Newborn Screening Technology: A Compendium Resource

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The Challenge

- The ACHDNC has to make complex decisions in a rapidly changing domain
  - Screening methods
  - Diagnostic approaches
  - Treatment
- Advances in scientific discovery, knowledge, and technology progressing rapidly, especially for genetic disorders
- Risks and benefits (anticipated and known) of standard technology applications not the main focus of evidence reviews assessing *net* benefit of expand newborn screening

Goal (Revised)

Based on feedback from the ACHDNC and TEP:

- Need a living document to describe current and emerging NBS technologies:
  - *Compendium of Newborn Screening Technologies*
- Identify key technologies (TEP, Lit Search)
  - Screening and Confirmatory Testing
  - Treatments
  - Other related areas (e.g., Bioinformatics)

Goal *(Revised)*

- Describe key elements of each technology
  - Overview and application(s)
  - Regulatory status (as applicable)
  - Benefits and Risks/Harms (anticipated and known)
  - Cost and resource considerations (when available)
  - Ethical, Legal, Social Issues (as reported)
  - Key references for more information
- Baseline information
- Update-able

Key Technologies Identified

SCREENING	TREATMENTS	BIOINFORMATICS
Tandem Mass Spectrometry (MS/MS)	Allogenic Stem Cell Therapy	R4S CLIR
Targeted next-gen sequencing	Autologous Stem Cell Therapy	ClinGen
Targeted next-gen sequencing	ERT	
Fluorometry, enzymatic, DELFIA	ERT Intrathecal Injections	
Digital Microfluidics	ERT with Chemical Mods to Bypass Blood Brain Barrier	
Real Time-PCR	Oligonucleotide Therapies	
Whole Genome Sequencing	Gene Editing with Zinc-Finger Nucleases	
	Gene Editing with CRISPR/Cas9	

Template for Compendium Entries

- NBS Area (Screening/Treatment/Other)
- Technology Name
- Description
- Application(s) in newborn screening
  - Implementation status (e.g., States)
  - RUSP Conditions
- Benefits (outcomes, screening accuracy)
- Harms/Risks (outcomes/AEs/false positives, etc.)
- Costs or Resourcing
- Special Considerations (regulatory, ELSI, Implications)
- Key References

BASIC TEMPLATE for Review of Each Technology

SCREENING

(or TREATMENT or OTHER_____)

Digital Microfluidics Fluorometry

Description

Digital microfluidics is a lab-on-a-chip system that manipulates small, separate liquid droplets using electrical control of surface tension. This allows for automated control of droplet mixing, storage, transport, and analysis. Recently, digital microfluidic technology has been combined with fluorometric enzyme activity assays to generate a high-throughput, hands-off screening method for enzyme deficiency disorders, including lysosomal storage disorders (LSDs). This technology is marketed as the SEEKER system (Baebies, Inc). SEEKER quantitatively measures the activity of multiple lysosomal enzymes in dried blood spots to screen for LSDs.

Current Use/Applications

Piloted and used by Missouri (Reference: Hopkins et al 2015)

PMID: 25444528
DOI: 10.1016/j.jpeds.2014.09.023 (pubmed hyperlink)

Illinois – not yet published

Conditions (RUSP or other)

Pompe, Fabry, Gaucher, MPS I

Reported or Anticipated Benefits *Availability of evidence re: benefits (Y/N), brief summary*

- Comparison of MS/MS and DMF for LSDs discussed in Millington et al 2017, Gelb et al 2017 (both in Molecular Genetics and Metabolism).
- Anticipated benefits
  - Digital microfluidics for LSDs uses very small reagent volumes, reducing costs.
  - Digital microfluidics for LSDs is fully automated from blood spot extraction to display of results.
  - The SEEKER apparatus is small and portable.

Potential Harms or Risks *Availability of evidence re: harms or risks (Y/N), brief summary*

- Potential harms or risks, likelihood

Costs or Resources needed to operate/use technology

- Equipment: SEEKER, Baebies Inc.
- Cost: unknown.
- Reagents: digital microfluidic cartridges, enzyme activity reagents available from Baebies, Inc. Cost: unknown

Special Considerations *(include for each technology as applicable)*

FDA or Regulatory Status

- The SEEKER system was FDA approved for newborn screening in February 2017.

Other ELSI factors: not mentioned

Implications: *(e.g., to newborn screening, health care services, follow up, other):*

- New technology alternative to MSMS, cost difference in NBS TBD.
- "Lab-on-a-chip" offers portability, other possible translations to point-of-care testing

Key References

Reviews:

Schlein et al 2017 (Int J Neonatal Screen)

Gelb et al 2015 (Clinical Chemistry).

Primary Reports:

Hopkins et al 2015 (J Peds)

Sista et al 2013 (Clinica Chimica Acta)

Millington et al 2017 (Molecular Genetics and Metabolism)

Gelb et al 2017 (Molecular Genetics and Metabolism).

Technology Table example – Screening

TECHNOLOGY	INSTRUMENT	ASSAYS / TESTING APPLICATION(S)	FDA APPROVAL	CURRENT USE (STAGE PROGRAMS)
Tandem Mass Spectrometry (MS/MS)	Multiplex	-Core RUSP conditions -Multiplex applications for LSD enzyme activity, XALD		
Targeted next-gen sequencing	MiSeqDx (Illumina)	-CF 139-variant assay for newborn confirmatory testing and parental carrier testing	yes	
Targeted next-gen sequencing	Ion AmpliSeq (Thermo Fisher)	-CF panel		
Fluorometry, enzymatic, DELFIA	GSP Genetic Screen Processor (Perkin Elmer)	-PKU -CF -CAH -biotinidase deficiency -CH -G6PD -Galactosemia		
Digital Microfluidics	SEEKER (Baebies)	-MPSI -Pompe -Gaucher -Fabry	yes	
	FINDER (Baebies)	-point-of-care testing for bilirubin	in development	
Real Time-PCR	EnLite Neonatal TREC Kit (Perkin Elmer)	-SCID -SMA		
EMERGING				
Whole Genome Sequencing				

Questions, Comments, or Suggestions?