DuchenneConnect: The Power of Registry Data

Holly Peay
Overview

• Update on DuchenneConnect
• Review of recent publication
• Review of soon-to-be submitted manuscript: Collaboration with Stan Nelson and team at UCLA
Update on DuchenneConnect

• Registrants:
  – More than 2000 living males with DBMD
  – Most from United States, but worldwide participation
2011-2012 Recruiting for Clinical Trials (as of July 2012)

<table>
<thead>
<tr>
<th>Study Description</th>
<th># eligible people from registry who clicked on link</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK Exon 51 Skipping (DMD114876 Study)</td>
<td>4</td>
</tr>
<tr>
<td>DART EIM Trial</td>
<td>31</td>
</tr>
<tr>
<td>Duchenne/Tadalafil Study at Cedars-Sinai</td>
<td>41</td>
</tr>
<tr>
<td>IGF-1/Cincinnati</td>
<td>157</td>
</tr>
<tr>
<td>IMAGE DMD study (all three sites)</td>
<td>44</td>
</tr>
<tr>
<td>Becker Limb Perfusion Trial (UNC-CH)</td>
<td>2</td>
</tr>
<tr>
<td>Early Treatment of Cardiomyopathy (two sites)</td>
<td>35</td>
</tr>
</tbody>
</table>
Profile Survey

- Diagnosis and Family History
- Mobility, Walking and Sitting
- Steroids & Procedures
- Breathing
- Heart
- Back, Bone & Tendon
- Behavior & Learning
- Therapies
- Genetic Testing and Insurance
- Clinical Trials, Research & Registry Participation
Recent updates to profile

- Based on advice of multidisciplinary advisory committee (industry, neurology, cardiology, pulmonology, physical therapy, parent, individuals with DMD) and expressed needs of users
- Plan to add NeuroQoL elements before end of 2012
Expanded Resources for Families

• Annual registry report published to DuchenneConnect
• Fact sheets about ongoing and upcoming clinical trials
• Webinar series
• Access to genetic counselors
• Clinic care survey
Publishing Registry Data

• Descriptive data published by DuchenneConnect team

• Published in PLoS Currents Muscular Dystrophy, 2012

• Working with academic colleagues to use data to inform about natural history and care
Clinical Trial & Research Announcements 2010-2011

Studies Posted to Homepage

• Featured Studies & Updates 24
• Number of Pageviews Mean 975 views/study (range 123-3184)

Targeted Email Announcements

• Targeted Notification 11 studies
• Meeting Pre-Screen Criteria 1416 patients

Diagnosis of Participants (n=1756)

- **Duchenne**: 78%
- **Confirmed carrier**: 4%
- **Becker**: 7%
- **Possible carrier**: 2%
- **Blank**: 3%
- **Manifesting carrier**: 1%
- **Intermediate**: 5%

Ambulation of Participants (n=1575)

- Walk without assistive devices: 54%
- Walk with assistive devices: 13%
- Do not walk: 33%

Steroid Use Among Ambulatory Participants

Breathing Devices

Breathing Devices (n=211)

Cardiomyopathy (n=241)

Findings from the DuchenneConnect Registry: Using Your Data to Better Understand Duchenne

Stanley F. Nelson, MD
Center for Duchenne Muscular Dystrophy
Professor Human Genetics, Pathology and Laboratory Medicine, and Psychiatry
snelson@ucla.edu
www.facebook.com/cdmd.ucla
What is helping to treat DMD

• Supportive care: respiratory/PT
• Cardiac care for heart failure
• Medications
  – Steroids
  – ACE Inhibitors (like lisinopril)
  – Are there other factors?
  – What role do anti-oxidants/VitD/nutritional supplements play?
  – Can we explore this without long/small clinical trials?
DuchenneConnect Registry: Do we know that the data are typical?

Deletion 74%

Duchenne

Deletion - Small mutation 3%
Duplicatic 10%
Nonsense 8%
Splice site 3%

Fig 12. Mutation types reported by participants with Duchenne.** Duplication (small mutations), Insertion/deletion, Insertions and Other account for less than 3% of mutation types reported.

**DuchenneConnect DMD Mutation Spectrum**

1. Similar mutation spectrum
2. Similar age of diagnosis (4.8y V 4.9y(MDSTARNET))
3. Similar age at WC use (10.43y v 10.3y))

Relative to published data
Using DuchenneConnect data to assess therapeutic benefit of drugs/supplements

- Use Age at Wheelchair use as measure of severity
- Correlate each drug/supplement usage with severity
- Assess if combinations are correlated with severity
- Interpret potential for treatment benefit from single drugs and combined agents
- Advantages: Largest cohort for such interpretations, assesses actually used treatments
- Disadvantages: Not tightly controlled, unknown drug doses/timing
### Summary of supplements/drugs in 384 DMD patients after WC age

<table>
<thead>
<tr>
<th>Supplement/Drug</th>
<th>Mean Age at WC</th>
<th>Number Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ace Inhibitors</td>
<td>11.07937</td>
<td>189</td>
</tr>
<tr>
<td>steroids</td>
<td>11.1761</td>
<td>159</td>
</tr>
<tr>
<td>VitaminD</td>
<td>11.47126</td>
<td>87</td>
</tr>
<tr>
<td>Calcium</td>
<td>11.67901</td>
<td>81</td>
</tr>
<tr>
<td>CoenzymeQ10</td>
<td>11.58</td>
<td>50</td>
</tr>
<tr>
<td>VitaminC</td>
<td>11.30769</td>
<td>26</td>
</tr>
<tr>
<td>VitaminE</td>
<td>12.09091</td>
<td>11</td>
</tr>
<tr>
<td>Magnesium</td>
<td>12.72727</td>
<td>11</td>
</tr>
<tr>
<td>CreatineMonohydrate</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Melatonin</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Protandim</td>
<td>12.42857</td>
<td>7</td>
</tr>
<tr>
<td>L.Arginine</td>
<td>11.16667</td>
<td>6</td>
</tr>
<tr>
<td>GreenTeaExtract</td>
<td>13.4</td>
<td>5</td>
</tr>
<tr>
<td>VitaminA_Beta.Carotene</td>
<td>12.25</td>
<td>4</td>
</tr>
<tr>
<td>B.50Complex</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>GrapeSeedExtract</td>
<td>11.66667</td>
<td>3</td>
</tr>
<tr>
<td>HGH</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Juven</td>
<td>11.33333</td>
<td>3</td>
</tr>
<tr>
<td>L.Carnitine</td>
<td>9.333333</td>
<td>3</td>
</tr>
<tr>
<td>Selenomax</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td><strong>No drugs/supp reported</strong></td>
<td><strong>9.6y</strong></td>
<td><strong>136</strong></td>
</tr>
</tbody>
</table>
Duchenne Connect
N=2285

Duchenne Muscular Dystrophy
N=1396

Becker Muscular Dystrophy
N=128

Other (Unknown, Carrier, At risk)
N=761

Country

US
N=972

*Other oecd
N=229

Non oecd
N=195

Mean Age of Diagnosis

4.12 yrs N=963

3.50 yrs N=185

Mean: 4.02 yrs N=1164

Mean Age at Wheelchair:
10.49 yrs
N=384

Remove non-WC user (n=711)

Remove outliers (N=69)

STEROID USE
(Deflazacort, Prednisone)

CARDIOMYOPATHY
(Medication (i.e. Perindopril))

VITAMINS AND SUPPLEMENTS
(Vitamin D, Calcium, Coenzyme Q, ..)

Center for Duchenne Muscular Dystrophy
Wide variation in age at wheelchair use provides ability to determine effect of drugs

Age at start of Wheelchair use
(OECD Countries with DMD Diagnosis, N=384)

MEAN AGE: 10.54 years
DC data observe steroids EFFECT

<table>
<thead>
<tr>
<th></th>
<th>Number Observations</th>
<th>Mean Wheelchair Age (years)</th>
<th>Sd (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never Used Steroids</td>
<td>107</td>
<td>9.88</td>
<td>2.18</td>
</tr>
<tr>
<td>Current Steroid User</td>
<td>159</td>
<td>11.18</td>
<td>2.65</td>
</tr>
</tbody>
</table>

Never Used Steroids verses Current Steroid User
Wicoxon test P-value = 2.1e-05

Wheelchair Bound Age with Corticosteroid Usage

- Never used corticosteroids
- Current user corticosteroids
Fraction of DMD Patients able to walk: effect of steroids (n=1089 patients)
Corticosteroids Usage: Deflazacort and Prednisone

Wheelchair Age of Deflazacort and Prednisone

<table>
<thead>
<tr>
<th></th>
<th>Number Observations</th>
<th>Mean Wheelchair Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deflazacort</td>
<td>82</td>
<td>11.62</td>
</tr>
<tr>
<td>Prednisone</td>
<td>77</td>
<td>10.70</td>
</tr>
</tbody>
</table>

Deflazacort vs Prednisone
Wilcoxon test P-value: **0.03217**

<table>
<thead>
<tr>
<th></th>
<th>Deflazacort</th>
<th>Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Dose</td>
<td>11.5 years</td>
<td>11.02 years</td>
</tr>
<tr>
<td>(N=68)</td>
<td>(N=56)</td>
<td></td>
</tr>
<tr>
<td>Other Dose</td>
<td>12.37 years</td>
<td>9.85 years</td>
</tr>
<tr>
<td>(N=11)</td>
<td>(N=13)</td>
<td></td>
</tr>
</tbody>
</table>

Dosage ANOVA P-value: 0.1413
Identifying effects of other treatments based on age of Wheelchair Bound

Mean Age at Wheelchair: 10.49
N=384

**Perindopril or similar**
N=197

STERIOD USE

Never used Steroids
N=124

Previously used Steroids
N=110

Currently using deflazacort
N=76

Currently using prednisone
N=75

SUPPLEMENTS

Vitamin D
N=88

Calcium
N=76

Coenzyme Q10
N=39

Vitamin C
N=32

Vitamin E
N=15

Magnesium
N=11

Melatonin
N=7

Creatine monohydrate
N=7

Protandim
N=5

SUPPLEMENTS

Calcium
N=53

Vitamin D
N=54

Coenzyme Q10
N=22

Vitamin C
N=12

Creatine monohydrate
N=6

Vitamin E
N=6

Protandim
N=5
Do ACE Inhibitors impact severity of skeletal muscles in DMD?

*ACEI category includes:
  - Aceon (Perindopril)
  - Captopril (Capoten)
  - Enalapril (Vasotec)
  - Lisinopril (Prinivil, Zestril)
  - Losartin (Cozaar)
  - Ramipril (Altace)

<table>
<thead>
<tr>
<th></th>
<th>Number Observations</th>
<th>Mean Wheelchair Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taking ACEI</td>
<td>196</td>
<td>11.02</td>
</tr>
<tr>
<td>Not Taking ACEI</td>
<td>199</td>
<td>10.06</td>
</tr>
</tbody>
</table>

ACEI vs No ACEI
P-value=0.000064

<table>
<thead>
<tr>
<th></th>
<th>Never Used Steroids</th>
<th>Current Steroid User</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number Observations</td>
<td>Mean Wheelchair Age (years)</td>
</tr>
<tr>
<td>Taking ACEI</td>
<td>50</td>
<td>10.08</td>
</tr>
<tr>
<td>Not Taking ACEI</td>
<td>74</td>
<td>9.73</td>
</tr>
</tbody>
</table>

Amongst steroid users:
ACEI vs No ACEI
P-value= 0.0008325
Different ‘ACE Inhibitors’ correlate with age at wheelchair use similarly

All ACE Inhibitors: 11.08y

Losartan (Cozaar): 11.42y
Lisinopril (Zestril): 11.1y

No significant difference: both are correlated with longer ambulation
## Correlation of Supplements/Drugs with Age of Wheelchair Use

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Mean of Age of Wheelchair</th>
<th>SD of Age of Wheelchair</th>
<th>Number of Observations</th>
<th>Wilcoxon test P-value</th>
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</thead>
<tbody>
<tr>
<td>Ace Inhibitors</td>
<td>11.08</td>
<td>2.64</td>
<td>189</td>
<td>1.7e-05</td>
</tr>
<tr>
<td>Corticosteroids (Deflazacort or Prednisone)</td>
<td>11.18</td>
<td>2.65</td>
<td>159</td>
<td>2.1e-05</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>11.47</td>
<td>2.93</td>
<td>87</td>
<td>0.00045</td>
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<tr>
<td>Calcium</td>
<td>11.68</td>
<td>2.91</td>
<td>81</td>
<td>2.8e-05</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>11.87</td>
<td>3.16</td>
<td>47</td>
<td>0.00118</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>11.31</td>
<td>2.88</td>
<td>26</td>
<td>0.16908</td>
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<tr>
<td>Vitamin E</td>
<td>12.09</td>
<td>3.78</td>
<td>11</td>
<td>0.18466</td>
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<td>Magnesium</td>
<td>12.72</td>
<td>4.13</td>
<td>11</td>
<td>0.05743</td>
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<td>Melatonin</td>
<td>11.00</td>
<td>2.82</td>
<td>8</td>
<td>0.50611</td>
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<tr>
<td>Creatine Monohydrate</td>
<td>12</td>
<td>3.97</td>
<td>9</td>
<td>0.21608</td>
</tr>
<tr>
<td>Protandim</td>
<td>12.43</td>
<td>2.64</td>
<td>7</td>
<td>0.03466</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>12.25</td>
<td>3.4</td>
<td>4</td>
<td>0.23706</td>
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</table>
## Supplements - Confounded By Steroids?

<table>
<thead>
<tr>
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<th>Current Steroid User</th>
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<tbody>
<tr>
<td></td>
<td>Number Observations</td>
<td>Mean Wheelchair Age (years)</td>
<td>Number Observations</td>
<td>Mean Wheelchair Age (years)</td>
</tr>
<tr>
<td>Taking Calcium</td>
<td>7</td>
<td>10.1</td>
<td>58</td>
<td>11.91</td>
</tr>
<tr>
<td>Not Taking Calcium</td>
<td>100</td>
<td>9.8</td>
<td>101</td>
<td>10.75</td>
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<tr>
<td>Wilcoxon Test P-value</td>
<td>0.6923</td>
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<td>0.01104</td>
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<tr>
<td>Taking Vitamin D</td>
<td>8</td>
<td>10.6</td>
<td>55</td>
<td>12.02</td>
</tr>
<tr>
<td>Not Taking Vitamin D</td>
<td>99</td>
<td>9.8</td>
<td>104</td>
<td>10.73</td>
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<tr>
<td>Wilcoxon Test P-value</td>
<td>0.67451</td>
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<td>0.00456</td>
</tr>
<tr>
<td>Taking Calcium or Vitamin D</td>
<td>11</td>
<td>10.1</td>
<td>71</td>
<td>11.89</td>
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<tr>
<td>Not Taking Calcium or Vitamin D</td>
<td>96</td>
<td>9.8</td>
<td>88</td>
<td>10.60</td>
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<tr>
<td>Wilcoxon Test P-value</td>
<td>0.95441</td>
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<td>0.00462</td>
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<tr>
<td>Taking Calcium and Vitamin D</td>
<td>4</td>
<td>1</td>
<td>42</td>
<td>12.10</td>
</tr>
<tr>
<td>Not Taking Calcium and Vitamin D</td>
<td>103</td>
<td>9.8</td>
<td>117</td>
<td>10.85</td>
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<tr>
<td>Wilcoxon Test P-value</td>
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<td>0.00827</td>
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## Supplements - Confounded By Steroids?

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</thead>
<tbody>
<tr>
<td></td>
<td>Number Observations</td>
<td>Mean Wheelchair Age (years)</td>
</tr>
<tr>
<td>Taking Coenzyme Q10</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Not Taking Coenzyme Q10</td>
<td>101</td>
<td>9.69</td>
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<tr>
<td>Wilcoxon Test P-value</td>
<td>0.07912</td>
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<tr>
<td>Taking Antioxidant</td>
<td>7</td>
<td>10.71</td>
</tr>
<tr>
<td>without Coenzyme Q10</td>
<td>100</td>
<td>9.82</td>
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<tr>
<td>Wilcoxon Test P-value</td>
<td>0.57877</td>
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<tr>
<td>Taking Antioxidant</td>
<td>12</td>
<td>11.33</td>
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<tr>
<td>with Coenzyme Q10</td>
<td>95</td>
<td>9.69</td>
</tr>
<tr>
<td>Wilcoxon Test P-value</td>
<td>0.23009</td>
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</tbody>
</table>
Positive Effects of Combining Steroids and Supplements

DMD OECD Countries
Mean Age at Wheelchair:
10.49
N=384

None
9.6y

Deflazacort or Prednisone
11.18 years
N=159

Ace Inhibitors
11.93 years
N=90

Vitamin D
11.47 years
N=87

Calcium
11.68 years
N=81

Coenzyme Q10
11.87 years
N=47

Vitamin C
11.31 years
N=26

Creatine monohydrate
12 years
N=9

Protandim
12.43 years
N=7

Vitamin D
12.02 years
N=55

Calcium
11.91 years
N=58

Coenzyme Q10
12.19 years
N=32

Vitamin C
12.16 years
N=12

Creatine monohydrate
12.5 years
N=8

Protandim
12.43 years
N=7

Vitamin D
12.41 years
N=34

Calcium
12.5 years
N=35

Coenzyme Q10
12.73 years
N=22

Vitamin C
13.75 years
N=4

Creatine monohydrate
14 years
N=6

Protandim
13.8 years
N=5
Inferred Regimen

- Deflazacort/prednison
- ACE Inhibitor
- Vitamin D
- Calcium
- CoEnzyme Q10
- Vitamin C
- Creatine
- Antioxidant?
Concluding remarks

• More complete participation improves ability to provide comparative data

• More complete participation lessens potential sampling bias: **BUT ALMOST 10% of all US affected individuals included**
  – Need to improve integration with other country registries, harmonize data accrual and simplify parent participation

• More collected information may improve confidence in data by clinicians to help guide practice parameters

• Registry data provides a dimension of clinical information difficult to collect in clinical trials and individual physician practices
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