

# Unlocking the Clinical Trial Toolbox

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# Outcome Measures



- Tools that help us:
  - **Measure** changes in a disease
    - Often a number, to determine if time A is different than time B
  - For use in clinical trials (or in clinic)
- Ideally outcome measures should:
  - Be pertinent to FSHD
  - Be reliable – what you measure one day you measure the next
  - Sensitive to progression in FSHD
  - Inexpensive
  - Collected at multiple sites in the same way

# Right Tool for the Right Job

- Measuring gene expression won't tell you whether someone is experiencing pain
- Different tools are important at different times in the drug development process
- You need more than one tool to build a house



# Matching the Outcome Measure to the Study Aim

- Biomarkers for early studies
  - Shorter time course, fewer patients
  - Often looking at safety and dosing
- Strength measures and functional measures for early effectiveness studies
  - Longer studies, often more people needed
- Patient reported / quality of life outcomes become more important in later phase studies
  - Overall impact of a treatment, on both physical and psychological aspects of a disease

# Biomarkers

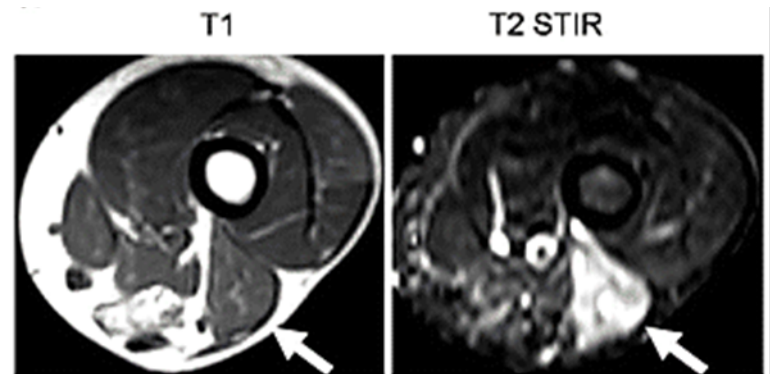
- Something you measure in blood or tissue: gene expression or proteins
- Other measurements, like neuroimaging, can also serve indirectly as a biomarker
- Important for:
  - Early studies, with small numbers of people
  - Monitoring early signals a drug might be working
  - Proof of concept – a drug is reaching its target
- Ideally a change in a biomarker early can be linked to a later change in the course of the disease

# Challenges: Biomarkers

- *DUX4* might seem like a good biomarker, but currently it is hard to measure directly
- Other genes affected by *DUX4* may be easier to measure
  - These 'downstream' changes appear to be more persistent
- Other proteins in serum either related to disease mechanism, or indirectly to other factors like muscle turnover, or oxidative stress may be useful
- However more work is needed to determine which molecular biomarkers will work best in FSHD

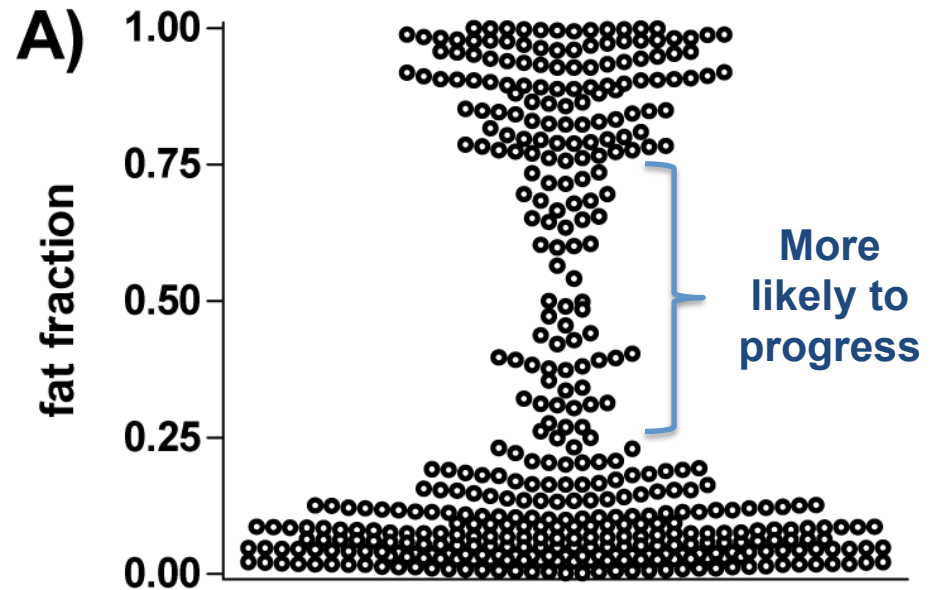
# MRI: non-invasive biomarker of disease progression?

- MRI uses magnetic fields and radio waves to look at the structure of muscle
- Changes on MRI might indicate active disease
  - May help target muscles at risk for progression
- MRI STIR+ muscles show increased expression of DUX4 downstream targets?



# MRI Continued

- Can also use MRI to measure lean muscle mass and fat content in muscle
- As muscles become weaker the fat content goes up
- Fat content might identify muscles at risk for progression



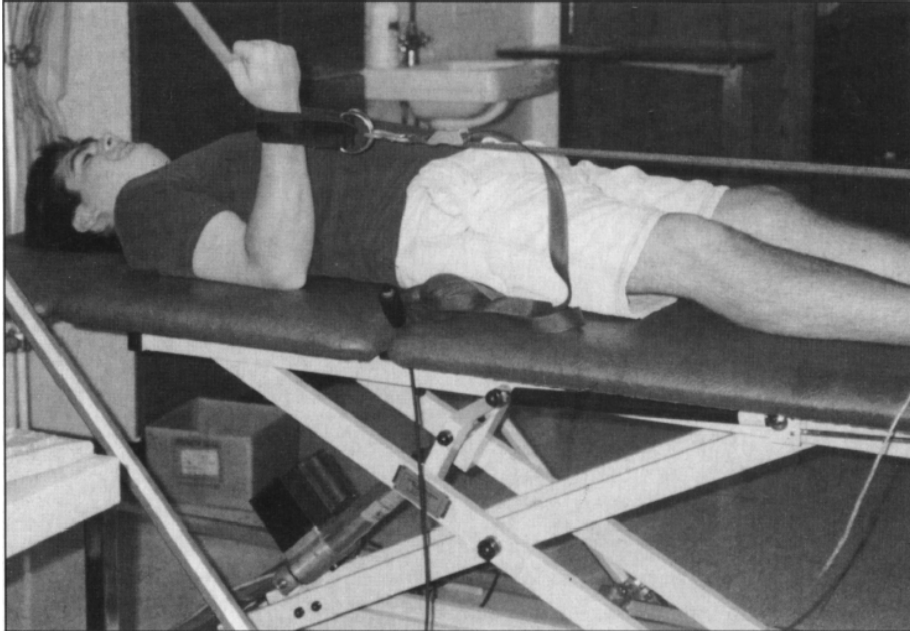


# Measuring Strength

- There two well studied methods for measuring strength in FSHD
  - Manual muscle testing (MMT)
  - Quantitative myometry (QMT)
- Strength would intuitively seem meaningful in a muscular dystrophy

# Background: QMT

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- Tests strength against fixed resistance
- Digital force transducer connected by an inelastic strap to metal frame
- Standardized positions for different muscles
- Can also use a handheld strength gage

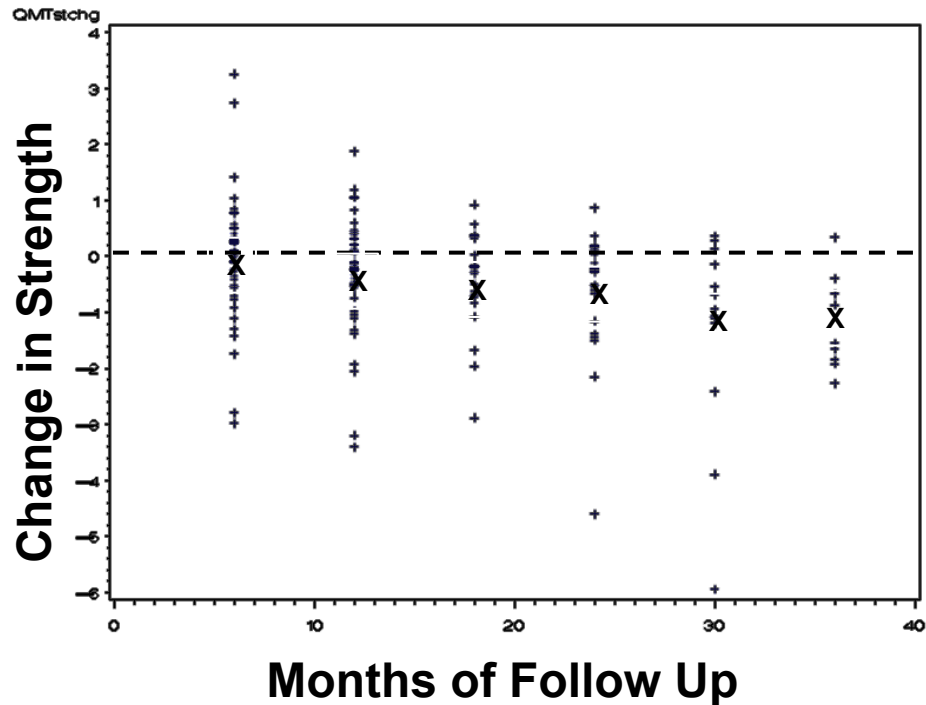
# Background: MMT

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- Manually test your ability to pull or push against resistance
- Standardized procedure for positioning
- MRC strength scale
  - Range: 5= normal strength; 3= against gravity but no resistance; 0 = no strength

# Natural History Combined Scores

- Both MMT and QMT are reliable and can be averaged across muscle groups to create combined score to follow progression over time
- MMT/QMT most sensitive measure to disease progression
- However small changes in strength can be difficult to put in 'clinical context'



# Functional Outcome Measures

- Tasks like:
  - Time to ascend 4 stairs
  - walk 30 feet
  - Lift objects over shoulder height
- FDA interested in outcomes which have correlate to activities in everyday life
- In FSHD: Moderate to strong relationship to disease severity or measures of strength
- But individually are not sensitive to progression in FSHD

# Patient Reported Outcomes

- Standardized questionnaires
  - SF-36
  - PROMIS 57
  - INQoL
- FSHD-Specific Health Inventory (Dr. Heatwole, URMIC)
  - Used patient interviews to determine the areas important to people with FSHD

## FSHD-HI Domains

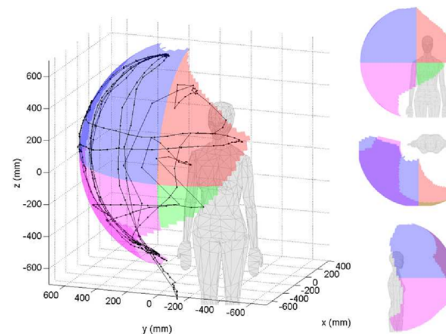
Problems with shoulders or arms  
Limitations with mobility or walking  
Inability to do activities  
Back, chest, or abdomen weakness  
Changed body image due to disease  
Fatigue  
Pain  
Decreased performance in social situations  
Problems with hands or fingers  
Decreased satisfaction in social situations  
Emotional issues  
Problems eating  
Difficulty thinking  
Communication difficulties

# In Development

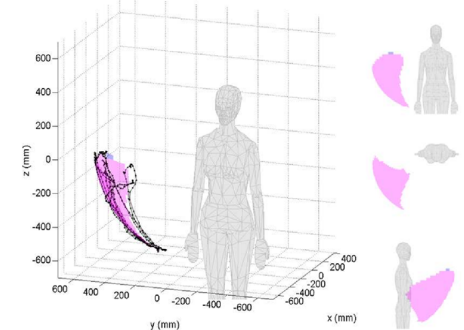
- Electrical impedance myography found to be a useful biomarker in other NM diseases
  - Impedance largely determined by muscle structure
- Reachable workspace using 3D camera system (Xbox Kinect)
- MRS to look at metabolites in muscles



Control Subject, RSA = 0.570



Subject #9 (FSHD), Brooke = 3, RSA = 0.115



# How Many People Are Enough?

- Depends on the **variability** of what you measure and **how big an effect** you think your therapy will have?
  - The smaller the variability or the larger the effect, the fewer people are needed for a clinical trial
- A better understanding of how our outcome measures work in FSHD will help us plan more efficiently for clinical trials



# Future Directions

- Current or planned outcome measure studies at the University of Rochester or Kansas
  - Disease-specific PRO and functional rating scale, and EIM (URMC, KUMC)
  - MRI and molecular biomarkers (URMC, KUMC)
- **Coordination** between sites is essential
  - Standardizing protocols - so we are all measuring things the same way
  - Building networks for future clinical trials

# Thank You

- FSHD patients and family members
- Your interest and support make our work possible!
- **Organizations**
  - FSHD Society
  - MDA Clinical Research Training Program
- **URMC**
  - Rabi Tawil, MD – mentor
  - Chad Heatwole, MD – collaborator
  - Kate Eichinger – PT
  - Shree Pandya – PT
  - Colleen Donlin-Smith – coordinator
- **KUMC**
  - Richard Barohn, MD – mentor
- **LUMC – the Netherlands**
  - Silvere van der Maarel - collaborator
- **Fred Hutchinson Cancer Center – Seattle**