Getting ready to test new targeted treatments for myotonic dystrophy

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Myotonic Dystrophy Foundation

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University of Rochester
Rochester, New York
“targeted therapy”
If a new targeted therapy for myotonic dystrophy was created, what effects could it have in a clinical trials

a) No effect
b) Slow down/stop the progression
c) Improvement
If a new targeted therapy for myotonic dystrophy was created, what effects could it have in a clinical trials

a) No effect
b) Slow down/stop the progression
c) Improvement

If there was a new drug for myotonic dystrophy, what should it do?
questionnaire
If you could pick one aspect of your condition that a drug would help, what would it be?

Person with DM1
Person with DM2
Family member
Interested person
if a drug made you better, would you be able to tell?
if a drug made you a little better (5%),
would you be able to tell?
if a drug made didn’t make you better, but stopped you from getting worse, would you be able to tell?
if a drug stopped you from getting worse, would you be able to tell in 2 months?
if a drug made didn’t make you better, but stopped you from getting worse, would that be worthwhile?
Choosing the best measurements

- Safe
- Acceptable to patients
- Not too costly
- Reliable
- Reflect something that’s important to a person’s life
- Responsive
  - Progression of the disease
  - To drug treatment
Natural History Study

Make a set of measurements in a group of people
No specific treatment
Repeat over time
# Study of Progression in DM (STOP DM)

<table>
<thead>
<tr>
<th>Name</th>
<th>Group Description</th>
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<tbody>
<tr>
<td>Richard Moxley</td>
<td>80 people with DM1</td>
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<tr>
<td>Charles Thornton</td>
<td>20 people with DM2</td>
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<tr>
<td>Chad Heatwole</td>
<td>20 healthy people</td>
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<td>Mike McDermott</td>
<td></td>
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<tr>
<td>Araya Puwanant</td>
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<tr>
<td>Masayuki Nakamori</td>
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<td>Jeanne Dekdebrun</td>
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<td>Kate Eichinger</td>
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<td>Shree Pandya</td>
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<td>Bill Martens</td>
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<tr>
<td>Nuran Dilek</td>
<td>Many different measurements</td>
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<tr>
<td>Bharati Shah</td>
<td>Muscle strength</td>
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<tr>
<td>Kirti Bhatt</td>
<td>Muscle function, myotonia</td>
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<td></td>
<td>EKG, questionnaires, EMG,</td>
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<tr>
<td></td>
<td>Muscle biopsy</td>
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What have we learned from STOP DM study

1. That it is possible to do a study
2. Which measurements are best for showing change
   • one answer: hand grip is best single measurement
3. How to measure myotonia
4. Very good biomarkers
5. Very good Patient Reported Outcome
Chad Heatwole and the DM-specific Patient Reported Outcome (MDHI)

1. Years in the making
2. In accordance with methods/recommendations FDA
3. Input from hundreds of people affected by DM
4. Extensively validated
5. Just published
Finding good biomarkers

- Laboratory measurements
- Using samples from people
- Showing that:
  - Drug went to the right place
  - Had the intended effect
Biomarkers

1. Muscle biopsy
2. Specimen placed in BioBank (if person gave permission)
3. Lab analysis
Biomarkers

1. Muscle biopsy
2. Specimen placed in BioBank (if person gave permission)
3. Lab analysis

- Largest, most intensive study of muscle biopsies in muscular dystrophy
- First study to systematically compare changes in biomarkers with changes of strength
- Results compared to DM1 mouse models
- How did the biomarker respond to treatment in mice
Biomarker measurements in muscle biopsies

• Big effect
• Quite precise
• Correlated with muscle weakness
• Similar changes in DM mice
• In DM1 mice, changes are completely normalized by antisense drug
Comments and Recommendation of Reviewer
This is a very comprehensive and detailed look at splicing patterns in DM and the findings show novelty in enlarging the number of DM-affected splice events and by providing insight into the functional correlation with splicing misregulation. *The major weakness of this manuscript is the shear bulk of information presented to potential readers. Only a select group of researchers would consider wading through all of this material after publication.*
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**Splicing Biomarkers of Disease Severity in Myotonic Dystrophy**

Masayuki Nakamori, MD, PhD, 1,2 Krzysztof Sobczak, PhD, 1,2 Araya Puwanant, MD, 1 Steve Welle, PhD, 3 Katy Eichinger, DPT, 1 Shree Pandya, DPT, 1 Jeanne Dekdebrun, MS, 1 Chad R. Heatwole, MD, 1 Michael P. McDermott, PhD, 1,4 Tian Chen, MA, 4 Melissa Cline, PhD, 5 Rabi Tawil, MD, 1 Robert J. Osborne, PhD, 1 Thurman M. Wheeler, MD, 1,4 Maurice Swanson, PhD, 6 Richard T. Moxley III, MD, 1 and Charles A. Thornton, MD 1,2,7
Scrambling toward trial readiness:
Myotonic Dystrophy Clinical Research Network

1. Like minded researchers
2. Additional natural history data
3. Further validation of PRO and biomarkers
4. Multicenter experience
Scrambling toward trial readiness:
Myotonic Dystrophy Clinical Research Network

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NIH
Advocacy
Myotonic Dystrophy Foundation
MDA
Marigold Foundation

Companies
Isis
Biogen Idec
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1. Ohio State University
   • Kissel, Arnold, King

2. Kansas University Medical Center
   • Barohn, Dimachkie, Herbelin

3. University of Florida
   • Ashizawa, Subramony

4. Stanford University
   • Day, Hagerman

5. University of Rochester
   • Moxley, Thornton, Heatwole, Pandya, Eichinger
Scrambling toward trial readiness:
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Initial study:

• 100 people
• 3 study visit over 1 year
• Measurements of DM1 severity
• Biomarker