Review of Newborn Screening Technologies

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Duke Clinical & Translational Science Institute

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

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This presentation is the "tasting menu"

NBS Technologies Review – Technical Expert Panel (TEP)

Specialty Area	TEP Member
Clinical Experts	**Nancy D. Leslie, MD** Cincinnati Children's Hospital Medical Center Division of Human Genetics
	Joanne Kurtzberg, MD Pediatric Blood and Marrow Transplant Program/ Carolinas Cord Blood Bank Duke University Medical Center
	Cynthia Powell, MD Pediatric Genetics & Metabolism UNC Hospital
Public Health Laboratories	**Scott M. Shone, Ph.D** Center for Newborn Screening, Ethics, and Disability Studies RTI International
	Patrick V. Hopkins NBS Laboratory Manager Missouri State Public Health Laboratory
National Research & Regulatory	**Amy Brower, PhD** National Coordinating Center /Newborn Screening Translational Research Network American College of Medical Genetics and Genomics
	Kellie B. Kelm, Ph.D. Office of In Vitro Diagnostic Devices Evaluation & Safety U.S. Food and Drug Administration

Evidence Review Group (ERG)

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

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 *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 *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 *Dystrophin* gene for DMD
  - targeting *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!

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