



Fulcrum  
Therapeutics

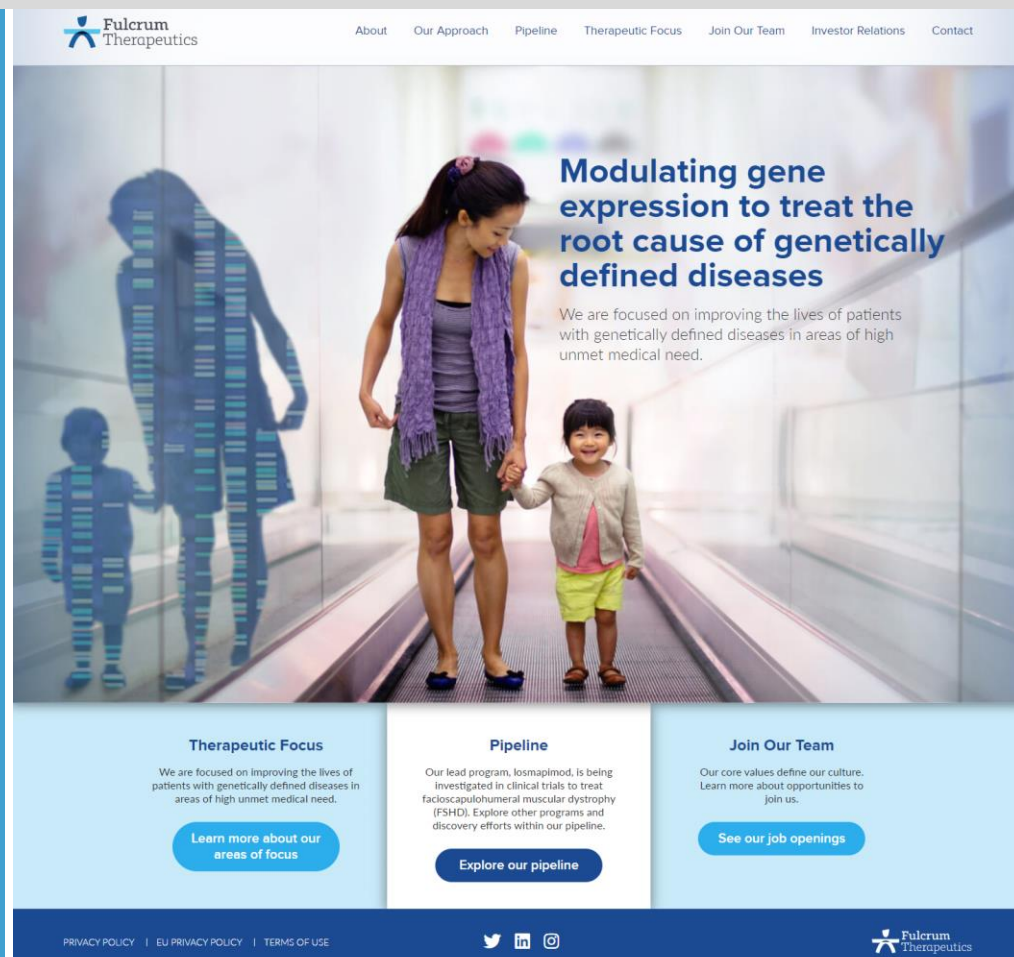
# Quantitative Muscle Analysis in FSHD using Whole-Body MRI: Composite Muscle Measurements for Cross-Sectional Analysis

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## Michelle Mellion, M.D.

- Sr. Medical Director, FSHD – Fulcrum Therapeutics
- Board Certified Neurologist with subspecialty training in Neuromuscular Disease
- I am not presenting any data related to ReDUX4 and cannot take any questions related to the recently concluded randomized controlled ReDUX4 clinical trial.



The screenshot shows the Fulcrum Therapeutics website. The header includes the company logo and navigation links: About, Our Approach, Pipeline, Therapeutic Focus, Join Our Team, Investor Relations, and Contact. The main banner features a woman and a child walking on a glass walkway, with the headline "Modulating gene expression to treat the root cause of genetically defined diseases" and a sub-headline: "We are focused on improving the lives of patients with genetically defined diseases in areas of high unmet medical need." Below the banner are three columns: "Therapeutic Focus" (with a button "Learn more about our areas of focus"), "Pipeline" (with a button "Explore our pipeline"), and "Join Our Team" (with a button "See our job openings"). The footer contains links for Privacy Policy, EU Privacy Policy, and Terms of Use, along with social media icons and the company logo.

Fulcrum Therapeutics

About Our Approach Pipeline Therapeutic Focus Join Our Team Investor Relations Contact

### Modulating gene expression to treat the root cause of genetically defined diseases

We are focused on improving the lives of patients with genetically defined diseases in areas of high unmet medical need.

#### Therapeutic Focus

We are focused on improving the lives of patients with genetically defined diseases in areas of high unmet medical need.

[Learn more about our areas of focus](#)

#### Pipeline

Our lead program, losmapimod, is being investigated in clinical trials to treat facioscapulohumeral muscular dystrophy (FSHD). Explore other programs and discovery efforts within our pipeline.

[Explore our pipeline](#)

#### Join Our Team

Our core values define our culture. Learn more about opportunities to join us.

[See our job openings](#)

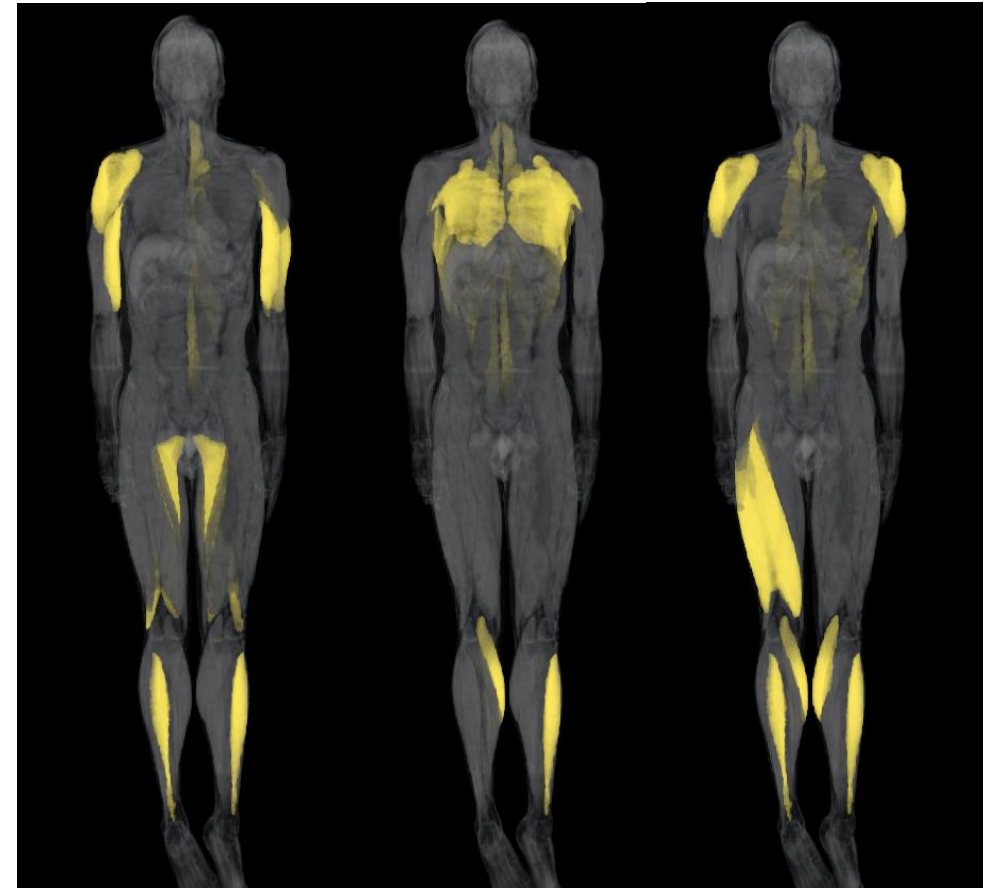
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Fulcrum Therapeutics

# Whole-Body MSK MRI

## Evaluation of FSHD Disease Heterogeneity and Progression

- WB-MSK-MRI Captures
  - Wholistic evaluation of skeletal musculature
  - Small quantitative changes in muscle health that correlate with functional measures
  - Disease Heterogeneity
- Non-invasive
- Minimal burden on patient participation
- Changes in MSK MRI may be detected earlier than changes in clinical outcome assessments (COAs)



Affected Muscle

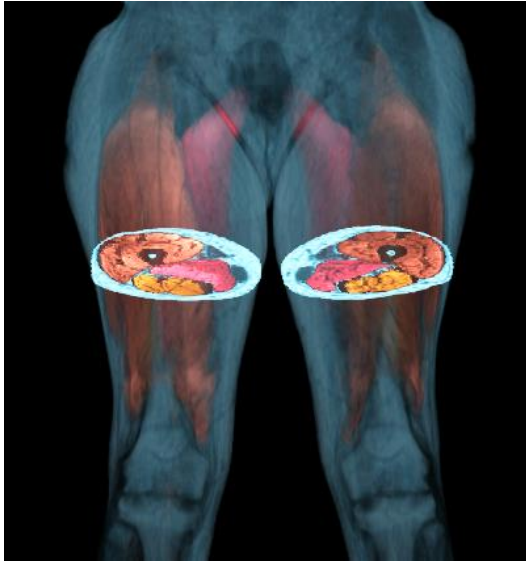
# Objective

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- 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
- Generate a regional composite measurement that can correlate with clinical outcome measures



# New Paradigm of Image analysis in NMD



**Imaging a slice(s) of  
select muscles in lower  
limbs**



**Imaging of whole  
muscle, proximal to  
distal, in the whole body**

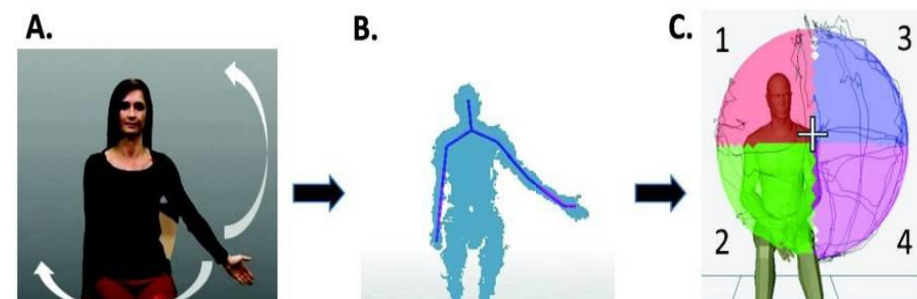
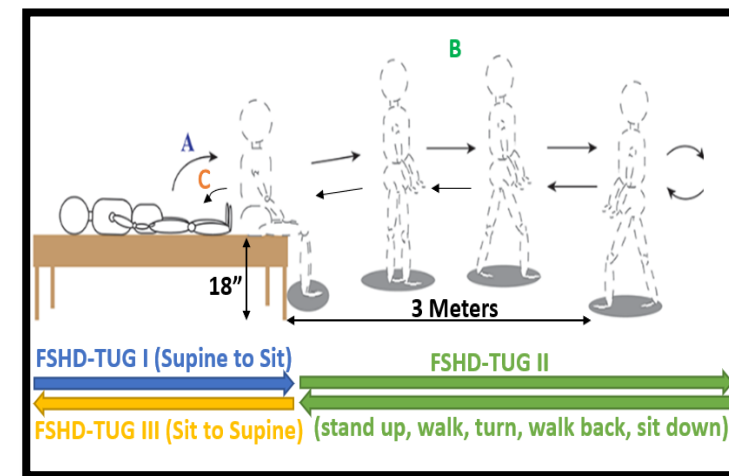
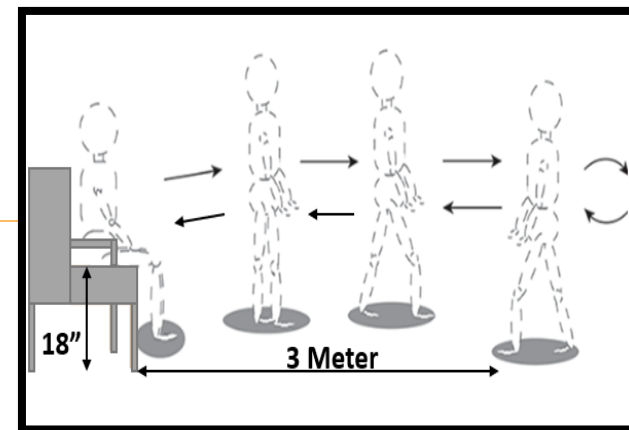


**Personalized set of  
muscles to follow over  
time**



# Study Design

- Two Visits 4-12 weeks apart
- Assessments included
  - WB-MSK-MRI
  - Muscle Biopsy
    - Results presented in Ronco, et al. A Biomarker of DUX4 Activity to Evaluate Losmapimod Treatment Effect in FSHD Phase 2 Trials. At 2020 Virtual MDA Clinical and Scientific Congress.
- Clinical Outcome Assessments
  - TUG
  - FSHD TUG
  - Reachable Work Space



# Main Inclusion Criteria

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- Age 18-65 years old
- Confirmed diagnosis of FSHD1 with 1-7 repeats
- CSS 2 to 4 on Ricci's scale (range 0-5)
- Presence of STIR positive signal in at least one leg muscle eligible for muscle biopsy

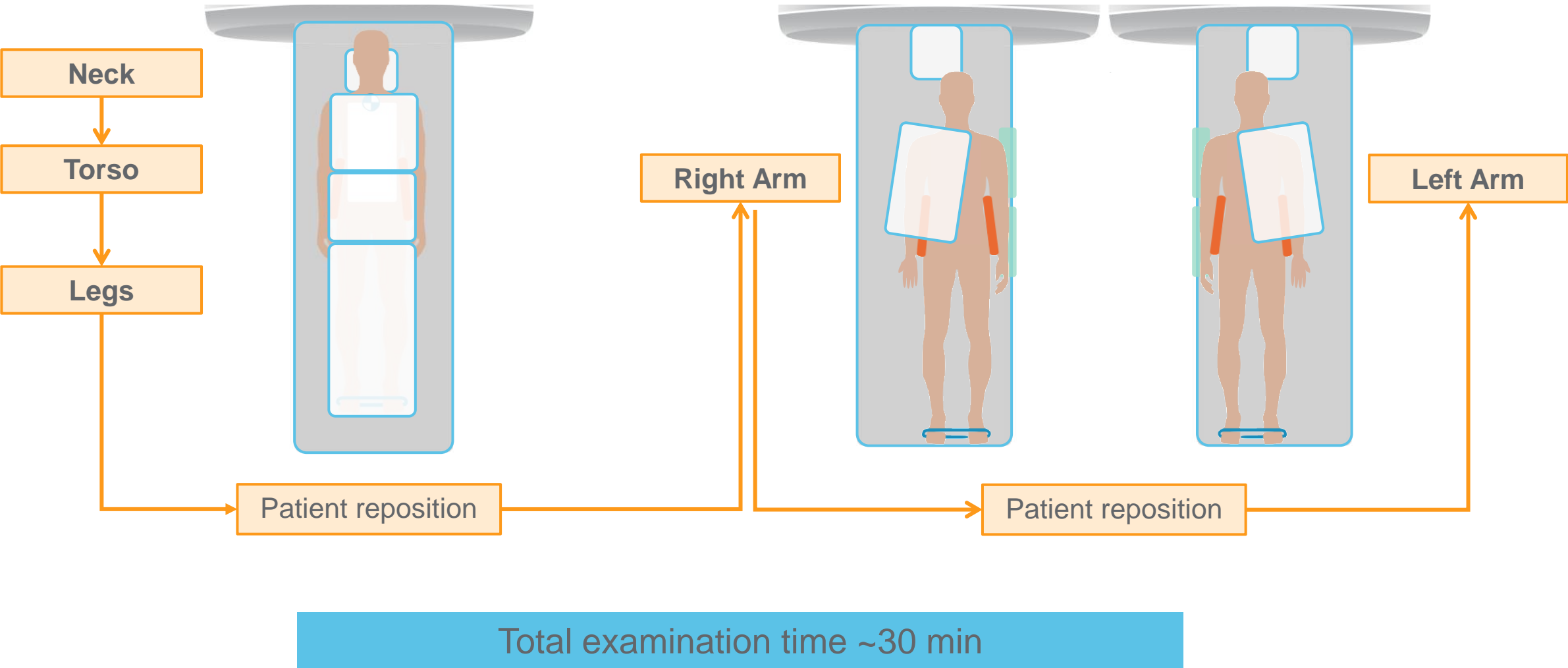
# Subject Demographics (N=17)

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Variable	Mean(SD); range
Age	49.4 (13.02); 23-65
Gender (Female) %	29.4%
Clinical Severity Score (CSS)	3.0 (0.71); 2-4
Average Repeats	5.2 (1.46); 3-7



# Imaging Protocol for Whole Body MRI



# Skeletal Muscle MRI

## Muscles Studied- 18 muscles bilaterally; 36



### Neck

- Supraspinatus
- Infraspinatus
- Subscapularis
- Teres Minor

### Legs

- Quadriceps
- Hamstrings
- Adductors
- Tibialis Anterior
- Gastrocnemius Medialis

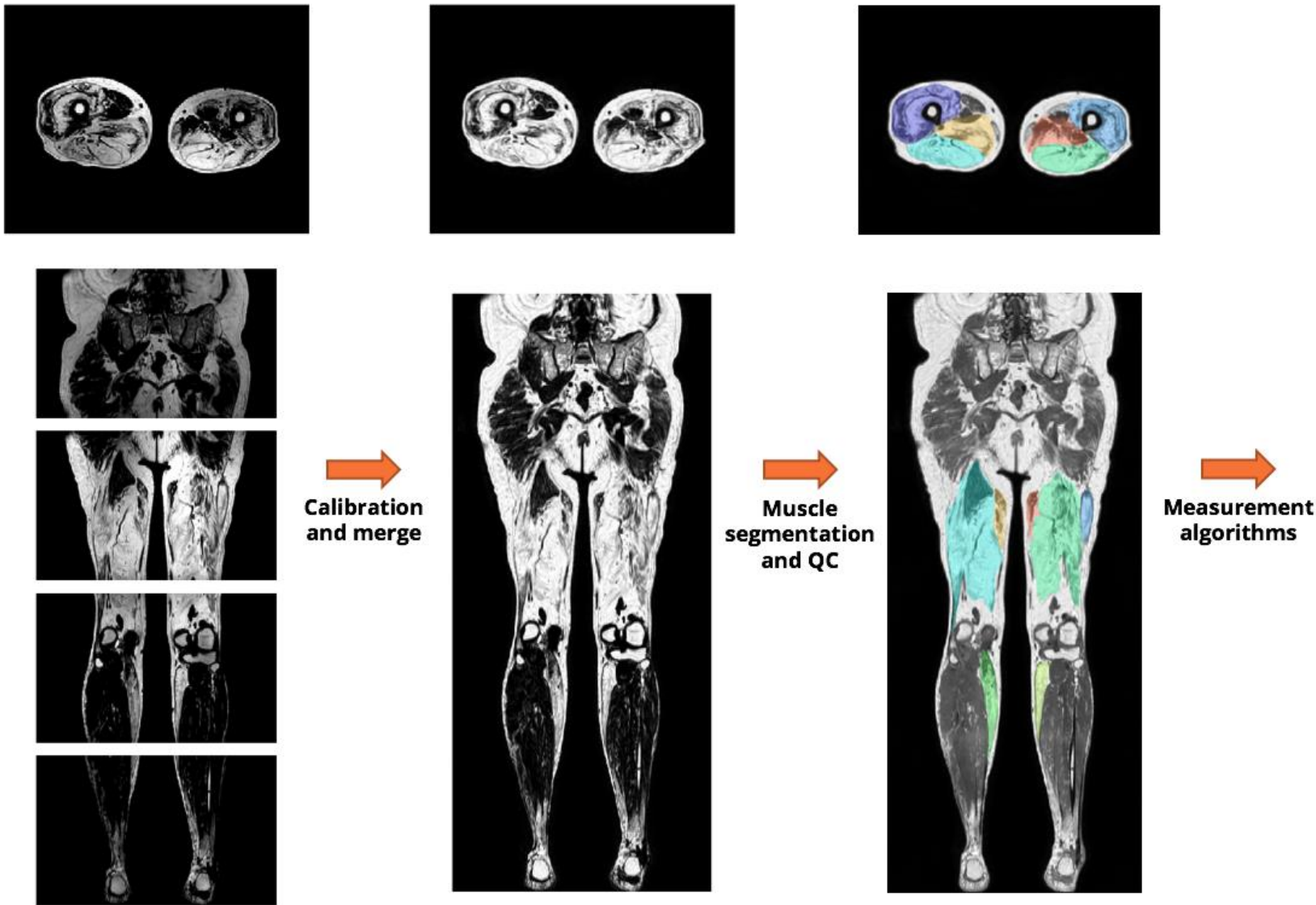
### Torso

- Pectoralis Major
- Rhomboideus
- Latissimus Dorsi & Teres Major
- Trapezius
- Serratus Anterior
- Paraspinal (C3-Sacrum)

### Arm

- Deltoid
- Biceps Brachii
- Triceps Brachii

# Image Analysis



# Quantitative Muscle Measurement

- **LEAN MUSCLE VOLUME (cL)**



- *A measurement of the amount of lean/contractile muscle tissue*

- **MUSCLE FAT INFILTRATION (%)**

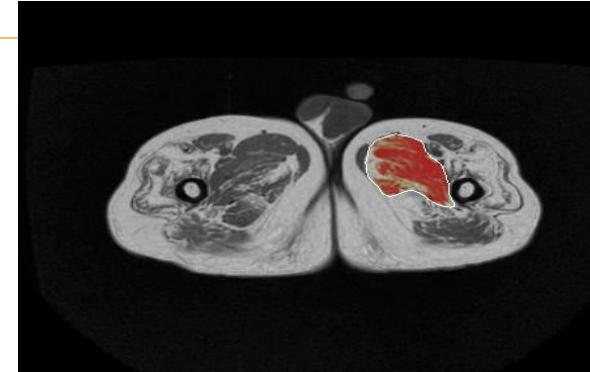



- *A measurement of the diffuse fatty infiltration in the leaner/functioning parts of the muscle definition.*


- **MUSCLE FAT FRACTION (%)**

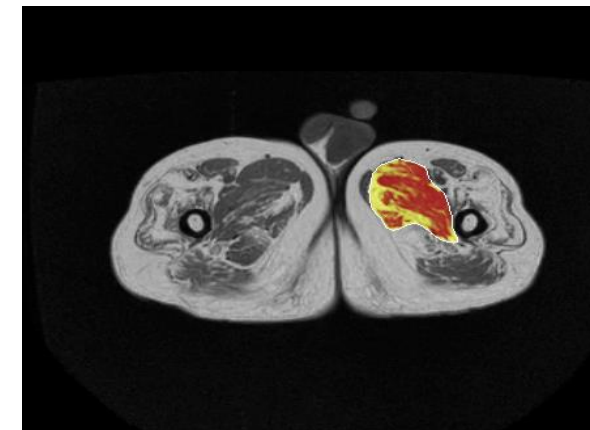
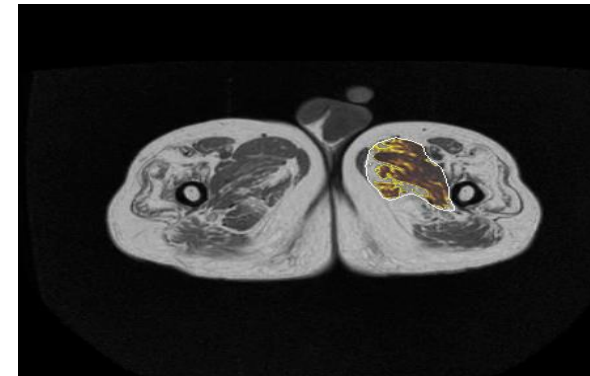


- *A measurement of the overall fattiness of the muscle. Used to identify affected muscles or follow a muscle-to-fat replacement progress in muscle dystrophy*



 = Lean

 = Fatty



# Muscles Analyzed

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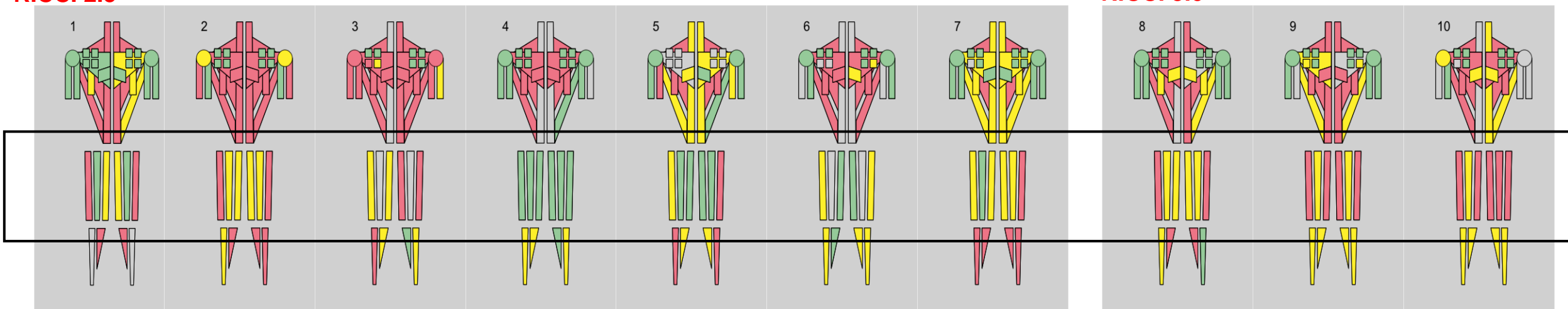
- 478 out of 612 muscles analyzed
- 134 not analyzable
  - 64 Image Artifacts
    - Technical issues; e.g. streak artifact
  - 70 due to complete fat replacement



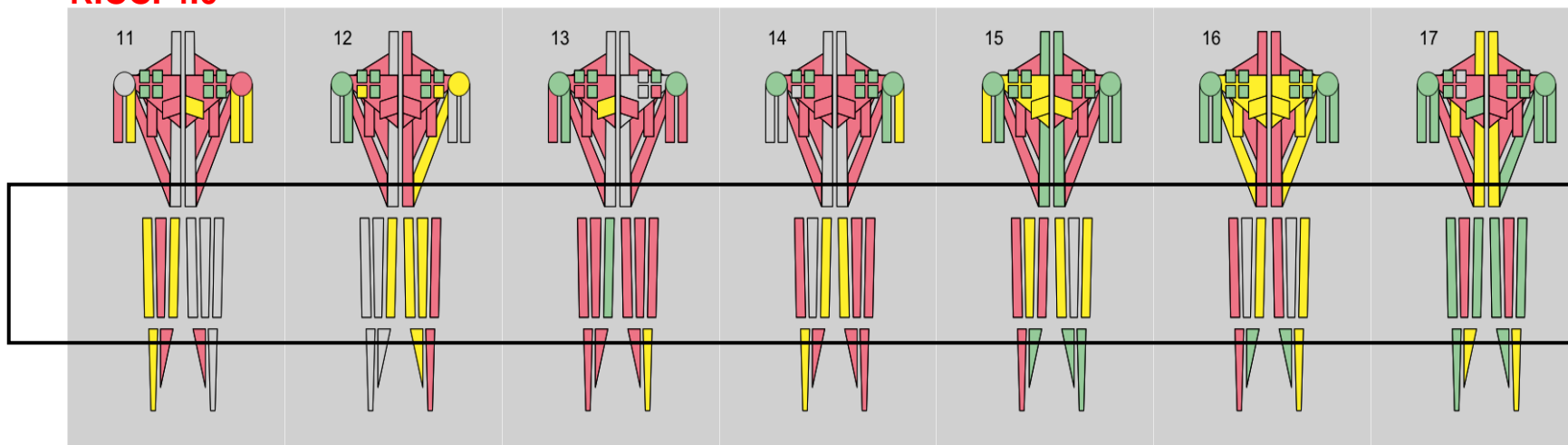
# WB-MSK-MRI Captures Disease Heterogeneity

**RICCI 2.5**

**RICCI 3.0**



**RICCI 4.0**



**Normal**

- Muscles do not appear to be affected by disease
- MFF  $\leq 10\%$

**Intermediate**

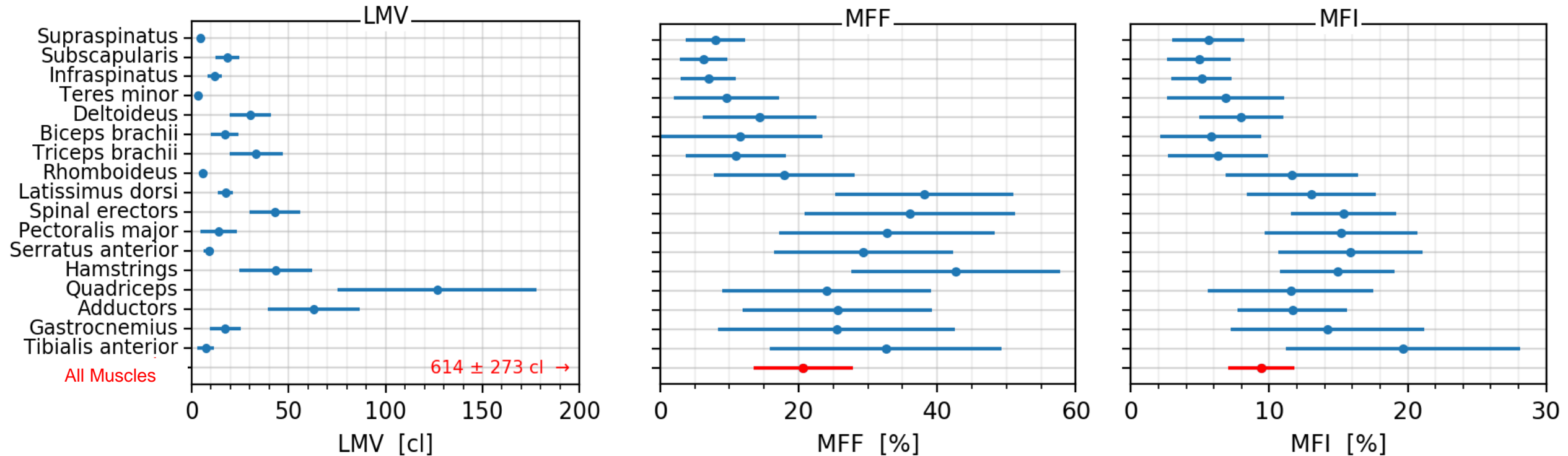
- Muscles clearly affected by disease, but not so severely fat replaced to have lost all function
- MFI  $\geq 10\%$ ; MFF  $\leq 50\%$

**End-Stage**

- Muscles severely fat replaced and have likely lost a most if not all function
- MFF  $\geq 50\%$

**Excluded due to image artefacts**

# Quantitative Muscle Measurement is Consistent with FSHD Pattern

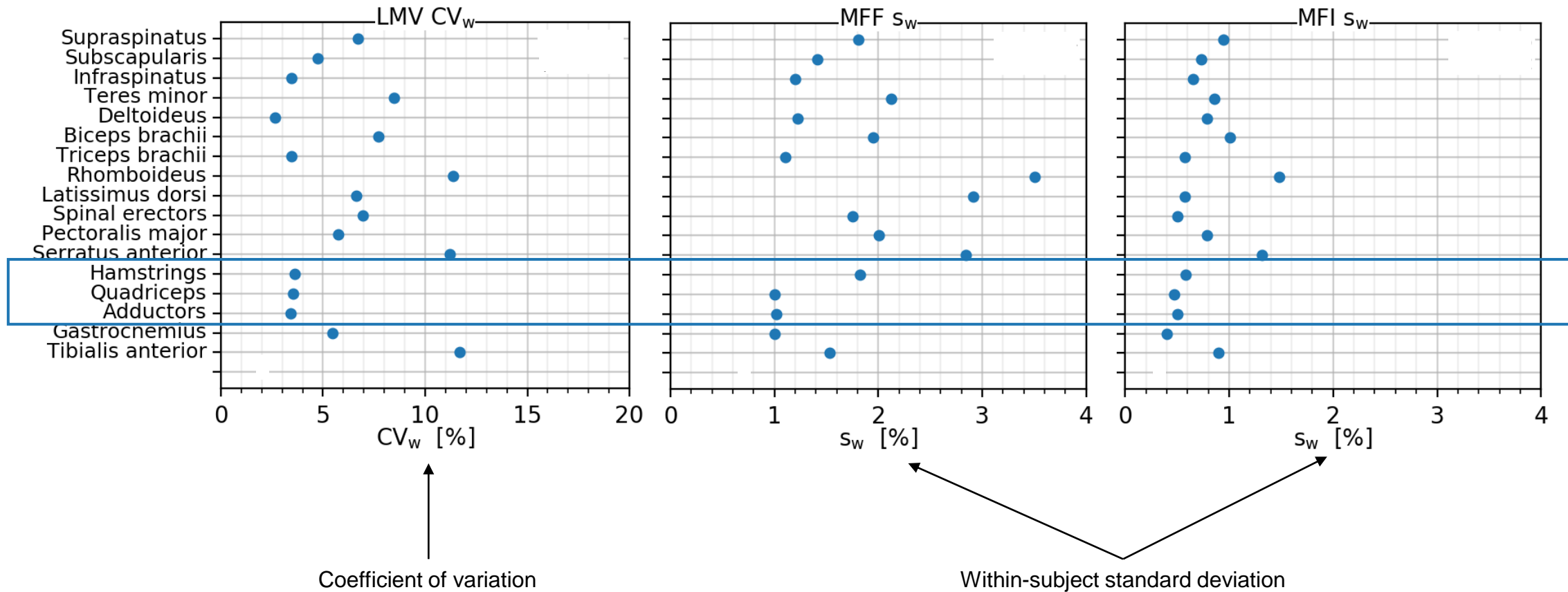


Circle and lines correspond to mean  $\pm$  one standard deviation

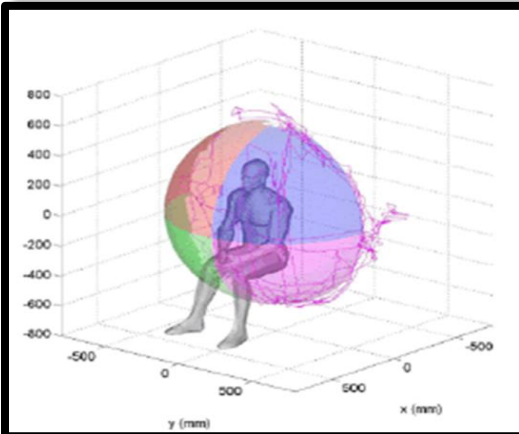
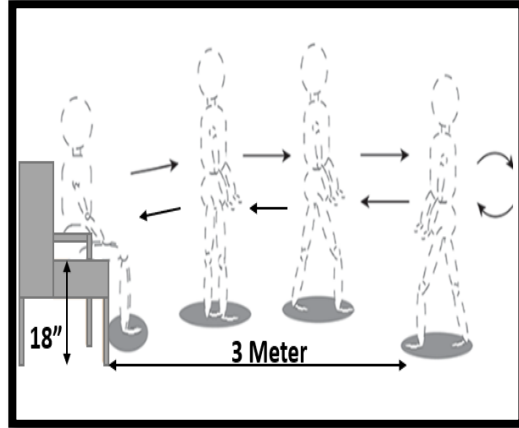
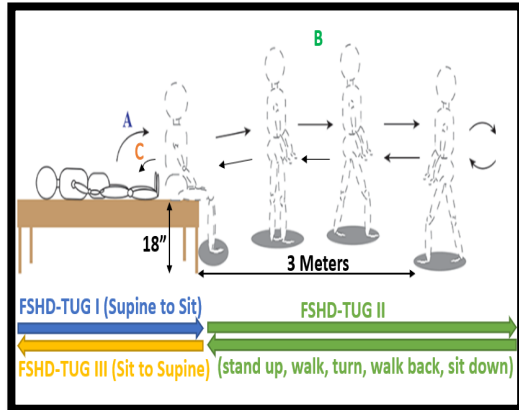


# Good Reproducibility for All Muscle Measurements

- Good reproducibility across all muscles
- Higher reproducibility in larger muscles

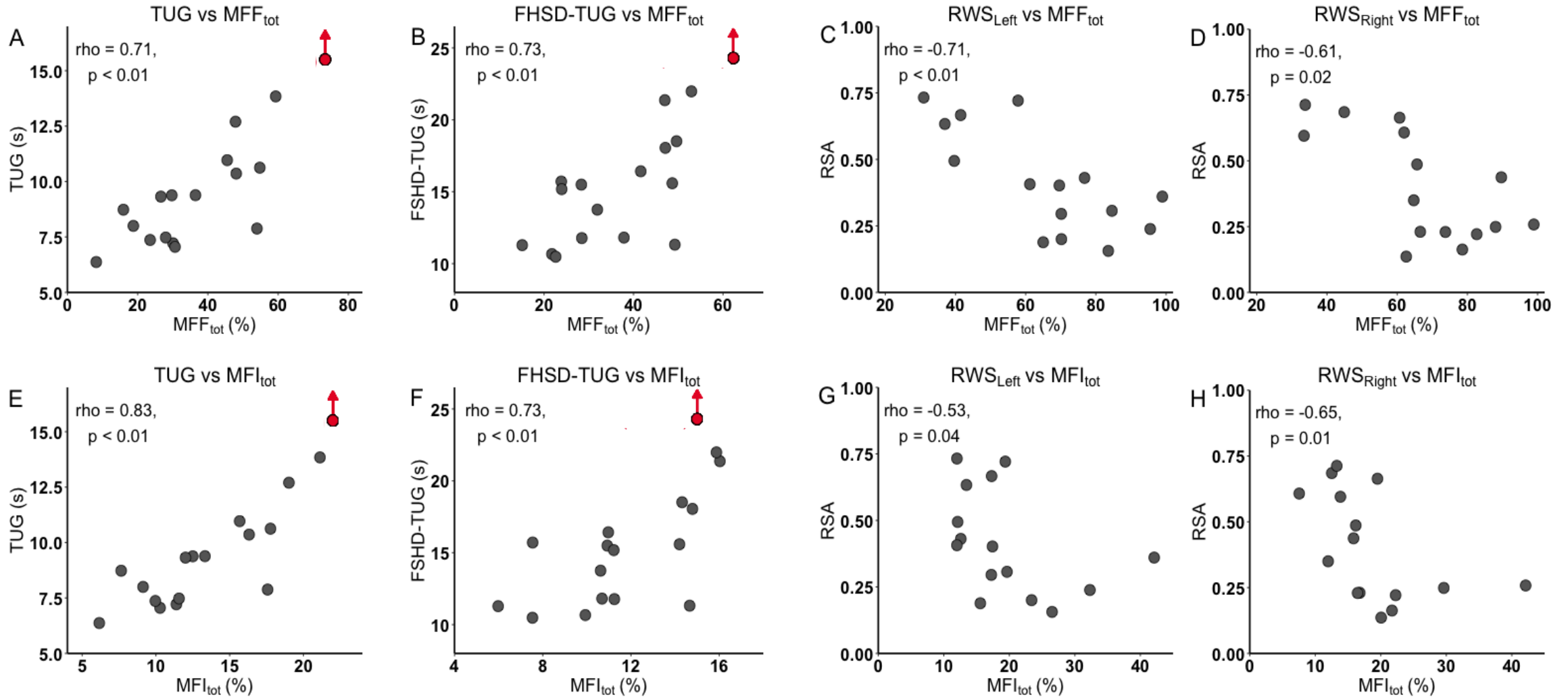


# Regional Composite Measurement ( $MFF_{tot}$ & $MFI_{tot}$ )



Test	Muscles		
	<u>Upper Extremity</u>	<u>Trunk</u>	<u>Lower Extremity</u>
<b>FHSD TUG</b>	Supraspinatus Infraspinatus Subscapularis Teres Minor Deltoid Biceps Brachii Triceps Brachii	Pectoralis Major Rhomboides Latissimus Dorsi & Teres Major Trapezius Serratus Anterior Paraspinal (C3-Sacrum)	Quadriceps Hamstrings Adductors Tibialis Anterior Gastrocnemius Medialis
<b>Classic TUG</b>	N/A	N/A	Quadriceps Hamstrings Adductors Tibialis Anterior Gastrocnemius Medialis
<b>RWS</b>	N/A	Pectoralis Major Rhomboides Latissimus Dorsi & Teres Major Trapezius Serratus Anterior	N/A

# Regional Composite Measurements ( $MFF_{tot}$ & $MFI_{tot}$ ) Show Strong Correlations with TUG, FSHD TUG and Moderate Correlations with RWS

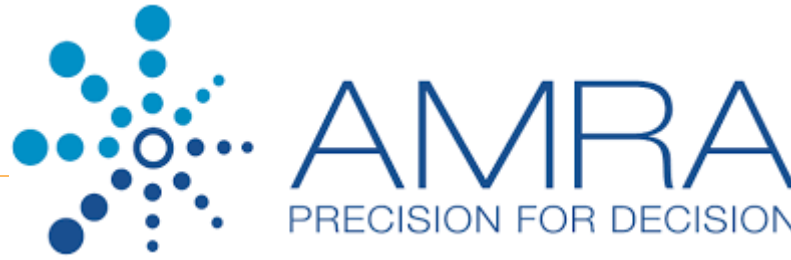


# Summary

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- Developed WB-MSK- MRI protocol
  - Currently being performed in all Phase 2 clinical trials of losmapimod
- Reproducibility of quantitative muscle measurements was excellent
- Strong cross-sectional correlation between Regional Composite Measurement ( $MFF_{tot}$  &  $MFI_{tot}$ ) and TUG, FSHD-TUG and RWS.
- **Whole Body-MSK MRI can capture the heterogeneity and provide important information about disease severity as it correlates with FSHD relevant clinical endpoints.**

# Thank you!



- ALL PATIENTS WITH FSHD

- Participating Sites



Kennedy Krieger Institute



**Radboudumc**  
university medical center



UNIVERSITY *of* WASHINGTON

- Collaborators



**UC Irvine**