

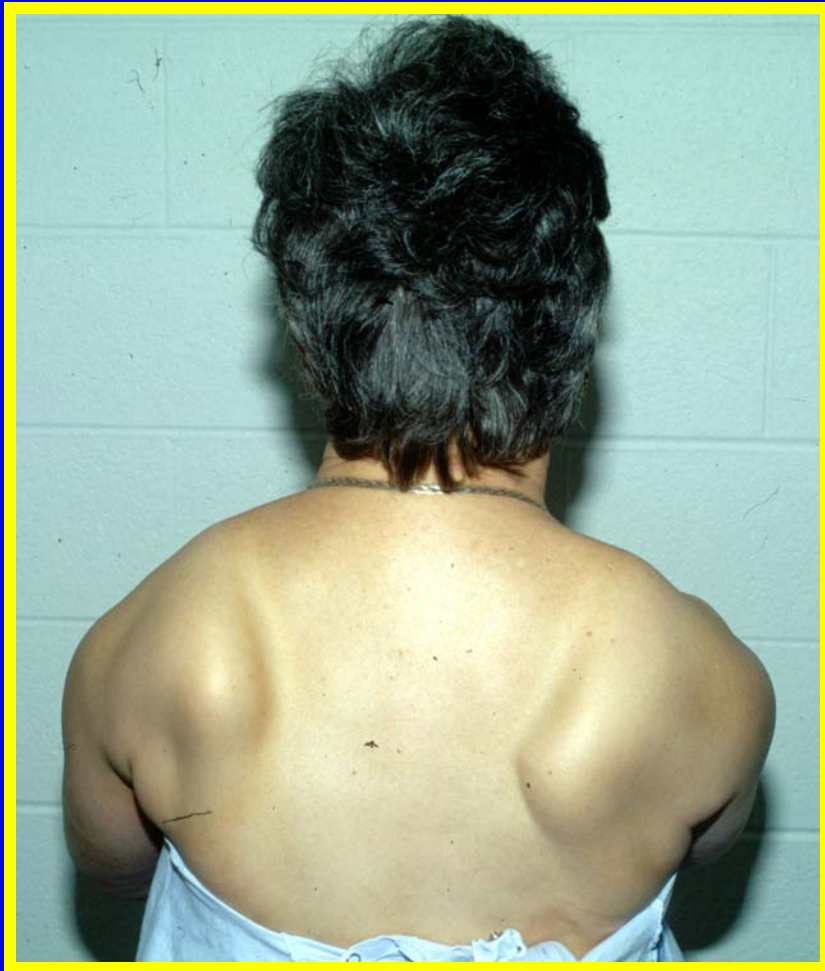
***Taking Stock of Natural History
Data in FSH Dystrophy:
The Good, Bad, & Missing***



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FSH Dystrophy

Overview & Epidemiology



- Autosomal dominant linked to chromosome 4q35 in 1991
 - 20-30% sporadic
- 3rd most common MD
 - Prevalence ~1:20,000
 - 1:15,000 in Utah; 50% in one kindred
 - NIH-FSHD Registry – 472 patients entered since 1/02

FSH Dystrophy

Clinical Features



- Symptoms begin < age 20 in ~80% of patients
 - Much variability
- Typically begins in face
 - Orbicularis oris, oculi, zygomaticus
- Subtle/absent in ~4%
- ~ 20-30% asymptomatic

FSH Dystrophy

Clinical Features



- Shoulder weakness presenting c/o in 80%
 - Lat. dorsi, lower trap, rhomboids, serratus
- Tibialis ant.-foot drop
- Abdominal weakness
- Asymmetric, variable
 - Study megascores

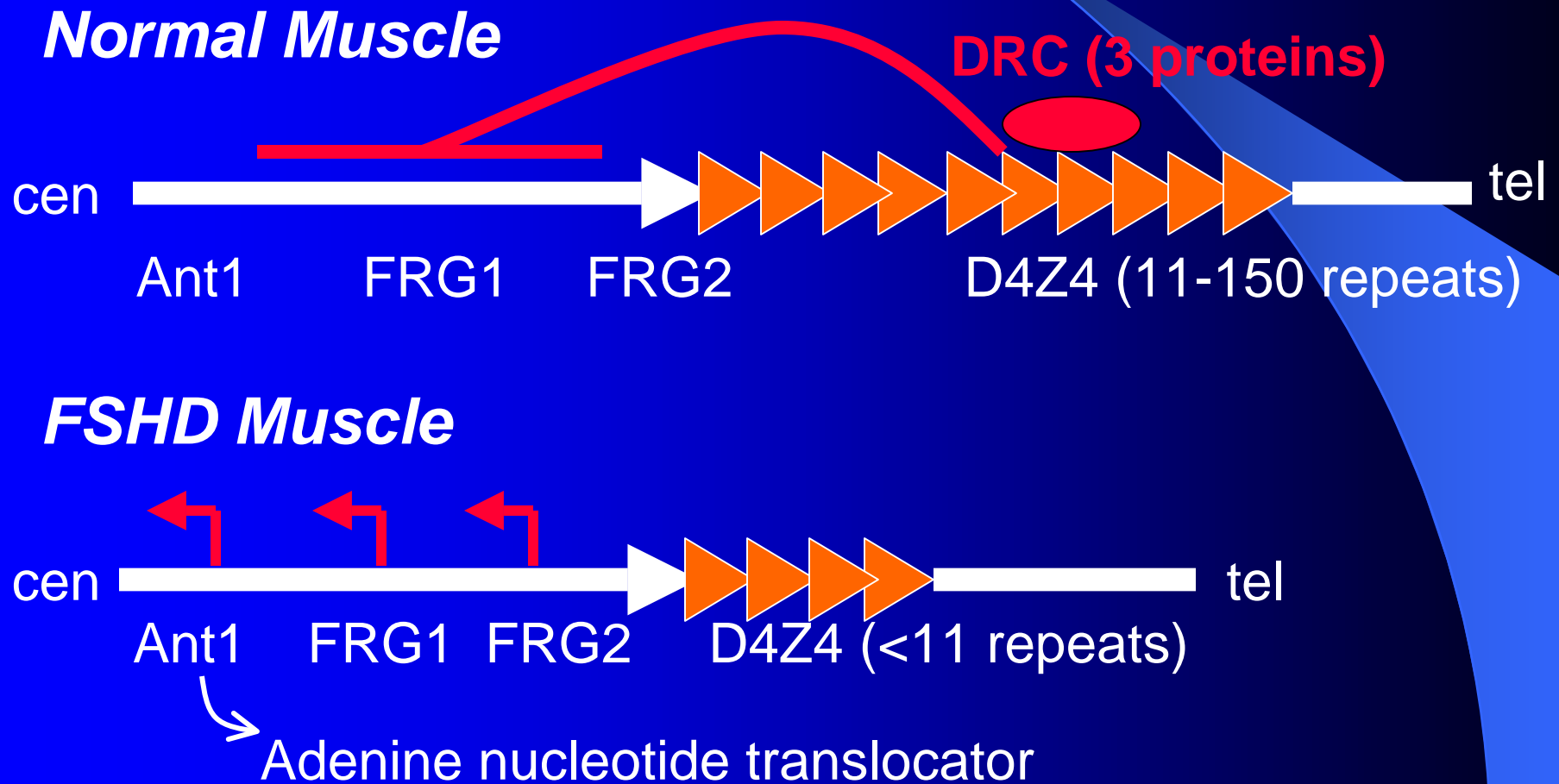
FSH Dystrophy

Genetics

- Probe p13E-11 detects EcoR1/BlnI “small fragment” on 4q35 (A allele *only*)
 - ~95-98% of all FSHD (FSHD1A)
 - Normal 38-300 kb; FSH < 35 kb
- Deletion of 3.3 kb repeated sequence (D4Z4) with heterochromatin features
- Fragment size correlates inversely to severity
- No genes found in deleted repeat area

“Inappropriate Gene Activation in FSHD”

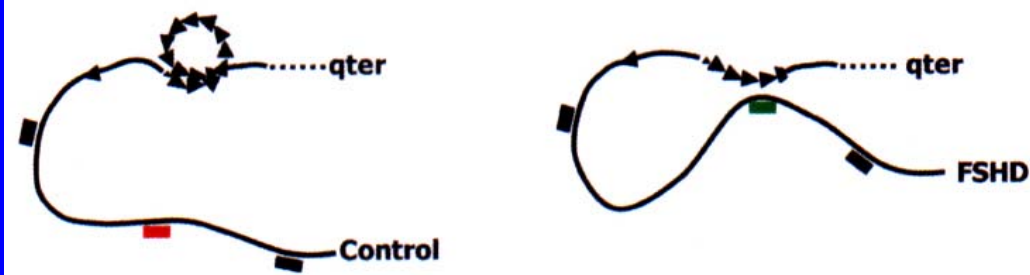
Gabellini et al, Cell - August 2002



D4Z4 Pathogenesis of FSHD

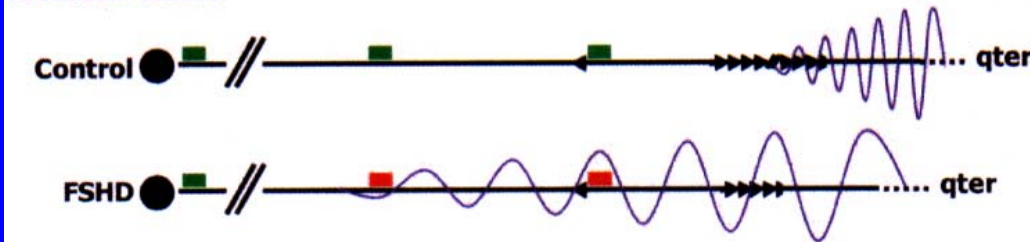
van der Maarel & Frants, 2005

Cis-looping model



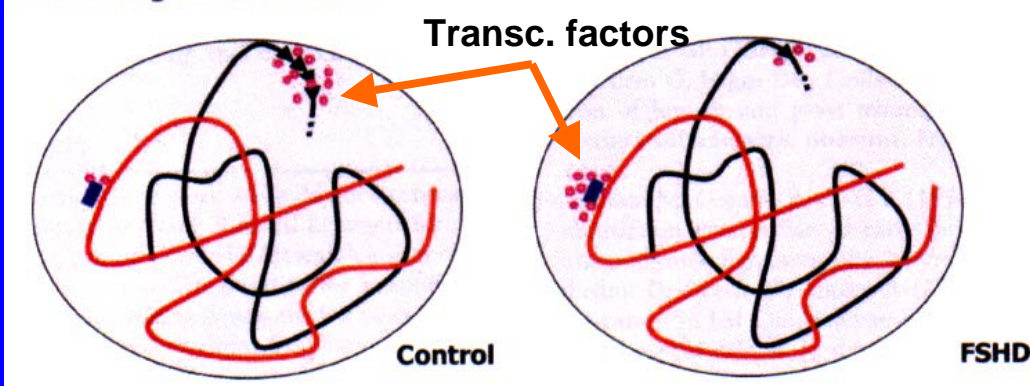
Increased expression
- distant genes

Insulator model



Decreased expression
- local genes

Nuclear organization model



Nuclear envelope dx.
- local, distant genes
- Affect myogenic differentiation

The FSH-DY Group

Natural History Studies

- Begun in 1989 at OSU, Rochester
 - Became part of Muscle Study Group
- Develop protocols to assess natural hx.
 - Genotype/phenotype correlations
 - Conduct therapeutic trials
- Evaluated 300 patients in >70 families
- Conducted 3 clinical trials
 - DB-RCT of albuterol

FSHD Natural History Studies

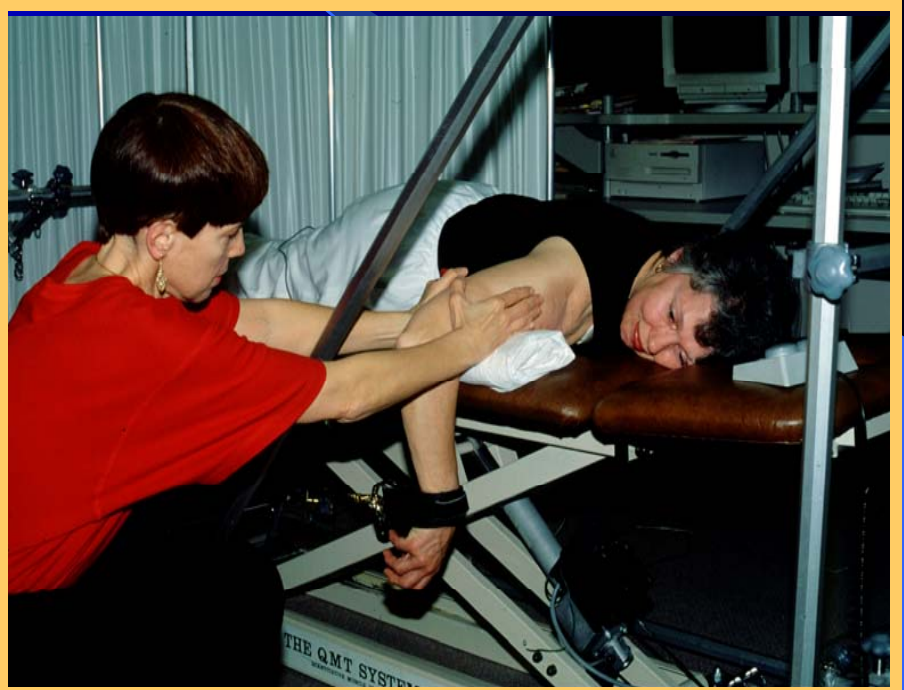
Parameters Assessed

- 81 patients seen q 6 mos for 3 years
 - Pre-DNA testing, clinical criteria
- 18 muscle groups (9 per side) tested
 - MMT (10-point composite AMS)
 - MVICT scores (regression analysis to normals, composite z-score)
- Muscle mass (24 hr urinary Cr excretion)
- Functional testing – PFTs, timed tests
- Arm (9) & leg (5) functional grades

Muscle Testing Technique



Hip Extension
(MMT)



Sh. External Rotation
(MVICT)

Prospective Studies in FSHD

The FSH-DY Group; Neurology

Facioscapulothumeral muscular dystrophy (FSHD): Design of natural history study and results of baseline testing

1994

R. Tawil, MD; M.P. McDermott, PhD; J.R. Mendell, MD; J. Kissel, MD;
R.C. Griggs, MD; and the FSH-DY Group*

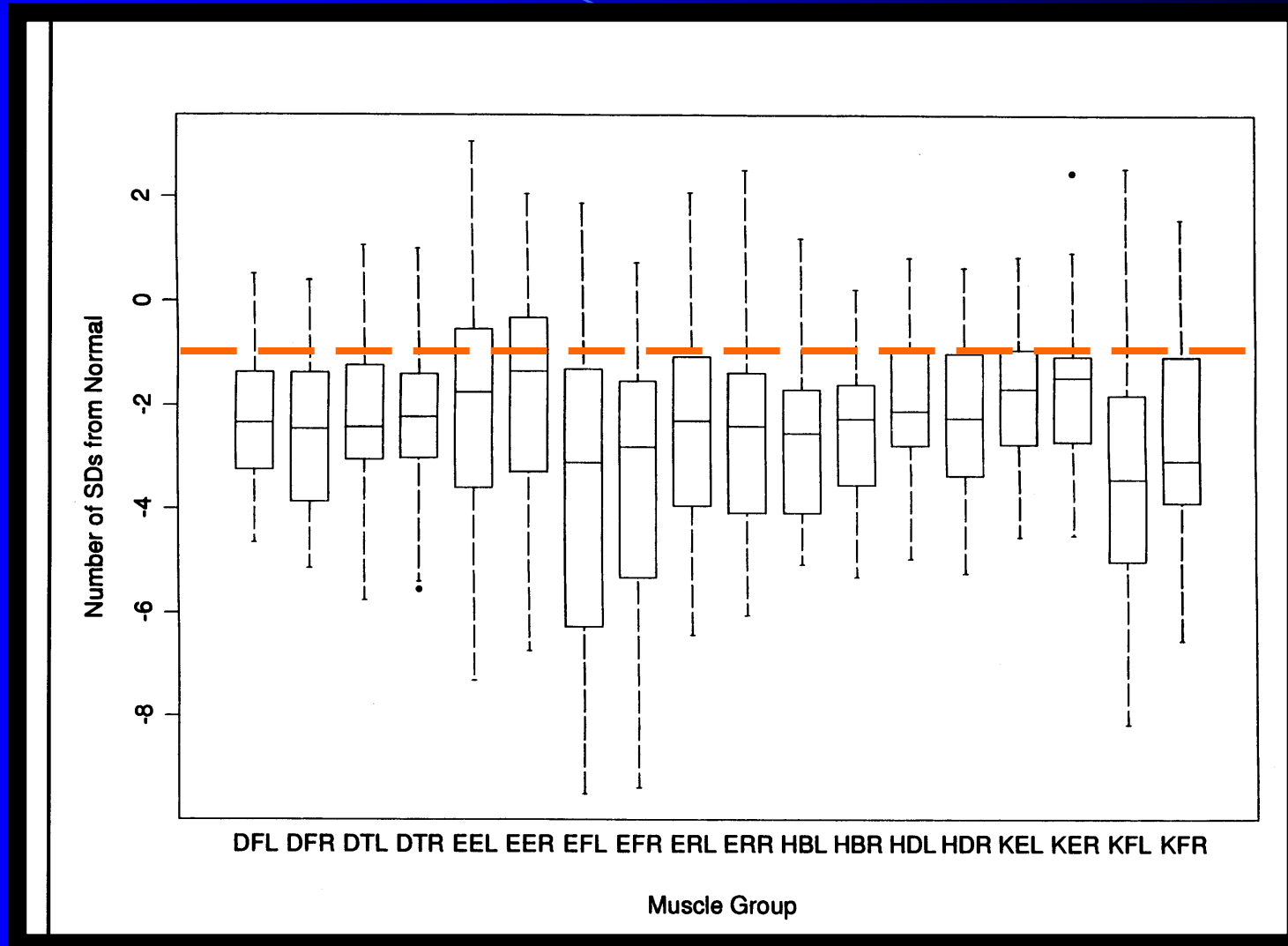
A prospective, quantitative study of the natural history of facioscapulothumeral muscular dystrophy (FSHD):

1997

Implications for therapeutic trials

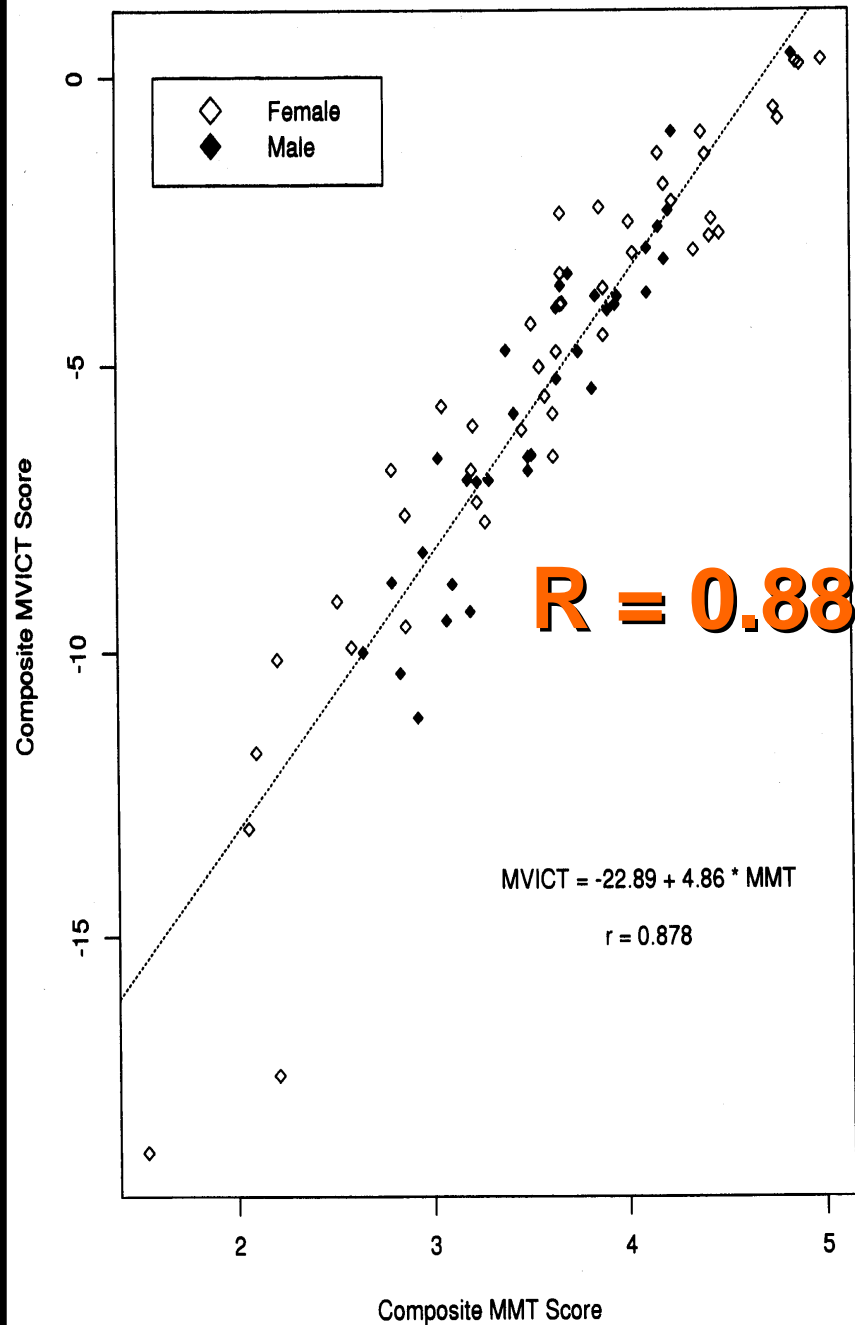
The FSH-DY Group*

MVICT Muscle Scores - FSHD



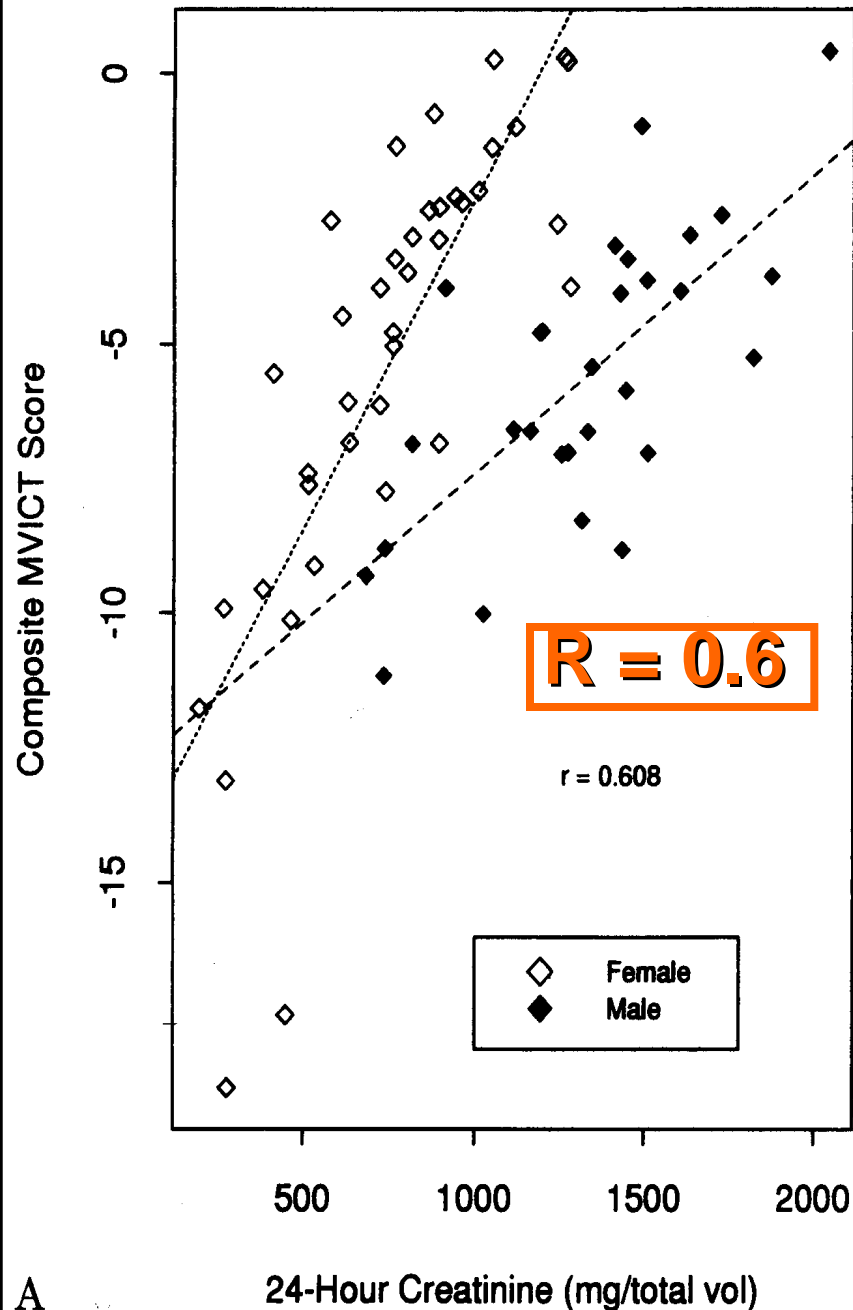
Results similar for MMT

MMT/MVICT Correlation



- Any disease severity
- True for males *and* females
- True at all time points
- Which best for clinical drug trials?

Strength - Muscle Mass Correlation



- True for both MMT & MVICT ($r=0.6$)
- Different slopes for men & women
- Subsequently shown for DEXA muscle mass
- ? Surrogate marker for clinical trials?
 - Not in albuterol study

Change in Strength Over Time

The FSH-DY Group, Neurology, 1997

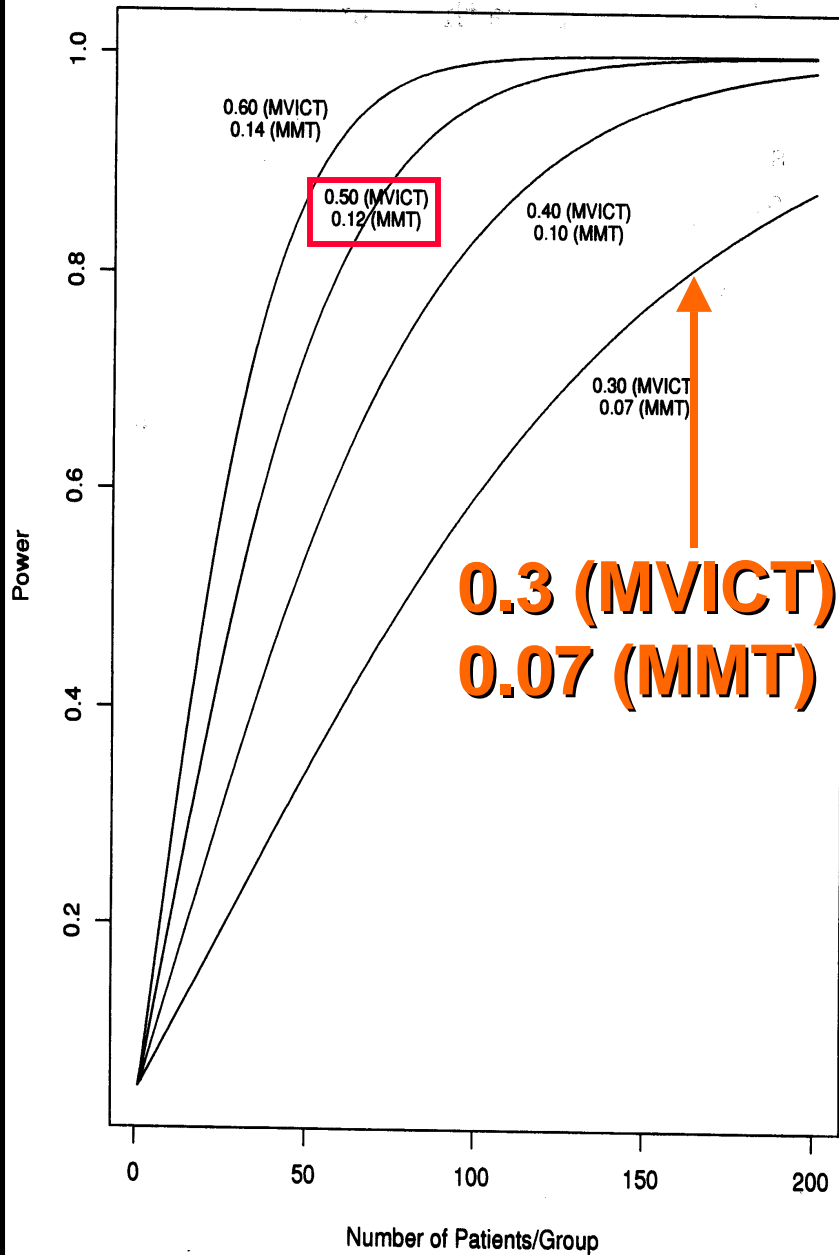
Table 3 Longitudinal changes in composite muscle strength scores

Variable	Composite MVICT score				Composite MMT score			
	<i>n</i>	Mean	SD	<i>p</i> -value	<i>n</i>	Mean	SD	<i>p</i> -value
Change from baseline to								
6 months	48	-0.02 ^a	1.06	0.91	48	-0.05	0.19	0.09
12 months	50	-0.29	0.96	0.04	47	-0.07	0.23	0.05
18 months	22	-0.44	0.89	0.03	17	-0.09	0.16	0.04
24 months	23	-0.62	1.11	0.01	20	-0.16	0.27	0.01
30 months	13	-1.32	1.81	0.02	7	-0.27	0.23	0.02
36 months	9	-1.20	0.85	0.003	8	-0.31	0.23	0.007

^a Negative values indicate a decline in strength from baseline.

1) No change at 6 months. 2) MMT = MVICT

Power Curves



- For PR-DBPCT, need 160 patients/group to detect disease arrest with 80% power
 - A lot of patients!
- 50 patients/group, detect +0.5 MVICT, 0.12 MMT units

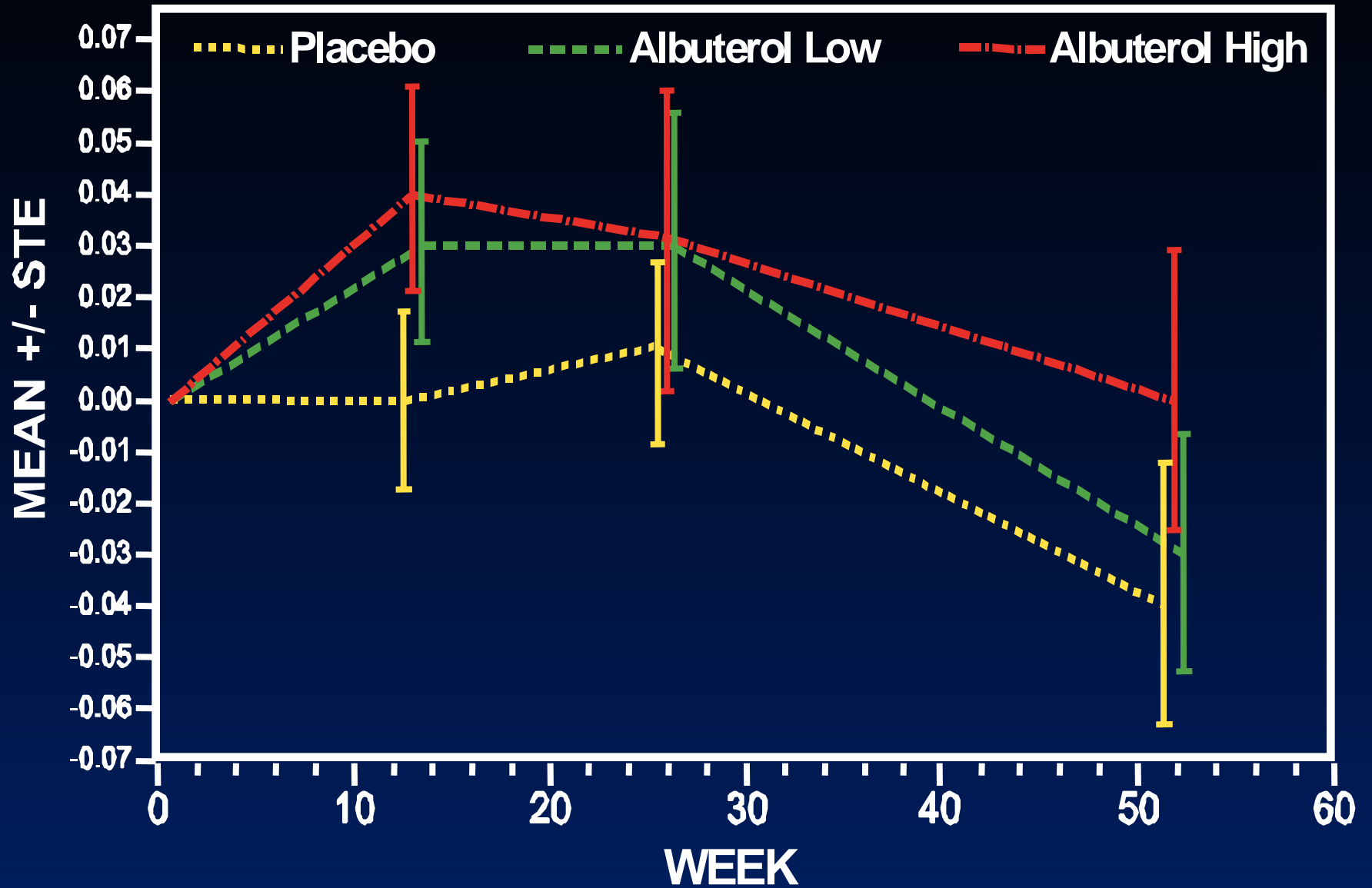
FSH Dystrophy

Therapeutic Avenues

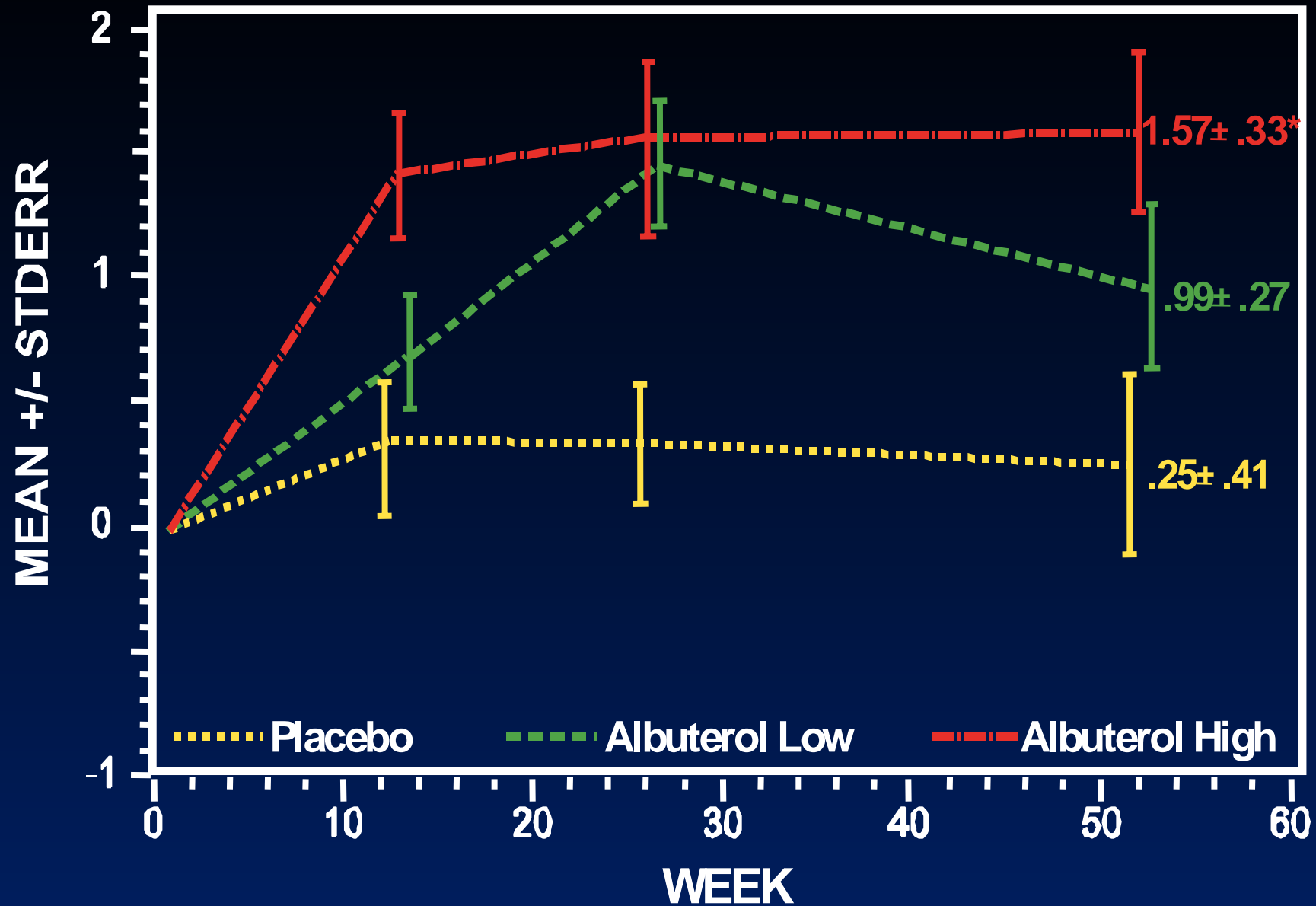
<u>Author</u>	<u>Year</u>	<u>Agent</u>	<u># Pts.</u>	<u>Dur.</u>	<u>Effect</u>
Tawil*	1997	Pred.	8	12	NS
Walter	2000	Creatine	12	8	NS
FSH-DY	2001	Albuterol	90	52	NS
van der Kooi	2004	Albuterol Exercise	65	26	NS
Wyeth	2005	Myo-029	36	24 (36)	

* Not DB-RCT

Change in Avg MMT



Change in Average Lean Body Mass by DEXA



* P=.006

Functional Testing



- Forced vital capacity
- Pinch dynamometer
- Timed function tests
 - Climb 4 stairs
 - Walk 30 feet
 - Sip 6 oz water
 - Rise from chair
- Arm (9) and leg (5) functional *grades*

Functional Testing

- Standard deviations too high
 - Jamar dynamometer for pinch
 - Sip 6 oz. water from a cup
- Not change enough over natural hx. study
 - Forced vital capacity
 - Walk 30' & climbing 4 standard stairs
 - Functional grades
- **Simply NOT capturing useful data**
 - Financial, practical, ethical implications

FSH Dystrophy

Burden of Disease

- Does not shorten life
 - 1% of 800 Dutch patients needed ventilatory support (Wohlgemuth, 2004)
- 50% get *symptomatic* pelvic weakness
 - 10-20% need wheelchair
- Long periods of stable strength
 - Variable severity and progression
- “Affects every aspect of my life”
 - No functional scale or QOL measures

FSH Natural History Studies

The Good

- Solid strength data on progression extending up to three years out
 - Standardized methods for MMT & MVICT
 - Permits detailed power calculations
 - Validated in two PR-DBPC clinical trials
- Linear relationship between MMT, MVICT
- Linear relationship for **both** with muscle mass

FSH Natural History Studies

The Bad & Missing

- Patients enrolled based on *clinical* criteria
 - No data for asymptomatic/atypical patients
- Data past two yrs based on very small #s
 - ? if long term stable periods really exist
- How to account for asymmetry and variability for muscle megascores
 - May be masking clinical effect
- Don't know what "clinically significant" strength change is
- **No validated FRS or QOL measures!**

The FSH-DY Group Members

The Ohio State University

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Funding Agencies

MDA, NIH, State of New York

Leg Functional Grades

1. Walks, stairs without assistance
2. Walks, stairs with railing
3. > 4 seconds for standard stairs
4. Walks, out-of-chair, but no stairs
5. Walks, no chairs, stairs

Arm Functional Grades

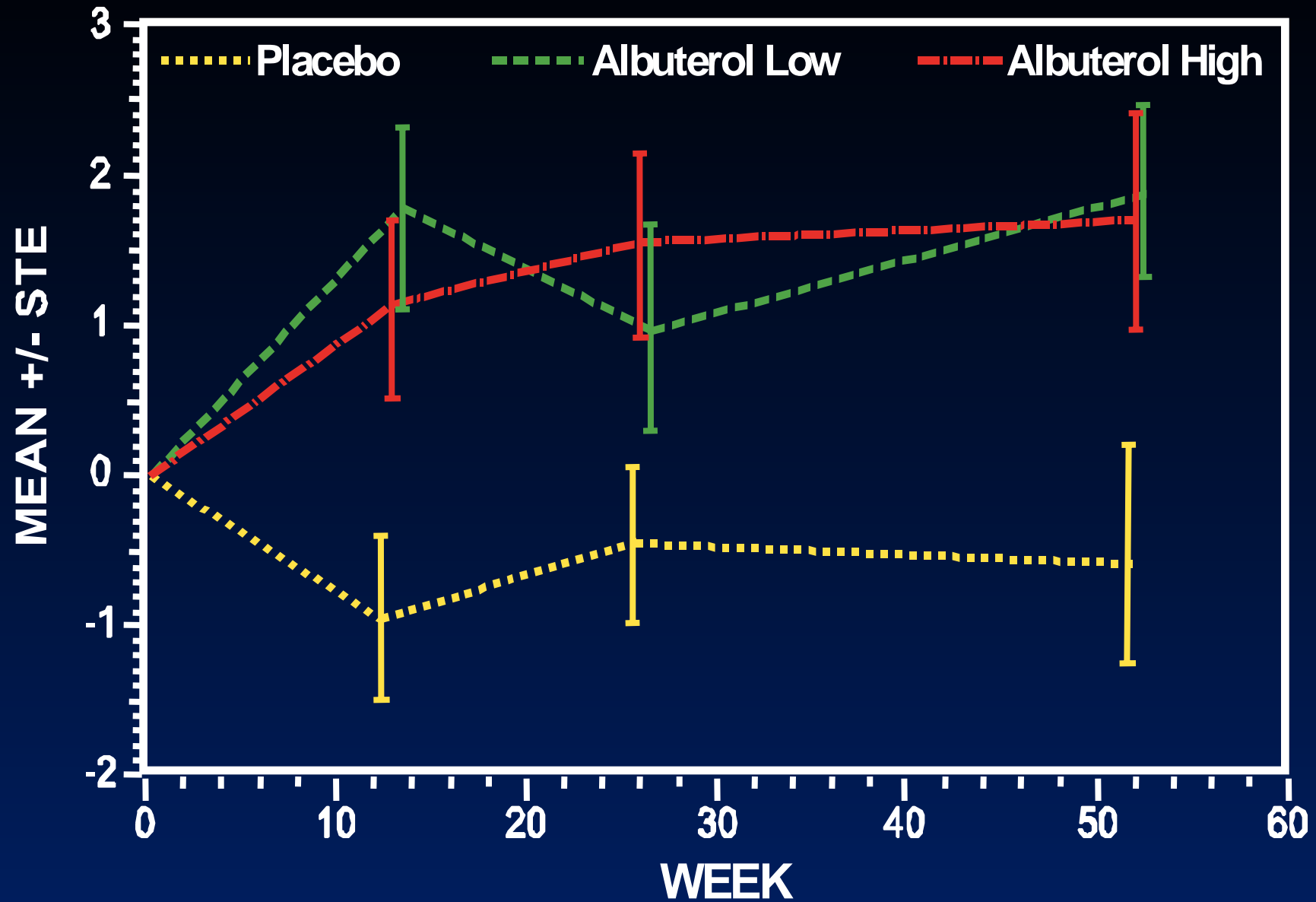
1. Abducts full circle, arms straight
2. Abducts full circle, arms flexed
3. Abducts $>90^\circ$ on trunk
4. Abducts $>90^\circ$ on trunk, but $<45^\circ$
5. Cannot abduct $> 45^\circ$, but can raise glass
6. Two hands to raise glass
7. Can raise hand to mouth, but no glass
8. No hand to mouth, but handles objects
9. No useful hand function

FSHD Natural History

Muscle Groups Tested

- Assess 9 muscle groups testable by *both* MMT and computerized MVICT:
 - Elbow flexion and extension
 - Shoulder abductors and external rotators
 - Horizontal abduction and adduction
 - Knee flexors and extensors
 - Ankle dorsiflexors
- Test both sides (18 groups total)

Change in Avg Grip Score



MVICT Score Standardization

- Regression model constructed relating log (MVICT score) to age, sex, height
 - Based on 168 *normal controls*
 - Model constructed for *each* muscle
- Pts. score =
$$\frac{\text{actual} - \text{predicted score}}{\text{estimated SD for model}}$$

MVICT Score

Example

- For left elbow flexor in male:

$$Y = -292.25 - (2.29 \times \text{age}) + (3.46 \times \text{ht})$$

- Age 39.9, 171 cm pt. scoring 163 newtons

$$Y = -292.25 - (2.29 \times 39.9) + (3.46 \times 171.0) \\ = 228.57 \text{ newtons}$$

- $Z = \frac{163.0 - 228.57}{25.60} = -2.56 \text{ SD units}$
25.60 (estimated SD for that muscle)

MVICT Score

Standardization

- Score represents the # SDs below average “normal” for age, height, sex
- Composite score easily derived by *averaging* individual scores for all 18 muscles
- Regional scores also easy to determine
 - Arm or leg regional scores

MVICT Standard Dev Score

Advantages

- Same conceptual strategy as MMT
 - “Real” weakness compared to normals
- Avoids giving undue weight to large muscles
 - eg. KE 0-700 newtons; EE 0-200 newtons
- Superior to “percent predicted normal”
 - Compensates for inherent variability in tests
- Uses normals for calculation of megascores
 - Can be used for other diseases

FSHD Muscle Testing

Conclusions

- MMT = MVICT for global, composite scores
 - MVICT > MMT for single, regional muscles
- Both useful in conducting therapeutic trials
 - Which is “best” in documenting improvement is unclear, and awaits successful agent
 - Expanded #s muscles currently being tested
- Better functional measures are needed

Change in Strength Scores

<u>Time</u>	<u>N</u>	<u>Δ MVICT</u>	<u>P</u>	<u>Δ MMT</u>	<u>P</u>
6 mo.	48	-0.02 \pm 1.06	0.91	-0.05 \pm .19	.09
12 mo.	50	-0.29 \pm 0.96	0.04	-0.07 \pm .23	.05
18 mo.	22	-0.44 \pm 0.89	0.03	-0.09 \pm .16	.04
24 mo.	23	-0.62 \pm 1.11	0.01	-0.16 \pm .27	.01
30 mo.	13	-1.32 \pm 1.81	0.02	-0.27 \pm .23	.02
36 mo.	9	-1.20 \pm 0.85	0.003	-0.31 \pm .23	.007

FSHD Natural History Trial

- **Spectrum of disease-** have not covered well
 - Atypical (~2-5%) and asymptomatic (~25%) need to follow-up ALL of them
 - Pediatric/infantile patients
 - FSHD phenotype with negative 4q35
- **Demographics-**
 - ? racial preference
 - Better disease ascertainment

FSHD Natural History Trial

- **Outcome measures**
 - Primary outcome - FRS to be validated
 - Compared to strength data
 - ? across diseases - doubtful
 - Quality of life measures – good in theory but how to validate (InQoI)?
- **Long-term studies – X-sectional/retrospective**
 - Milestone data needed (death, wheelchair)
 - Prognostic factors

FSHD Natural History Trial

- **Genetic Information** - genetic confirmation for all
 - ? borderline deletions
 - Centralized genetic testing facilities
- **Adverse Events/Complications**
 - Heart, sensorineural deafness, retinal vascular events, oropharyngeal involvement, pain, orthopedic pathology, depression and psych issues need definitive answers