Implementation of Newborn Screening for Duchenne Muscular Dystrophy

Michele A. Lloyd-Puryear, MD, PhD¹, Stuart J Moat, PhD², Amy Brower³, PhD, Annie Kennedy¹, Petra Furu⁴, Michael Watson, PhD³, Jerry R Mendell, MD⁵

¹Parent Project Muscular Dystrophy
²Wales Newborn Screening Laboratory, University Hospital of Wales, Cardiff, UK.
³American College of Medical Genetics and Genomics
⁴PerkinElmer International
⁵Nationwide Children’s Hospital, Paul D. Wellstone Muscular Dystrophy Cooperative Research Center
Early Identification of Duchenne Through Newborn Screening

- The identification of affected newborns prior to the onset of clinical symptoms may improve health outcomes and maximize the benefits of existing and new therapies.

- Early treatment has the potential to prevent muscle deterioration, fibrosis and other damage.
Presentation Outline

• Disease Overview
• Interventions and Treatments
• PPMD Newborn Screening Efforts
  – Steering Committee and Workgroups
  – PKI-PPMD project
• Proposed Pilot
• Next Steps
Presentation Outline

• Disease Overview
• Interventions and Treatments
• Newborn Screening
  – RUSP Process
  – Early Identification
  – Completed Pilots
  – Proposed Pilot
• Next Steps
About Duchenne Muscular Dystrophy

- X-linked, pediatric neuromuscular disease, with onset in early childhood
- Incidence rate: 1:5000 boys (30% spontaneous)
- Diagnosis: 4 years of age [mean]
- Predictable course
- Progressive loss of function
- 100% lethal - mean age of death, 28
Presentation Outline

• Disease Overview
• Interventions and Treatments
• Newborn Screening
  – RUSP Process
  – Early Identification
  – Completed Pilots
  – Proposed Pilot
• Next Steps
<table>
<thead>
<tr>
<th>DRUG</th>
<th>PRECLINICAL</th>
<th>PHASE I</th>
<th>PHASE I/II</th>
<th>PHASE II</th>
<th>PHASE III</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXONDYS 51 (ETEPLIRSEN) [SAREPTA]</td>
<td></td>
<td></td>
<td>GRANTED ACCELERATED APPROVAL SEPTEMBER 2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEFLAZACORT [MARATHON PHARMACEUTICALS]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>APPROVAL FEBRUARY 2017</td>
</tr>
<tr>
<td>SPIRONOLACTONE &amp; EPLERENONE [OHIO STATE UNIVERSITY]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRANSLARNA™ (ATALUREN) [PTC THERAPEUTICS]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIVINOSTAT (ITF2357) [ITALFARMACO]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAXONE® (IDEBENONE) [SANTHERA]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRP-4045/SRP-4053 [SAREPTA]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COENZYME Q10 &amp; LISINOPRIL [US DEPARTMENT OF DEFENSE]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF-06252616 [PFIZER]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FG-3019 [FIBROGEN]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS-065/NCNP-01 [NS PHARMA]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAMOROLONE (VBP15) [REVERAGEN]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAT-1004 [CATABASIS]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EZUTROMID (SMT C1100) [SUMMIT PLC]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLLISTATIN GENE TRANSFER [NATIONWIDE CHILDREN’S]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS-986089 [BRISTOL MYERS SQUIBB]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MYOBLAST TRANSPLANTATION [CHU DE QUÉBEC]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAP-1002 [CAPRICOR]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GENE TRANSFER OF MICRO-DYSTROPHIN [NATIONWIDE CHILDREN’S]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Duchenne Treatment: Major Approaches

- Glucocorticoids
- Exon Skipping

There is no cure, but physical therapy and medications, such as corticosteroids, can help control symptoms and improve quality of life.
Exon-Skipping Approach

SKIPPING EXON 51 ENABLES PRODUCTION OF FUNCTIONAL DYSTROPHIN PROTEIN (targets dystrophin region where skipping 51 corrects 13% of DMD mutations).
Completed Pilots

- CA 10/54K; 1:5400
- OH 6/38K; 1:6291
- CA 10/54K; 1:5400
- UK 63/335K; 1:5266
- UK 0/2K; 0
- WG 78/350K; 1:4589
- NZ 2/10K; 1:5000
- BG 51/281K; 1:5514
- CY 5/30K; 1:6002
- FR 7/37K; 1:5330
- PA 10/49K; 1:4900

10 Countries
36 Years
~1.8M Newborns
344 Cases
1:5000
Presentation Outline

• Disease Overview
• Interventions and Treatments
• PPMD Newborn Screening Efforts
  – Steering Committee and Workgroups
  – PKI-PPMD project
• Proposed Pilot
• Next Steps
Proposed Pilot

Steering Committee
- PPMD
- Clinical Centers
- Enrollment & Consent
- Education
- Assay Development
- Assay QA/QC
- Diagnostic Algorithm
- State Pilots
- Long-Term Follow-Up

NBSTRN Coordination and Tools

Analytical and Clinical Validation
- CDC’s NSQAP
- Proficiency Testing
- Quality Control
- Validation of New Tests

State Pilots

Screen Positive Newborns
- Case Count
- Case Report

Diagnosed Newborns, LTFU and Health Outcomes
- Case Characteristics
- Cases Per Center

Screening
- Pilots/Screening in 2016
- No Screening

Parent Project MD.org
## Key Components for Duchenne Pilot

<table>
<thead>
<tr>
<th>Component</th>
<th>Responsible Party(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment/Enrollment and Approach to Consent</td>
<td>PPMD</td>
</tr>
<tr>
<td>Engagement of Clinical Centers and Specialists</td>
<td>Clinical Centers</td>
</tr>
<tr>
<td>Identification of State Program(s)</td>
<td>NBSTRN</td>
</tr>
<tr>
<td>Education Materials – Family, Provider</td>
<td>PPMD</td>
</tr>
<tr>
<td>Assay Analytical and Clinical Validation</td>
<td>Perkin Elmer</td>
</tr>
<tr>
<td>Assay QA/QC</td>
<td>CDC/R4S</td>
</tr>
<tr>
<td>Screening Assay Laboratory Protocol</td>
<td>State Program + PE</td>
</tr>
<tr>
<td>Diagnostic Algorithm – Case Definition</td>
<td>NBSTRN + PPMD</td>
</tr>
<tr>
<td>LTFU and Health Outcomes</td>
<td>NBSTRN + Clinical Centers</td>
</tr>
</tbody>
</table>
Workgroup Analysis: Key Considerations

• X-linked, Female Carriers

• Communication of Results
  – Screen Positive ➔ State NBS to Pediatrician
  – Diagnosed Cases ➔ Muscular Dystrophy Clinics

• Treatment
  – Molecularly Targeted/ Requires Sequencing
  – Clinical Trials for New Therapies

• Outcomes
  – Clinical Measures

• Refinement of the CK screening assay
Screening Newborns for DMD

1. **USUAL CARE**
   - Undiagnosed
   - Diagnosed

2. **NEWBORN SCREENING**
   - Positive Screen
   - Negative Screen

3. **DIAGNOSIS**
   - Short-term follow-up

4. **SCREENING & SHORT-TERM FOLLOW-UP: NET BENEFITS & HARMS**

5. **TREATMENT & LONG-TERM FOLLOW-UP**
   - Treatment & Long-term follow-up

6. **INTERMEDIATE MEASURES**

7. **PRIMARY HEALTH OUTCOMES**

8. **SECONDARY OUTCOMES**

9. **TREATMENT & LONG-TERM FOLLOW-UP: NET BENEFITS & HARMS**

10. **HEALTH CARE SYSTEM**
    - Population
    - Health care service system -- public and private

PUBLIC HEALTH – NEWBORN SCREENING PROGRAMS & LABORATORIES
Informed Consent Process for DMD NBS

- **State NBS Program**
  - DMD NBS Result
    - Screen Positive / Negative
      - Dx to State
      - Dx to PCP
    - Screen Positive
      - Consult with NM clinic
      - Consult with NBS program
      - Consult with neuromuscular clinic
      - Early Intervention Programs
      - Family support
  - Consult Act Sheet
    - Disorder Identified
      - Consult with NBS program
      - Consult with neuromuscular clinic
      - Early Intervention Programs
      - Family support
  - Neuromuscular Clinic
    - Diagnostics
      - Diagnosis (results to parents/PCP/state)
      - Referral for therapy
      - Consultation with pediatrician
      - Family support

- Registry for LTFU
Limitations of the CK enzyme test

Creatine Phosphate + ADP $\xrightarrow{CK}^\text{CK}$ Creatine + ATP

- **False negatives**
  - CK - marker of other disease processes
  - Lack of assay standardisation
    - Stability of enzyme activity in bloodspots at room temperature
    - Long term reproducibility/sustainability with reagents
Creatine kinase assays

• Enzyme activity – total CK activity/and non-specific
• CK – isoenzyme (MM, MB & BB forms)
• **CK-MM found in skeletal muscle**
  – Greater specificity
  – Greater stability at room temperature
• Cardiff and PerkinElmer collaborated to develop a kit utilizing an immunoassay
Cardiff /PPMD-PKI and CA Biobank Project

• PKI with the assistance of PPMD certified clinics in CA, obtained the required CDPH informed consent for use of the RDBS from CA biobank from DMD subjects [Poster P-098]
  – Goal is to collect 200 confirmed positive specimens to be included in assay development and clinical studies
• 40 consent forms collected to date
• **First CA samples:** Results in favor of the CK-MM assay vs enzyme activity
  – All DMD cases are clearly separated from the normal population with the CK-MM assay, whereas see overlap with enzymatic assay.
  – False positives/false negatives=0
Presentation Outline

• Disease Overview
• Interventions and Treatments
• Newborn Screening
  – RUSP Process
  – Early Identification
  – Completed Pilots
  – Proposed Pilot

• Next Steps
Next Steps

• Complete CK Assay Validation Studies
• Convene Meeting of Stakeholders to Discuss Model of Pilot: October 2017
• Development of Care Guidelines/CDEs for newborns: January 2018
• Initiate Pilot
• Report Findings to Community including ACHDNC
• Submit RUSP Nomination Form