Newborn Screening: View from a Clinician, Federal Advisory Committee contractee, (and Stalwart Supporter)

Nancy S. Green, MD
Associate Professor of Pediatrics
Associate Dean for Clinical Research Operations
Columbia University Medical Center

Genetic Alliance
8/20/2013
Outline

- Overview of NBS
- Impact of technology
- Expansion:
  - What’s pushing forward?
  - What’s holding back?
  - Comments
Newborn Screening Is a System

- **Hospital**: Collection of specimens
- **State Dept. of Health**: Laboratory
- **DOH & Primary care**: Follow-up
- **Specialty**: Diagnosis
- **Specialty**: Therapy

*Electronic data & records*
“Newborn screening should be conducted only when science and technology can serve both the individual and the public good.”

NBS Task Force Report 2000
~12,500 children are diagnosed through screening annually including >5000 with hearing loss

Cost: $30 per infant (2003 estimate)

CDC MMWR 2012

*Screening is based on PHENOTYPE to minimize uninformative results
NBS: Defined by Available Technology

- PKU: Bacterial inhibition assay – 1960’s
NBS: Defined by Available Technology

WHAT’S NEW?

• Mass spectrometry
  – Metabolic conditions
  – LSDs

• DNA-based analysis:
  – Specific mutations (several)
  – Functional assay (SCID)
  – Sequencing: targeted genes (limited)
  – Sequencing: whole genome/exome??
Previously, disorders in screening panels varied widely between states: Several states piloted screening for disorders prior to adoption by others states.

**New opportunities for NBS, through discovery, new technologies and therapies.**

**RAPIDLY EXPANDING!**

**PILOT PROGRAMS IN NEWBORN SCREENING**

Kenneth Pass,1* Nancy S. Green,2 Fred Lorey,3 John Sherwin,3 and Anne Marie Comeau,4

1Wadsworth Center, NYS Department of Health, Albany, New York
2March of Dimes, White Plains, New York
3Genetic Disease Branch, California Department of Health Services, Richmond, California
4New England Newborn Screening Program, Department of Pediatrics, University of Massachusetts Medical School,
“Newborn Screening: Toward a Uniform Screening Panel and System”

Established the 1st national recommendations on conditions to be screened by state-based programs:

29 specific conditions based on a set of criteria
Authorizing Legislation

- Title XXVI of the “Children’s Health Act of 2000” enacted three sections of the Public Health Service (PHS) Act:
  - Established the Advisory Committee on Heritable Disorders in Newborns and Children
  - Additional legislation for funding: 2008
  - Committee meetings: 2004 – 2013
  - To date, the Committee has focused efforts on NBS
HHS Secretary’s Advisory Committee: Nomination process for new conditions

Process: Nomination and Evidence based deliberation

Committee Report: Advancing the current recommended panel of conditions for newborn screening

Nancy S. Green, MD1, Piero Rinaldo, MD, PhD2, Amy Brower, PhD3, Colleen Boyle, PhD, MS4, Denise Dougherty, PhD5, Michele Lloyd-Puryear, MD, PhD6, Marie Y. Mann, MD, MPH6, Rodney R. Howell, MD7, for the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

The Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children is charged with advising the Secretary of the US Department of Health and Human Services in areas relevant to heritable conditions in children, especially newborn screening (NBS). This report describes the formulation by the Committee of a new process to nominate and review conditions to the recommended universal NBS panel. Nominations are currently being solicited. Committee review will adhere to the fundamental principles of being transparent, broadly accessible, evidence-based and consistent for all of the proposed conditions across the process. Genet Med 2007;9(11):792–796.

Key Words: newborn screening, genetic screening, evidence-based review, heritable disorders, nomination process
Nomination form is available on the HRSA website


<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>Screening and Diagnostic tests</th>
<th>Pilot results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SECTION I – CONDITION INFORMATION**

**SECTION II – EVIDENCE-BASED INFORMATION**

**SECTION II, PART A**

**SECTION II, PART B**

**TEST**

<table>
<thead>
<tr>
<th>Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation, positive predictive value, false positive rate, analytical specificity, sensitivity.</th>
</tr>
</thead>
</table>

**POPULATION-BASED PILOT STUDY**

<table>
<thead>
<tr>
<th>Location of Prospective Pilot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Newborns Screened</td>
</tr>
<tr>
<td>Number of Screen Positive Results</td>
</tr>
<tr>
<td>False Positive Rate; False Negative Rate (if known)</td>
</tr>
<tr>
<td>How is diagnosis confirmed (clinical, biochemical, etc.)</td>
</tr>
</tbody>
</table>

**LIST OF REFERENCES**

Limited to 20 references from scientific journals to support statements on un/published data; references may be written statements from other investigators.

1
2
3
4
Screened conditions should be:

- Medically serious
- Understood from population-based assessment
- Screening test works
- Diagnosis is possible
- Children needing treatment are identifiable
- Treatment is effective and available

Now: “Public Health Feasibility and Readiness”
Example: The Case for SCID
Early Infant Transplant (N=113)

RH Buckley *Ann Rev Immunol* 2004
Outcome of Nominations – as of May 2013

Recommended:
1) SCID (severe immune deficiency) (2010)
2) Critical congenital heart defects (2010)
3) Pompe Disease (2013)

Several others were not recommended due to:

Questions about:
Effectiveness of screening and/or treatment
NBS: WHAT IS COMING SOON?

• Fragile X – *What Treatment?*
  – What benefit to affected children?

• Spinal Muscular Atrophy –
  - Pending results of treatment trials

• Lysosomal Storage Diseases –
  – Hematopoietic transplant – Risk-Benefit?

• *Whole genomic sequencing from bloodspots?*
What is holding NBS back?

1) Discovery: Screening tests, new treatments
2) $$$ for Research and Public Health - at Federal and State levels
3) Federal Advisory Committee: Re-authorizing legislation: *in limbo*!
4) Public ambivalence…
Dried Bloodspot Repositories
Public-private controversies:

Example: Residual Bloodspot Specimens

Issue: Resource for piloting new disorders versus Privacy concerns from parents

Consequences: Texas destroyed 5.3 million newborn samples... MN is next.

State Responses: Increased outreach to parents
From a clinician’s perspective: How should NBS expand to better meet the needs* of children and their families?

*Current and future Information from NBS should be useful to the affected child.
**Neonatal screening by DNA microarray: spots and chips**

_Nancy S. Green and Kenneth A. Pass_

Abstract | Newborn screening (NBS) is a public-health genetic screening programme aimed at early detection and treatment of pre-symptomatic children affected by specific disorders. It currently involves protein-based assays and PCR to confirm abnormal results. We propose that DNA microarray technology might be an alternative, most prominently for treatment stratification of certain malignancies and for pharmacogenetic assessment of commonly used medications (for example, the AmpliChip CYP450 test; see Online links box). Newborn screening (NBS) is a public-health genetic screening programme that is aimed at early detection and treatment of...

<table>
<thead>
<tr>
<th>Limitations in 2005</th>
<th>In 2013+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete coverage</td>
<td>Probably OK</td>
</tr>
<tr>
<td>Imperfect genotype-phenotype correlations</td>
<td>YES</td>
</tr>
<tr>
<td>Generates too much information (TMI)</td>
<td>YES</td>
</tr>
<tr>
<td>Other (Consumer, Provider, etc.)</td>
<td>YES</td>
</tr>
</tbody>
</table>
My thoughts:

• Public health service must serve the public.
  ➢ The future: New treatments, diagnoses, disease modifiers.
• Research is intrinsic to NBS and must serve public health.
• These 2 functions must be mutually supportive.
  ➢ The “TMI” of genomic testing: What risks are acceptable?
  Risks: Interpretation difficulties, parental autonomy, burden of information
However, some things won’t change...

Thank you for your attention!

Any questions?

K. Pass, NY NBS