

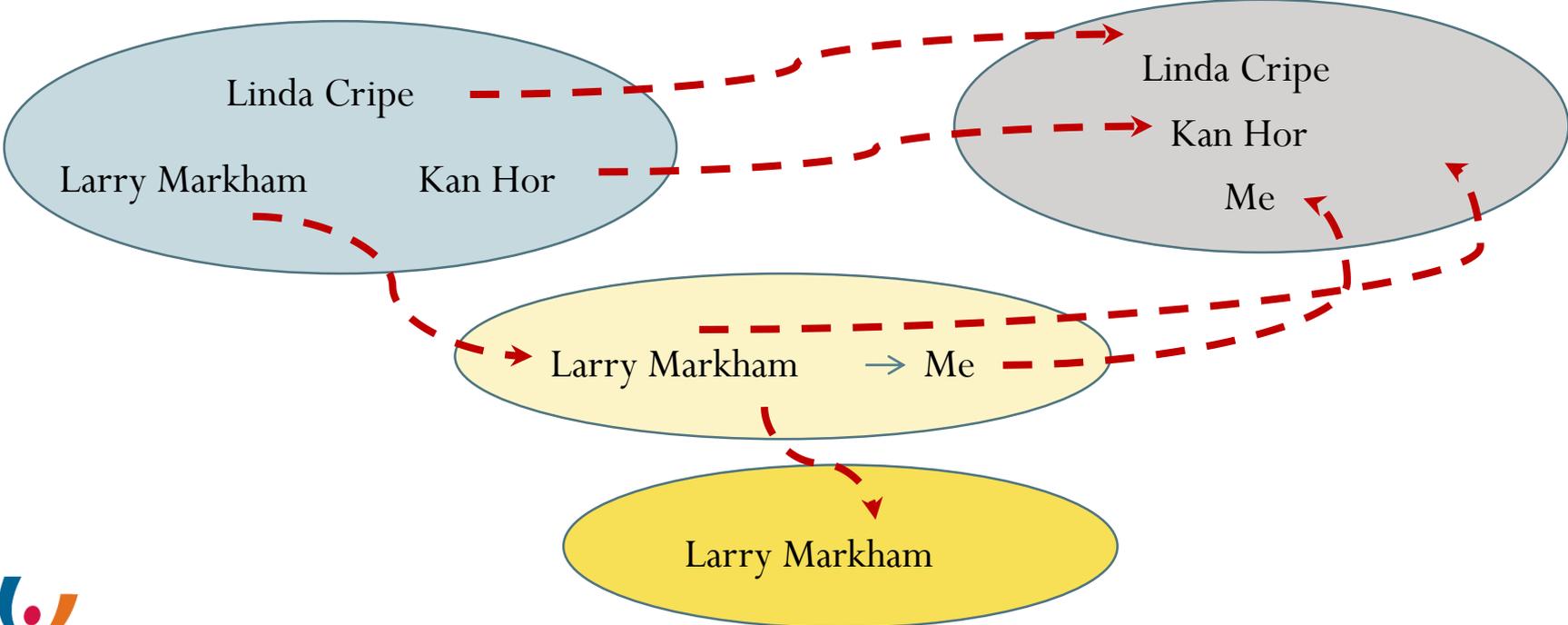
Determine the incidence and prognosis of clinically significant cardiac, skeletal muscle, and cognitive impairment in carriers of Duchenne and Becker Muscular Dystrophy

Parent Project Muscular Dystrophy  
National Meeting 2018  
Scottsdale, Arizona

May Ling Mah, MD MS  
No disclosures



# Past History is Important



Where you come from is important (circa 1978)



# Acknowledgements (Part 1)

- I know this is hard . . .
- The idea of “carried” disease
- Despite this, 100 women (and counting) have participated in our study.



# What we think we know

- Often cardiac disease is the only manifestation
- Definition of cardiac disease is unclear
- Diagnostic tool has been echocardiogram
- Newer studies suggest much higher incidence of cardiac and non-cardiac problems at a younger age than previously published

NMD 1999, 2003; Lancet 1999; JAMA 1996



# What is Known: Basis for Expression of DMD in Carriers

- Some carriers have reduced production of dystrophin
- X-Chromosome **Inactivation** of the normal allele (chromosome) associated with clinical manifestation
- Bottom Line: There is a basis for the existence of the “disease” of carrier cardiomyopathy



Viggiano E, et al. Clin Genet 2013



# The Knowledge Gap

You Are Here



What is  
Known

Treatment



# Where to do we really start?

Major Gap in carrier cardiac disease knowledge...

You can not treat what you do not know

No clear treatment recommendations or benefits based on current findings

## This is Step One

To define disease prevalence and severity

Gives us the knowledge to determine the need, type  
and timing of treatment as well as to monitor efficacy



# Impact of diagnosis

- Psychosocial (positive and negative)
- Is there a lead-time impact for treatment?
- Is there a role for standard “heart failure” treatment in this population?
  - Myopathic process compounded
    - Age
    - Acquired Disease
    - Impact of Own-Health and Caregiver Stress



Acquired  
Heart  
Disease  
Risks

**How do these  
different areas  
affect cardiac disease in  
DMD Carriers?**

Cardiac Disease

Genetics

Neuromuscular  
Disease

Pregnancy

Caregiver  
and Health-  
Related  
Stress

Cognitive

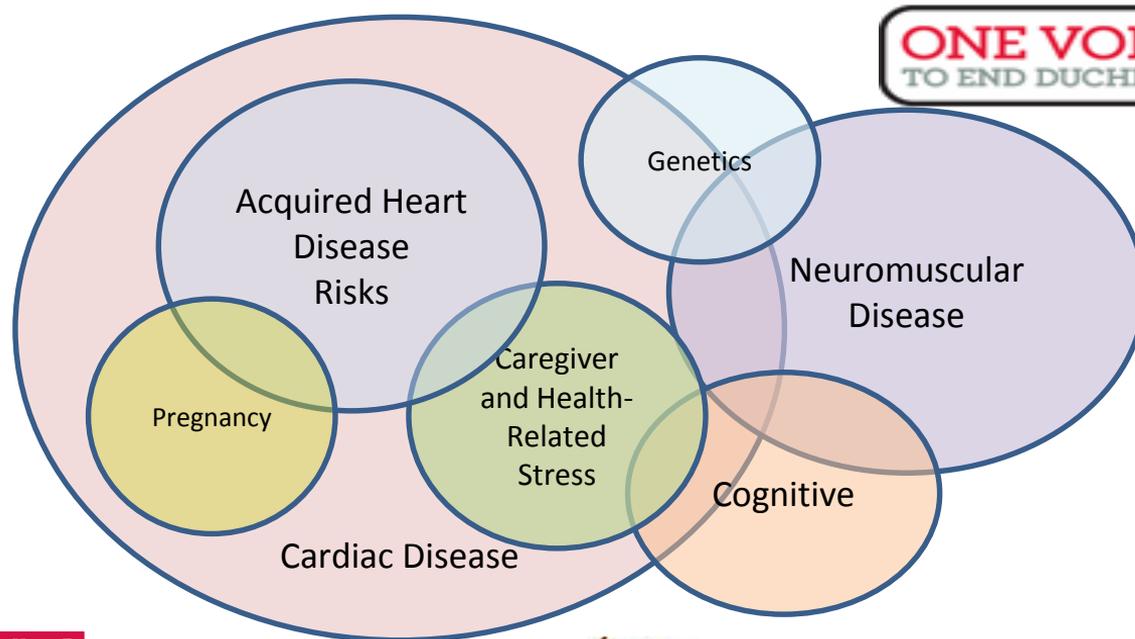


*Design a Study to*



# Define Carrier Cardiomyopathy

Determine incidence and prognosis of clinically significant cardiac, skeletal muscle and cognitive impairment in carriers of DMD and BMD



**ONE VOICE**  
TO END DUCHENNE

Parent Project  
Muscular Dystrophy

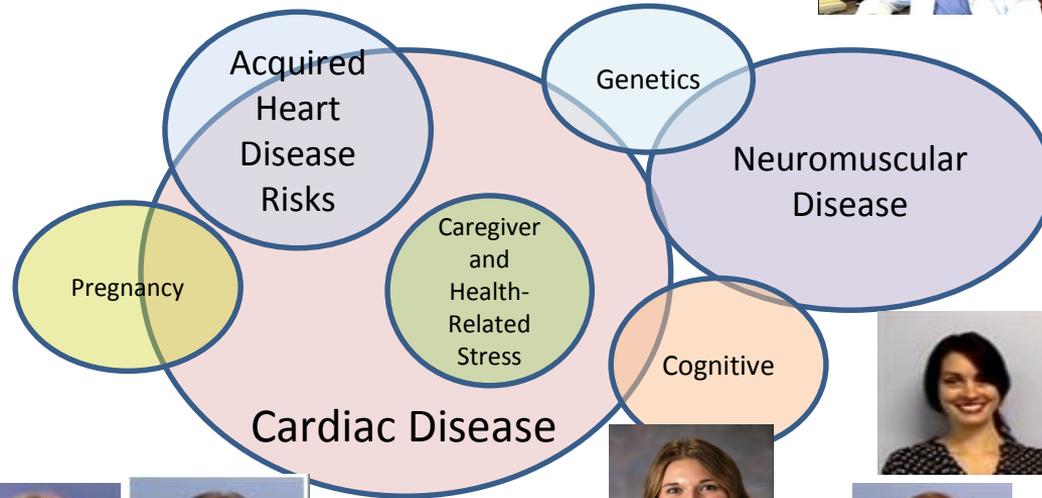
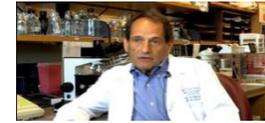


# The DMD Carrier Study Team

Cardiology



Neurology



Exercise Physiology



Psychology



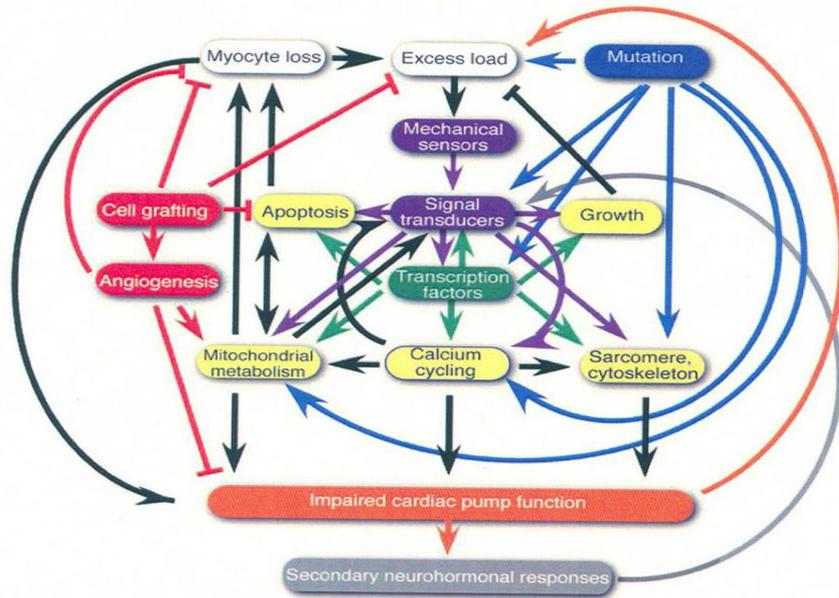
Research  
Coordination



NATIONWIDE  
CHILDREN'S

*When your child needs a hospital, everything matters.™*

# What is “Heart Failure?”



- Complicated - the heart fails to meet the needs of the body
- Does **NOT** mean the heart has “failed” or stopped working
- Occurs when cardiac function is poor **but** can occur with normal function and increased demand
- Body’s response at first helpful but eventually causes harm

# Prevalence of Carrier Cardiomyopathy

- It Depends . . .
- Lack of current definition of
  - “Manifesting”
  - “Non-manifesting”



# How is this study different?

## Large case-control study

- 100 DMD/BMD carriers moms
- 50 DMD/BMD non-carrier moms
- 25 DMD/BMD carrier non-moms
- 25 healthy controls with normal CK

## Longitudinal Design

- Anticipation for 3-5 years of data
- Control population for “normal” parameters

## Wholistic look at the patient

- Necessarily Interdisciplinary

## Treadmill Testing

- Has not been done in carriers

## Technical Improvements

- Backbone of imaging is cardiac MRI
- Novel techniques



# Carrier cardiomyopathy has been defined by...

- ~~Cardiac enzymes~~
- ~~Echocardiogram (ultrasound)~~
- Cardiac Magnetic Resonance Imaging (cMRI)
- **Exercise Treadmill Testing?**
  - **First test of functional status in carriers**

# Study Visits

- Three study visits are completed over the course of two days each (Day 0, Year 1, Year 2)
- Each time point consist of the following components:

Day 1 (~4-5 hours)		
Biobehavioral Measures (90min)	Neuromuscular Measures (60min)	Physical Therapy Measures (60min)
Cognitive testing	Vitals (Ht, Wt, BP, etc.)	6 Minute Walk Test
Qualitative Interview	Medical History	Quantitative Myometry
Hair Sample	Manual Muscle Testing	ACTIVE-Seated
	Blood draw and urine sample	Time to rise
Day 2 (~3 hours)		
Cardiology Measures		
Cardiac MRI with and Without Contrast (45-60 minutes)	Treadmill Stress Test (60-90 minutes)	



# Enrollment Thus Far

- Current status
  - 100 women tested
  - 54 Confirmed Somatic Carriers
  - 20 Confirmed Nonsomatic Carriers
  - 26 Healthy Controls
- Interim Analysis (March 2018)
  - 85 women tested
  - 46 Confirmed Somatic Carriers
  - 18 Confirmed Nonsomatic Carriers
  - 18 Healthy Controls



# Treadmill Exercise Testing

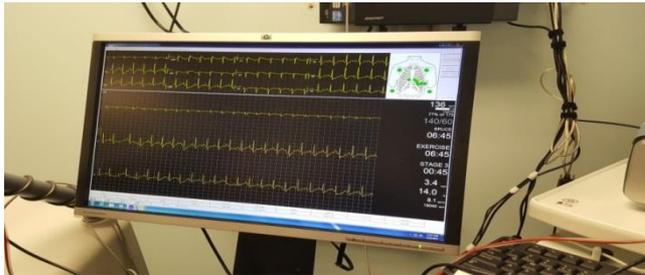
- Typical utility is to define functional capacity in patients and to exclude ischemic heart disease
- Carriers are highly functional, treadmill exercise testing will add value to traditional 6-minute walk test to help further define those “with” and “without” manifestation
- Offers detailed information on
  - Functional capacity
  - Hemodynamic response to exercise
  - Effort



# Treadmill Demystified



1. Set-up: EKG, Face Mask
2. Obligatory Selfie/Facebook Post
3. Run (see next)
4. Data Collection



# Treadmill Exercise Testing



# So what do you get out of me wearing that crazy mask?

- $\dot{V}O_2$  -Maximal oxygen consumption
  - The maximum amount of oxygen that a person can use during exertion
  - Good indication of how well the heart, lungs, blood vessels and muscles work together
  - Recognized as an indication of a person's fitness level (how much energy does your body give you to exercise?)
- $\dot{V}E/\dot{V}CO_2$  – fine tunes this measure for more cardiac specific measure
- RER – what effort did you give me? Did you give me a full effort?



# Results

- Average age was 41.9 years (range 28-63)
  - Did not differ between the three groups
- Maximal oxygen consumption ( $\dot{V}O_2$  max)
  - Not different between somatic and non-somatic DMD moms
  - Significant difference noted between DMD moms and controls (almost one standard deviation difference)
  - Translation: being a DMD mom meant that you had lower general fitness level compared to controls\*



# Results

- VE/VC02
  - NO DIFFERENCE in the cardiac-centered measure
  - The heart was not the specific limiting factor
- RER
  - Full efforts were given by 100% of participants and was not different

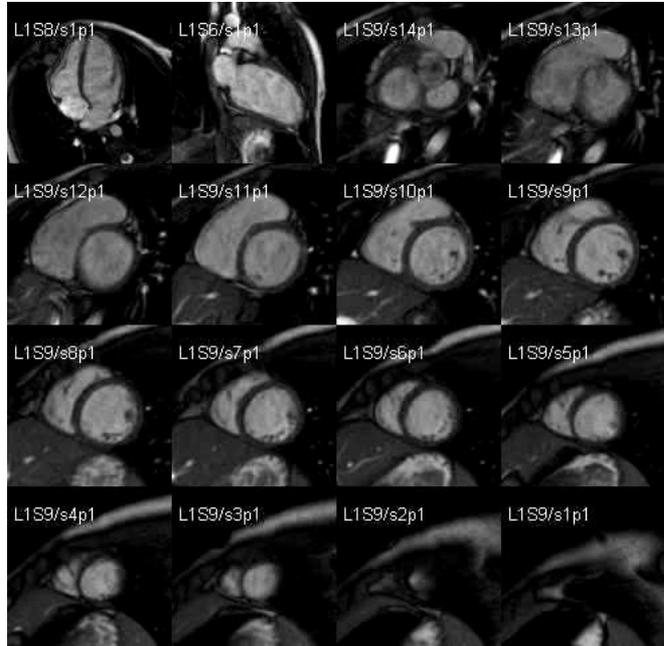


# Results: Arrhythmia (unexpected)

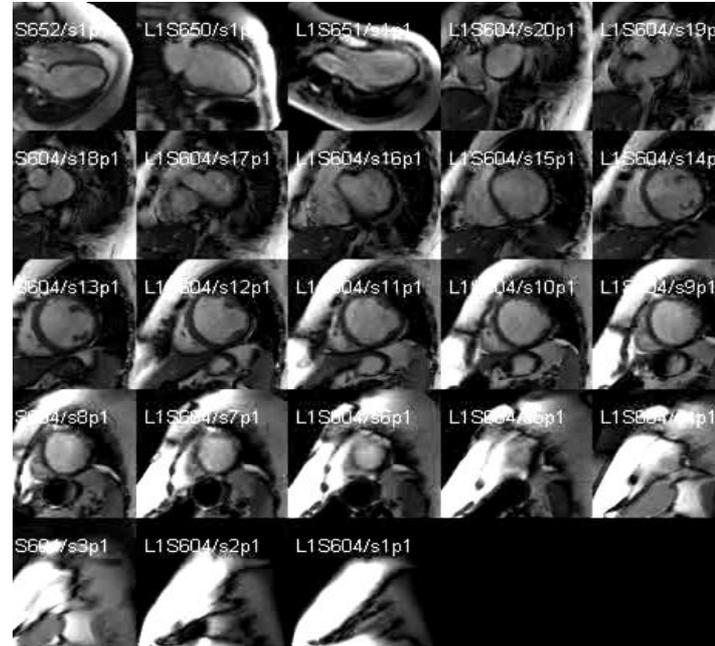
- Premature Ventricular Contractions during exercise differed
- Known to be a marker of heart muscle “irritability”
- Seen in non-DMD (dilated) cardiomyopathy studies
- Early beats are noted during exercise in 50% of somatic patients (25/49)
- This was significantly different in comparison to the healthy controls and non-somatic patients
- Correlation between those with early beats on treadmill testing and fibrosis is pending!



# Cardiac MRI

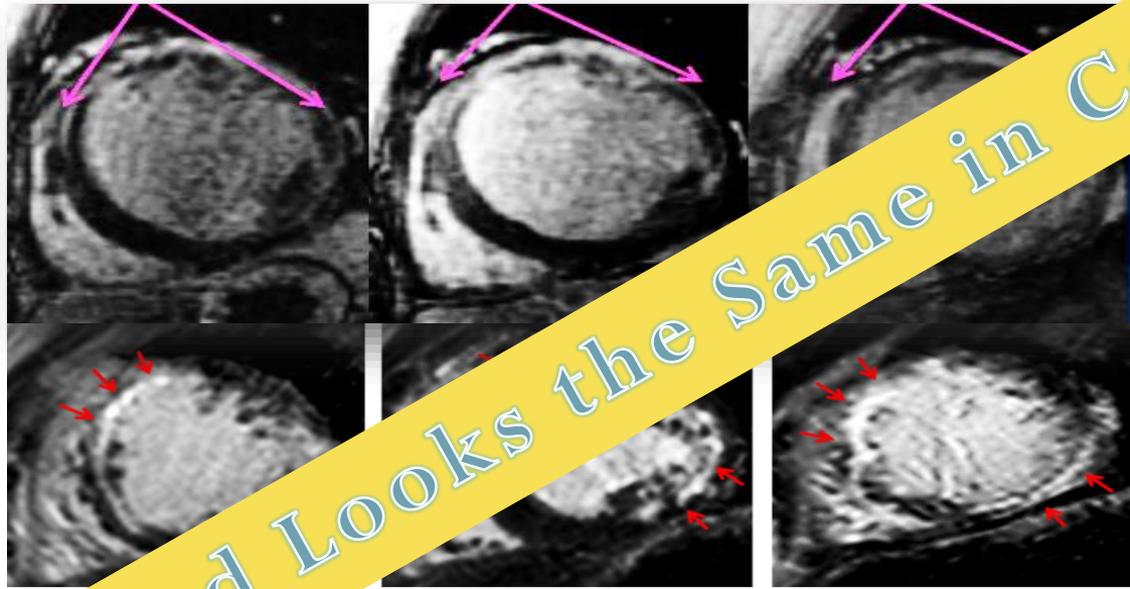


Normal EF



Abnormal EF

Myocardial fibrosis/scar pattern unique to DMD (outside region) compared to heart attack (inside region)



DMD Scar

Heart Attack Scar

And Looks the Same in Carriers

# Results

- Global functional assessment of ventricular systolic function by CMR were normal in all cohorts and did not differ among groups.
- Fibrosis (subepicardial late gadolinium enhancement pattern) was demonstrated in **47%** (23/46) of somatic patients and **5%** (1/18) non-somatic patients ( $p=0.0003$ ) and none in control subjects.



# Aging is Rough . . .

- Age matters
  - Ventricular ectopy with exercise
    - Mean 44.2 yrs vs. 39.5 yrs in those who did not ( $p=0.041$ )
  - LGE by CMR
    - Mean 45.5 yrs vs 37.8 yrs, ( $p=0.004$ )



# Defining Carrier Cardiomyopathy

## Stress and Cardiomyopathy

- Stress biomarkers are elevated among otherwise healthy young women caring for children with significant challenges
- These biomarkers are linked with mitochondrial dysfunction in cells of the heart
- Could stress accelerate cardiomyopathy?



# Acknowledgements

ParentProjectMD.org

LEADING THE  
FIGHT TO  
END DUCHENNE

Parent Project  
Muscular Dystrophy



# Acknowledgements (continued)

- So back to things we “carry”
- This is an extremely dedicated group of families
- RESILIENCE
  - May or may not come out in the data
  - IS absolutely true
  - And IS the most important thing you carry for your children

