Gene Sequencing in Public Health Newborn Screening: Are We Ready?

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Texas Timeline in Newborn Screening Technologies

- 1960: Bacterial-inhibition assay PKU
- 1970: Automatic puncher
- 1980: Radio-immunoassay CH
- 1990: 2nd-tier Rapid flow analysis PKU/total Gal
- 2000: 2nd-tier Molecular assay (PCR-RFLP) SCD
- 2010: MS/MS Multiple metabolic disorders
- 2010: Molecular assay (Real-Time PCR) SCID
- 2010: 2nd-tier LC MS/MS CAH
- 2010: Fluorometric assay Phe/total Gal
- 1990: Fluorometric immunoassay CH, CAH
- 1980: Electrophoresis Sickle Cell Disorders (SCD)
Gene Sequencing Timeline in Routine Newborn Screening

- **2004**
  - Hemoglobinopathies: Texas begins HBB sequencing 3rd tier test

- **2005**
  - Krabbe: NY begins GALC sequencing 2nd tier

- **2006**
  - Advent of Next Gen Sequencing

- **2007**
  - X-ALD: NY begins ABCD1 sequencing 3rd tier

- **2008-2012**

- **2013**
  - Cystic Fibrosis: WI begins CFTR Next Gen sequencing/genotyping 2nd tier
  - X-ALD: CA begins ABCD1 sequencing 3rd tier

- **2014**
  - MPS 1 (IDUA): NY: 2nd tier
  - Krabbe, Pompe & MPS 1 (GALC, GAA & IDUA): NJ: 2nd tier
  - Pompe, MPS 1, X-ALD (GAA, IDUA, & ABCD1): New Eng: 2nd tier
  - Pompeo & MPS 1 (GAA, IDUA): MN: 2nd tier
  - Pompe (GAA): WI: 2nd tier
  - VLCAD (ACADVL): TX: 2nd tier
  - Cystic Fibrosis Next Gen Seq: NY: 3rd tier
NBS Molecular Subcommittee

• The mission of the subcommittee is to ensure continuity and responsible growth of emerging molecular technologies within the newborn screening public health environment.

• WA, MI, CA, NY, MN, IA, WI, TX, MA, PR, CA(2) – expertise and a community of collaboration
NBS Molecular Subcommittee

• Molecular Quality Improvement Program
• NBS Molecular Workshops
• Molecular Assessment Program
• Molecular Resources Website
• Paradigm for NBS Molecular Pilots
• Presentations to the Community
APHL Molecular Testing Survey
Current Status
Molecular Testing Survey Data

Survey Field Date: January, 27, 2017
Survey Close Date: March 3, 2017

<table>
<thead>
<tr>
<th>NBS Programs Surveyed</th>
<th># of Completed Surveys</th>
<th>Completion Rate</th>
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<tbody>
<tr>
<td>53</td>
<td>48</td>
<td>90.60%</td>
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Current Status of Molecular Testing in NBS Programs

- Yes, within our lab/in-house (2.1%)
- Yes, performed by another lab or program - please list the laboratory(ies) (33.3%)
- No, we do not currently perform molecular assays (64.6%)

2017 APHL ANNUAL MEETING and state health government environmental laboratory conference
Molecular Testing Platforms Used

- Real Time PCR: 80.9%
- Luminex: 57.4%
- Allele Specific PCR (ARMS): 17.0%
- Probe based allelic discrimination PCR (TaqMan/LightCycler): 14.9%
- Sanger DNA Sequencing: 12.8%
- GenMark: 10.6%
- Other - please specify: 8.5%
- Restriction Fragment Length Polymorphism (RFLP): 8.5%
- Illumina MiSeq Next Generation Sequencing: 6.4%
- Illumina MiSeq Next Generation Sequencing for detection of mutation panels: 6.4%
- No molecular methods used: 0.0%
- ThermoFisher Ion Torrent Next Generation Sequencing: 0.0%
2017 Gene Sequencing in Public Health Newborn Screening Meeting

February 16-17, 2017 in Atlanta, GA

- Sponsored by APHL, in collaboration with CDC and HRSA
- Primary invitees were NBS Laboratory Directors, Managers and Follow Up Coordinators from states and territories across the U.S.
- >40 States and >120 participants
- 13 presentations and 4 breakout sessions
The purpose of this meeting is to convene pertinent stakeholders to discuss the current status of gene sequencing in newborn screening, and identify barriers and solutions for the successful incorporation of gene sequencing into newborn screening.
ARE WE READY?

Challenges and Barriers Identified
Common Barriers Identified

• Knowledge barriers / gap / personnel skillsets
• Cost / funding / resources
• Reporting – VOUS, consistency, change of urgency
• Information technology and bioinformatics
• Laboratory specific – instruments, space, workflow, timeliness
• Follow-up specific – education, LTFU
• Decision making
Potential Solutions Identified
How to address identified barriers?

• Many creative ideas
• Develop mobile app, e.g. education, health records, updates
• National call center or genetic librarian
• Google alert
How to address identified barriers?

• Education
  • NBS specific training courses
  • Education materials, web resources, video
  • Increase awareness of NBS in schools
  • NBS fellowship or graduate training

• Utilize, explore, and develop resources
  • Other public health programs
  • Other states
  • Other organizations
  • Use of regional laboratory
How to address identified barriers?

• Communication and information sharing
  • Within the program
  • With the stakeholders
  • With other states
  • Conferences

• Establish infrastructure and guidelines
  • Cost effectiveness analysis
  • In-house or regional laboratory
  • LIMS system specifications and bioinformatics
  • NBS variant database
  • Reporting content and timeline
  • Long term follow-up
What do NBS programs need to think through to determine if gene sequencing is of value to their programs?

• Definition of NBS
• Value or benefit added
  • Patient and family, providers, follow-up, lab
• Other consequences
• Cost effectiveness
• Generic and disorder-specific guidelines
• Gather stakeholder inputs
Current Resources Available

• APHL/CDC Molecular Training Workshop
• Sources of NBS Molecular QA/QC Materials
• Molecular Assessment Program
• Molecular Resources Website
• Technical assistance
  • Peer Network Resource Centers
  • CDC Newborn Screening and Molecular Biology Branch
• NBS specific variant database
• ....................
Thank you!