Newborn Screening Pilot Studies

Presented to the ACHDNC

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• The NBSTRN is an NICHD funded contract, awarded to ACMG in September 2008 and after open recompete in September 2013 and 2018.

• The NBSTRN will maintain, administer and enhance resources to support investigators with projects related to newborn screening for:
  - New technologies
  - New Conditions
  - New treatments and management approaches
Research Areas Related to Newborn Screening Pilot Studies

• Obtaining an unbiased understanding of rare genetic conditions
  • Population-based pilot testing of new NBS tests
• Validating new tests and treatments in asymptomatic newborns that allows for NBS expansion
Much Learned from Ongoing NBS Pilot Studies

- Currently coordinating multistate pilots for:
  - SCID (Complete)
  - Pompe (Complete)
  - MPS1 (Complete)
  - X-ALD
  - SMA
  - Duchenne Muscular Dystrophy +
  - Next??
Pilot Study Systems

- Sue Berry, Piero Rinaldo, Amy Brower, Bob Currier, NBSTRN Steering and Pilot Study workgroup

- What are the Measures of Progress of a Pilot Study?
  - Sufficient data for ACHDNC to make informed decisions

- What’s coming, what’s changing, what’s needed to deal with challenges?
  - Understand statistics around rare diseases at the population level
  - How to meet the capacity needs
    - Systems
    - Workforces
Problems Emerging in the NBS Pilot Study System

• The R & D pipeline is full
  • Several conditions are ready for pilot studies
  • New drug pipelines are growing
  • NBS and medical genetics workforces are strained
  • Funding is limited

• Targets of newborn screening are changing
  • Pharmaceutical pipeline full of treatments that target a disease subgroup
  • Systems are overloaded with off target services
    • false positives impact individuals
    • carrier rates can be very high for some conditions

• Rare diseases at the populational level challenge our current clinical trial ‘system’ for genetic screening.
  • Very hard to know when you know enough
• Disorders with already available analyte data (e.g., amino acids, often low)
  • proximal urea cycle disorders (OTC, CPS, NAGS)
    • Low citrulline and ratios by MS/MS; treated by medical foods and drugs
  • remethylation disorders (MTHFR, Cbl E, G)
    • low methionine and other intermediate pathway related biomarkers
  • Conditions with low valine, leucine, and isoleucine like branched chain kinase
  • Conditions with low serine/glycine like 3-phosphoglycerate dehydrogenase def.
  • Several formerly “secondary conditions” may be candidates for RUSP
• More LSDs
More Molecularly Screened Target Conditions are Emerging

- Cancer predispositions
  - RB (retinoblastoma)
  - TP53 (Li-Fraumeni)

- Infectious diseases
  - HIV
  - TOXO
  - CMV

- Molecular phenotypes, yes/no questions, or targeting genes
Targets of NBS and Treatment are Changing

- Severe and early onset forms of conditions are often the impetus for considering screening for a condition
- New therapeutics aimed at subtypes of diseases are growing
- Individualized treatments are coming fast
<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Disease Patient Subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaperones</td>
<td>Change conformation of a defective protein</td>
</tr>
<tr>
<td>RNA-directed exon skipping</td>
<td>Brings out of frame mutations leading to premature stop codons back into frame for more complete protein</td>
</tr>
<tr>
<td>Readthrough</td>
<td>Allows RNA to read through a premature stop codon due to nonsense variants (e.g. DMD)</td>
</tr>
<tr>
<td>Pre-mRNA splicing modifiers</td>
<td>Increases amount of functional protein (e.g. SMN2 to generate more functional SMN protein)</td>
</tr>
<tr>
<td>RNA interference</td>
<td>siRNA silences or downregulates genes via mRNA</td>
</tr>
<tr>
<td>Substrate reduction therapy</td>
<td>Enzymatic modification of specific enzyme substrates</td>
</tr>
</tbody>
</table>
Targets of Treatment are Changing

- New therapeutics aimed at subtypes of diseases
  - Exon 51 skipping (read-through) for DMD
  - Chaperone therapies

- Gene therapies
  - AAV and Lenti virus treatments are coming fast
    - Safety profiles are very positive

- Ultimately, primary targets should be the forms for which treatment outcome is assessed in pilots
The Challenge of Assessing Clinical Validity of Rare and Clinically Variable Diseases

• Rare diseases in prospective population-level pilot studies require latitude in statistical power
  • Incidence of disease, proportional distribution of mutations, and genomic background on which variants operate vary across populations
  • Requires extensive data sharing to maximize

• Variability in time of treatment and disease onset requires ongoing data collection

• Monitoring of performance of screening tests over time requires ongoing data collection

• Curating genetic variation before formal screening begins
Goals of Pilot Study: Statistical Considerations

• Generate sufficient data such that:
  • there is a high likelihood that the screen for the condition will perform as it did in the pilot study.

• Generate statistically robust data to make a well-informed decision of whether to add the condition to the RUSP
  • Measures of the progress of the pilot study over time
  • Should there be a minimum PPV that is acceptable for NBS conditions?
  • Should the incidence of the treatable form of the condition be considered?

All while accommodating the unique needs of rare diseases to ensure access when data is limited
• How Much Pilot Study Data Do We Need
  • How likely is that the test performs in routine use as it did in pilot studies?
  • Are there criteria by which a proposed screening test fails?

• Statistical perspective in coming slides
  • Confidence intervals (CI) provide a measure of the uncertainty of a result
    • A 10% difference between lower and upper CIs is a general target

• Coefficient of variation (CV) is a measure of the spread of data (standard deviation) around the average
  • A CV of 10% or less is a general target
Relatively Small Pilots Define False Positive Rate

Incidence: 1:10,000; Detection rate 100%; PPV 20%, False positive rate 0.05%

<table>
<thead>
<tr>
<th>PILOT STUDY SIZE</th>
<th>95% CI</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>25,000</td>
<td>(0.022%, 0.078%)</td>
<td>28.3%</td>
</tr>
<tr>
<td>50,000</td>
<td>(0.030%, 0.070%)</td>
<td>20.0%</td>
</tr>
<tr>
<td>75,000</td>
<td>(0.034%, 0.066%)</td>
<td>16.3%</td>
</tr>
<tr>
<td>100,000</td>
<td>(0.036%, 0.064%)</td>
<td>14.1%</td>
</tr>
<tr>
<td>150,000</td>
<td>(0.039%, 0.061%)</td>
<td>11.5%</td>
</tr>
<tr>
<td>200,000</td>
<td>(0.040%, 0.060%)</td>
<td>10.0%</td>
</tr>
</tbody>
</table>
Determining Detection Rate Requires Very Large Pilots

Incidence:1:10,000; Detection rate 100%; PPV 20%; False positive rate 0.05%

<table>
<thead>
<tr>
<th>Cases Detected</th>
<th>95% CI</th>
<th>Population Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>(70%, 100%)</td>
<td>100,000</td>
</tr>
<tr>
<td>30</td>
<td>(90%, 100%)</td>
<td>300,000</td>
</tr>
<tr>
<td>60</td>
<td>(95%, 100%)</td>
<td>600,000</td>
</tr>
<tr>
<td>120</td>
<td>(97.5%, 100%)</td>
<td>1,200,000</td>
</tr>
<tr>
<td>300</td>
<td>(99%, 100%)</td>
<td>3,000,000</td>
</tr>
</tbody>
</table>
Larger Numbers are Needed to Define PPV

Incidence: 1:10,000; Detection rate 100%; PPV 20%, False positive rate 0.05%

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<thead>
<tr>
<th>PILOT STUDY SIZE</th>
<th>95% CI</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>100,000</td>
<td>(7.2%, 26.1%)</td>
<td>28.3%</td>
</tr>
<tr>
<td>150,000</td>
<td>(9.0%, 24.4%)</td>
<td>20.0%</td>
</tr>
<tr>
<td>200,000</td>
<td>(10%, 23.2%)</td>
<td>16.3%</td>
</tr>
<tr>
<td>250,000</td>
<td>(10.7%, 22.6%)</td>
<td>14.1%</td>
</tr>
<tr>
<td>300,000</td>
<td>(11.2%, 22.1%)</td>
<td>11.5%</td>
</tr>
<tr>
<td>350,000</td>
<td>11.6%, 21.7%</td>
<td>10.0%</td>
</tr>
</tbody>
</table>
As Incidence Decreases, the PPV Decreases

- Incidence: 1:10,000; Detection rate 100%; PPV 20%
- False positive rate 0.05% (125 cases), Pilot Study Size 250,000

<table>
<thead>
<tr>
<th>INCIDENCE</th>
<th>TRUE POSITIVE CASES</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 5,000</td>
<td>50</td>
<td>28.57%</td>
</tr>
<tr>
<td>1 in 10,000</td>
<td>25</td>
<td>16.67%</td>
</tr>
<tr>
<td>1 in 25,000</td>
<td>10</td>
<td>7.41%</td>
</tr>
<tr>
<td>1 in 50,000</td>
<td>5</td>
<td>3.85%</td>
</tr>
<tr>
<td>1 in 125,000</td>
<td>2</td>
<td>1.57%</td>
</tr>
<tr>
<td>1 in 250,000</td>
<td>1</td>
<td>0.79%</td>
</tr>
</tbody>
</table>
**PPV is Maintained as False Positive Rate Decreases**

Pilot size 250,000; Incidence: 1:10,000; Detection rate 100%; False positive rate 0.05%, **PPV 20%**

<table>
<thead>
<tr>
<th>INCIDENCE</th>
<th>TRUE POSITIVE CASES</th>
<th>FALSE POSITIVE CASES</th>
<th>FALSE POSITIVE RATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 5,000</td>
<td>50</td>
<td>200</td>
<td>0.080%</td>
</tr>
<tr>
<td>1 in 10,000</td>
<td>25</td>
<td>100</td>
<td>0.040%</td>
</tr>
<tr>
<td>1 in 25,000</td>
<td>10</td>
<td>40</td>
<td>0.016%</td>
</tr>
<tr>
<td>1 in 50,000</td>
<td>5</td>
<td>20</td>
<td>0.008%</td>
</tr>
<tr>
<td>1 in 125,000</td>
<td>2</td>
<td>8</td>
<td>0.0032%</td>
</tr>
<tr>
<td>1 in 250,000</td>
<td>1</td>
<td>4</td>
<td>0.0016%</td>
</tr>
</tbody>
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Managing False Positive and Off-Target Rates

- Carriers can be important to a screened individual for some conditions (e.g. X-linked)
  - Can be confounded when variants are associated with a wide range of disease severity
  - Can be less individually important for others (autosomal recessives)
    - Need functional EHRs to make it useful for infants eventual family planning
- 2nd tier biochemical vs. molecular tests can minimize carrier identification family recontact
- Use of alternative risk assessment tools (e.g., CLIR)
Workforces Misaligned

- Medical Geneticist and Newborn Screening Program shortages
- Limited comfort with genetics services among non-genetics trained providers
- Analytical and clinical complexity of screening results are separating
How Can we Meet the Capacity Demands?

• Delegate responsibilities for off-target results after Public Health mandate is met
• Multiplex pilot studies
• Virtual pilot studies
• Ensure adequate workforces to meet growing demands
• Evolve a system in which the limited data available for screening for rare diseases can be developed in an controlled and organized way
• Consider alternative financing models that involve a broader range of stake holders.
Systems for Enhancing Capacity When Rare Disease Science is Moving Rapidly

• Regulatory Mechanisms
  • Models systems such as for ensuring rare disease treatment development and availability
    • Orphan Drug Act provided incentives for rare disease drugs
      • Postmarket surveillance to ensure that expected performance is maintained (i.e., DATA SHARING)
    • Need similar model for rare disease diagnostics and screening

• Reimbursement Systems
  • Maximizing evidence development
    • Coverage with evidence development (what’s not covered)

• Distribution of responsibilities to minimize duplication of effort and meet stakeholder needs
Resources to Enhance Translational Capacity

• Public funding limited

• Centralized data sharing in the absence of robust clinical EHRs is limited without incentives

• Public Private Partnership models
  • Risk sharing models (e.g., PPMD-funded DMD pilot in NY)
  • Patient driven data sharing works for those clinically affected but is limited for asymptomatic people with risks
  • Managed Entry Agreements (MEAs) to share the cost of uncertainty as in Europe for oncology drugs
NBSTRN
Newborn Screening Translational Research Network

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