

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

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**COLUMBIA UNIVERSITY
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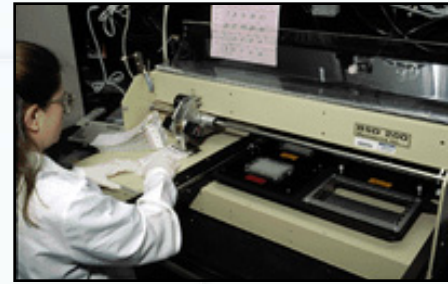
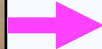
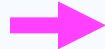
Discover. Educate. Care. Lead.

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

Impact of Newborn Screening - U.S.

**~12,500 children are diagnosed
through screening annually**
including >5000 with hearing loss

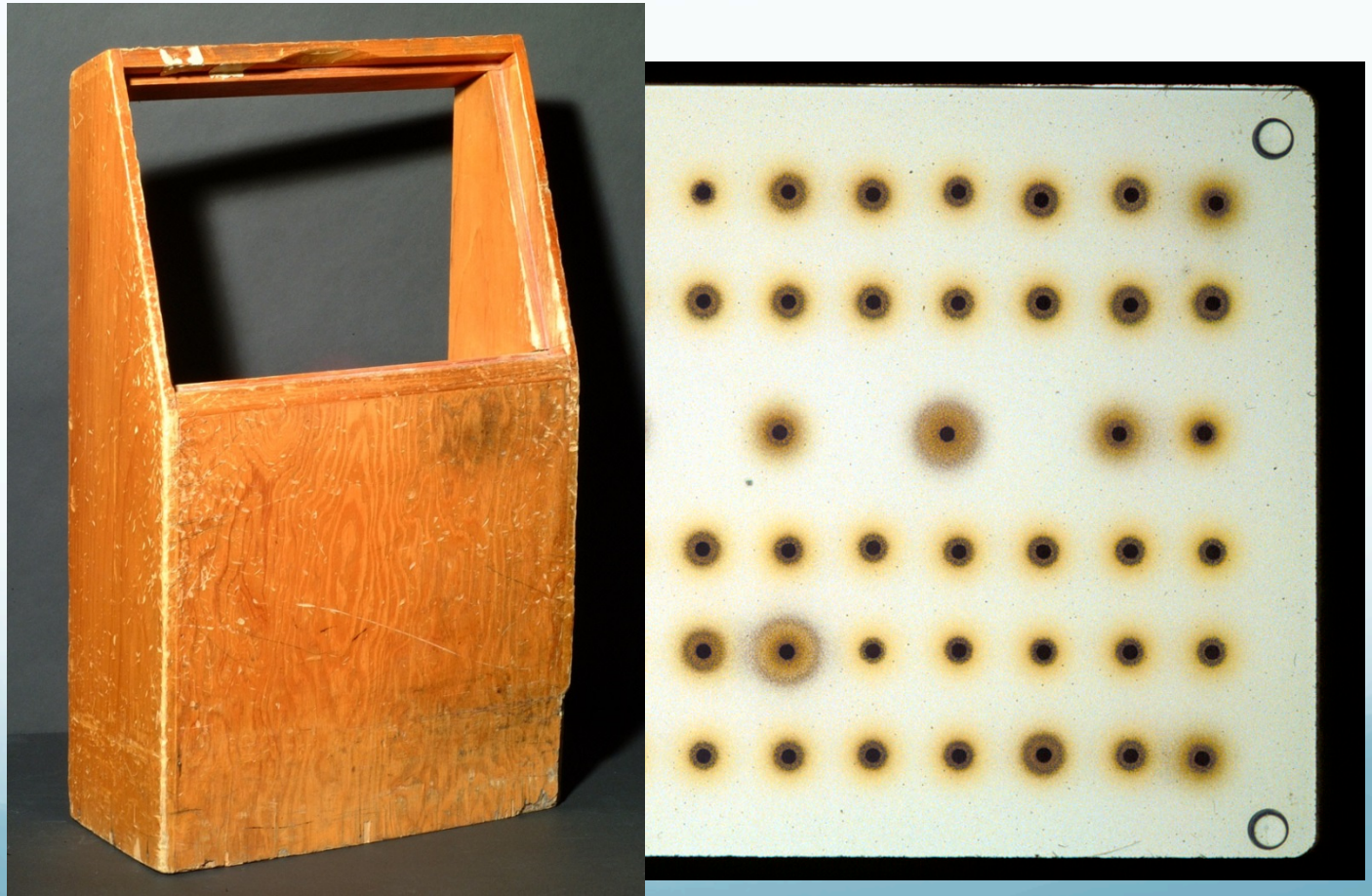
Cost: \$30 per infant (2003 estimate)

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?? ←



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

RAPIDLY EXPANDING!

**Previously, disorders in screening panels varied
widely between states: Several states piloted screening
for disorders prior to adoption by others states.**

MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES
RESEARCH REVIEWS 12: 293-300 (2006)



PILOT PROGRAMS IN NEWBORN SCREENING

Kenneth Pass,^{1*} Nancy S. Green,² Fred Lorey,³ John Sherwin³, and
Anne Marie Comeau,⁴

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⁴New England Newborn Screening Program, Department of Pediatrics, University of Massachusetts Medical School,

2005 Report: American College of Medical Genetics



“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



Advisory Committee on Heritable Disorders in Newborns and Children

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

(2007)

brief report

November 2007 • Vol. 9 • No. 11

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

Nancy S. Green, MD¹, Piero Rinaldo, MD, PhD², Amy Brower, PhD³, Coleen 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

<http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/nominatecondition/nominationform.pdf>

SACHDNC Form for Nomination of a Condition for Inclusion in the Uniform Screening Panel

DATE	
NAME OF NOMINATOR AND ORGANIZATION (include professional degrees)	
CO-SPONSORING ORGANIZATIONS (include professional degrees)	
*Note: Please reference each statement number listed in Section I, Part A	

Condition, Treatment, Screening and Diagnostic tests, Pilot results, References

TREATMENT	
Modality	Drug(s), diet, or other treatment.
Urgency	How soon after birth or onset of disease?
Efficacy (Benefits)	Extent of prevention or improvement of difficulty with acceptance of condition?
Availability	Limits of availability?
Potential Harms of Treatment	Potential medical or other harm?

TEST	STATEMENT	
Clinical Validation	Location, duration, size, preliminary results of past/ongoing pilot study for clinical validation, positive predictive value, false positive rate, analytical specificity, sensitivity.	
	POPULATION-BASED PILOT STUDY	STATEMENT
Analytical Validation	Location of Prospective Pilot	
	Number of Newborns Screened	
	Number of Screen Positive Results	Positive by primary test vs. 2 nd tier test if applicable.
	False Positive Rate; False Negative Rate (if known)	False positive by primary test vs. 2 nd tier test if applicable.
Considerations of Screening and Diagnostic Testing	False positives, carrier status, etc.	
Potential Secondary Findings	Detection or suggestion of other conditions	
	Number of Infants Confirmed with Diagnosis	How is diagnosis confirmed (clinical, biochemical, molecular)?

SECTION I – CONDITION INFORMATION

SECTION I, PART A

CONDITION	
Nominated Condition	
Type of Disorder	
Screening Method	
Gene	
Locus	Include ClinVar link if applicable
OMIM or other names for condition	Include Genetics Home Reference link if applicable
Case Definition	
Incidence	Determined by what method(s):
Timing of Clinical	Relevance of the timing of newborn screening

SECTION II – EVIDENCE-BASED SCREENING

- For a nominated condition to be included in the Uniform Screening Panel, the following criteria must be met:
1. Validation of the laboratory test
 2. Widely available confirmatory test (see Section II, Part B)
 3. A prospective population-based study

SECTION II, PART A

TEST	
Screening test(s) to be used	Description of the multi-analyte panel
Modality of Screening	(Dried blood spot, etc.)
Does the screening algorithm include a second tier test? If	(Dried blood spot, etc.)

SECTION II, PART B

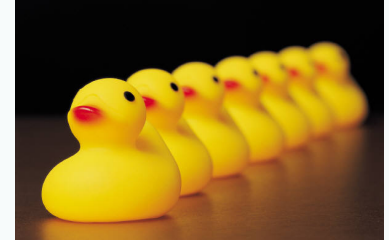
CONFIRMATORY TESTING	
Clinical and Analytical Validity	Quantitative or qualitative?
Type of test and/or sample matrix (blood, radiology, urine, tissue sample, biophysical test)	

LIST OF REFERENCES	
Limited to 20 references from scientific journals to support statements on un/non-published data, references may be written statements from clinical investigators.	
1	
2	
3	
4	

Considerations for Committee Review

Screened conditions should be:

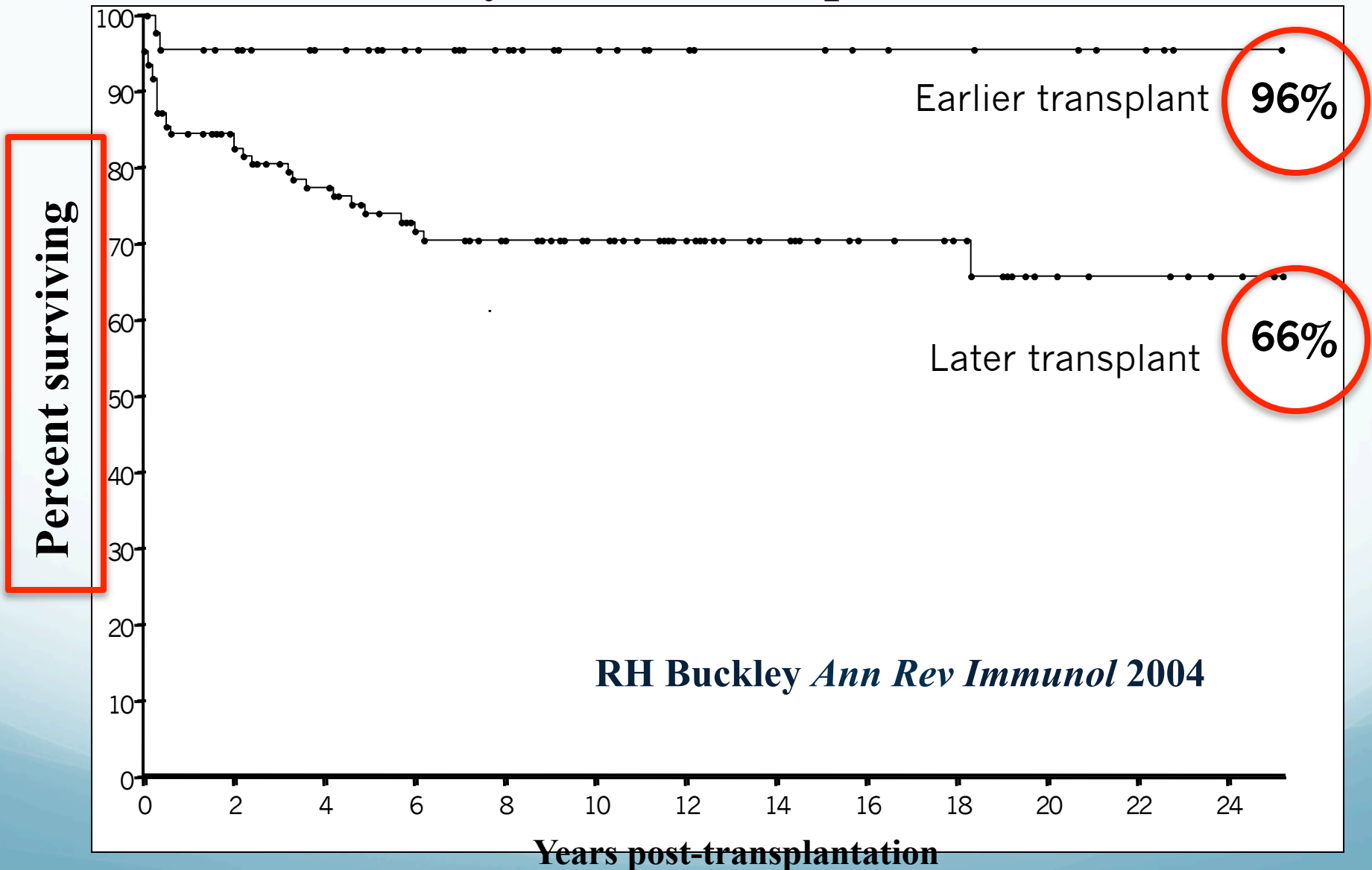
- Medically serious
- Understood from population-based assessment
- Screening test works
- Diagnosis is possible
- Children needing treatment are identifiable
- Treatment is effective and available



Now: “Public Health Feasibility and Readiness”

Example: The Case for SCID

Early Infant Transplant (N=113)



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.**



OPINION

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

use, most prominently for treatment stratification of certain malignancies³ 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

Limitations in 2005

- Incomplete coverage
- Imperfect genotype-phenotype correlations
- Generates too much information (TMI)
- Other (Consumer, Provider, etc.)

In 2013+

Probably OK

YES

YES

YES

Whole genomic sequencing from bloodspots?



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...



K. Pass, NY NBS

**Thank you
for your
attention!**

***Any
questions?***