clinical trial readiness

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Clinical Trial Readiness?

- We as a community are **stakeholders** in the process of drug development
  - We need to facilitate therapeutic development not just for the trials which are active now, but for all drugs that may benefit people with FSHD
- We need the tools in place, so we can be confident
  - We do not throw out drugs which might work
  - We do not approve drugs that will not help
- Ensure all stakeholders take part in the conversation
  - Industry
  - Academia
  - FSHD advocacy groups
  - People with FSHD, and their family members

Why Plan Now

URMC Patient Day! 2016

2nd Clinical Trial Preparedness Workshop

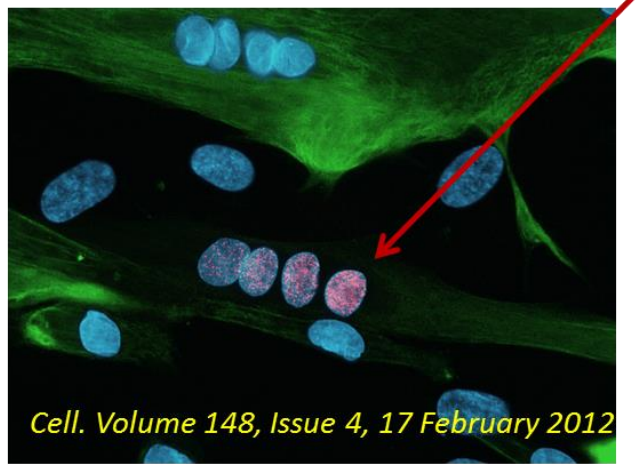
- From a practical POV there's a lot of work that needs to be done
  - Ensure standard techniques for how we measure things
  - Address gaps in understanding of what happens clinically over time
  - Develop tools for clinical trials, and make sure results are consistent when implemented across multiple locations
  - Figure out what features predict how fast the disease changes: e.g. mutation, age, gender
- Advocate nationally (internationally) for resources to pursue research and cures
- Without people volunteering for studies we cannot make progress
  - Your participation means a lot!!!!

Innovation and Collaboration

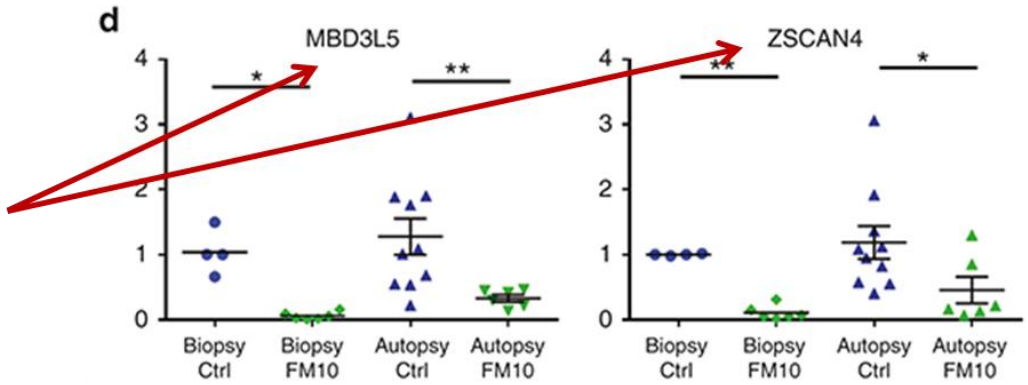
- Early on we need people working independently
  - Thinking of new ways to measure the disease
  - Thinking of new avenues for treatments
  - Thinking outside the box
- But ultimately we need people to then come together to test these new ideas in large groups of people (we need to prepare)
  - We want things that work for all people with FSHD
  - To ensure our assumptions about what our tools measure and how they measure it are true
- If we can agree on common approaches we can accelerate drug development
  - Examples: Duchenne Muscular Dystrophy, Spinal Muscular Atrophy
  - By joining together as a community they were able to hasten overall drug development

Getting Ready for Clinical Trials: Tools

- We've made advances in our clinical trial tools, but for each there is work that needs to be done
- Biomarkers: blood, tissue, other
  - Proof a drug is reaching its target



Downstream Targets of DUX4



Chen et al. *Molecular Therapy* (2016); **24** 8, 1405–1411.

Getting Ready for Clinical Trials: Tools

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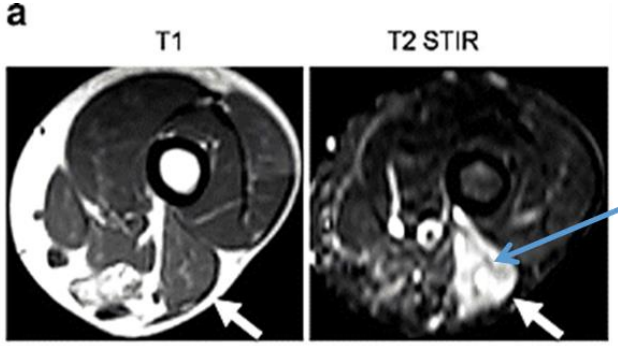
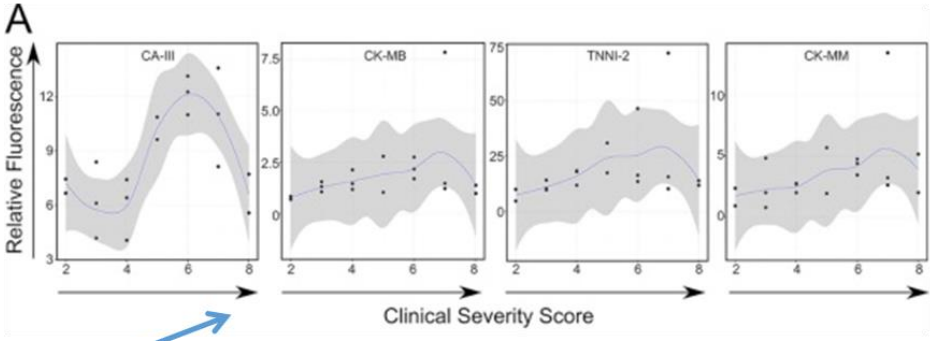
  - Proof a drug is reaching its target
  - Monitoring disease activity



Frisullo, G., et al. (2011) J Clin Immunol 31(2): 155-166.

MRI Can Measure:
Inflammation
Fat
Fibrosis

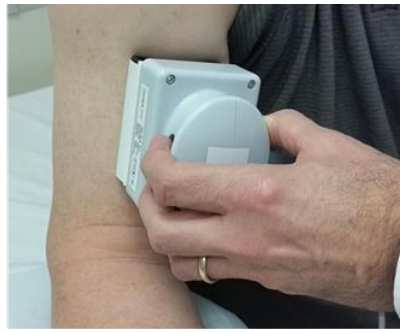


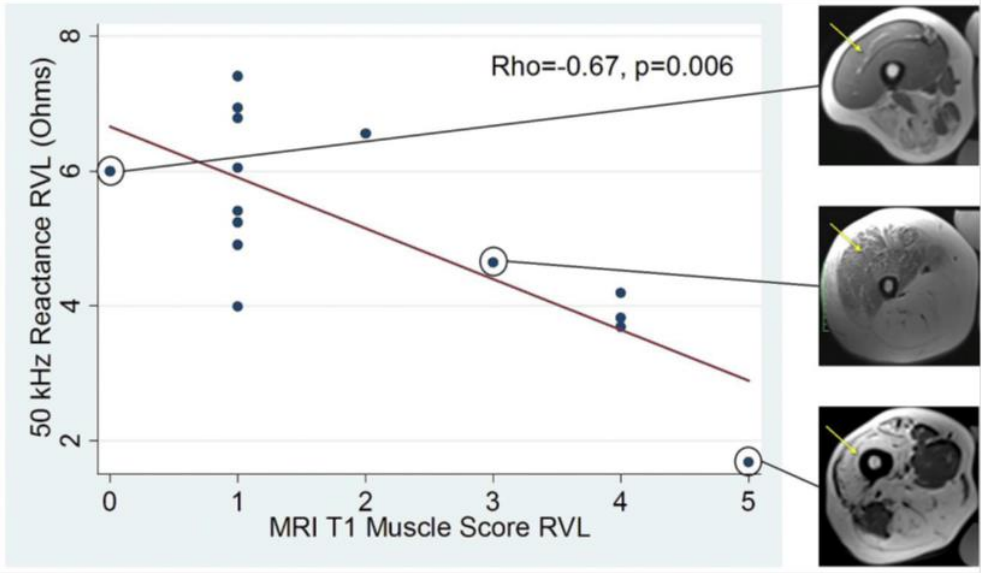
Petek, et al. Neuromusc Dis. (2016) Volume 26, Issue 7, 405–413

Serological Proteins
Which Might Track with Disease Activity

Getting Ready for Clinical Trials: Tools

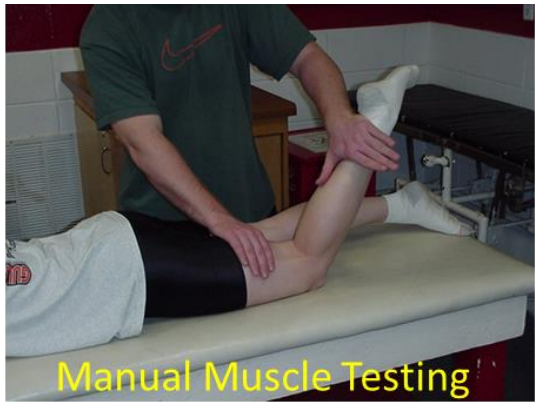
- We've made advances in our clinical trial tools, but for each there is work that needs to be done
- Biomarkers: blood, tissue, other
  - Proof a drug is reaching its target
  - Monitoring disease activity
  - Monitoring physiological changes
- Biomarkers important for early studies: as early signals, before we see changes in strength or function
- But before we can use them:
  - Need to standardize the technique
  - Show we can get consistent results from multiple centers
  - Understand how they naturally change in people with FSHD over time

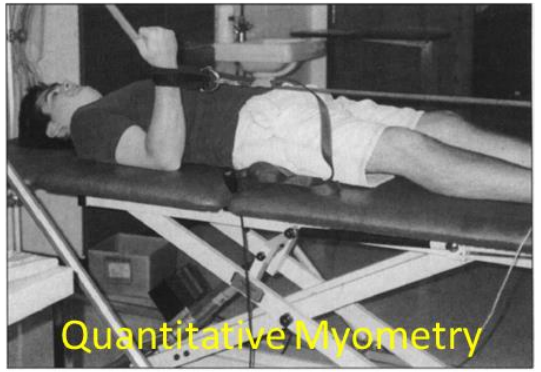




Getting Ready for Clinical Trials: Tools

- Strength and Function
- There are many techniques for measuring individual muscle strength


Manual Muscle Testing


Quantitative Myometry


Force During Movement


Handheld Dynamometry

Getting Ready for Clinical Trials: Tools

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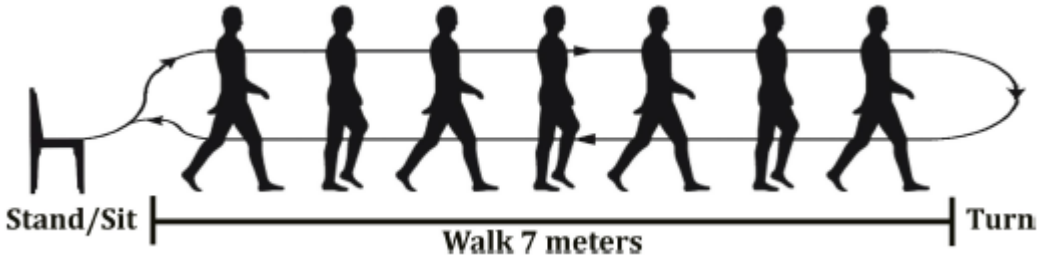
- Standard functional tasks include things like how fast you can go 30 feet, get out of a chair, climbing 4 stairs, or how far you walk in 6 minutes



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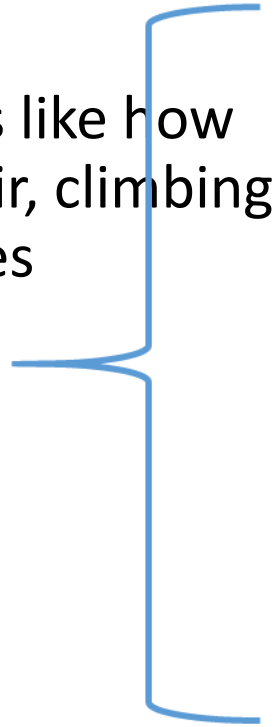
- Can combine tasks into a composite



North Star Ambulatory Assessment

Hammersmith Motor Ability Scale

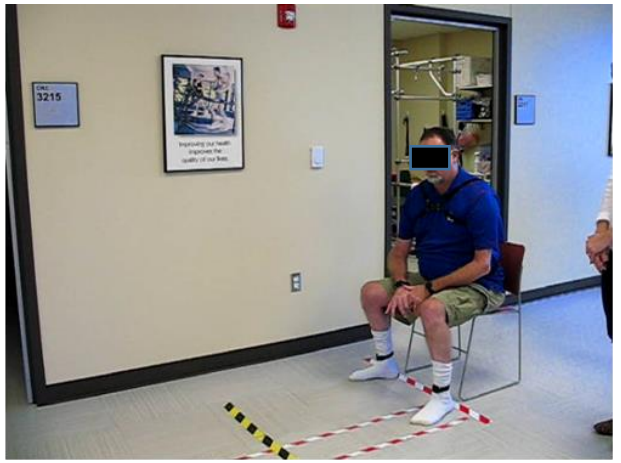
Performance Upper Limb Module

Motor Function Measure

FSHD – Composite Measure

Getting Ready for Clinical Trials: Tools

- Strength and Function
- There are many techniques for measuring individual muscle strength
- Standard functional tasks include things like how fast you can go 30 feet, get out of a chair, climbing 4 stairs, or how far you walk in 6 minutes
- Can combine tasks into a composite
- Can instrument a functional task
- There is still work that needs to be done:
  - We need to standardize our equiptment and procedures
  - Train our evaluators
  - Ensure we understand the relationship to genetics, age, gender, baseline functional status



Get Up and Go Motion Metrics	Normative Mean n=84 (SD)	FSHD Total n=17 (SD)	Number Outside Normative 95% CL (%)
Total Duration (seconds)	16.6 (2.2)	27.4 (7.1)	16 (94.1)
Stride length (%stature)	84.8 (5.8)	77.4 (8.1)	12 (70.6)
Stride velocity (%stature/s)	80.3 (8.9)	58.6 (12.8)	17 (100)
Cadence (steps/min)	113.4 (8.7)	90.1 (13.7)	16 (94.1)
Double support (%)	22.2 (4.1)	31.5 (7.5)	16 (94.1)
RoM Knee (degrees)	57.6 (3.7)	61.2 (7.4)	13 (76.5)
RoM Knee Assymetry (| Diff R-L |)	0	5.5 (3.6)	-
ROM Trunk Horizontal (degrees)	9.4 (2.6)	10. 0 (9.8)	4 (23.5)
ROM Trunk Sagital (degrees)	4.3 (1.0)	6.8 (3.0)	13 (76.5)
RoM Arm (degrees)	20 (8.3)	14.1 (6.2)	13 (76.5)
RoM Arm Assymetry (| Diff R-L |)	0	11.5 (10.7)	-
Turn: Duration (seconds)	1.9 (0.3)	3.2 (1.9)	15 (88.2)

Getting Ready for Clinical Trials: Tools

- Patient-reported outcomes
- Ask the question how a treatment impacts someone's life
- These can be standard instruments like: the Short-Form 36, the Individualized Neuromuscular Quality of Life Scale, the PROMISE scales
- Or disease specific
- Still need to:
  - Establish common instruments which cover full range of disability
  - Understand the normal variability from year to year
  - Determine if there are differences from region to region, culture to culture

Individual Interviews with people with FSHD

The FSHD Health Inventory

- 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

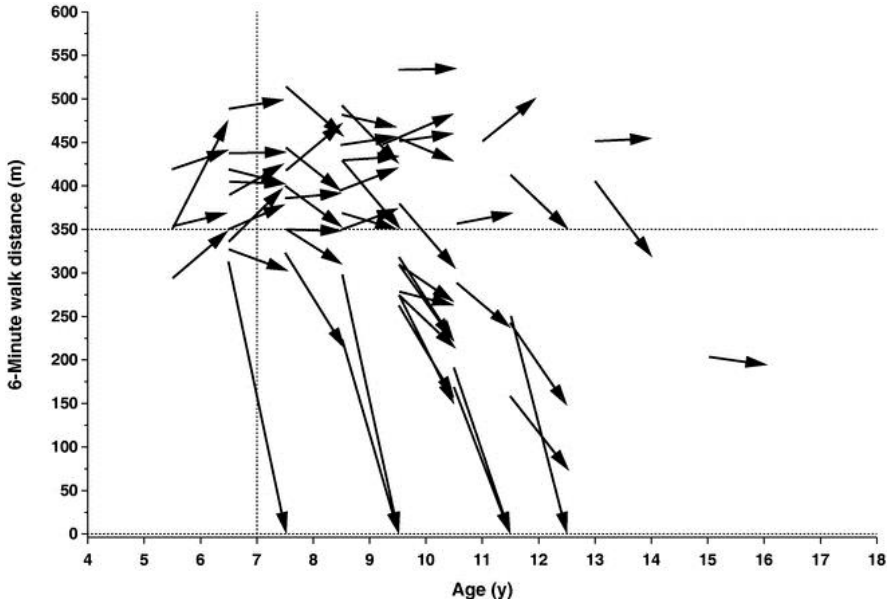
Developed by Chad Heatwole, MD

Survey sent to > 300 people with FSHD

Ranked symptoms by prevalence and impact on their lives

Getting Ready for Clinical Trials: Understanding disease progression

- The ability to understand the normal progression of FSHD and how it impacts the types of tools we choose for measurement can:
  - Help prevent us from rejecting a drug or therapy when it may actually work (example: DMD)
  - Help us design more efficient clinical trials
  - Reduce the burden on individuals participating, by allowing us to reduce the number of people required for early phase studies
  - Help us design confirmatory trials
- There are still several gaps in our understanding which need to be addressed:
  - How does genetics, baseline functional status, demographics influence rates of progression?
  - Are there simple tools we can use to 'predict' how someone might do over the next year?



McDonald CM, et al. Muscle Nerve. 2013 Sep;48(3):343-56.

Getting Ready for Clinical Trials: How big a change is meaningful

- Ultimately understanding how big a change would be meaningful can help make the argument for approval of a drug
- Short of hard outcomes like mortality, or time to requiring a wheelchair, or non-invasive ventilation we need other ways to determine how big a change would be meaningful
- This will depend on what the treatment is for
  - For example a drug designed to help with pain does not need to improve how you walk
- We can try and understand this using statistical techniques, by using questionnaires, or by relating a change in one measurement to a change in another
- Your voice / your opinion is important!!!

Future Directions

- We have collaborated with 7 large academic centers across the US, the FSH Society, and private funding to form an **FSHD Clinical Trial Research Network**
  - Our goal: to hasten therapeutic development for FSHD
  - We plan to work with drug companies, researchers, advocacy groups, and people with FSHD
  - To address gaps in our understanding of the natural history of FSHD, or the tools we use to measure changes in FSHD
  - To make large clinical data sets available to anyone with an interest in developing therapies for FSHD
- This network is getting started now and your participation can make a difference – you can contact me, my coordinator, or the FSH Society to find out how to take part

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