Review of Newborn Screening Technologies

Alex R. Kemper, MD, MPH, MS
K.K. Lam, PhD

Presented to the Advisory Committee on Heritable Disorders in Newborns and Children

August 4, 2017
Background

- Technologies used in newborn screening are complex and advancing rapidly
- AC decisions depend on understanding current technologies and anticipating future developments
Overarching Goals

• To describe
  • Screening methods
  • Confirmatory methods
  • Treatment

• Key elements
  • Overview and application
  • Analysis of benefits and risks
  • Costs
Overarching Goals

• To describe
  • Screening methods
  • Confirmatory methods
  • Treatment

• Key elements
  • Overview and application
  • Analysis of benefits and risks
  • Costs

This presentation is the “tasting menu”
<table>
<thead>
<tr>
<th>Specialty Area</th>
<th>TEP Member</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Experts</strong></td>
<td><strong>Nancy D. Leslie, MD</strong>&lt;br&gt;Cincinnati Children’s Hospital Medical Center&lt;br&gt;Division of Human Genetics</td>
</tr>
<tr>
<td><strong>Joanne Kurtzberg, MD</strong></td>
<td>Pediatric Blood and Marrow Transplant Program/&lt;br&gt;Carolinias Cord Blood Bank&lt;br&gt;Duke University Medical Center</td>
</tr>
<tr>
<td><strong>Cynthia Powell, MD</strong></td>
<td>Pediatric Genetics &amp; Metabolism&lt;br&gt;UNC Hospital</td>
</tr>
<tr>
<td><strong>Public Health Laboratories</strong></td>
<td><strong>Scott M. Shone, Ph.D</strong>&lt;br&gt;Center for Newborn Screening, Ethics, and Disability Studies&lt;br&gt;RTI International</td>
</tr>
<tr>
<td><strong>Patrick V. Hopkins</strong></td>
<td>NBS Laboratory Manager&lt;br&gt;Missouri State Public Health Laboratory</td>
</tr>
<tr>
<td><strong>National Research &amp; Regulatory</strong></td>
<td><strong>Amy Brower, PhD</strong>&lt;br&gt;National Coordinating Center /Newborn Screening Translational Research Network American College of Medical Genetics and Genomics</td>
</tr>
<tr>
<td><strong>Kellie B. Kelm, Ph.D.</strong></td>
<td>Office of In Vitro Diagnostic Devices Evaluation &amp; Safety&lt;br&gt;U.S. Food and Drug Administration</td>
</tr>
</tbody>
</table>
# Evidence Review Group (ERG)

<table>
<thead>
<tr>
<th>ERG Members</th>
<th>Role</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alex R. Kemper, MD, MPH, MS</td>
<td>Chair</td>
<td>Nationwide Children’s Hospital</td>
</tr>
<tr>
<td>Anne M. Comeau, PhD</td>
<td>State NBS Public Health Program</td>
<td>New England NBS Program, University of Mass Medical School</td>
</tr>
<tr>
<td>Nancy S. Green, MD</td>
<td>Clinical Expert</td>
<td>Department of Pediatrics, Columbia University Medical Center</td>
</tr>
<tr>
<td>Scott Grosse, PhD</td>
<td>Federal Advisor; NBS Expert</td>
<td>CDC</td>
</tr>
<tr>
<td>Jennifer A. Kwon, MD</td>
<td>Clinical Expert in Long-term Follow up</td>
<td>University of Rochester Medical Center, Department of Neurology and Pediatrics</td>
</tr>
<tr>
<td>Jelili Ojodu, MPH</td>
<td>Public Health Impact Task Leader</td>
<td>NBS &amp; Genetics, Association of Public Health Laboratories</td>
</tr>
<tr>
<td>Lisa Prosser, PhD</td>
<td>Decision Analysis Leader, NBS Health Economist</td>
<td>Health Management &amp; Policy/ SPH; Pediatrics/Univ of Michigan Med School</td>
</tr>
<tr>
<td>Susan Tanksley, PhD</td>
<td>State NBS Public Health Program</td>
<td>Newborn Screening Laboratory TX Department of State Health Services</td>
</tr>
<tr>
<td>K.K. Lam, PhD</td>
<td>Project Leader</td>
<td>Duke University</td>
</tr>
</tbody>
</table>
Screening and Confirmatory Testing

- Tandem Mass Spectrometry (MS/MS)
- Digital Microfluidics
- Molecular Tests
  - Polymerase Chain Reaction (PCR)
  - Targeted Gene Sequencing
  - Next-Gen Sequencing
- New Instrumentation
  - Genetic Screening Processor (GSP)
  - Point-of-Care Testing
Tandem Mass Spectrometry (MS/MS)

• Lysosomal storage disease screening
  • Ceramide detection with targeted high resolution mass spec
  • Potential markers for Pompe disease, Gaucher disease, adenosine deaminase deficiency, purine nucleosidase phosphorylase deficiency, X-ALD, Wilson disease, GAMT, and DMD
  • Might help reduce false positives and improve assessment of the degree of involvement
Molecular Tests

- DNA-based assays for screening and confirmatory testing
- Polymerase Chain Reaction (PCR)
  - SCID first-tier screening – detection of T-Cell Receptor Excision Circles (TREC)
  - SMA first-tier screening – detect copies of SMN1 gene
- Targeted Gene Sequencing
  - Sanger sequencing
  - Second-tier or confirmatory testing (e.g., Pompe disease, MPS I, X-ALD, MCAD, Galactosemia, SMA)
  - Next-gen sequencing panels
  - Cystic fibrosis Illumina panel – sequences all protein coding regions and intron/exon boundaries of the CFTR1 gene
  - SCID panel
- Whole Exome/Genome Sequencing
  - On-going pilot studies exploring the use of WES/WGS for newborn screening and for diagnostic dilemma
New Instrumentation

- **Digital Microfluidics**
  - Lab-on-chip
  - Work needed to understand relative benefit compared to other approaches, like MS/MS
  - Could be used for point-of-care newborn screening

- **Genetic Screening Processor (GSP)**
  - High throughput batch analyzer for quantitative or qualitative measurement of neonatal screening samples on 96-well microplates
  - Automates processes
  - Significant interest within state newborn screening programs
  - Trials planned to measure CK
Now Switching to Treatment
Hematopoietic Cell Therapy

• Infusion of either autologous (from patient) or allogeneic (from matched donor) hematopoietic stem cells (HSCs) to address insufficient enzyme activity or cell type

• Umbilical cord blood offers benefits (availability, lower risk of GVHD, lower risk of infection)

• Gene editing technologies targeting and attempting to fix the genetic lesions in defective autologous cells are in clinical trials (will discuss more)
Enzyme Replacement Therapy

- Replaces deficient enzyme activity
- Can be neutralized by antibodies
- To cross the blood-brain barrier
  - Intrathecal injections
  - Chemical modifications
  - Combined with other treatments (e.g., HCT)
Antisense Oligonucleotide Therapy

- Short single-stranded nucleic acid molecules that bind to mRNA
- Can modify mRNA splicing or alter translation to protein
- Nusinersen for Spinal Muscular Atrophy
  - alters splicing of \textit{SMN2} mRNA to include exon 7 and produce functional SMN protein
  - administered by intrathecal injection (6 doses in first year, followed by every 4 months thereafter)
- Eteplirsen for Duchenne Muscular Dystrophy
  - alters splicing of \textit{Dystrophin} mRNA to exclude pathogenic exon51 (13\% of DMD cases) and produce short but functional Dystrophin protein
  - administered by IV infusion once weekly
- Others in development
  - targeting other exons of \textit{Dystrophin} gene for DMD
  - targeting \textit{MeCP2} mRNA to reduce levels in Rett Syndrome
Targeted Gene Therapy

• **Gene Editing** – Using programmable DNA nuclease to correct mutations or introduce functional gene copies
  • Zinc Finger Nucleases (ZFN)
    • Clinical trials for MPSI and MPSII using ZFNs to introduce wildtype enzyme genes into hepatocytes
    • single intravenous injection is expected to provide lifetime production of functional enzymes
  • CRISPR/Cas9
    • Animal studies for correcting sickle cell mutations

• **Gene Replacement** – using viral vectors to introduce functional gene copies
  • Lentiviral
    • *ex vivo* gene transfer into hematopoietic or other stem cells
  • Adeno-associated virus (AAV)
    • *in vivo* gene transfer into somatic cells of specified tissues or organs
    • Phase 1 clinical trials for SMA and DMD
Questions or Comments?

Thank you!

Alex Kemper
alex.kemper@nationwidechildrens.org

K.K. Lam
Ashley Lennox (PhD Candidate)
Emily Miller, PhD

Duke CTSI