Universal Screening for Metabolic Disorders
Historical Context and Adverse Outcomes

Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

Jeffrey P. Brosco MD PhD
Associate Professor, Clinical Pediatrics
Mailman Center for Child Development
University of Miami

December 19, 2006

Introduction

- Objective: “In the early history of universal NBS for metabolic disorders (PKU), is there evidence that substantial numbers of children with false positive results had medically adverse outcomes?”
- The short answer
- The long answer
  - Critical historical context for this committee
  - The questions you face are remarkably similar to 1960s

Methods

- Review of the historical literature on MR, NBS
- Review of relevant current issues for expanded NBS
- Narrow definition of medically adverse outcomes
  - Focus on death and permanent disability (developmental)
  - Did not include psychosocial consequences of FP results
- Comprehensive review of literature on six conditions
  - congenital hypothyroidism, phenylketonuria, congenital adrenal hyperplasia, galactosemia, sickle cell disease, and maple syrup urine disease
- Oral history interviews

Selected Conditions

Condition	Year NBS Possible	Year NBS First Implemented
PKU	1961 – Guthrie test created and available for mass NBS (Guthrie 1996)	1967 - 37 U.S. states had widespread screening (Guthrie 1996)
Congenital Hypothyroidism	1972 – Dussault created first CH screen (Dussault 1997)	1974 – mass screening in Quebec (Dussault, Coulombe et al. 1975)
Galactosemia	1964 – Guthrie (Guthrie 1968) introduces bacterial metabolite inhibition assay for galactosemia	1964 – galactosemia screening incorporated into the Massachusetts Newborn Screening Program for Metabolic Disorders (Shih, Levy et al. 1971)
Syphilis	1916 – Wasserman test and treatment available to prevent vertical transmission (Brandt 1985)	1938 – laws enacted to universally screen pregnant women for syphilis (Brandt 1985)
Congenital Adrenal Hyperplasia	1937 – able to detect peculiar chemicals in the urine of CAH patients (Butler and Marrian 1937)	1977 – screening first performed in Alaska (Pang and Shook 1997)
Sickle Cell Disease	1961 – sickle cell detectable by starch gel electrophoresis (Pearson 1989)	1976 – first statewide sickle cell screening program done in NY (Guthrie 1989)
Maple Syrup Urine Disease	1964 – Guthrie bacterial inhibition assay made available for NBS (Naylor and Guthrie 1978)	1973 – over 3 million infants routinely screened for MSUD (Levy 1974)

Methods: Literature Review Strategy

- On-line/Database
  - PubMed, Ovid
  - CALLCAT (database for University of Miami)
  - Google (to access web sites such as CDC and OMIM)
- Keywords: Specific conditions/synonyms plus:
  - + false positive
  - + adverse events
  - + injury
  - + adverse outcomes
  - + history
  - + newborn screening
- Manual (Textbooks, Books/articles by historians)
- Organic
  - References of references retrieved
  - Authors' names searched for relevant articles

Methods: Oral History

- Interview approach
  - Semistructured interviews
- Interviewees
  - Prominent clinicians and researchers
  - Asked each interviewee who else we should interview
- Interviews were taped and partially transcribed
- Key information reviewed with interviewee to assure accuracy

Results of Literature Search

- There are no population-based data or disease registries for NBS conditions in the early years of NBS programs in the US
- There is no data, even informal follow-up, of false positive results in the early years of NBS programs

Results of Literature Search

- **Sickle Cell Disease** – no cases of adverse medical outcomes from treatment of false positive results
- **Galactosemia** – no cases of adverse medical outcomes from treatment of false positive results
- **Maple Syrup Urine Disease** – no cases of adverse medical outcomes from treatment of false positive results
  - Tornqvist (1996) reported one case of a child with MSUD developing deepithelialization of the cornea, along with skin and intestinal symptom; perhaps due to an isolated deficiency of isoleucine

Literature Search Results
Congenital Adrenal Hyperplasia

- Mendilaharzu (1973)
  - 23 day-old boy in NY presented with shock; diagnosed CAH
  - Cushing syndrome after years treatment with corticosteroids
  - Treatment withdrawn at age 5 years: he had rapid catch-up growth and dramatic change in physical appearance, but lost sight in right eye and had pituitary ACTH abnormality
  - Misdiagnosis rather than false positive (not universal screening)
- Decsi, Kosztolanyi et al. (1990)
  - Hungarian team described “treatment-induced injury” in a child with true CAH
  - Cortical blindness in infant who developed enteritis and severe but transient hypertension; related to overdose of steroids?

Literature Search Results
Congenital Hypothyroidism

- No published reports of iatrogenic injury to a child falsely diagnosed as having CH from screening programs
- Fisher (1979) noted that some infants demonstrate “transient hypothyroidism,” and receive treatment for weeks to months before normal thyroid functioning is discovered
- He reported no long-term consequences for these children of the early treatment with thyroxine

Literature Search Results
PKU

- **Rouse** (1966) described two children admitted to pediatric wards at the University of Texas, Galveston, for failure to thrive.
- Both children had initial results suggesting PKU but no follow-up testing to confirm the diagnosis; it is not clear if the confusion began with result of a NBS program
- After several months of formulas low in phenylalanine, both infants developed the known effects of restricting this essential amino acid
  - Listless, poor gain weight, severe eczematous rashes
- Symptoms resolved within days of starting a whole milk formula, but both infants continued to demonstrate developmental delay
- Rouse concluded: “These cases reflect the fallacy of institution of phenylalanine restriction before a definitive diagnosis of phenylketonuria is established.”

Literature Search Results
PKU

- Moncrieff (1961) reported the case of an infant at Great Ormond Street Hospital in London; the child had indeterminate test results and was treated for PKU because of high serum levels of phenylalanine which normalized with a restricted diet
- Child continued to have poor growth, restlessness, and a skin rash despite weeks of close follow-up that included adjustments to the diet and careful attention to serum and urine test results
- All symptoms resolved when “half-cream dried milk” begun, and over the next few months the child thrived and maintained normal serum levels of phenylalanine despite the lack of a restrictive diet
- Her developmental quotient was reported as 103 at age 14 months.

Literature Search Results
PKU

- Many reports of children with PKU suffering adverse medical consequences as clinicians struggled to manage protein restriction
  - Seizures (Woolf, 1955)
  - Hypoglycemia (Dodge, Mancall et al. 1959)
  - Failure to thrive (Moncrieff, 1961)
  - Rash (Wilson and Clayton 1962)
  - Megaloblastic anemia (Royston and Parry 1962)
  - **Death** (Holt, 1963)
  - Wilson (1962) noted second-hand reports of deaths:
    - "From contacts with other pediatricians it has become apparent that … in some instances there has been a fatal outcome."

Literature Search Results
PKU

- No case reports after 1970 of adverse medical events
- 1970 Hanley et al reported still having considerable difficulty in balancing the nutritional needs of the growing infant with the need to keep phenylalanine levels low
  - 19% of children treated for PKU before six months of age had IQs less than 75 by age five year (6/32)
- Problems with metabolic variants, “heterozygotes,” “transient hyperphenylalanine,” LBW - tyrosine
  - Are these “false positives”?

Oral History Results

NAME	POSITION	Key Notes
Harvey Levy	NBS program Massachusetts	Does not recall medically adverse cases from false positives except those reported by Rouse; does not recall many such discussions/reports at meetings.
Richard Koch	NBS program California	No personal experience with adverse outcomes, but heard that "some babies got hurt that way." Believes key was confirming positives obtained from screening tests.
Ed McCabe	NBS program Colorado	Recalls one [unreported] case of a child with FTT who came to his clinic at a year of age after treatment for false positive for PKU; also recalls "half a dozen" children with MR from PKU because of false negatives. Emphasizes that hyperphenylalanine (not classic PKU) poorly understood early on.
Selma Snyderman	NBS program New York	Infants referred to her on the PKU diet by physicians who did not do confirmatory tests; she would stop diet and retest to distinguish among classic PKU, variants, and false positives. No long-term consequences for child who were false-positive or hyperphenylalanine variants.
W. Harry Hannon	Newborn Screening CDC	No personal experience with adverse medical outcomes from false positives in screening for PKU.

Oral History Results

Norman Fost	Pediatrician, Ethicist	No first-hand knowledge of adverse outcomes; His sources on adverse medical outcomes include Bessman, Paul, Edelson, Cooper, AAP committees, NAS report

Sam Bessman	Biochemist, U. Maryland	Early critic of NBS, especially PKU programs. Not interviewed due to illness.
Marvin Mitchell	NBS, Massachusetts	Not interviewed because little experience with PKU and no experience with adverse medical outcomes.

Short Answer

- "In the early history of universal NBS for metabolic disorders (PKU), there is **no** evidence of substantial numbers of children with false positive results who had medically adverse outcomes"
  - Likely no publication bias
  - How do you define a "false positive"?
  - Why is there no evidence?
    - No population-based data available
      - US has never been good at keeping such data

Complicated Answer

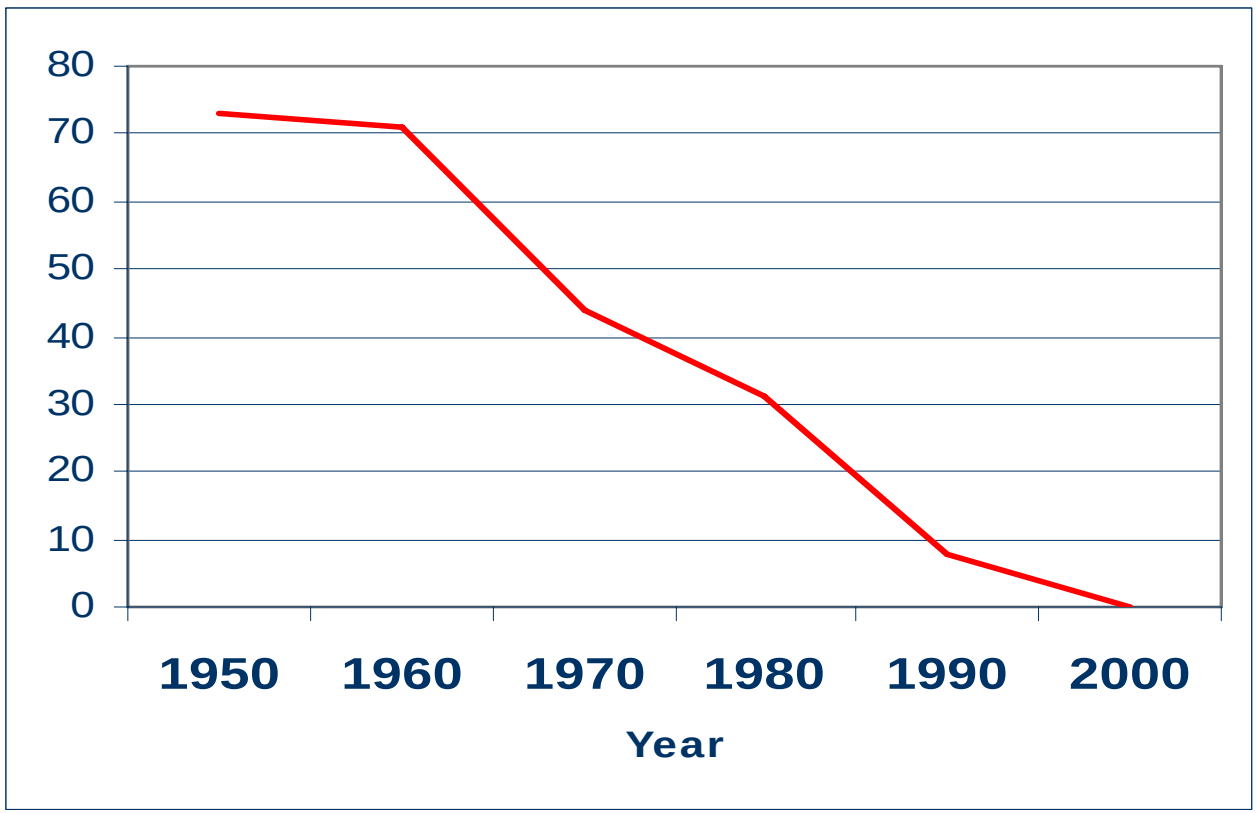
- History does not tell us what to do, but the PKU story in particular is fascinating and relevant
- In many ways, we now face questions about expanded NBS that our counterparts faced in the early years of implementing NBS for PKU

Standard Story of PKU

- 1934 Asjborn Folling reported high levels of phenylpyruvic acid in urine associated with MR
- 1939 George Jervis found substance in urine of 50 persons with MR at the Village State School in Thiells, NY
  - Jervis found similar cases in other institutions
- 1950s Horst Bickel and colleagues speculated that restricting phenylalanine in diet could prevent MR
  - Effective only when begun before symptoms appeared
  - Feasible only in younger siblings of affected individuals
- Early 1960s Robert Guthrie introduced a semi-quantitative phenylalanine assay applied to a drop of dried blood

Phenylketonuria

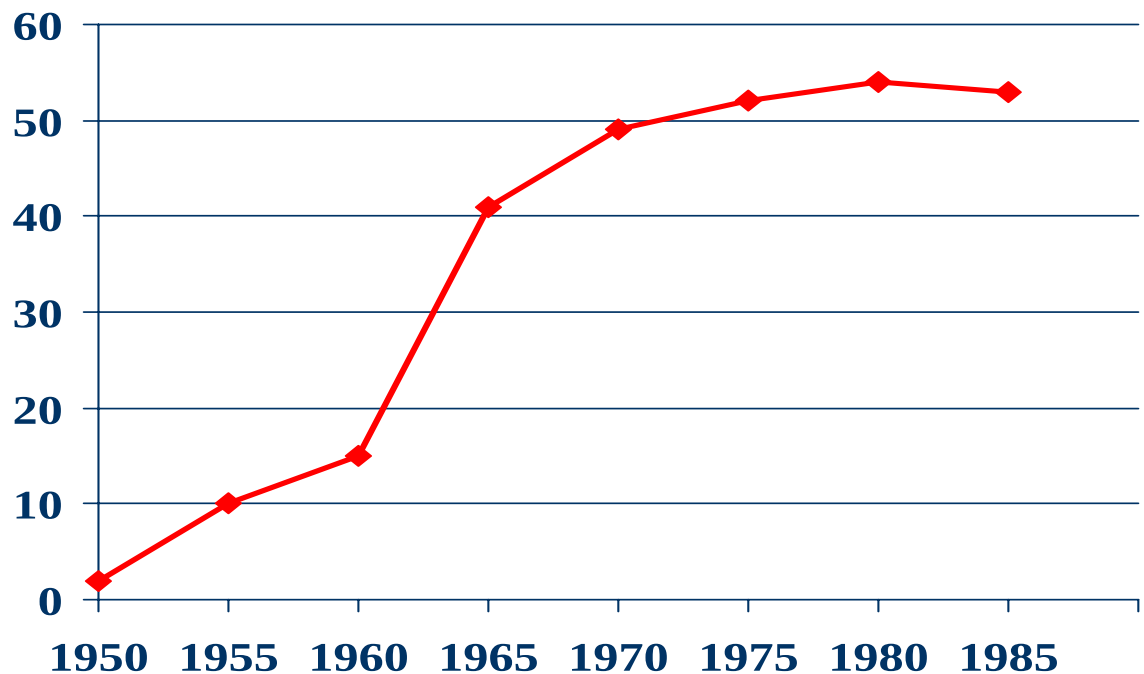
Incidence of MR per 1 million births (Brosco et al, 2006)



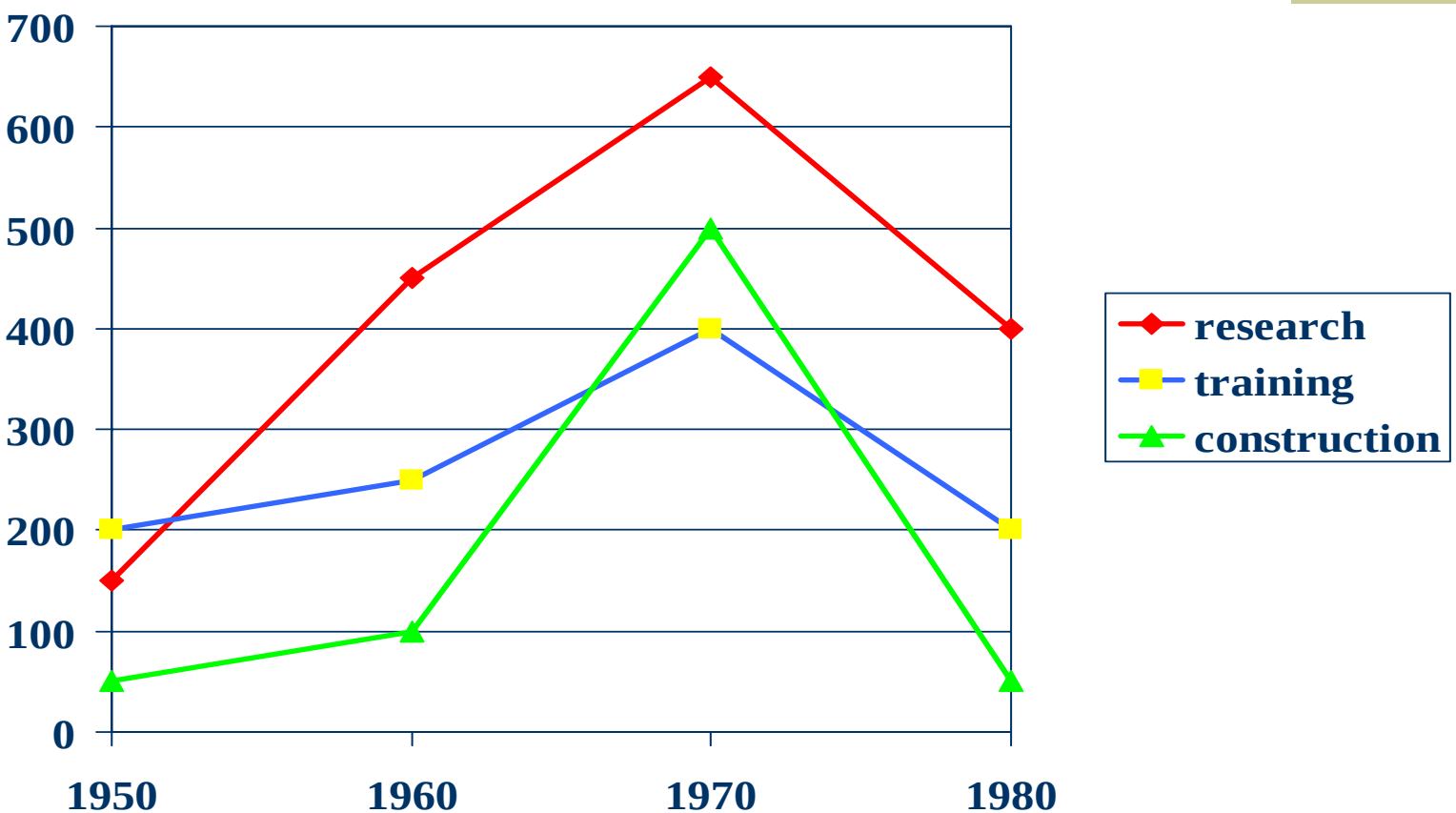
Historical Context for NBS in 1960s

- Declining infant and child mortality
  - IMR was over 200/1000 live births in 1900; 23 in 1960
- Faith in science/technology
  - 1950s Polio vaccine
  - Federal investment in research, 1940s-50s
- Early disability rights movement
  - State MR/DD institutions - a problem for generations
  - 1930s-40s Families changed our ideas of disability
  - Kennedy family (and others) in government
    - Kennedy Panel on MR, 1962

Federal MR Programs



Federal Spending on MR



Historical Legacy You Face
American Approach to NBS: State Laws

- PKU NBS implemented state by state in 1960s/70s
  - Every state has its own approach to PKU/NBS programs
  - First laws depended on local politics; heroes and villains
  - Specific NBS laws supported by US Children's Bureau, NARC
- Federal government just emerging as force in medicine
  - Medicare/Medicaid in late 1960s
- Medicine very different just 40 years ago
  - Very little, if any, training in genetics/metabolism
  - Most doctors were male, solo practitioners, generalists
  - MDs didn't trust government
    - 1974: 18% of PCPs supported federal registry for PKU

Assessment of PKU NBS in 1966

- 27 states with NBS programs; 1 million infants tested; many treated
- Exciting time, but many problems for metabolic experts
  - Labs - no quality standards; great geographic variation (FP, FN)
  - Not clear that every baby tested and getting appropriate treatment
  - Treatment is trickier than originally thought
    - How much phenylalanine in the diet?
    - Malnutrition and “missing” nutrients
  - Treat infants with intermediate values of phenylalanine?
    - Metabolic variants, transient hyperphenyluria, heterozygotes?
  - What is causing the brain damage?
    - Some infant with classic PKU lab results and no problems without treatment; others with MR despite treatment

Assessment of PKU NBS in 1966

- US Children's Bureau sponsors "consensus conference"
  - Most of the world's leaders in PKU gathered in MN
  - Discussions worth reading - these scholars engaged/passionate
- Sam Bessman and others concerned that no controlled experiments done, but most participants considered such an approach unethical
- Joseph Cooper as "outsider" (political scientist at Howard)
  - Watches the debate and basically says: Wait a minute. You're telling me that you don't know? Children starving, no health care, Vietnam war, streets burning, and we've got mandatory state laws to do something we're not sure about?
- 1966 Conclusion: need for more research; continue with PKU NBS
- 1972 Criticism persists so NAS reviewed genetic screening programs and affirmed value of NBS and PKU in particular

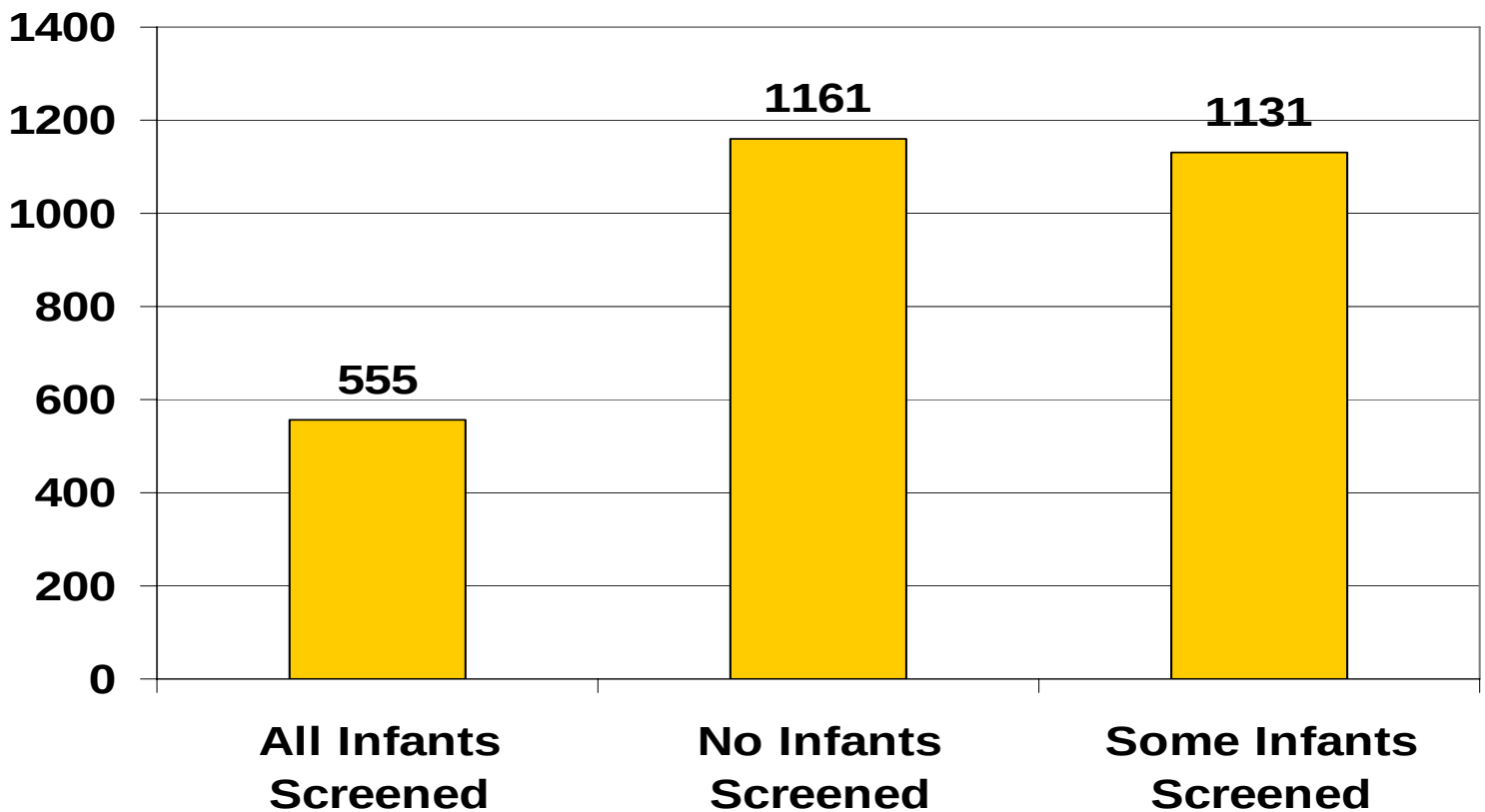
Historical Experiment

- What if we had been more systematic in collecting data on NBS from the beginning? What might have been the outcome? Would there be evidence for medically adverse outcomes for FP?
  - In the context of the early 1960s, PKU registry was not possible
- There was no registry, but there was a “natural experiment”
  - Step-wise introduction of NBS by states 1961-66
  - We can infer outcomes based on small studies
  - We can imagine what a registry might have revealed
- Warning: these are very “soft” numbers, but they give us some notion of whether early introduction of universal screening for PKU was likely to have been beneficial or harmful on balance

Risks/Benefits PKU NBS (1961-65)

NOT FOR CITATION	Infants Screened	Infants Not Screened
Number of newborns	1,000,000	1,000,000
Number born with PKU	65	65
False positives (FP)	6452	0
TP with MR or Death	21	58
FP with MR or Death	6	0
Total with MR or Death	**28**	**58**

Infants with MR/Death (1961-65)



Reflections on Early History of NBS

- PKU story is not unique in history of medicine
  - Diabetes and discovery of insulin did not result in immediate cure (technological fixes usually bring new problems)
- Questions in early 1960s similar to those of today re expansion of NBS to other conditions
  - Until we do NBS at least in some large population, we don't know everything we need to know (natural history, variants)
    - Delays mean some children do not receive benefit
    - Moving ahead may lead to some harms, wasted effort
    - Value of screening for conditions with no current treatment
  - Need for uniform national standards; coordinated plan

Reflections on Early History of NBS

- This is NOT the early 1960s: we have no excuse for not carefully studying expansion of NBS programs
  - Following all TPs and at least some (if not all) FPs
  - Coordination/sharing data
- Current debate partly about values/experience
  - Clinicians value their personal experience of children harmed by failure to prevent MR
  - Ethicists/epidemiologists more comfortable with the “greatest good for the greatest number” kinds of arguments
  - Beware the “inward vision/outward glance” problem that has characterized medicine in the US for the last 100 years

Lessons Learned

1. As expanded newborn screening moves forward, we must carefully review results at frequent intervals (every year)
   - Population-based follow of TPs and FPs
   - Outcomes include physical, psychological, and family factors
2. Available treatment may not be a critical factor in deciding which conditions to include: there is value in understanding the natural history—especially of variant conditions—because treatment usually carries some risks
3. Beware the “inward vision/outward glance” problem that has characterized medicine in the US for the last 100 years: there are nearly 10 million children without health insurance in the US

Acknowledgements

- Michael I. Seider, Angela C. Dunn, Lee M. Sanders, and Diane Paul
- Grant Support:
  - Robert Wood Johnson Foundation General Scholar Program; Grant number 033954
  - DHHS/HRSA/MCHB Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children; Subcontract number 06-C210-01