Newborn Screening: The Future Is Here

Ed McCabe, MD, PhD
Senior Vice President and Chief Medical Officer
March of Dimes Foundation
Overview

• NBS and the March of Dimes
• Advocacy for Improving NBS
• NBS Deserves a “Culture of Safety”
• DNA Sequencing in NBS
• Summary
NBS AND THE MARCH OF DIMES
March of Dimes Mission

- To improve the health of babies by preventing birth defects, premature birth, and infant mortality
- NBS fits into the categories related to
  - Birth Defects
  - Infant Mortality
Newborn Screening (NBS)

- 4 million babies are born each year in the USA
- Every one of those babies has access to testing for a number of disorders
- NBS protects babies from disorders associated with disabilities and death by early identification and interventions
- NBS saves lives!
Newborn Screening (NBS)

- Was originally based on a heel stick blood sample taken before discharge from the nursery
- Now includes
  - Hearing testing for hearing loss
  - Pulse oximetry for critical congenital heart disease
Newborn screening tests developed through March of Dimes research

- 1961: PKU
- 1977: Congenital Adrenal Hyperplasia
- 1979: Congenital hypothyroidism
- 1984: Biotinidase Deficiency
ADVOCACY FOR IMPROVING NBS CONSISTENCY AND PARENT EDUCATION
NBS Advocacy

• Proliferation of tests led to a state-by-state patchwork
• MOD advocated for policies to promote more uniformity
• Developed annual NBS Report Cards
Newborn Screening For All Babies

March of Dimes Newborn Screening Report Cards Held States Responsible and Drove Change

*Green states are those offering: 9 or more tests in 2004
21 or more tests in 2008
SDACHDNC

• Chartered in April 2013
  ▪ “to advise the Secretary regarding... effectively reducing morbidity and mortality in newborns and children having, or at risk for, heritable disorders”
  ▪ Includes
    o “most appropriate application of universal newborn screening tests, technologies, policies, guidelines and standards”
  ▪ Functions previously undertaken by SACHDNC
RUSP

• 31 Disorders
  ▪ 29 Blood spot-based
  ▪ 2 Functional tests
• Recommendations for uniformity
• Brings a discipline to addition of disorders to NBS
Newborn Screening Consumer Education
CLSI Education

Based on CLSI Standard NB501

Making a Difference Through Newborn Screening:
Blood Collection on Filter Paper

Based on CLSI Standard NB501-A6
Newborn Screening Saves Lives
Reauthorization Act of 2013

• Introduced into the
  - House: H.R. 1281 - Passed May 2014
  - Senate: S. 1417 - Passed January 2014

• Renews federal programs and state grants
• Supports parent and provider education
• Ensures laboratory quality and surveillance activities
• Reauthorizes the SACHDNC for 5 years
• MOD nominated
NBS: MOD Approach

• Select a Bold Problem
  - Reduce death and disability from birth defects

• Plan Strategically
  - Develop advocacy initiatives
  - Hold states accountable

• Solve Effectively
  - More robust and uniform NBS system
NBS DESERVES A “CULTURE OF SAFETY”
NBS Is a Complex System

• Many targeted disorders are rare
• Large number of individuals are involved in the NBS system
  ▪ But most will not be involved in identification of an affected individual
  ▪ Do not understand the NBS system and their impact
• Unusual events in a complex environment provide the opportunity for errors at the many steps in the system
High Reliability Organization

• HRO paradigm is a key feature of system safety

• HROs exist in “target rich” environments
  ▪ Inherently risky and unsafe
  ▪ Where consequences of errors are enormous and prevent experimentation

NBS: Adverse Events and System’s Failures

• Many disorders targeted by NBS can strike the affected neonate within days of birth
  ▪ Delays can result in death or disabilities
• Therefore, many states require NBS samples to be sent to the laboratory within 24 hours of collection
• MJS reported that delays occurred even when insurance or the state would have covered more timely delivery
Reasons for delays:

- Hospitals collecting multiple specimens over days before sending them to the laboratory
  - Process known as “batching”
- State NBS laboratories closed on weekends and holidays
- Lack transparency about transit times
- State programs vary widely
High Reliability Organizations

• Provide reliability through infrastructure that
  ▪ Prevents adverse events by anticipation
    ○ Examples: to identify, map and mitigate risk in an anticipatory manner
  ▪ Is resilient by containing these events
    ○ Examples: to recognize and contain errors before they spread and cause failure

• Provide optimally reliable outcomes by continuous quality improvement (CQI)
NBS and Culture of Safety
Continuous Quality Improvement

• Example from California reported in MJS
  ▪ California newborn screening program visited each hospital and reviewed practices every 2 years
  ▪ Visit of one hospital identified NBS sample batching as a problem
  ▪ Immediately corrected according to subsequent data monitoring

• Shows value of having CQI practices in place to identify errors, providing for prevention and resilience, characteristics of an HRO and a culture of safety
Newborn Screening Quality Improvement

- Publications on “Culture of Safety” in NBS
- NBS Quality Improvement Work Group
- NBS Quality Awards to State Health Officials:
  - Establish policies of full transparency and 95% transit times of 72, 48 or 24 hours
  - Robert Guthrie NBS Award for full transparency and 95% transit goal of 24 hours

Continuous Improvement

March of Dimes
• If your State Health Official has established a policy of full transparency and 95% transit by 72, 48 or 24 hours:
  ✓ Nominate for a NBS Quality Award
     ➢ Will be vetted by ASTHO
  ✓ Additional Awards will be announced in December 2014

• Encourage your hospitals to set their own goals to prevent “Deadly Delays’ for their babies
Inaugural Newborn Screening Quality Award – 72 Hours

Will Humble, MPH
Director, Arizona Department of Health Services
Estimate of Missed Children

• We estimated the number of children missed by NBS
  ▪ Using data from Holtzman et al. (Pediatrics 1986)
  ▪ A minimum of 80-120 babies missed per year
    ○ Resulting in unnecessary morbidity and mortality
NBS Culture of Safety

• NBS is a complex system prone to errors

• Errors represent
  ▪ Missed babies
  ▪ Avoidable morbidity and mortality
  ▪ Human factors problems

• We have known these issues since at least 1986
DNA SEQUENCING IN NBS
Incorporating DNA Sequencing into NBS

• The Human Genome Project is leading to cheaper DNA sequencing
• DNA is present in the NBS dried blood spots (DBS)  
  McCabe et al. 1986
• NIH has funded four grants to determine if DNA in the DBS can be sequenced and the implications of this
NICHD and NHGRI Grants

- Each of these sites will consider three areas of interest
  - Genomic sequencing from the NBS dried blood spots (DBS) and analysis of the sequence data
  - Investigation of impact of these data on patient care
  - Ethical, legal and social implications of the use of genomic sequence information in newborns
Examples from Funded Projects

- Identify and overcome technical challenges in sequencing DNA from DBS
- Determine optimal approaches for returning results to physicians and families
- Evaluate whether sequencing information complements NBS results and improves care
- Reduce sequencing results turnaround to 50 hours and determine impact on diagnosis and care in the NICU
Adverse Drug Events

- ADEs have a significant impact
  - Overall incidence in US hospitals estimated at 6.7% or >2MM/yr
  - Fatal ADEs estimated at 0.3% or >100,000 excess deaths/yr
    Nussbaum et al. Genetics in Medicine, 6th & 7th editions, 2001 & 2007
- Nearly 2% of US hospital admissions experience a preventable ADE
  - Results in an increased cost of $4,700/admission or ~$2B
    IOM, To Err Is Human: Building a Safer Health System, 2000
- Therefore, there are sizable numbers in morbidity, mortality and healthcare costs attributable to ADEs
Pharmacogenomics

- Uses genome-wide assessment technologies
  - To personalize therapeutic selection and dosage to improve drug
    - Safety
    - Efficacy
  - To reduce preventable adverse drug events (ADEs)
- Should NBS DNA sequencing include known ADE allele associations?
  - Would go beyond disease conditions
NBS & DNA Sequencing: Ethical, Legal and Social Implications

- Which sequence variants should be reported in the context of NBS?
  - All identified?
  - All with known associations for
    - Diseases?
    - Other sequence variants, e.g. ADEs?
  - Only those for which knowledge and intervention can impact morbidity and mortality in childhood?
  - Only those on the current NBS recommended uniform screening panel (RUSP)?
Should NBS Samples Be Analyzed in the Third Trimester?

• Even if samples can be analyzed routinely by 5 days of age
  ▪ Some babies will become critically ill before that time

• Is there a way to prevent the inevitable “Deadly Delays” in NBS?
Should NBS Samples Be Analyzed in the Third Trimester?

- If high quality fetal DNA can be obtained for sequencing in the mother’s third trimester blood
- If NICHD studies show DNA sequencing efficacious
- Then should fetal DNA be sequenced to determine appropriate services?
SUMMARY
Summary

• NBS is 51 years old
  ▪ Incredibly powerful
  ▪ Need to work as a community to
    o Improve the culture of safety
    o Reduce missed babies

• Adding new technologies will not prevent systems failures
Summary

• We must be relentless advocates for NBS
  ▪ Federal: NBS Reauthorization Act
  ▪ State: Attacks on “privacy” grounds
THANK YOU