Welcome to Iowa City!

SENATOR PAUL D. WELLSTONE

MD COOPERATIVE RESEARCH CENTER

NIH

National Institutes of Health

UNIVERSITY of IOWA CARVER COLLEGE OF MEDICINE

University of Iowa Health Care

University of Iowa Children's Hospital

University of Iowa Health Care

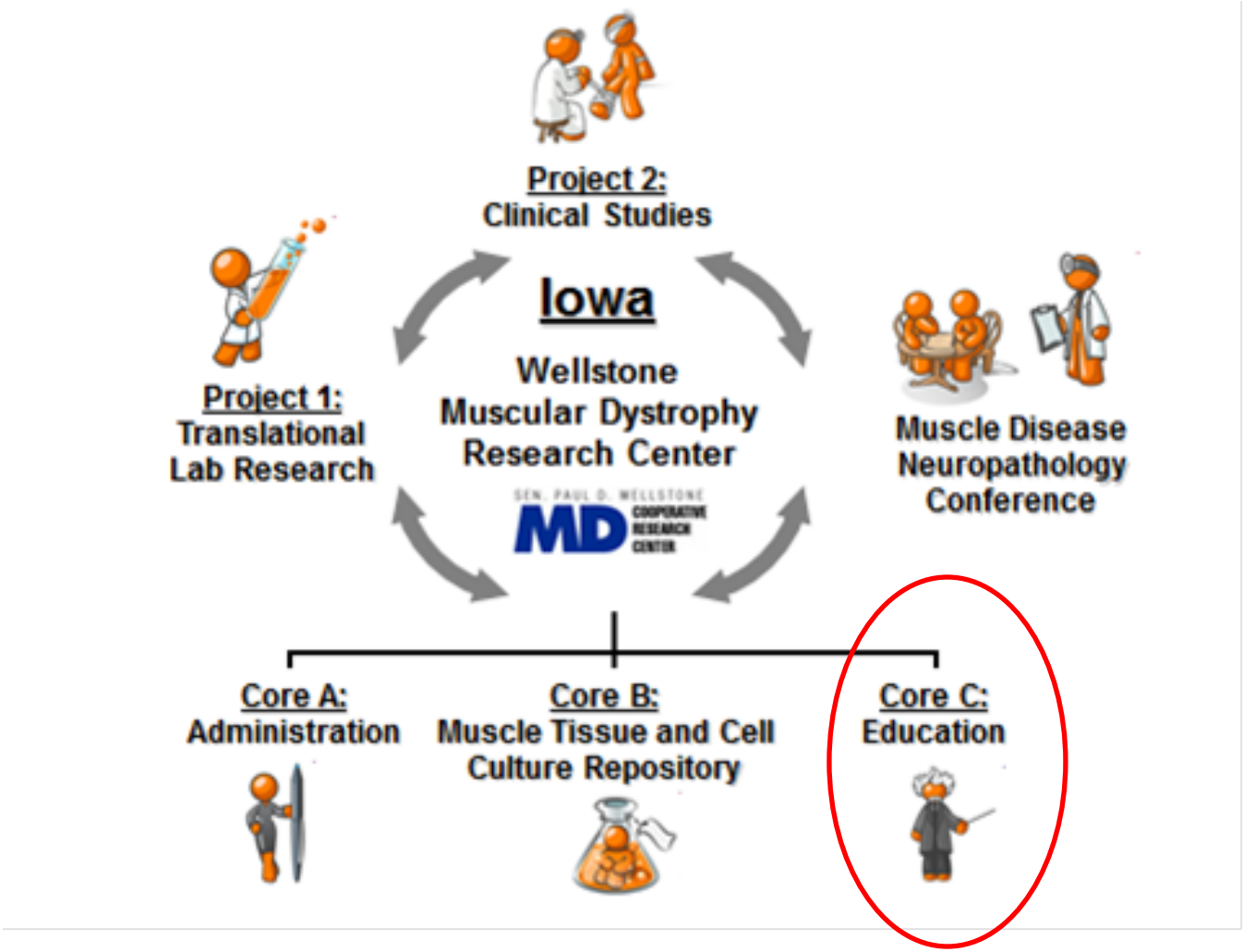
Thank you to those who make this conference possible

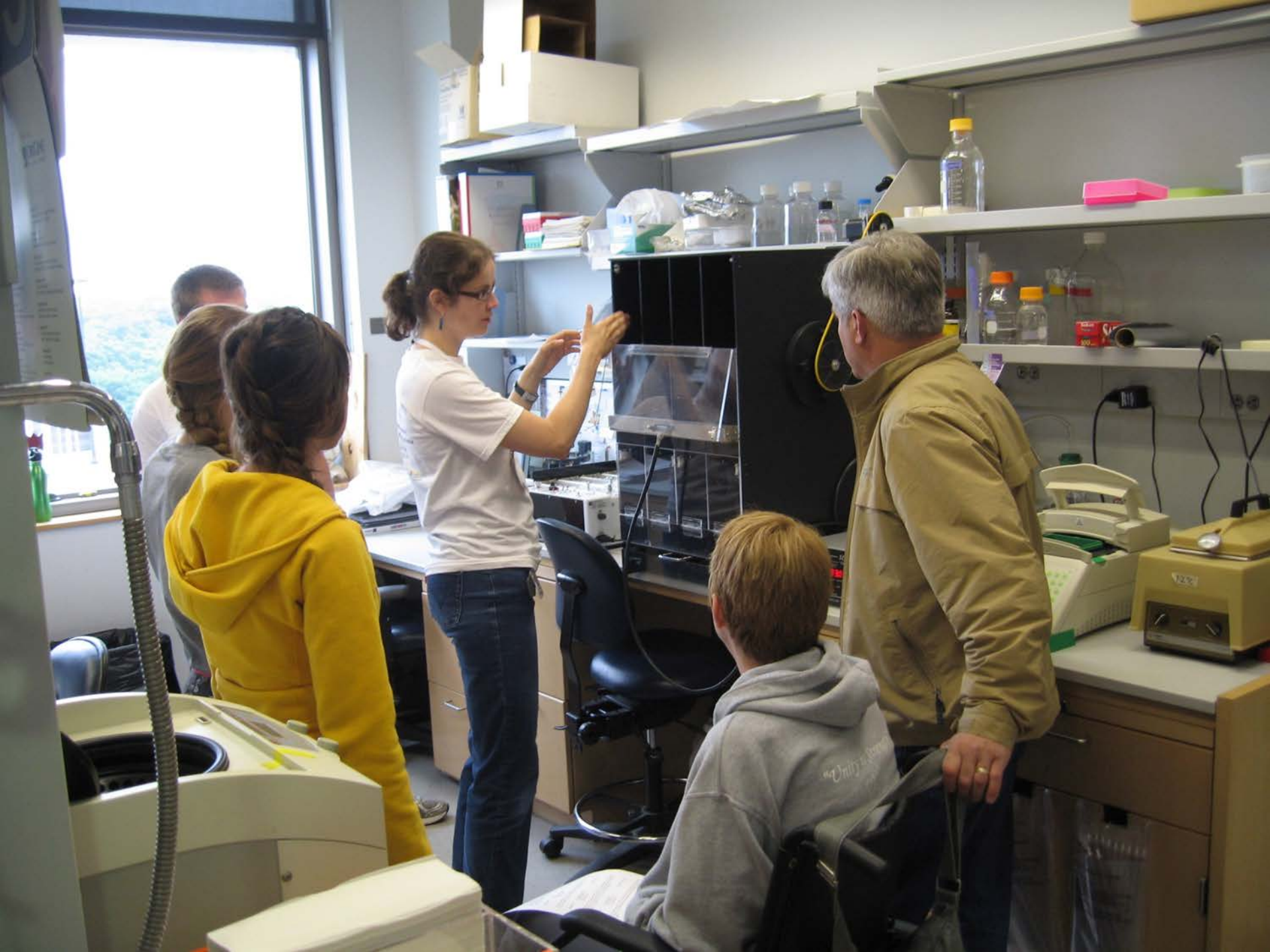
- Carrie Stephan
  - Research coordinator
  - Event planner
  - Everything else
- Meghan Lawler
  - Administrative assistant
  - Event planner
- Bekah Walker
  - Dr. Campbell's administrative assistant
  - Artist and designer of this year's t-shirts
- Students and trainees
- Lab personnel
- Volunteer child supervisors
- Speakers (volunteers)
- Volunteers to help with study evaluations
- NIH and foundations for providing funding

Meghan, Shelley, and Carrie

Supervision of children

Iowa Wellstone Muscular Dystrophy Center



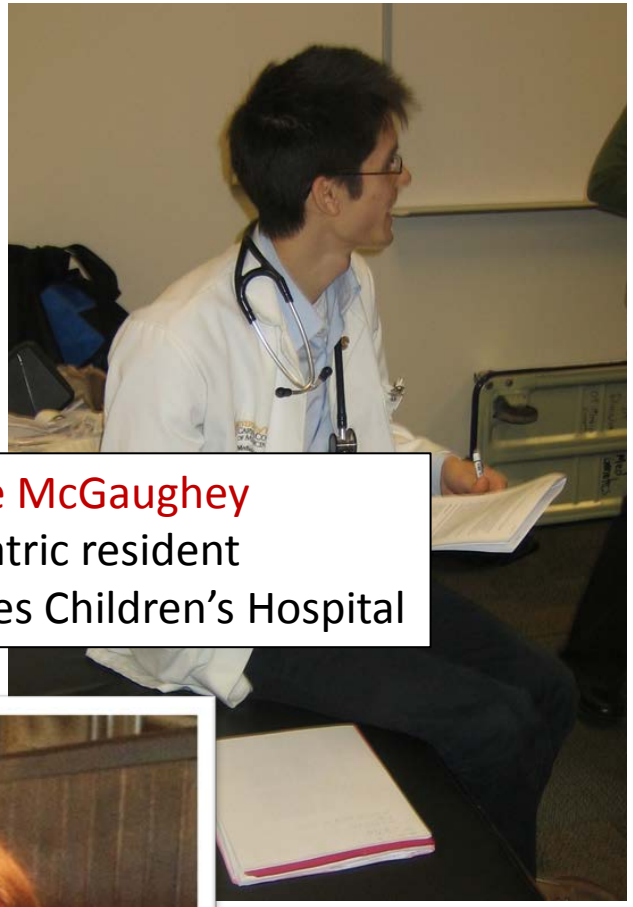


Iowa Wellstone Center Clinical Fellowship

- Why?
  - There is a shortage of pediatric neurologists and particularly of those with expertise in neuromuscular disease.
- The Wellstone Center supports one medical student fellow per year
  - One year taken out of medical school training
  - Focus on neuromuscular diseases (particularly dystroglycanopathies)
  - Opportunity for clinical and basic research

Iowa Clinical Fellows

Jamie Eskuri
Child neurology resident
Boston Children's Hospital



Steve McGaughey
Pediatric resident
Barnes Children's Hospital

Not pictured:
Braden Jensen
This year's fellow!

Cameron Crockett
Medical student
University of Iowa
Future child neurology resident

Katie Lutz
Child neurology resident
University of Iowa
Children's Hospital

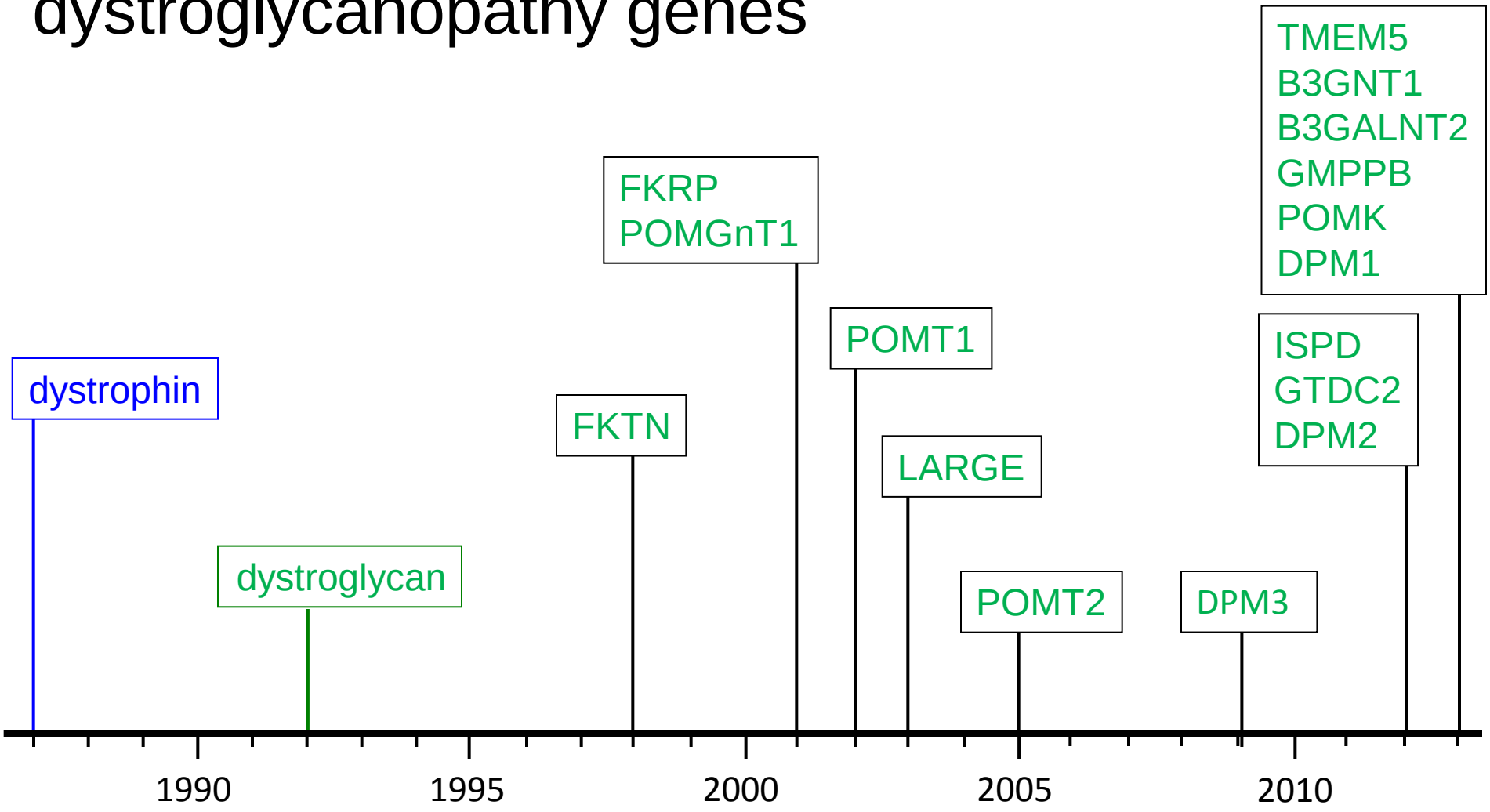
Clinical trial readiness in the dystroglycanopathies

- Project began 9 years ago, only studying patients with FKRP mutations
- Now there are ~17 dystroglycanopathy genes known and the patient population is greatly expanded.

Congenital muscular dystrophy
Weakness in infancy, possibly with brain and eye involvement

Limb girdle muscular dystrophy
Onset of weakness in adulthood

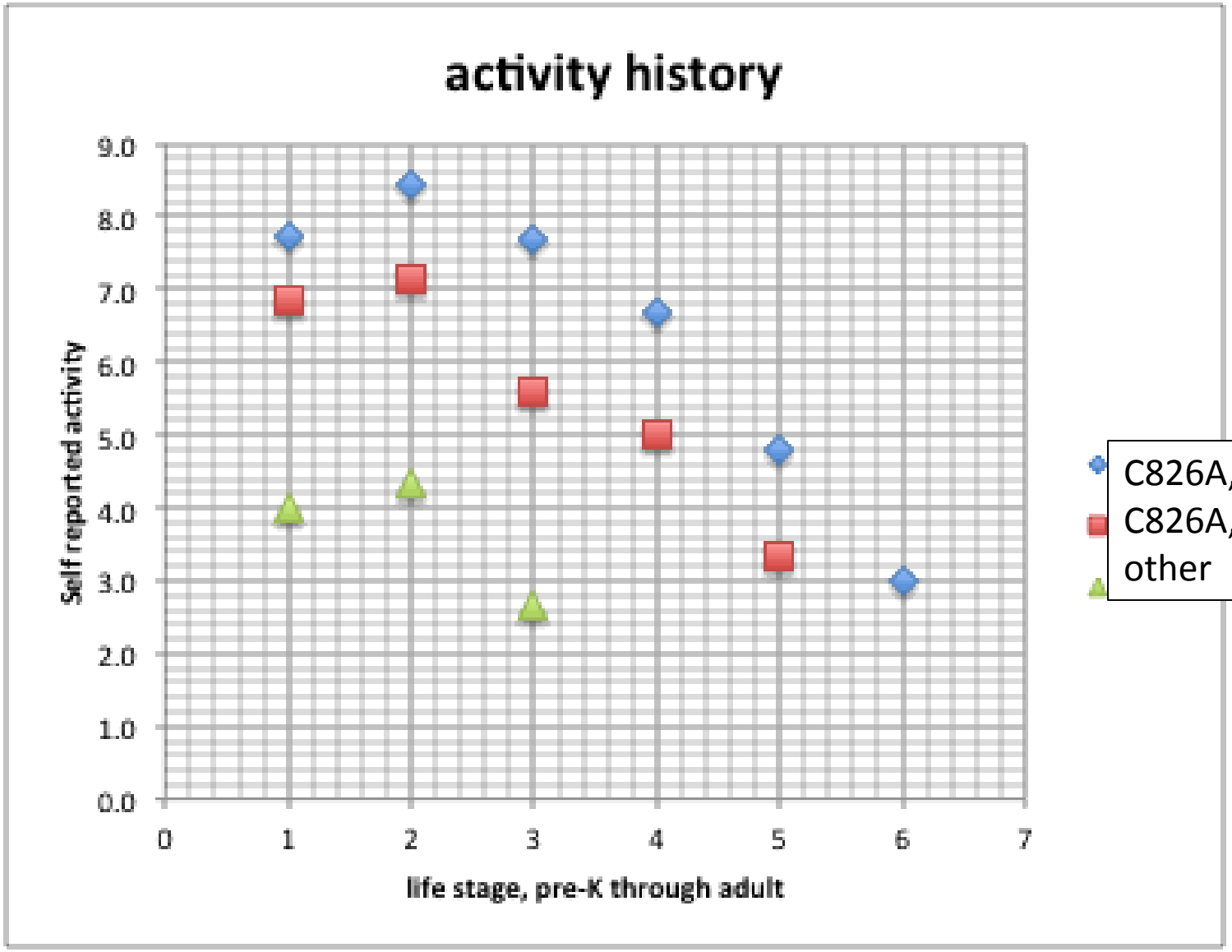
Identification of dystroglycanopathy genes



Clinical trial readiness in the dystroglycanopathies

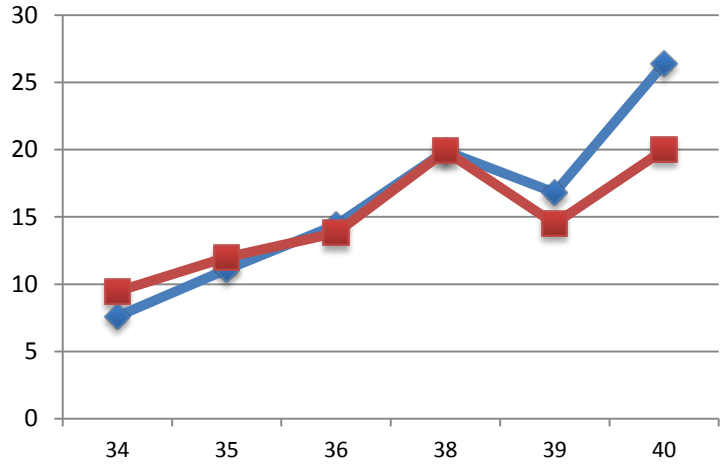
- Many ways to approach the information you have contributed to this study
- Overall goal: Learn about the natural history of this group of diseases
  - Identify outcome measures
    - Reproducible
    - Minimal equipment
    - Change fairly rapidly
  - Answer clinical questions
    - Muscle weakness-rate of progression, degree of weakness
    - Heart
    - Breathing
    - GI/GU symptoms
    - Quality of life
    - What else are you interested in???

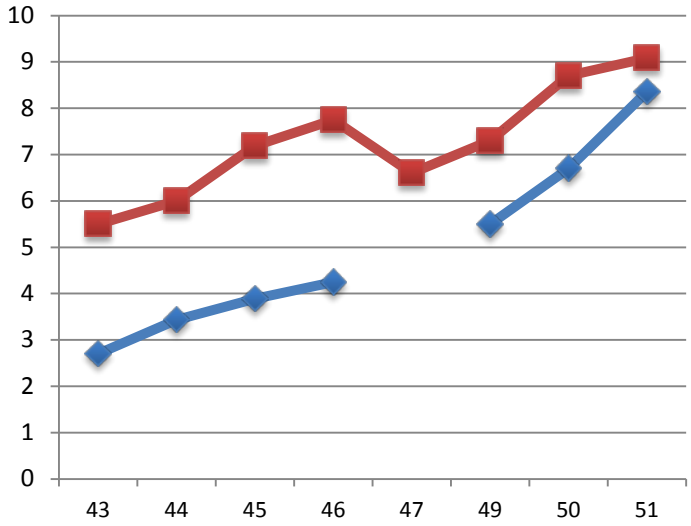
Self reported activity vs genotype

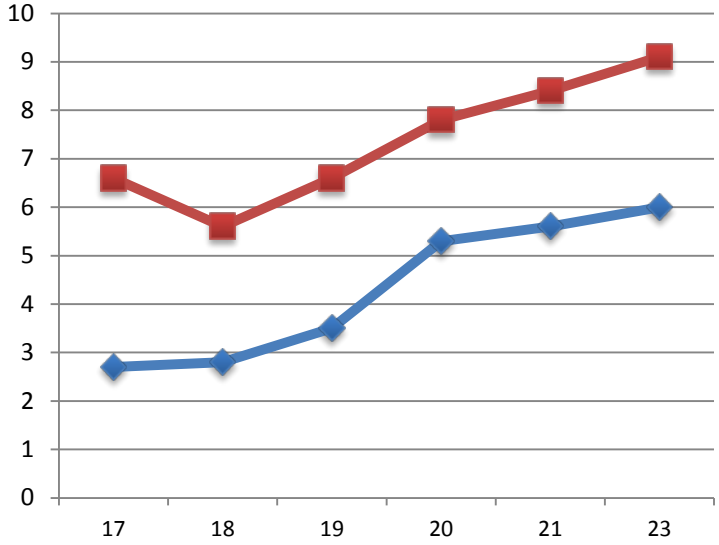


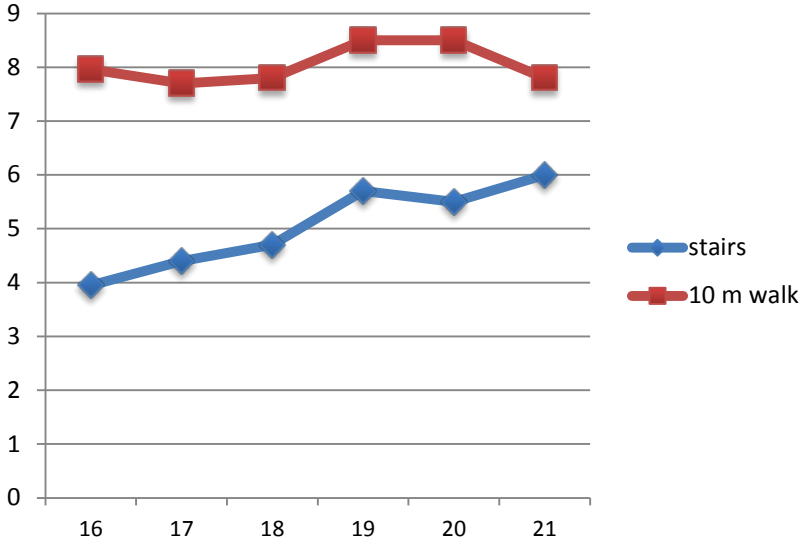
Pattern of change is similar across measures

Comparing 10 m walk with climb 4 stairs

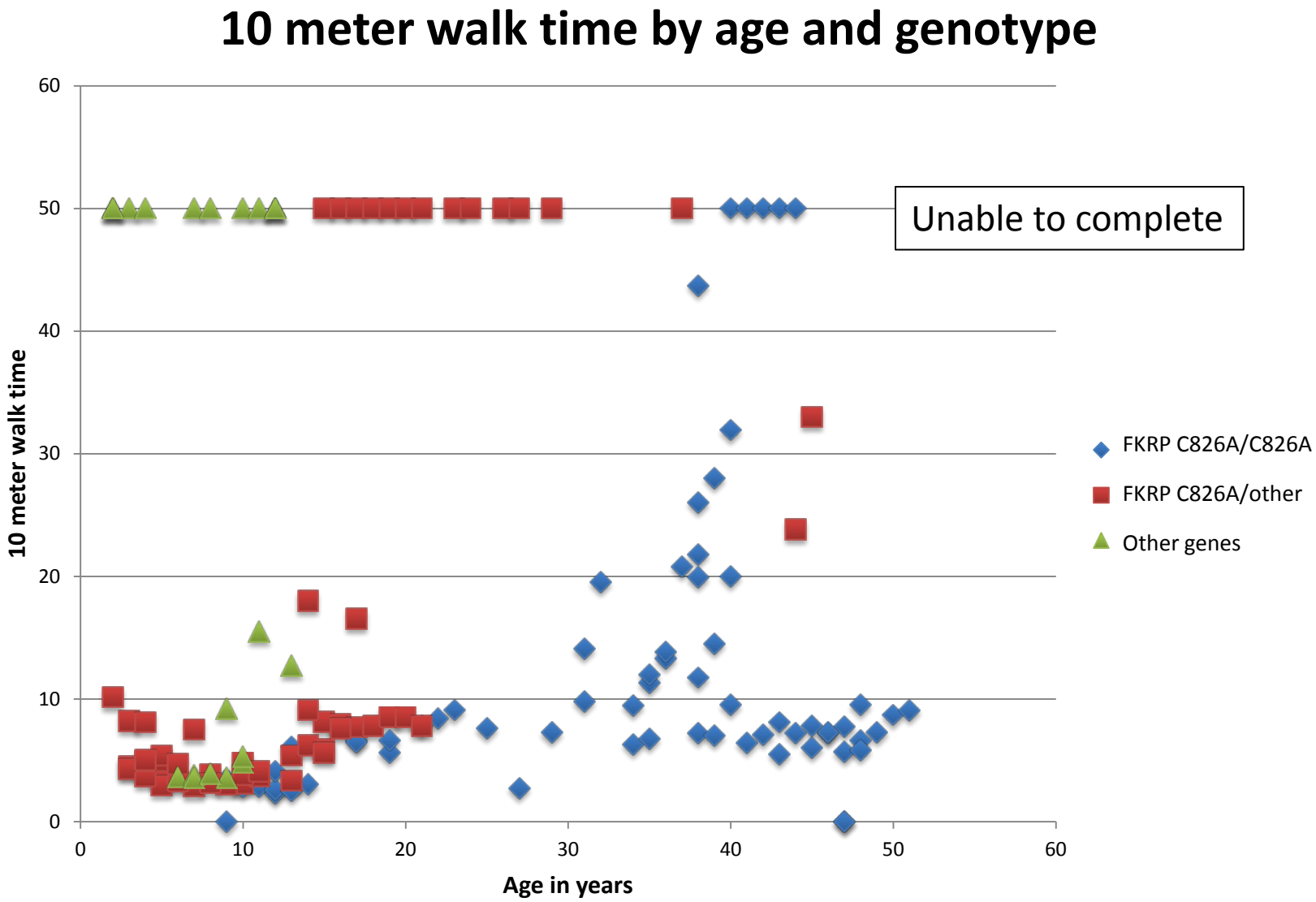




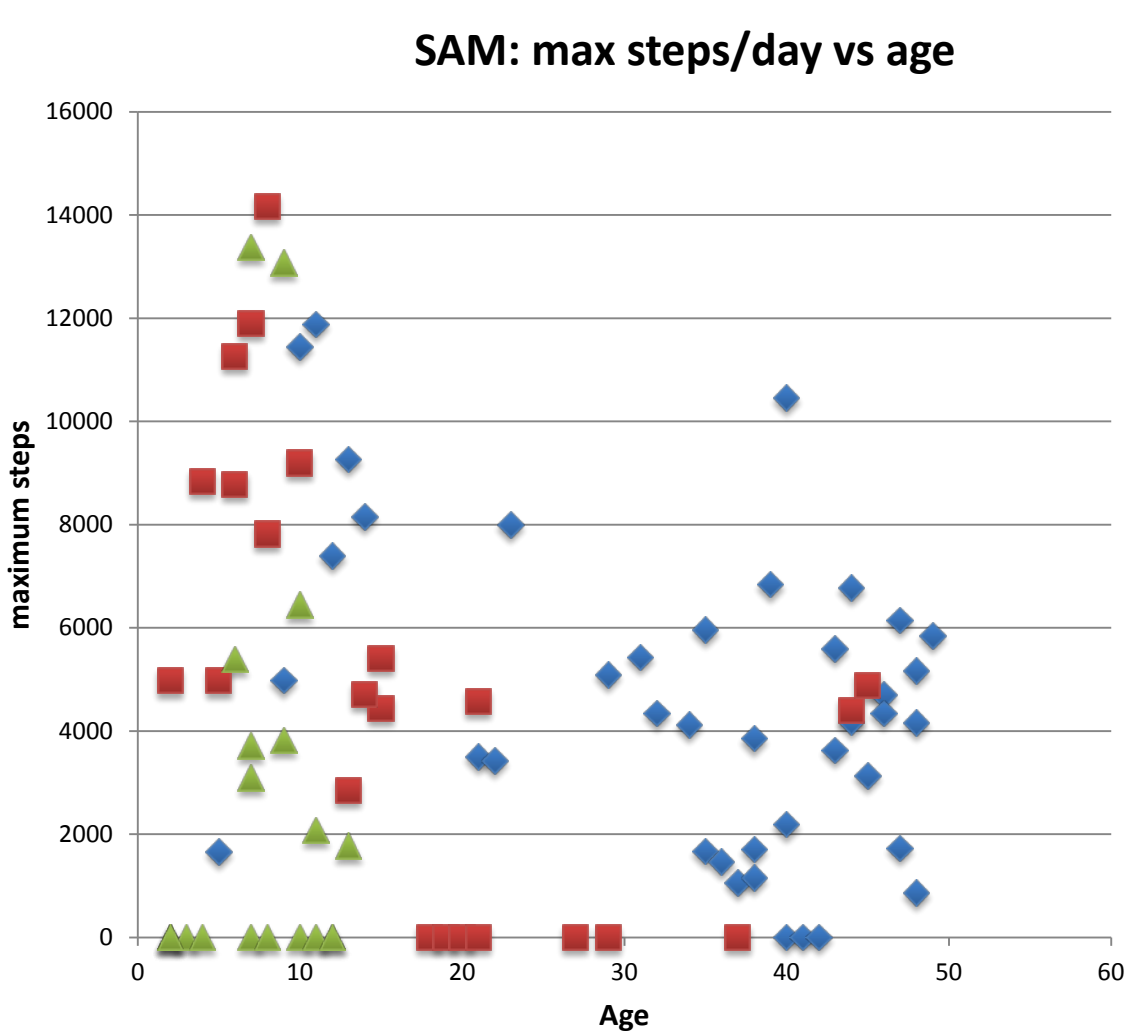




Walking time for the whole group



Step Activity Monitor



Not walking independently

FKRP C826A/C826A

2/23 (9%)

FKRP C826A/other

3/20 (15%)

Other

7/15 (50%)

Heart, the literature

- Retrospective European series of individuals with congenital muscular dystrophy due to dystroglycanopathy (mean age 9.3 yrs)
  - Many without specific genetic mutation
  - 5/115 with dilated cardiomyopathy
    - 3-FKPR (23%),
    - 1-POMT1 (7%)
    - 1-POMT2 (1%)
      - Neuromuscul Disord. 2012 Aug;22(8):685-9. 2012.05.006.
- LGMD2I (FKRP mutations, onset after infancy)
  - 2/11 (18%)
    - J Neurol Neurosurg Psychiatry. 2009 Dec;80(12):1405-8.
  - 14/23 (60%)
    - Neuromuscular Disorders 18 (2008) 650–655

Conclusions
(K. Lutz, submitted for publication)

- Our data support the recommendation for regular monitoring of heart function in people with dystroglycanopathies.
- Consideration should be given for the use of cardioprotective medications in this population.

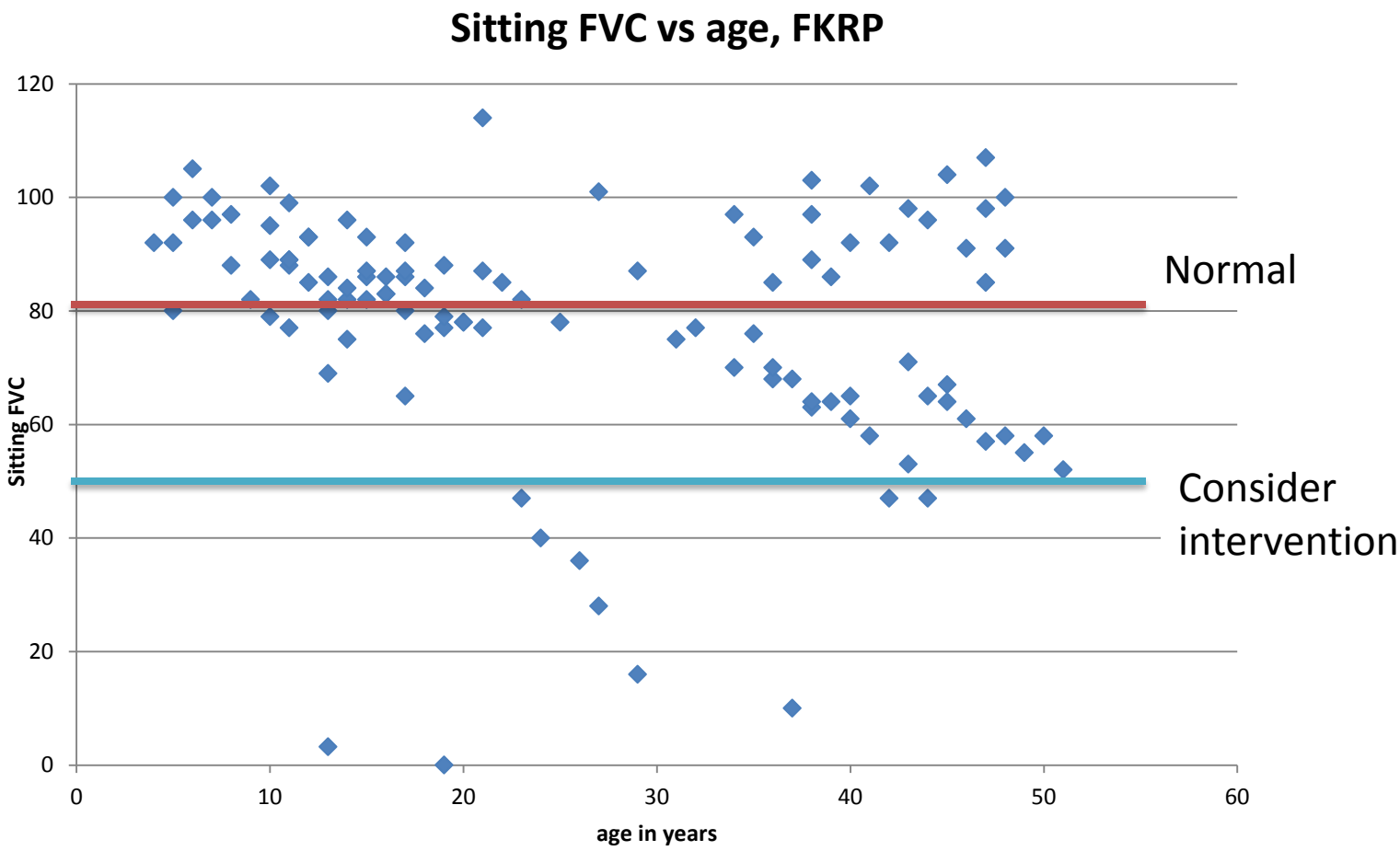
Respiratory function, the literature

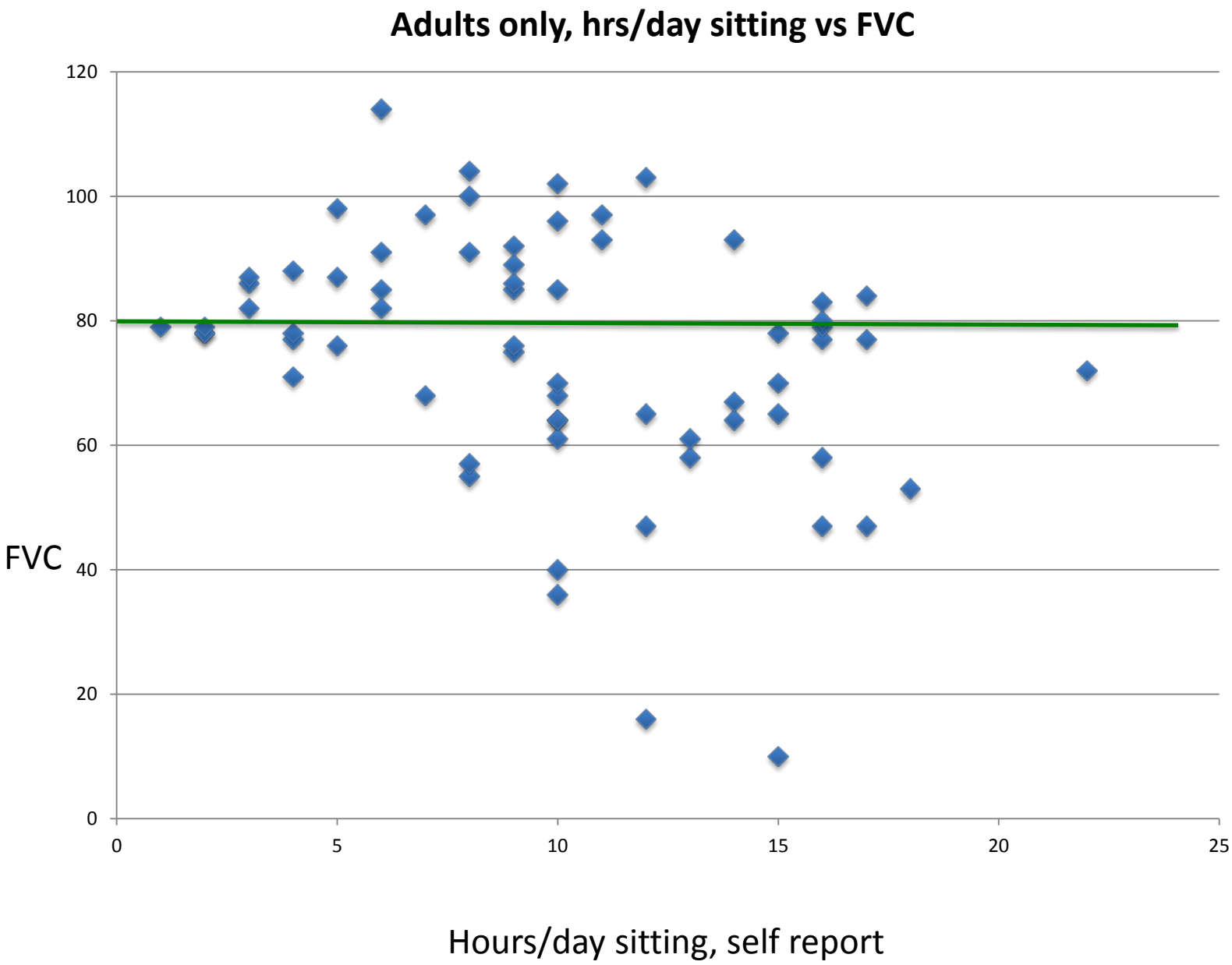
- European study—congenital muscular dystrophy
  - 13 getting respiratory support of some type (11%)
    - 7-unknown gene
    - 3-FKRP (6 m, 9 yrs, 13 yrs) 23%
    - 3-POMT2 (2 yrs, 7 yrs, 19 yrs) 3%
      - Neuromuscul Disord. 2012 Aug;22(8):685-9.
- LGMD2I
  - 5/14 (36%) with respiratory support
    - NEUROLOGY 2003;60:1246–1251
  - 6/11 (55%) FVC<50% predicted
    - J Neurol Neurosurg Psychiatry 2009;80:1405–1408

Our data, respiratory function

- LGMD2I
  - 4/43 (9%) with FVC <50% predicted
- Other mutations:
  - 1/6 (17%) of those able to cooperate with FVC <50% predicted.

Sitting FVC vs Age

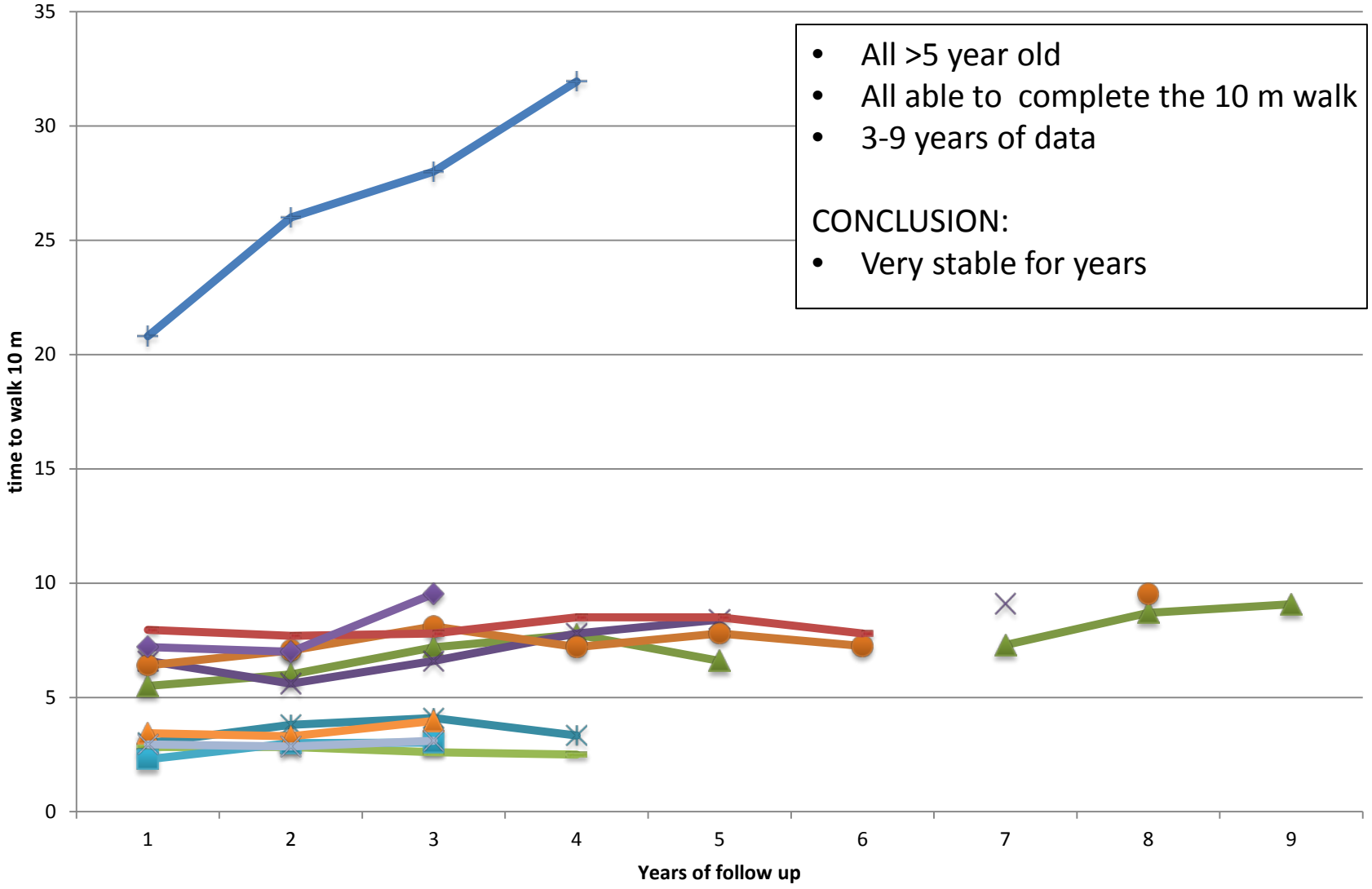



Adults only, hrs/day sitting vs FVC
120
100
80
60
40
20
0
FVC
0
5
10
15
20
25
Hours/day sitting, self report

Clinical trial readiness in the dystroglycanopathies

- Overall goal: Learn about the natural history of this group of diseases
  - Identify outcome measures
    - Reproducible
    - Minimal equipment
    - Change fairly rapidly
  - Answer clinical questions
    - Muscle weakness-rate of progression, degree of weakness
    - Heart
    - Breathing
    - GI/GU symptoms

10 m walk time for individuals over time; outcome measure?



Biomarker study

- Collaboration with Sebahattin Cirak, MD
- Why?
  - Clinical outcome measures are often slow to change
  - Clinical outcome measures can be highly variable
  - Difficult to measure in young children, individuals with cognitive impairment
- Try to find a laboratory test that changes faster or more reliably than the clinical measures
  - Blood
  - Urine
  - Imaging (MRI, ultrasound)
  - You are invited to give blood for this study today!!

Thank you for your participation!

Please complete your evaluation forms