Newborn Screening History
The Early Days

- 1902 – Garrod - Originated the phrase “Inborn Error of Metabolism”

- 1934 – Følling - Identified PKU as an inborn error associated with mental retardation - diaper test - ferric chloride - presence of phenylpyruvic acid in urine

Source: http://www.pkuworldlink.org/history.html
Newborn Screening History
The Early Days

- **1953 - Bickel - PKU dietary treatment** - Published the results of dietary therapy and formula treatment developed by himself, Evelyn Hickmans, John Gerrad, and Louis Woolf in the medical journal *Lancet*.

- **1959 - Guthrie - Filter paper test for PKU** - Developed a simple, inexpensive test with blood on filter paper for early detection of PKU (and other disorders). Early detection and treatment prevents the harmful effects of PKU.

Source: http://www.pkuworldlink.org/history.html
Newborn Screening
History of PKU

◆ 1930’s: dietary treatment was proposed
◆ 1950’s: dietary treatment became available
  – greatest cognitive improvement seen in youngest patients

Fig 19. Contrast—untreated and treated phenylketonurics. The 11-year-old boy is severely retarded, whereas his 2½-year-old sister, diagnosed in early infancy and promptly treated with the mind-saving diet, is normal.\(^7\)

*Pediatrics, 105:89, 2000.*
Earliest Reference Dried Blood Spots?

Mayan Mural 780 AD - Bonampak, Mexico - “Letting drops of blood fall on paper that will be burned to conjure the gods”

National Geographic 1995
1957: First reported use of a paper punch device to obtain standardized aliquots of dried blood from filter paper.

Source: Pellegrino J, Brener, Z., Revista Brasileira de Malariologia e Doencas Tropicais 1958:39-44. [Rio de Janeiro, Brazil]
Newborn Screening History

1959  – Guthrie – Began working on PKU method
1961  – Guthrie – Reported his bioassay for PKU (1963) using dried blood collected on filter paper
Newborn Screening History
Lessons Learned

Specimens punched and transferred manually
Newborn Screening History
Lessons Learned

1960s – Phillips (USA), Thalhammer (Austria) –
Began to develop automated tray scanning
Later Generation Punch Machines
Newborn Screening History


Brief Newborn Screening History - DNA


Brief Newborn Screening History – MS/MS


Brief Newborn Screening History

- **1930s** – Diaper Test for PKU
- **1950s** – Treatment for PKU
- **1960s** – Filter paper test for PKU, research, automated filter paper punching
- **1970s** – Thyroid testing, sickle cell testing, CAH testing, expanded metabolic testing
- **1980s** – Computerized data management and tracking, automation research
- **1990s** – DNA from filter paper, MS/MS techniques, CF studies, infectious diseases (HIV), hearing.
- **2000s** – Extended multiplexing, privacy (HIPAA), continued expanded screening
The Paradigm Shift:

“Technology Driven”

Analyte Screening by Multiplex Assays –
Hemoglobins - Isoelectric Focusing, HPLC
Metabolics - Tandem Mass Spectrometry
What is a tandem mass spectrometer?
Newborn Screening Challenges - MS/MS

- Significant “paradigm shift” – MS/MS is expensive, complex and can detect disorders for which no effective treatment is available
- Sudden expansion of presumptive positive cases - Multiple disorders detected – most disorders are very rare – natural disease course poorly understood
- Confusion as to how many disorders/conditions are detectable by MS/MS – the “numbers game”
- Detection of “mild/variant” forms of diseases (e.g. SCAD, MCAD) that may not require treatment
- Staff re-training for unfamiliar and difficult roles
- Significant stress on financial and personnel resources that are already limited
Newborn Screening is a SYSTEM!
Newborn Screening Process

1. Warm Heel
2. Puncture Heel
3. Absorb Blood
4. Air Dry / Send to Lab
Newborn Screening Process (continued)

5. Receive Specimens
6. Punch Specimens
7. Perform Testing
8. Record/Report Info.
NNSGRC INFRASTRUCTURE

HRSA Project Officer

NNSGRC Office – Austin

Executive Director
[Genetics Program Director]
Administrative Assistant
Program Coordinators (1.5)

Executive Advisory Committee
Includes 3 Center Administrators, 2 HRSA Advisors, 1 CDC Advisor
1 Consumer Liaison

NBS Technical Consultation Team
Genetics Technical Consultation Team

Project Advice Committees
Various Subcontracts
AAP Newborn Screening Task Force

◆ Approved by:
  – AAP Board of Directors
  – AAP Committee on Genetics
  – AAP Committee on Fetus and Newborn
  – Medical Home Initiatives for Children with Special Needs-Project Advisory Committee
  – AAP Task Force on Newborn and Infant Hearing
Congressional Interest - Equality

U.S. Government Accounting Office
March 2003

Response to Senate Request
One Approach

HRSA Contract
National Policy Development for NBS Test Selection

American College of Medical Genetics

Scoring Criteria

- Incidence
- Difficulty of diagnosis (birth)
- Disease impact
- Test sensitivity/specificity
- Test characteristics
- Treatment availability & cost
- Treatment efficacy
- Benefits to individual
- Benefits to family & society
- Mortality prevention
- Diagnosis availability
- Management availability
- Simplicity of therapy
## HRSA Contract
National Policy Development
for NBS Test Selection

American College of Medical Genetics

Completed January 2005

<table>
<thead>
<tr>
<th>CRITERIA INCLUDED IN THIS SURVEY</th>
<th>CATEGORIES</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of condition</td>
<td>&gt;1,500</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>&gt;1,25,000</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>&gt;1,00,000</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>&gt;75,000</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>&lt;1,100,000</td>
<td>0</td>
</tr>
<tr>
<td>Phenotype clinically identifiable at birth</td>
<td>&lt;25% of cases</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>&lt;50% of cases</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>&lt;75% of cases</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Always</td>
<td>0</td>
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<tr>
<td>Burden of disease if untreated</td>
<td>Profound</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Minimal</td>
<td>0</td>
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<tr>
<td>Does a sensitive AND specific screening test currently exist?</td>
<td>YES</td>
<td>200</td>
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<tr>
<td></td>
<td>NO</td>
<td>0</td>
</tr>
<tr>
<td>Test characteristics</td>
<td>Dobble in neonatal blood spots OR by a simple, in-</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>nursery physical method</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High throughput (&gt;=200/year/TE)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Cost (supplies + equipment) per test &lt;10</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Multiple markers in same analysis</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Detection of secondary targets</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Utilizes a multiplex platform</td>
<td>20</td>
</tr>
<tr>
<td>Availability of treatment</td>
<td>Inexpensive and widely available</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Expensive OR limited availability</td>
<td>50</td>
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<tr>
<td></td>
<td>Expensive AND limited availability</td>
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</tr>
<tr>
<td></td>
<td>To prevent ALL negative consequences</td>
<td>100</td>
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<tr>
<td></td>
<td>To prevent MOST negative consequences</td>
<td>50</td>
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<tr>
<td></td>
<td>To prevent SOME negative consequences</td>
<td>50</td>
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<tr>
<td></td>
<td>Treatment efficacy not proven</td>
<td>0</td>
</tr>
<tr>
<td>Potential efficacy of existing treatment</td>
<td>Clear scientific evidence that intervention IN THE FIRST WEEKS OF LIFE maximizes outcome</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Early intervention improves outcome</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>No evidence of improved outcome</td>
<td>0</td>
</tr>
<tr>
<td>Benefits of early intervention (INDIVIDUAL OUTCOME)</td>
<td>Early intervention improves benefits (education, understanding prevalence and natural history, cost effectiveness)</td>
<td>100</td>
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<tr>
<td></td>
<td>Early intervention improves benefits</td>
<td>50</td>
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<tr>
<td>Benefits of early intervention (FAMILY &amp; SOCIETY)</td>
<td>No evidence of benefits</td>
<td>0</td>
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<tr>
<td>Early diagnosis and treatment prevent mortality</td>
<td>YES</td>
<td>100</td>
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<tr>
<td></td>
<td>NO</td>
<td>0</td>
</tr>
<tr>
<td>Diagnostic confirmation</td>
<td>Widely available</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Reduced availability</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Available only in a few laboratories</td>
<td>0</td>
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<tr>
<td>Clinical management</td>
<td>Widely available</td>
<td>100</td>
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<tr>
<td></td>
<td>Reduced availability</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Available only in a few centers</td>
<td>0</td>
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<tr>
<td>Simplicity of therapy</td>
<td>Very high</td>
<td>200</td>
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<tr>
<td></td>
<td>High</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>0</td>
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Max score 1000
Education - Policy Makers

ACMG Report on Newborn Screening

May 2006
<table>
<thead>
<tr>
<th>Uniform Panel (Primary Targets)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MS/MS</strong></td>
</tr>
<tr>
<td><strong>(9)</strong></td>
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<tr>
<td>IVA</td>
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</table>

## Secondary Targets

<table>
<thead>
<tr>
<th>OA</th>
<th>Acylcarnitines</th>
<th>MS/MS</th>
<th>Amino acids</th>
<th>Hb Pathies</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cbl C,D</td>
<td>M/SCHAD</td>
<td>Hyper-PHE</td>
<td></td>
<td>Variant Hb</td>
<td>GALE</td>
</tr>
<tr>
<td>2M3HBA</td>
<td>SCAD</td>
<td>TYR-II</td>
<td></td>
<td></td>
<td>GALK</td>
</tr>
<tr>
<td>IBG</td>
<td>MCKAT</td>
<td>BIOPT (BS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2MBG</td>
<td>GA-II</td>
<td>TYR-III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3MGA</td>
<td>CPT-IA</td>
<td>ARG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAL</td>
<td>CPT-II</td>
<td>BIOPT (REG)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CACT</td>
<td></td>
<td>MET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DE REDUCT</td>
<td></td>
<td>CIT-II</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ACMG – Developed ‘Just in Time’ Guidance for Physicians – ACT Sheets

- Utilized recognized experts to develop actions to be taken upon receipt of screening results.
- Developed flow diagrams leading to diagnosis with understanding that they were templates that would likely need specialist support.
- Published on website.
Welcome to the National Newborn Screening and Genetics Resource Center (Genes-R-US), Genetic and Newborn Screening Resource Center of the United States.

The National Newborn Screening and Genetics Resource Center (NNSGRC) is a cooperative agreement between the Maternal and Child Health Bureau (MCHB), Genetic Services Branch and the University of Texas Health Science Center at San Antonio (UTHSCSA), Department of Pediatrics.

We provide information and resources in the area of newborn screening and genetics to benefit health professionals, the public health community, consumers and government officials.

Links of Special Interest

Papers and Reports


ACT Sheets (ACMG)


Related Links

Brochure for Parents: Model developed for state use based on parent focus groups

Brochure for Providers: Model developed for state use based on provider focus groups

Laboratory Services: Additional non-state newborn screening laboratory services
STATE MAP PAGE
Newborn Screening

Select the state initials on the map or the state name in the table below for newborn screening information.

Please contact Sue Triesch with questions, or with updates/corrections to state information. (512-454-6419) E-mail: triesch@uthscsa.edu

Click here for information on Regional Genetics and Newborn Screening Regional Collaboratives
National Project

Update Training on Added Conditions

[MS/MS, DNA (CF)]
Laboratory Service Delivery Models
States Using Contract Screening Laboratories (Public and/or Commercial/Non-profit)
U.S. Newborn Screening Conditions Required – August, 2008
(Conditions available as an option to a selected population are not counted – Must be universally required)
NNSGRC Consultative Reviews

‘Expert’ Assistance to state health departments to evaluate and improve the newborn screening program at the state level.

A valuable external review system using experts in laboratory, follow-up, administration, quality assurance and medicine to address specific program needs at the request and invitation of a public health screening program.
HRSA-Supported Quality Improvement Reviews
(Since 1987)
CLSI Standard LA04-A5 Package 2008
“Blood Collection on Filter Paper for Neonatal Screening Programs, Approved Standard”

- 3-Year shelf life for paper
- Better illustrations/descriptions
- 3-Month inventory of collection devices
Newborn Screening Quality Assurance Program

• Services provided:
  – Filter paper QC
  – Reference materials
  – QC materials
  – Proficiency testing
  – Consultation and network resource support

• Partners
  – Association of Public Health Laboratories
  – > 61 domestic screening laboratories
  – > 470 laboratories in > 72 countries
478 Laboratories in 72 Countries
U.S. Newborn Screening

2nd Screen Study

Status as of June 2008

Not Universally Required
Universally Required
Strongly Recommended (>85% compliance)
Challenges in newborn screening uniformity in U.S.

- National Mandate? – States left to decide
- Consent or Dissent? – All but 3 mandate screening without consent
- 1 screen or 2 screens – 8 States mandate 2 screens – may be important for CH, CAH, MS/MS
- Financing? – 5 States supported by gov’t. while others have fee – fees vary from $10 - $139
- Treatment? – Smaller states lack local specialists
<table>
<thead>
<tr>
<th>Condition</th>
<th>Screening Test(s) to be used</th>
<th>Modality of screening</th>
<th>Clinical validation</th>
<th>Laboratory performance metrics</th>
<th>Confirmatory testing</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>(Reference required. By pilot screening or clinical identification?)</td>
<td>(Dried blood spot, physical or physiologic assessment, other)</td>
<td>(Location, duration, size, preliminary results of ongoing pilot study for clinical validation)</td>
<td>(Sensitivity, specificity, etc.)</td>
<td>(Reliability, etc.)</td>
<td>(False positives, carrier detection, invasiveness of method, other)</td>
</tr>
<tr>
<td>Timing of clinical onset</td>
<td>(Relevance of this)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of disease</td>
<td>(Morbidity, disability, mortality)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>(Drug(s), diet, replacement therapy, transplant, other)</td>
<td>(How soon after birth treatment needs to be initiated to be effective)</td>
<td>(Extent of prevention)</td>
<td></td>
<td>(Any limits of availability)</td>
<td>(Potential medical or other ill effects from treatment)</td>
</tr>
</tbody>
</table>

**References**

<table>
<thead>
<tr>
<th>Key References (Specific citations - limit to 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
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<td>7</td>
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<td>8</td>
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<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>11</td>
</tr>
</tbody>
</table>

**Submission Information**

- **Submit nominee to:**
  - Mathematics and Science Branch
  - 5000 Fisher Lane, Suite 130N-10
  - Rockville, MD 20852
  - 301-443-8500
  - 301-443-8500

- **Contact Information:**
  - **Name:**
    - Michael A. Lass-Pamela, M.D., Ph.D.
  - **Position:**
    - Chief, Genetics Services Branch
  - **Address:**
    - 5000 Fisher Lane, PM 130N-10
    - Rockville, MD 20852
    - 301-443-8500
    - 301-443-8500

- **Submission Checklist:**
  - Cover letter by proponent
  - Nomination form
  - Copy of references listed on this form

- **Comments:**
  - Nomination of condition (page 2)
Examples of Candidate Conditions for Expansion of Uniform Panel (in alphabetical order)

- CDG type Ib
- CMV
- DMD
- G6PD
- Fabry disease
- FHC
- HIV
- Krabbe disease
- Pompe disease
- SCID
- SMA
- Toxoplasmosis
- Wilson disease
- Many (?) others……
1st Conference of Asia Pacific Regional Newborn Screening Network for Developing Programs
Cebu, Philippines – April 5 -7, 2008
International NBS Listserv Available

http://genes-r-us.uthscsa.edu
http://www2.uthscsa.edu/nnsis/
http://www.marchofdimes.com/peristats/