Duchenne Newborn Screening in the U.S.

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Duchenne Muscular Dystrophy

- X-linked
- Incidence 1 in 5000 live male births
- All races and ethnicities
- ~2/3 spontaneous mutation
- Carriers can manifest symptoms; not well understood or characterized – great variability
Duchenne Muscular Dystrophy

Not just a muscle disease...

Cardiac * pulmonary * endocrine * GI/GI * cognition * psychological health * bone * and more

ParentProjectMD.org
Dystrophin Covers and Protects Muscle

Dystrophin Positive

Negative
Consequences of Absent Dystrophin

- The process continues with scar tissue replacing lost muscle fibers causing muscular dystrophy.
Fibrosis and Muscle Fiber Loss Occurs at Early Age in DMD
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

• Goal: Facilitate early identification of muscle weakness in children ages of 6 months to 5 years
• Tools:
  – Motor Surveillance Aid
  – Motor Delay Algorithm (screening and referral)
  – Video Library showing manifestations of weakness
  – Supporting materials available on www.childmuscleweakness.org

** Funded through a grant by CDC NCBDDD to PPMD, led by Kathy Mathews, MD & Holly Peay, PhD
Composition of Neuromuscular Task Force

Representatives from:
- American Academy of Pediatrics
- American Academy of Neurology
- Association of Academic Physiatrists
- Childhood Neurology Society
- American Academy of Physician Assistants
- National Association of Pediatric Nurse Practitioners
- National Association of Community Health Centers
- American Physical Therapy Association
- American Academy of Physical Medicine and Rehabilitation
- American Occupational Therapy Association
- American Speech Language Hearing Association
- National Society of Genetic Counselors
- National Coalition for Health Professional Education in Genetics
- CDC
- HRSA
- Parent Project Muscular Dystrophy
- Muscular Dystrophy Association
- Cure CMD
- SMA Foundation
- Families of SMA

ParentProjectMD.org
Task Force Yield

- 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
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 occurs.

Current DMD Dx Trends in U.S.

- Duchenne Connect
  Mean age of dx = 4

- CDC MD STARnet
  Mean age of dx = 4
Duchenne Newborn Screening – Where Are we in the U.S. today?

• State of Duchenne research
• Ohio pilot
• Duchenne NBS Steering committee
• Questions to be answered
• NBSTRN engagement
• Ck kit laboratory validation program
• NBS workgroups
• Expanded pilot planning – launch 2017
# CURRENT DUCHENNE CLINICAL TRIALS, September 2015

<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>
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<tbody>
<tr>
<td>CATENA (SANTHERA)</td>
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<td>DRISAPERSEN (BIOMARIN)</td>
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<td>IDEBENONE (SANTHERA)</td>
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<td>ATALUREN (PTC THERAPEUTICS)</td>
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<td>ETEPLIRSEN (SAREPTA)</td>
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<td>TADALAFIL (ELI LILLY)</td>
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<td>EPIGALLOCATECHIN-GALLATE (CHARITE UNIVERSITY, BERLIN)</td>
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<td>EPLERENONE (NATIONWIDE CHILDREN'S)</td>
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<td>HT-100 (HALO)</td>
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<td>PRO 44 (BIOMARIN)</td>
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<td>ANTI GDF-8 (PFIZER)</td>
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<td>FOLLISTATIN/AAV GENE THERAPY (NATIONWIDE CHILDREN'S)</td>
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<td>PRO 45 (BIOMARIN)</td>
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<td>PRO 53 (BIOMARIN)</td>
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<td>SMCT-1100 (SUMMIT PLC)</td>
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<td>CAT 1004 (CATABASIS)</td>
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<td>ISOFEN (PPMD ONLUS)</td>
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</table>
## DUCHENNE TRIALS QUEUED UP FOR 2015

<table>
<thead>
<tr>
<th>DRUG</th>
<th>TARGET</th>
<th>GOAL</th>
<th>COMPANY/INVESTIGATOR</th>
<th>TIME LINE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NBD PEPTIDE</strong></td>
<td>Blocks IkB in the NF-kB pathway</td>
<td>Reduce inflammation, boost muscle growth</td>
<td>Dennis Guttridge at Nationwide Childrens and TheraLogics</td>
<td>Need to complete IND-enabling toxicology; Seeking partner for trial</td>
</tr>
<tr>
<td><strong>GALGT2 GENE TRANSFER</strong></td>
<td>Muscle membrane-extracellular matrix interface</td>
<td>Decrease muscle injury</td>
<td>Paul Martin and Kevin Flanigan, Nationwide Children’s</td>
<td>Need to complete GMP manufacturing run; Phase I in 2015</td>
</tr>
<tr>
<td><strong>MINI-DYSTROPHIN GENE TRANSFER</strong></td>
<td>Muscle membrane-extracellular matrix</td>
<td>Decrease muscle injury</td>
<td>Jerry Mendell, Nationwide Children’s</td>
<td>2015</td>
</tr>
<tr>
<td><strong>BIGLYCAN</strong></td>
<td>Muscle membrane-extracellular matrix</td>
<td>Decrease muscle injury</td>
<td>Justin Fallon, Tivorsan</td>
<td>Phase I in 2015</td>
</tr>
<tr>
<td><strong>VBP-15</strong></td>
<td>NF-kB pathway</td>
<td>Blocks inflammation and stabilizes membrane</td>
<td>Reveragen</td>
<td>Phase I started in 2015; Phase 2 in late 2015</td>
</tr>
<tr>
<td><strong>CAT-1004</strong></td>
<td>NF-kB pathway</td>
<td>Blocks inflammation</td>
<td>Catabasis</td>
<td>Phase I/II in 2015</td>
</tr>
<tr>
<td>(+)-EPICATECHIN</td>
<td>Mitochondria</td>
<td>Improve energettics</td>
<td>Cardero</td>
<td>Phase I/II in 2015</td>
</tr>
<tr>
<td>TAMOXIFEN (ORAL SERM)</td>
<td>Estrogen Receptor</td>
<td>Not Known</td>
<td>Lee Sweeney</td>
<td>Phase I/II 2015; need a clinical collaborator</td>
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<tr>
<td><strong>DEFLAZACORT</strong></td>
<td>Anti-Inflammatory</td>
<td>Extended Access Program for approval in US</td>
<td>Marathon</td>
<td>EAP in 2015</td>
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<tr>
<td><strong>SRP-4045</strong></td>
<td>Exon 45 Skip</td>
<td>Restores dystrophin</td>
<td>Sarepta</td>
<td>Phase I/II 2015</td>
</tr>
<tr>
<td><strong>SRP-4053</strong></td>
<td>Exon 53 Skip</td>
<td>Restores dystrophin</td>
<td>Sarepta</td>
<td>Phase I/II 2015</td>
</tr>
<tr>
<td><strong>BMS-986089</strong></td>
<td>myostatin</td>
<td>Increases muscle mass</td>
<td>Bristol Myers Squibb</td>
<td>Phase I/II 2015</td>
</tr>
</tbody>
</table>
Duchenne Treatment: Three Major Approaches

- Glucocorticoids
- Exon Skipping
- Mutation Suppression

2 new product reviews anticipated in U.S. before end of 2015 – 2 possible in Q1 2016

first time ever for Duchenne
Summary of Glucocorticoids in DMD

- Efficacy demonstrated in six randomized controlled studies done (inclusive of 266 DMD)
  - 5 pred vs placebo
  - 1 deflzct vs placebo

- All randomized controlled glucocorticoid trials showed improved strength and function in DMD
MD STARnet & Corticosteroids

Corticosteroids & Cardiomyopathy

- Mean age of onset of CM = 14.3 years
  - 15.2 years in corticosteroid-treated
  - 13.1 years in non-treated
- By 14.3 years, 63% of non-treated males had developed CM
  - Versus 36% of treated
- For every year of treatment, the probability of developing CM decreased by 4%

Corticosteroids & Ambulation

- Type: 64.1% - prednisone, 22.3% - deflazacort, and 13.6% received both
- Average duration of treatment before losing ambulation - 3.4 years
- Mean age at loss of ambulation:
  - Untreated – 10.3 years
  - Short-term treated (3 months – 3 years) – 9.5 years
  - Long-term treated – 12.3 years
Corticosteroids in Infants?

- CDC Care Considerations for Duchenne recommend use of steroids beginning after motor skill development has plateaued between 4-6; some clinicians treat more aggressively – literature lacking

- Anne Connolly, Wash U leading a 5 Center study of 25 very young boys (ages 1 – 30 months) on weekend dose steroid regimen (ongoing), outcome measures include the North Star Functional Assessment & Bayley III
SKIPPING EXON 51 ENABLES PRODUCTION OF FUNCTIONAL DYSTROPHIN PROTEIN (targets dystrophin region where skipping 51 corrects 13% dystrophin)
Mutation Suppression

Ribosome

Stop Codon Mutations
- UAA
- UGA
- UAG

Gentamicin or Ataluren - Premature stop complex
14 year old with Duchenne enrolled in Eteplirsen trial
Duchenne Newborn Screening – Where Are we in the U.S. today?

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- **Ohio pilot**
- Duchenne NBS Steering committee
- Questions to be answered & priorities
- NBSTRN engagement
- Ck kit laboratory validation program
- NBS workgroups
- Expanded pilot planning – launch 2017
Phase I: Establish Range of CK within Population

- Ohio of Health (ODH)
- Analyzed 30,547 anonymous dried blood spots
  - DNA analysis on DBS for CK exceeding threshold (>600 U/L)
  - all 79 exons screened for deletions/point mutations

Funding support received from NCBDDD
Screening Newborns

- NBS implemented at 43 birthing hospitals throughout the state of OHIO
- 18,000 newborns screened, with 58 above threshold (>600)
- DMD mutation found in one newborn with CK=2003

Extending Screening

- Increased sample size throughout State of OHIO to 37,749
- 3 additional newborns with DMD mutations, again with CK > 2000
- Total 6 newborns with DMD mutations
<table>
<thead>
<tr>
<th>Gender</th>
<th>CK U/L</th>
<th>Gene</th>
<th>Mutation</th>
<th>Frame</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>2462</td>
<td>DMD</td>
<td>Del ex50</td>
<td>Out</td>
</tr>
<tr>
<td>Male</td>
<td>2675</td>
<td>DMD</td>
<td>Del ex5-41</td>
<td>In</td>
</tr>
<tr>
<td>Male</td>
<td>2003</td>
<td>DMD</td>
<td>Del ex8-9</td>
<td>Out</td>
</tr>
<tr>
<td>Male</td>
<td>2466</td>
<td>DMD</td>
<td>Del ex45</td>
<td>Out</td>
</tr>
<tr>
<td>Male</td>
<td>2791</td>
<td>DMD</td>
<td>Del ex45-48</td>
<td>Out</td>
</tr>
<tr>
<td>Male</td>
<td>2688</td>
<td>DMD</td>
<td>Del ex4-7</td>
<td>Out</td>
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<tr>
<td>Year of report</td>
<td>Country</td>
<td>Findings</td>
<td>Incidence</td>
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<tr>
<td>1979</td>
<td>New Zealand</td>
<td>10,000 screened</td>
<td>1:5,000</td>
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<td></td>
<td></td>
<td>2 DMD found</td>
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<td>1982</td>
<td>Edinburgh, UK</td>
<td>2,336 screened</td>
<td>0</td>
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<td></td>
<td></td>
<td>No DMD found</td>
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<td>1986</td>
<td>West Germany</td>
<td>350,000 screened</td>
<td>1:4,589</td>
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<td></td>
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<td>78 DMD found</td>
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<td>1988</td>
<td>Manitoba, Canada</td>
<td>54,000 screened</td>
<td>1:5,400</td>
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<td>10 DMD found</td>
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<tr>
<td>1989</td>
<td>Lyon, France</td>
<td>37,312 screened</td>
<td>1:5,330</td>
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<td>7 DMD found</td>
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<tr>
<td>1991</td>
<td>Western Pennsylvania, USA</td>
<td>49,000 screened</td>
<td>1:4,900</td>
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<td>10 DMD found</td>
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<tr>
<td>1998</td>
<td>Cyprus</td>
<td>30,014 screened</td>
<td>1:6,002</td>
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<td>5 DMD found</td>
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<tr>
<td>2006°</td>
<td>Antwerp, Belgium</td>
<td>281,214 screened</td>
<td>1:5,514</td>
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<td></td>
<td></td>
<td>51 DMD found</td>
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<tr>
<td>2011</td>
<td>Wales, UK</td>
<td>335,045 screened</td>
<td>1:5,266</td>
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<td>63 DMD found</td>
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<tr>
<td>2012</td>
<td>Ohio, USA</td>
<td>37,749 screened</td>
<td>1:6,291</td>
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<tr>
<td></td>
<td></td>
<td>6 DMD found</td>
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*DMD, Duchenne muscular dystrophy.*
Prior Duchenne NBS Community Conferences

Early Detection & Screening of Neuromuscular Diseases Conference
Eunice Kennedy Shriver National Institute of Child Health and Human Development
March 2009

MDA Muscle Disease Symposium on Newborn Screening
Jerry Mendell, MD & Michele Lloyd-Puryear, MD PhD
Muscle & Nerve, July 2013
Duchenne Newborn Screening – Where Are we in the U.S. today?

- State of Duchenne research
- Ohio pilot
- **Duchenne NBS Steering committee**
- Questions to be answered & priorities
- NBSTRN engagement
- Ck kit laboratory validation program
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- Expanded pilot planning – launch 2017
Duchenne NBS Steering Committee Membership

Michele Lloyd-Puryear, PPMD
Annie Kennedy, PPMD
Jerry Mendell, Nationwide Children’s

Anne Connolly, Wash U
Fred Lorey, Retired CA Public Health Dept
Bob Currier, CA Public Health Department
Jeff Brosco, MD, Univ of Miami, NBSTRN
Michele Caggana, NY Public Health Department
Micki Garski, Legacy of Angels Foundation
Don Bailey, Fragile X Foundation
R. Rodney Howell, MDA
Kristen Stephenson, MDA
Meduhri Hegde, Emory University
Pending, Parent of a Child w/ DMD

Michael Watson, ACMG NBSTRN*
Tiina Urv, NICHD*
Petra Furu, Perkin Elmer*
Julie Bolen, CDC*
Amy Brower, NBSTRN*
*non-voting members

ParentProjectMD.org
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Newborn Screening SYSTEM

- Prenatal Education
- Screening
- Diagnosis and Short-Term Follow-Up
- Clinical Care and Long-Term Follow-Up

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Screening Newborns for DMD

1. Usual Care

2. Newborn Screening

3. Diagnosis

4. Screening & Short-Term Follow-Up: Net Benefits & Harms

5. 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. Healthcare System

PUBLIC HEALTH – NEWBORN SCREENING PROGRAMS & LABORATORIES

POPULATION

HEALTH CARE SERVICE SYSTEM -- PUBLIC AND PRIVATE
Key Questions

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
Questions to Answer

• **Treatments**
  • 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?
    – We now have demonstrated treatments [glucocorticoids and exon skipping] that change the natural history of disease
      • There are multiple randomized double blind clinical trials using daily prednisone, deflazacort and high dose weekend prednisone that show unequivocal efficacy.
      • Treatments delay progression and prolong ambulation. Evidence that scoliosis is prevented.
      • Recent studies have also shown that exon skipping will increase distance walked on the 6 minute walk test and increase dystrophin expression in muscle.
      • New generation of morpholinos demonstrates successful rescue of dystrophin expression in novel mutations
      • Delayed onset of cardiomyopathy associated with steroid use
Treatments

• Except for current steroid study (inclusive of ages 1 to 30 months, Connolly), newborns have not been treated with current therapies

• **Therefore, pilot may have to include a clinical trial arm**
  
  – Benefits & Harms—Treatment & Long-Term Follow-up
  
  – 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?
Duchenne Newborn Screening – Where Are we in the U.S. today?

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Questions to Answer?

• Establish Regionalization?
  – An opportunity to use an established analytical infrastructure
  – Proven to accelerate clinical validation, foster data sharing, peer comparison, and ultimately performance improvement

• The implementation of DMD screening could be facilitated by supporting the creation of a dried blood spot virtual repository of DMD cases & related disorders

• What is the cost of the screen? Of diagnosis?
PPMD’s Duchenne Connect
International Registry

Established by Parent Project Muscular Dystrophy in 2007, with assistance from the NIH, the CDC, and Emory Genetics
Part of PCORnet

DuchenneConnect Registry
Median age of Diagnosis = age 4

10 countries with highest participation in DuchenneConnect
Goal is to create a national network of centers that provide standardized care in alignment with the Standards of the Certified Duchenne Care Center Program and in agreement with the CDC Care Considerations.
197 MDA Clinics; MDA DMD Registry in ~20 Clinics
Partnership with NIH Newborn Screening Translational Research Network

- Refine CK screen to lower false positives, confirm analytic utility and validity seen in Ohio pilot
- Establish clinical utility and validity more firmly
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Questions To Answer

- **Evaluating the Screening Test**
  - What analytic markers are associated with DMD that can be used in population-based screening?
  - What screening tests can be used to find these markers?
  - What is the analytic validity of the screening tests for DMD? If the marker is present in dried-blood spots, will it be found?
  - What is the clinical validity of available screening test algorithms in dried-blood spots?
  - If a screening test is positive, how likely is it the child has DMD (e.g., what is the expected “positive predictive value” [PPV] in newborn screening)?
  - Are those most likely to benefit from early treatment identified by screening?
PerkinElmer CK assay Validation Project

Planning Underway

Retrieve 200 DBS from select Duchenne clinical sites in California
Informed consent for DBS retrieval

Match controls with DBS in same timeframe as DMD DBS [600]
PerkinElmer to run assays
  Test for CK performed with traditional assay
  Test for CK performed using assay designed by Stuart Moat
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Duchenne Newborn Screening Workgroups

• Outreach & Education – HCP & Patient Community
• Clinical Care Considerations & Follow Up for Pre-Symptomatically Identified Infants with DMD
• Laboratory Test Validation & Refinement (including Screening algorithm development)
• NBSTRN Integration: Clinical Integration Group (CIG) & Longitudinal Pediatric Data Resource (LPDR)
• Bioethical & Legal Considerations
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Duchenne Newborn Screening Pilot Expansion

**Identified Priorities**

2015/2016 Pilot Planning

Outreach to States

Clinical Infrastructure Readiness

Ethical Issues Recommendations

Educational Materials & Outreach/Support Infrastructure for Patient Community

Educational Materials & Training/Support Resources for HCPs

NBSTRN resource utilization/integration with DMD registries

Securing Pilot Funding – federal & private grants

Collaborations with federal agency partners

Laboratory test/assay refinement – PE validation program

Preparing existing clinical infrastructure – MDA Clinics & PPMD Certified Duchenne Care Centers

ParentProjectMD.org
Distribution of Results-Screening for DMD Panel

* Follow up Plan for Test Results:
  • *CK performed at NBS State Health Lab*
  • *Normal results sent to Family via Pediatric care provider.*
  • *Abnormal CK to Emory DNA Laboratory*
    – If DMD/BMD mutation found results to Family via MH and referred to DMD Clinic.
      • If female, parents see genetic counselor at DMD Clinic.
      • If other muscular dystrophy mutation found, family informed and sent to DMD Clinic.
      • If CK Elevated and no mutation found, the family is informed and patient advised to follow up in DMD Clinic for re-testing of CK.*
MD STARnet References


