Newborn Screening for Duchenne Muscular Dystrophy

Annie Kennedy
Parent Project Muscular Dystrophy
Why Newborn Screening for Duchenne?
The Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet)

- Population-based surveillance system
- Longitudinal surveillance for DBMD (2002-2011)
  - Arizona, Colorado, Iowa, Western New York, Georgia, Hawaii
- Cross-sectional pilot surveillance for all MD types (2011-2014)
  - Arizona, Colorado, Iowa, Western New York
- Longitudinal surveillance for all MDs (2014 - 2019)
  - Colorado, Iowa, Western New York, South Carolina, North Carolina – Piedmont region, and Utah/Nevada

Average age of diagnosis was 5 years. Unchanged in 20 years.

Average delay of 2.5 years between detected onset of symptoms and definitive diagnosis.

The National Task Force for Early Identification of Childhood Neuromuscular Disorders

- Provider Tools
- Community Assessment of ‘terms’ used when expressing concerns to physicians
- Aligns with AAP Bright Futures
- Motor Delay Algorithm
- Clinical Pearls
- Videos
- Resources for Talking with Families
- Cooperative outreach campaign

www.ChildMuscleWeakness.org

** Funded through a grant by CDC NCBDDD to PPMD, led by Kathy Mathews, MD & Holly Peay, PhD
Duchenne Newborn Screening in the U.S.

With life-altering treatments on the near horizon, the Duchenne community recognizes the need to identify boys with Duchenne who will derive optimal benefit from these emerging therapies as early as possible – before irreversible fibrosis and muscle deterioration occur.

• Are treatments available that make a difference in intermediate outcomes when the condition is caught early or detected by screening?

• Are treatments available that make a difference in health outcomes when the condition is caught early or detected by screening?
Early Intervention

24 boys w/ DMD 1 mo – 3 y, steroid naïve

Administered:
Bayley III Scales of Infant Development,
Adaptive Behavioral Subset of Bayley (ABS),
Expanded Hammersmith Functional Motorscales (HFMSE),
North Star Ambulatory Assessment

Found:
Mean gross motor and fine motor function = both p 6 .0001.
Mean cognitive comprehensive (p = .0002),
receptive language (p 6 .0001), expressive language (p = .0001).
All low compared to normal children.

Age was negatively associated with Bayley III gross motor, but not with fine motor, cognitive, or language scores.

HFMSE (n = 23) showed a mean score of 31 ± 13.
NSAA (n = 18 boys; 2.2 ± 0.4 years) showed a mean of 12 ± 5.
What We Carry
PPMD’s Carrier Initiatives

• **Strive Grant** (PTC Therapeutics) to raise awareness of carrier risk & related issues

• The **Female Side of Duchenne** carrier study at Nationwide Children’s
  – PPMD has teamed with Nationwide Children’s in Ohio to study 300 women. The study includes: the natural history of cardiac fibrosis, **skeletal muscle involvement**, the incidence of carriers having **cognitive and behavioral issues**, as well as document the relationship between **stress and stress biomarkers**, cardiac fibrosis, function and skeletal muscle involvement.

• We continue to provide **genetic counseling support** for women who are carriers or at-risk to be carriers
  – Exploring methods to improve access to carrier testing & subsidize the cost of carrier testing
<table>
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<tr>
<th>Treatment</th>
<th>Phase III</th>
<th>Phase II</th>
<th>Phase I/II</th>
<th>Pre-clinical</th>
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Completed NBS Pilots

10 Programs
36 Years
~1.8M Newborns
~300 Cases
1:5400
Key Questions and Issues for Newborn Screening System

1. Usual Care and Course
2. Screening and Short-Term Follow-Up
3. Diagnosis
4. Benefits & Harms - Screening & Diagnosis (unrelated to treatment)
5. Treatment and Long-Term Follow-up
6. Intermediate Outcome Measures
7. Primary Health Outcomes (Patient)
8. Secondary Outcomes (Patient, Caregivers)
9. Benefits & Harms - Treatment & Long-Term Follow-up
10. Health Care System Needs
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
- Sensitivity
- Specificity
- Positive Predictive Value
- Negative Predictive Value
- Positive Likelihood Ratio
- Negative Likelihood Ratio
- Test Characteristics

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

ParentProjectMD.org
## Key Components for Duchenne Pilot

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

Activities:
• reviewing Patient Community Outreach Materials from previous pilots
• refining Baby’s First Test Flow Chart
• Interviewing other patient communities with experience in NBS to assess best practices
• Developing materials for provider outreach (state labs, birthing centers, PCPs, etc)

Workgroup Members:
Micki Gartzke*, Legacy of Angels/ Save Babies Through Screening
Natasha Bonhomme*, Baby’s First Test
Mardee DeSantis, Duchenne community
Michelle Morgan, MDA
Ann Lucas, PPMD/Duchenne Connect
Joan Scott, HRSA
Annie Kennedy, PPMD
Samiah Al-Zaidy, Nationwide Children’s
Yaacov Anziska, SUNY-Downstate

Duchenne NBS SC

Care Considerations for Infants with DMD WG
Outreach & Education to Patients & HCPs WG
NBSTRN Integration and LPDR WG
Laboratory Test Refinement WG
Evidence Review WG
Ethical & Legal Considerations WG
Clinical Care Considerations & Follow Up for Pre-Symptomatically Identified Infants with DMD

Activities:
• Article published (Muscle & Nerve)
• Phase II underway to include additional organizations (AAP, ACMG)
• ACT sheet update in process

Workgroup Members:
Anne Connolly*, Washington University
Julie Bolen*, CDC
Valerie Cwik, MDA
Samiah Al-Zaidy, Nationwide Children’s
Kathi Kinnett, PPMD
Jennifer Kwon, U Rochester
Hoda Abdel-Hamid, U Pitt
Jerry Mendell, Nationwide Children’s
John Day, Stanford
Annie Kennedy, PPMD
Laboratory Performance

Activities:
- Recommended a project to test the traditional method of screening for CK vs use of an immunoassay
- PKI project underway in California in September 2017

Workgroup Members:
Harry Hannon*, CDC Foundation
Medhuri Hegde, PKI
Fred Lorey, Retired CA Public Health Dept
Bob Currier, CA Public Health Department
Michele Caggana, NY Public Health Department
Petra Furu, PerkinElmer
Stuart Moat, Wales
Victor DeJesus, CDC
Brad Therrell, NNSGRC
Michele Puryear, PPMD
Clinical Integration Group and Longitudinal Pediatric Data Resource Development

Activities:
- Creating Common Data Elements
- Created an LPDR from the PPMD data sets

Workgroup Members

Amy Brower*, NBSTRN
Ann Martin, PPMD
Lauren Webb, MDA
Richard Finkel, Nemours Children’s, FL
Michele Puryear, PPMD
Elizabeth Bower, Intern

Duchenne NBS SC
- Care Considerations for Infants with DMD WG
- Outreach & Education to Patients & HCPs WG
- NBSTRN Integration and LPDR WG
- Laboratory Test Refinement WG
- Evidence Review WG
- Ethical & Legal Considerations WG
Bioethical & Legal Considerations

Activities:
- Series of ELSI issues identified
- Papers in progress – ELSI considerations for NBS for DMD
- Working with NBSTRN ELSI group

Workgroup Members:
Aaron Goldenberg* Case Western
Tom Crawford* Johns Hopkins
Ed Goldman, WI/NBSTRN
Aaron Goldenberg
Angus Clarke UK
Michele Puryear, PPMD
Annie Kennedy, PPMD
Rodney Howell, Univ of Miami & MDA
Kristin Stephenson, MDA

• Jeff Brosco*, Univ of Miami, NBSTRN & Don Bailey, Fragile X Foundation served as WG members until recently when service on SACHDNC presented conflict
Evidence Review Workgroup

Activities:
• Compiled evidence for DMD NBS utilizing the ACHDNC nomination form

Workgroup Members
Melissa McPheeters*, Vanderbilt
Craig McDonald, UC Davis
Natalie Street, CDC MD STARnet
Ann Martin, PPMD DuchenneConnect
Michele Puryear, PPMD
Larry Charnas, Novartis
Holly Peay, RTI

Duchenne NBS SC
- Care Considerations for Infants with DMD WG
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Informed Consent Process for DMD NBS

- State NBS Program
  - Registry for LTFU
- DMD NBS Result
  - Screen Positive / Negative
  - Dx to State
- Pediatric Care Provider/and or Birthing Center
  - Dx to PCP
  - Screen Positive
  - Consult with NM clinic
- Neuromuscular Clinic
- Disorder Identified
  - Consult with NBS program
  - Consult with neuromuscular clinic
  - Early Intervention Programs
  - Family support
- Consult Act Sheet
- Diagnostics
  - Diagnosis (results to parents/ PCP/ state)
  - Referral for therapy
  - Consultation with pediatrician
  - Family support
Duchenne NBS Update

• Complete CK Assay Validation Studies: Ongoing; FDA approval of PKI kit expected Jan 2019
• PPMD Convened Meeting of Stakeholders to Discuss Model of Pilot: October 2017
• PPMD NBS ELSI Workgroup manuscripts accepted for publication IJNS January 20, 2018: “Duchenne Muscular Dystrophy, a Case Study for Examining Ethical and Legal Issues for Pilot for Emerging Disorders: Considerations & Recommendations”
• Initiate Pilot: Planning Underway/ Screening begin 2019
• Report Findings to Community including ACHDNC: Ongoing
• Submit RUSP Nomination Form: TBD