4 Repeats (n)	
1-3	2
4-9	15
Clinical Severity Score n (%)	
2.0	1 (5.9)
2.5	8 (47.1)
3.0	3 (17.6)
4.0	5 (29.4)
Ricci Score (Mean (SD))	3.0 (0.71)

Results

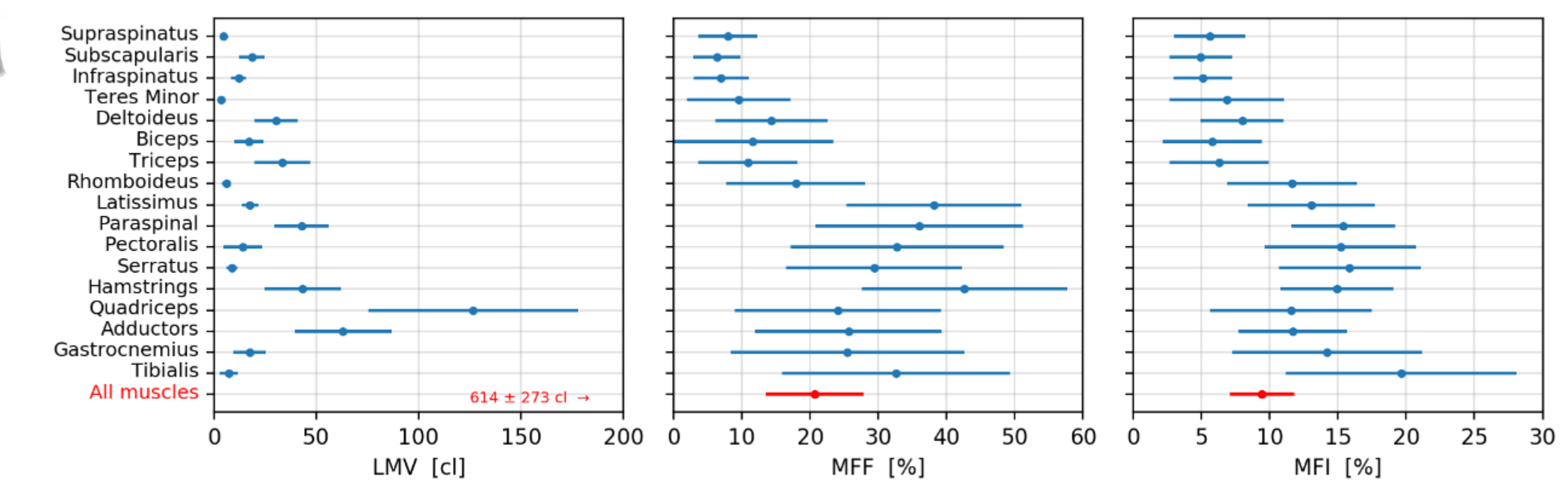
A. Average Baseline Muscle Involvement (N=17)



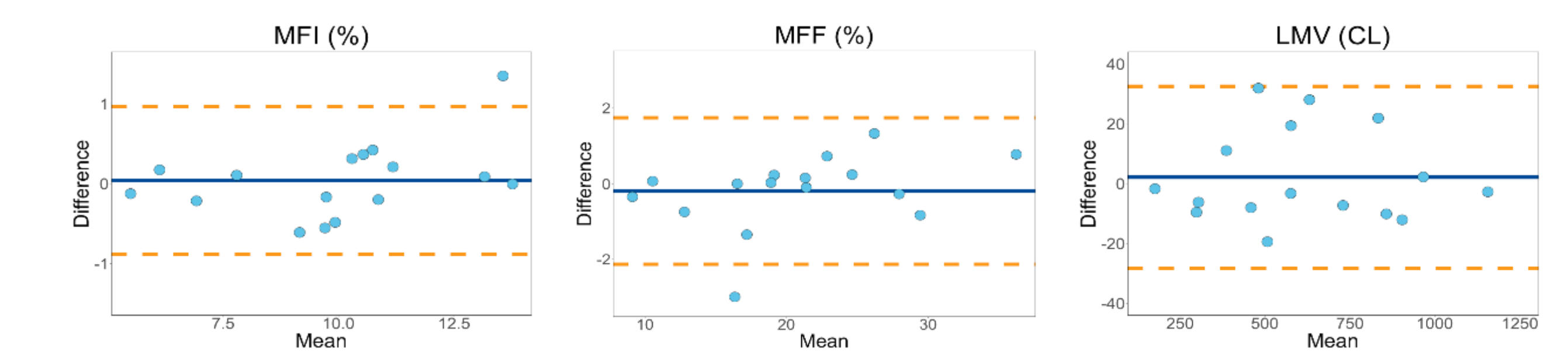
- Mean MFF < 15%
- Mean MFF 15 – 30%
- Mean MFF 30 – 50%
- Mean MFF > 50%

- Mean ± SD
- Only including muscles with MFF < 60%
- All trapezius muscles had MFF > 60%
- cl= centiliters

B. Descriptive Statistics



C. Repeatability



- All three measurements showed excellent repeatability 4-12 weeks apart
- The intraclass correlation coefficient was >0.97 for all 3 measurements

Conclusion

- We developed a quantitative whole-body muscle MRI protocol for longitudinal FSHD studies
 - Currently applied in Fulcrum Therapeutics phase 2 clinical trials of losmapimod.
- We measured three different biomarkers in all muscles/muscle groups, corresponding to:
 - Amount of functional muscle tissue (LMV)
 - Diffuse fat infiltration (MFI)
 - Total fat replacement (MFF)
- All three biomarkers showed excellent repeatability
- Mild to severe replacement of muscle tissue by fat was observed in all patients and in most muscles examined.
- Most affected muscles were the trapezius, serratus anterior, latissimus dorsi and hamstrings
- The rotator cuff muscles were not affected

References: (1) P38α Regulates Expression of DUX4 in a model of Facioscapulohumeral Muscular Dystrophy. LA Rojas et al, Journal of Pharmacology and Experimental Therapeutics 374 (3), 489-498. (2) MRI in Neuromuscular Diseases: An Emerging Diagnostic Tool and Biomarker for Prognosis and Efficacy. Julia R. Dahlqvist et al. Annals of Neurology 04 June 2020.