Newborn Screening: From RUSP to Reality

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Agenda

- From RUSP to Reality
  - RUSP
  - Why NBS is important to saving/improving lives, improving natural history knowledge, increasing awareness
  - Current list and diseases in consideration
  - The politics of NBS
  - What physicians can do to improve NBS in their states
  - Summary
- Learning objective: Explain how a disease becomes part of a NBS panel and why it helps patients

Surprising Statistics

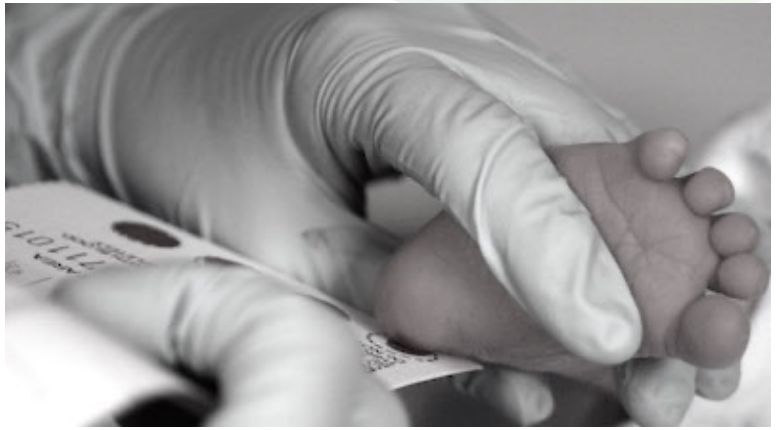
- Not So Rare
  - 3% of infants are born with a genetic problem
  - 0.5% of babies have an inborn error of metabolism
- Very Common Consequences
  - 40% of childhood mortality
  - 50% of childhood hospital admissions
  - 25% of adult hospital admissions

Newborn Screening

- Public health initiative
- Aimed at preventing
  - Mortality
  - Morbidity
  - Disabilities
- Metabolic/molecular screening on blood spots
- Other types of screening as point of care
  - Hearing
  - Pulse oximetry

The Test Case - PKU

- 1930’s
  - PKU identified as a cause of intellectual disability (George Jervis)
  - Early treatment could prevent symptoms (Horst Bickel)
- 1958: Bacterial inhibition assay developed (Robert Guthrie)
- 1961: Local (NY) newborn screening for PKU started
- 1962: State-wide screening for PKU began in MA with support from the National Association for Retarded Children



World Health Organization: 1968 Screening Criteria

- Treatable disease
- Detectable in newborns
- Simple collection method
- Suitable (simple) testing method
- Pre-symptomatic treatment beneficial
- Resources available for follow-up
- Public benefit and acceptance
- Cost/benefit ratio suitable

Recommended Uniform Screening Panel (RUSP)

- ACHRNC: Advisory Committee on Heritable Disorders in Newborns and Children curates the RUSP
- Established in 2003
- RUSP is dynamic with additions over time
- RUSP criteria
  - Specific and sensitive test available to detect disease
  - The health outcomes of the condition are well understood
  - Effective treatment is available
  - Identification of the condition could affect the future reproductive decisions of the family

Core RUSP

Metabolic disorders:

- Propionic acidemia
- Methylmalonic acidemia
- Isovaleric acidemia
- 3-Methylcrotonyl-CoA carboxylase deficiency
- 3-Hydroxy-3-methyglutaric aciduria
- Holocarboxylase synthase deficiency
- β-Ketothiolase deficiency
- Glutaric acidemia type I
- Carnitine uptake defect/carnitine transport defect
- Medium-chain acyl-CoA dehydrogenase deficiency
- Very long-chain acyl-CoA dehydrogenase deficiency
- Long-chain L-3 hydroxyacyl-CoA dehydrogenase def.
- Trifunctional protein deficiency
- Argininosuccinic aciduria
- Citrullinemia, type I
- Maple syrup urine disease
- Homocystinuria
- Classic phenylketonuria
- Tyrosinemia, type I

Endocrine Disorders

- Primary congenital hypothyroidism
- Congenital adrenal hyperplasia

Hematological Disorders

- S,S disease (Sickle cell anemia)
- S, βeta-thalassemia
- S,C disease

Other

- Biotinidase deficiency
- Critical congenital heart disease
- Cystic fibrosis
- Classic galactosemia
- *Pompe disease*
- Hearing loss
- *Severe combined Immunodeficiencies*
- *MPS Type 1*
- *X-linked Adrenoleukodystrophy*
- *Spinal Muscular Atrophy*

Secondary Disorders

Metabolic Disorders

- Methylmalonic acidemia with homocystinuria
- Malonic acidemia
- Isobutyrylglycinuria
- 2-methylbutyrylglycinuria
- 3-methylglutacoinic aciduria
- 2-methyl-3-hydroxybutyric aciduria
- Short-chain acyl-CoA dehydrogenase deficiency
- Medium/short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency
- Glutaric acidemia type II
- Medium-chain ketoacyl-CoA thiolase deficiency
- 2,4 Dienoyl-CoA reductase deficiency
- Carnitine palmitoyltransferase type I deficiency
- Carnitine palmitoyltransferase type II deficiency
- Carnitine acylcarnitine translocase deficiency
- Argininemia
- Citrullinemia, type II
- Hypermethioninemia
- Benign hyperphenylalaninemia
- Biopterin defect in in cofactor biosynthesis
- Biopterin defect in in cofactor regeneration
- Tyrosinemia, type II
- Tyrosinemia, type III

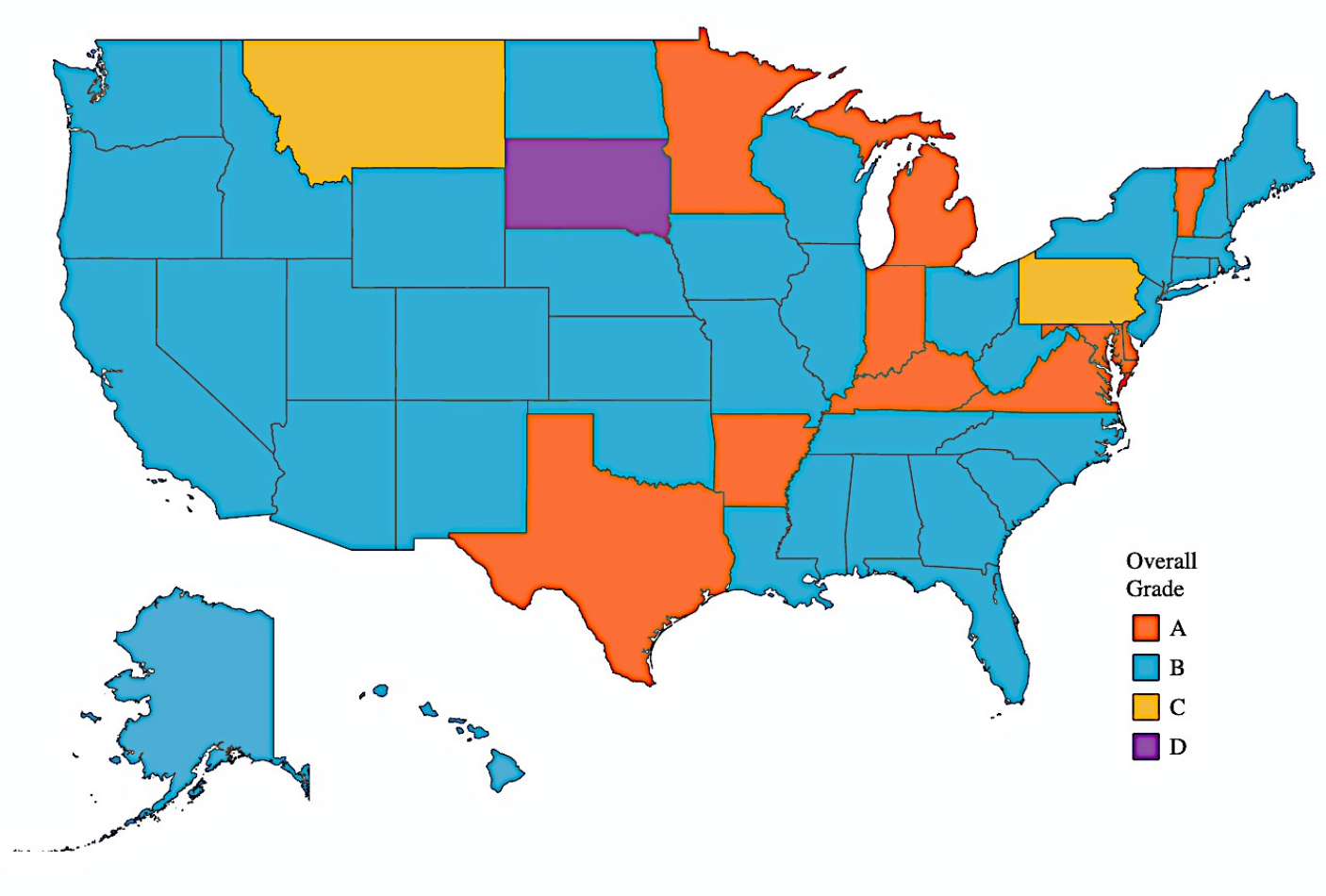
Hematological Disorders

- Various hemoglobinopathies

Other

- Galacto epimerase deficiency
- Galacto kinase deficiency
- T cell related lymphocyte deficiencies

Screening State by State – Most get a B average



- Screening is mandated by the states
- Addition of RUSP changes varies over time
- All states have different NBS screening panels

Figure adapted from NORD

The Politics of NBS

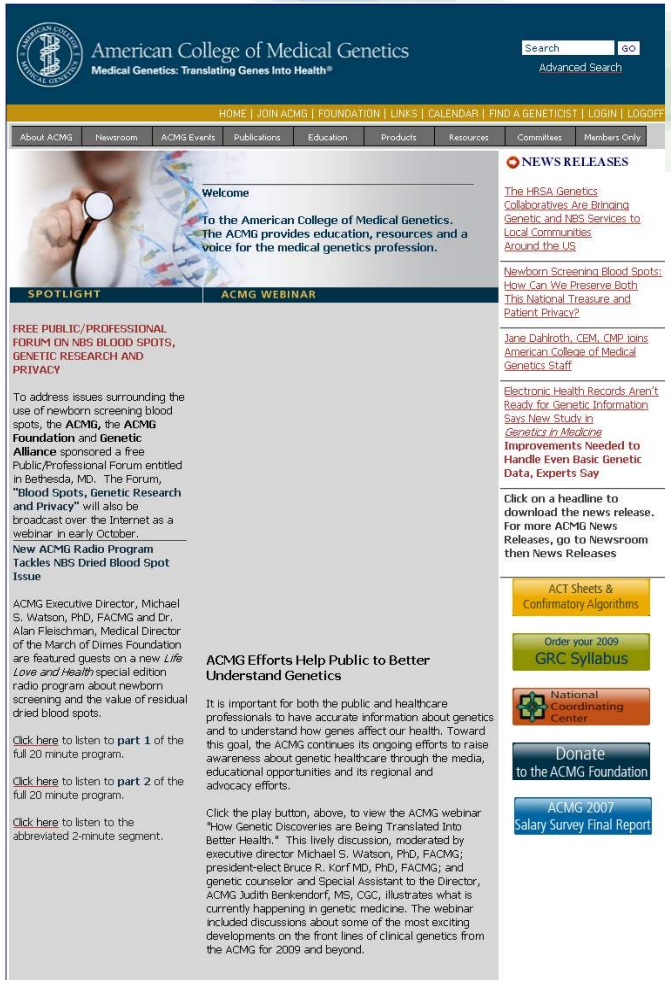
- Since State governments fund the tests, each addition to RUSP must be passed by State legislatures
- Funding must include
  - Testing machinery
  - Training of machinery
  - Training of data interpretation
  - Other training
- New legislation is often a team effort, involving clinicians, patient advocacy groups, testing, pharmaceutical companies, etc

Ethical Issues in NBS

- Burden of false positive and negative results
- Invasion of privacy
- Potential stigmatization
- Compulsory compliance and informed consent
- Violates right not to know
- Violates confidentiality

Responding to the Call

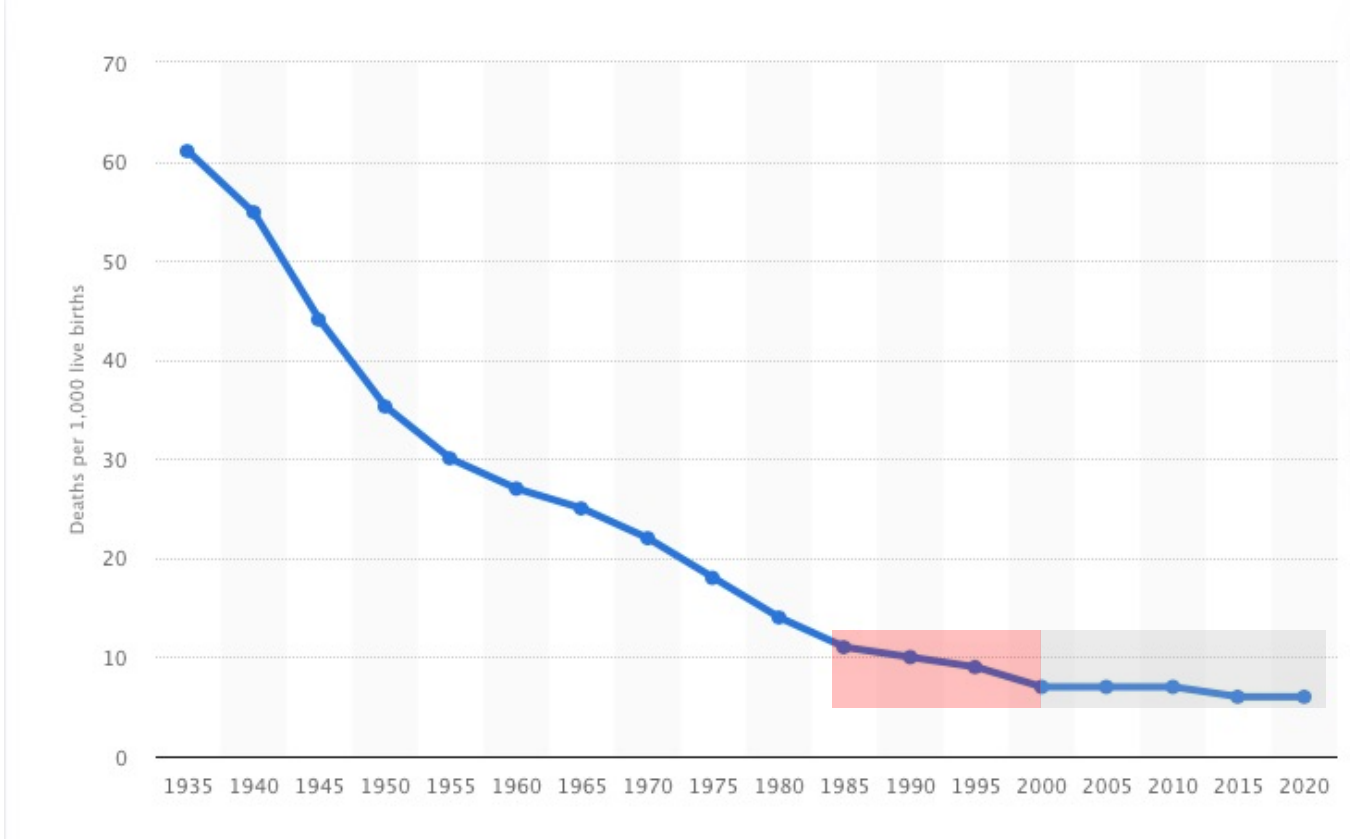
- Experts involved in newborn screening for endocrine, hematological, genetic, and metabolic diseases
- ACT sheets and diagnostic algorithms
- ACT sheets include
  - Information about the analytes and their clinical significance
  - Links to informational resources
  - Links to websites of regional subspecialists for consultation and referral



Next Generation NBS

- Non-IEM
- Non-genetic
- Non-newborn
- Non-traditional technology

US infant mortality 1935-2020



2020

Cause	%
Birth defects	20 (2/3 < 28 doa)
Preterm birth/low birth weight	18
Pregnancy complications	7
Sudden unexplained death	7
Injuries	5

Figures adapted from US DOH statistics

Next Generation NBS

First Author	Platform	Number of Genes Assessed	Samples	Study Population	Sensitivity	Specificity
Bhattacharjee, 2015(47)	NGS Gene Panel; and WES	126	36 subjects with known IEM - proband only	Amish and Mennonite	75% - without clinical information; 94% - with clinical information	Not addressed
Bodian, 2016(51)	WGS - Illumina; or Complete Genomics	163	1,696 neonates - trios	Family trios enrolled at Inova Fairfax Hospital	88.6% - concordance of NBS and WGS	Not addressed - for recessive disorders 2.9% with uncertain WGS results compared to 0.013% for NBS
Cho, 2017(52)	WES	307 total, 65 related to NBS	103 patients 81 - known patients 10 - carriers 12 - negative controls	Patients at Yonsei Severance Hospital, Republic of Korea	92.5% - with clinical information	Not addressed
van Campen, 2019(49)	NGS Gene Panel - NBS2	5	Healthy adults	Adults in the UK	Analytic sensitivity - 100%, disease samples not assessed	Analytic specificity - 99.96%, disease samples not assessed
Roman, 2020(101)	WES	466	106 newborns:	61 - healthy 17 - with an IEM 28 - with hearing loss	88% for IEM	Not addressed
Adhikari, 2020(60)	WES	78	1,012 individuals in the test set: 674 affected with an IEM, 338 unaffected and false positive on MS/MS NBS	IEM affected individuals from a birth cohort of 4.5 million newborns over 8.5 years in California	88% - 93.7% after clinical review of cases	98.4%

Summary

- RUSP is a recommendation
- Takes many years for a conditions to be added to RUSP
- Each State controls NBS
- NBS designed for diseases that are difficult to detect early but that early detection can guide treatment that can attenuate disease progression
- Financial issues
- Political issues
- Newer methods constantly finetuning outcomes
- Best to be part of the solution, rather than the problem