# Newborn Screening – Public Health Service, Research and Public Trust

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Deputy Director, New England Newborn Screening Program
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A National Conversation on Newborn Screening Research and Informed Consent
June 1-2 Washington, DC



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# Newborn Screening is

a public health program that

provides an opportunity for early identification and early treatment

of infants with conditions that otherwise would go unrecognized

prior to irreversible clinical damage.

# Newborn Screening is

highly successful.

~14,000 infants treated annually who otherwise would succumb to an illness that could have been treated

# 1997-98 Massachusetts DPH NBS Advisory Committee issues

Advocacy for addition of 21 conditions

Advocacy for emerging technologies

Public hearing comment

Evidence-based review –

- focus on condition, not technology

# 1998
# MA NBS Committee Recommendations

1. Keep focus on conditions
2. Add one (MCADD) to mandated list
3. **Offer** expanded screening for 20 others

    Collect data for further evaluation

    Report back to committee

    - Run Pilot NBS Program
    - Check with HSRBs
    - Ask for waiver of consent

# Human Subject Review

**2 independent HSRBs note:**

- No Mandate
- Data collection
- Evaluation of benefit

This is a study, requiring informed consent

**2 HSRBs also note:**

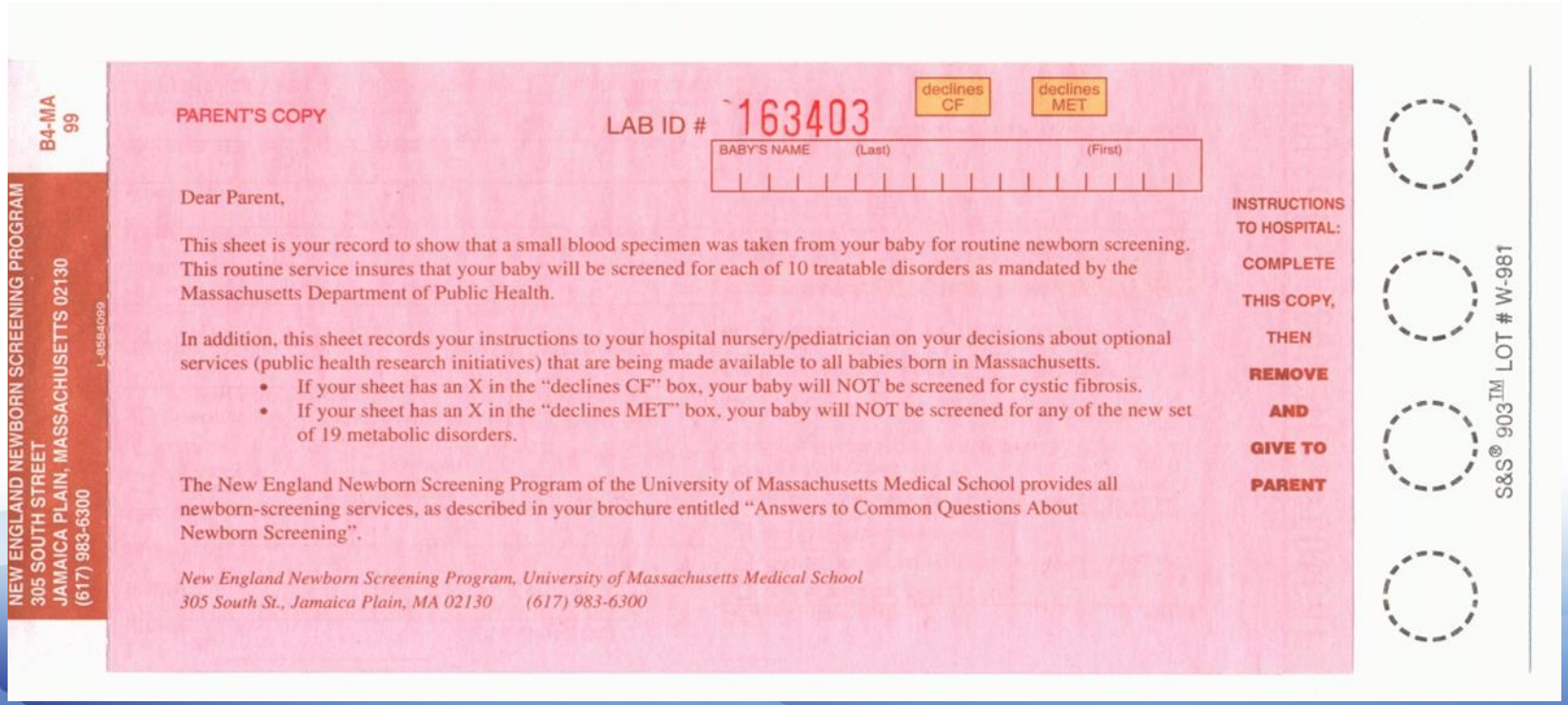
- Presumed benefit to infant
- Low risk- no additional blood and clinical follow up available
- Operational practicalities- informed consent for birth cohort

Verbal Informed Consent

OHRP buy-in

# Informed consent protocol

- Education via brochure
- Ask each infant's parent
- Provide parent with record of their decision



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305 SOUTH STREET
JAMAICA PLAIN, MASSACHUSETTS 02130
(617) 983-6300

L-0584099

PARENT'S COPY

LAB ID # 163403

declines CF

declines MET

BABY'S NAME (Last) (First)

Dear Parent,

This sheet is your record to show that a small blood specimen was taken from your baby for routine newborn screening. This routine service insures that your baby will be screened for each of 10 treatable disorders as mandated by the Massachusetts Department of Public Health.

In addition, this sheet records your instructions to your hospital nursery/pediatrician on your decisions about optional services (public health research initiatives) that are being made available to all babies born in Massachusetts.

- If your sheet has an X in the "declines CF" box, your baby will NOT be screened for cystic fibrosis.
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The New England Newborn Screening Program of the University of Massachusetts Medical School provides all newborn-screening services, as described in your brochure entitled "Answers to Common Questions About Newborn Screening".

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*305 South St., Jamaica Plain, MA 02130 (617) 983-6300*

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# …A word…

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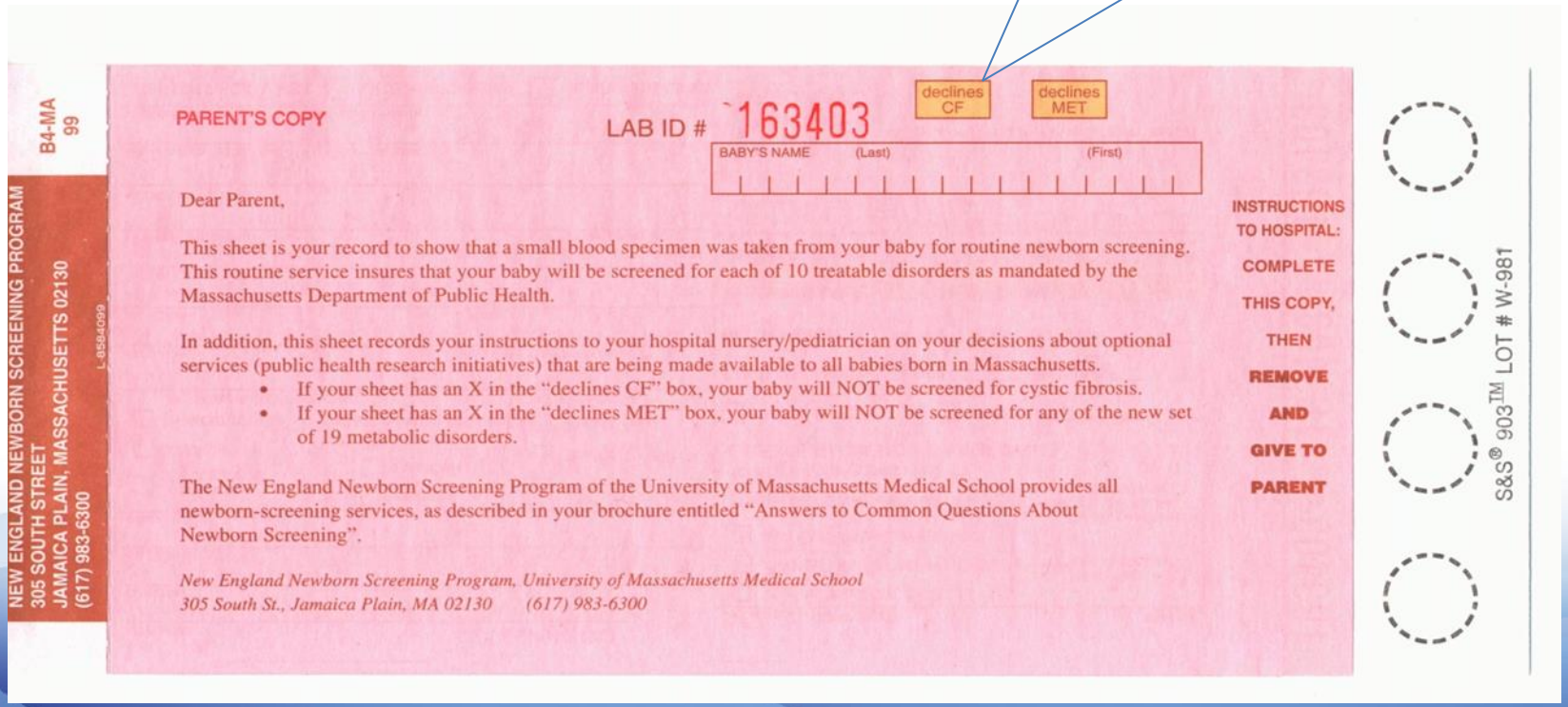

# MA NBS Pilot programs for CF and metabolics 1999–2009

| | | | |
|---|---|---|---|
| Total Number of Babies screened | > | **784,000** | |
| Total number declined | | **8,000** | **1%** |

# 2008
# MA NBS Committee Interim Conclusions

- DATA
  - Move some, not all conditions to mandatory panel

- CONSENT FORMAT
  - DO-ABLE
  - Disseminates knowledge about the service in general
  - PROVIDES FRAMEWORK FOR FUTURE QI / RESEARCH

# Experience

- CONSENT FORMAT
  - Simpler may be safer
  - Protocols included in competencies
  - Highest rates of declining in affluent communities
  - Disseminates knowledge about the service in PARTICULAR
    - Awareness of genetic testing among providers
    - Awareness of genetic testing among population
  - PROVIDES FRAMEWORK FOR FUTURE QI / RESEARCH

# SCID
# Severe Combined Immunodeficiency

- "…a treatable inherited lack of immunity…leading to death in early infancy unless immune reconstitution is provided."

- Bone Marrow Transplant
  Curative if successful
  50-95% success,
  increased success if prior to infection

  Alternative: early death

# 2009 forward
# Massachusetts SCID NBS Statewide Pilot

**ASSAY DEVELOPMENT**

**SCREENING IMPLEMENTATION**

**ALGORITHM REFINEMENT**

**TECHNOLOGY TRANSFER**

Grant # IV01-EH000362-03

Implementing SCID NBS with Multiplexed Assays in an Integrated Program Approach
CDC National Center for Environmental Health

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# Massachusetts and National Questions

- How would we define positive screen?
- Who would we recommend have flow cytometry?
- Who would we find?
- Would population-based clinical outcomes be as promising as originating treatment data?

# Continuation of the Pilot Consent Protocol Facilitated Expansion in Massachusetts.

## CF and metabolics 1999 -2009

| | | | |
|---|---|---|---|
| Total Number of Babies screened | > | **784,000** | |
| Total number declined | | **8,000** | **1%** |

## SCID 2009-present

| | | | |
|---|---|---|---|
| Total Number of Babies screened | > | **461,000** | |
| Total number declined | | **3,600** | **0.78%** |
| Year one declined | | | **1.6%** |

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Transplantation Outcomes for Severe Combined Immunodeficiency, 2000–2009

Sung-Yun Pai, M.D., Brent R. Logan, Ph.D., Linda M. Griffith, M.D., Ph.D., Rebecca H. Buckley, M.D., Roberta E. Parrott, B.S., Christopher C. Dvorak, M.D., Neena Kapoor, M.D., Imelda C. Hanson, M.D., Alexandra H. Filipovich, M.D., Soma Jyonouchi, M.D., Kathleen E. Sullivan, M.D., Ph.D., Trudy N. Small, M.D., Lauri Burroughs, M.D., Suzanne Skoda-Smith, M.D., Ann E. Haight, M.D., Audrey Grizzle, M.P.H., Michael A. Pulsipher, M.D., Ka Wah Chan, M.D., Ramsay L. Fuleihan, M.D., Elie Haddad, M.D., Ph.D., Brett Loechelt, M.D., Victor M. Aquino, M.D., Alfred Gillio, M.D., Jeffrey Davis, M.D., Alan Knutsen, M.D., Angela R. Smith, M.D., Theodore B. Moore, M.D., Marlis L. Schroeder, M.D., Frederick D. Goldman, M.D., James A. Connelly, M.D., Matthew H. Porteus, M.D., Ph.D., Qun Xiang, M.S., William T. Shearer, M.D., Ph.D., Thomas A. Fleisher, M.D., Donald B. Kohn, M.D., Jennifer M. Puck, M.D., Luigi D. Notarangelo, M.D., Morton J. Cowan, M.D., and Richard J. O'Reilly, M.D.

**N Engl J Med 2014;371:434-46.**
**DOI: 10.1056/NEJMoa1401177**

Original Investigation

# Newborn Screening for Severe Combined Immunodeficiency in 11 Screening Programs in the United States

Antonia Kwan, PhD, MRCPCH; Roshini S. Abraham, PhD; Robert Currier, PhD; Amy Brower, PhD; Karen Andruszewski, BS; Jordan K. Abbott, MD; Mei Baker, MD; Mark Ballow, MD; Louis E. Bartoshesky, MD; Francisco A. Bonilla, MD, PhD; Charles Brokopp, DrPH; Edward Brooks, MD; Michele Caggana, ScD; Jocelyn Celestin, MD; Joseph A. Church, MD; Anne Marie Comeau, PhD; James A. Connelly, MD; Morton J. Cowan, MD; Charlotte Cunningham-Rundles, MD; Trivikram Dasu, PhD; Nina Dave, MD; Maria T. De La Morena, MD; Ulrich Duffner, MD; Chin-To Fong, MD; Lisa Forbes, MD; Debra Freedenberg, MD; Erwin W. Gelfand, MD; Jaime E. Hale, BS; I. Celine Hanson, MD; Beverly N. Hay, MD; Diana Hu, MD; Anthony Infante, MD, PhD; Daisy Johnson, BSN; Neena Kapoor, MD; Denise M. Kay, PhD; Donald B. Kohn, MD; Rachel Lee, PhD; Heather Lehman, MD; Zhili Lin, PhD; Fred Lorey, PhD; Aly Abdel-Mageed, MD, MBA; Adrienne Manning, BS; Sean McGhee, MD; Theodore B. Moore, MD; Stanley J. Naides, MD; Luigi D. Notarangelo, MD; Jordan S. Orange, MD; Sung-Yun Pai, MD; Matthew Porteus, MD, PhD; Ray Rodriguez, MD, JD, MPH, MBA; Neil Romberg, MD; John Routes, MD; Mary Ruehle, MS; Arye Rubenstein, MD; Carlos A. Saavedra-Matiz, MD; Ginger Scott, RN; Patricia M. Scott, MT; Elizabeth Secord, MD; Christine Seroogy, MD; William T. Shearer, MD, PhD; Subhadra Siegel, MD; Stacy K. Silvers, MD; E. Richard Stiehm, MD; Robert W. Sugerman, MD; John L. Sullivan, MD; Susan Tanksley, PhD; Millard L. Tierce IV, DO; James Verbsky, MD, PhD; Beth Vogel, MS; Rosalyn Walker, MD; Kelly Walkovich, MD; Nolan E. Walter, MD, PhD; Richard L. Wasserman, MD, PhD; Michael S. Watson, MS, PhD; Geoffrey A. Weinberg, MD; Leonard B. Weiner, MD; Heather Wood, MS; Anne B. Yates, MD; Jennifer M. Puck, MD

*JAMA*. 2014;312(7):729-738. doi:10.1001/jama.2014.9132

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**Table 1. Classification of Conditions With Low T-Cell Receptor Excision Circles and Low T-Cell Numbers Found by Newborn Screening**

| | Definition of Condition | | |
|---|---|---|---|
| | CD3 T Cells/μL | Proliferation to PHA | Other Supporting Features |
| **Primary Targets of Newborn Screening** | | | |
| Typical SCID[a] | <300 (autologous) | <10% of normal | Detectable maternal T cells in peripheral blood; proven deleterious defect(s) in a known SCID gene |
| Leaky SCID[a] | 300-1500, few naive T cells | Reduced (10%-50% of normal) | No maternal T cells detectable; incomplete defect(s) in a known SCID gene |
| Omenn syndrome | Oligoclonal T cells | Reduced (10%-50% of normal) | Erythroderma, hepatosplenomegaly, eosinophilia, and elevated levels of serum IgE antibody |
| **Secondary Targets of Newborn Screening** | | | |
| Syndrome with low T-cell numbers | Recognized genetic syndrome that includes low T-cell numbers within its spectrum of clinical findings | | |
| Secondary T-cell lymphopenia | Congenital malformation or disease process without an intrinsic defect in production of circulating T cells | | |
| Preterm birth alone | Preterm birth and low birth weight, with low T-cell numbers early in life that normalize over time | | |
| Idiopathic T-cell lymphopenia, also called variant SCID | Low T-cell numbers without recognized cause; 6 programs used 300-1500 autologous T cells/μL plus evidence of functional immune cell impairment, while other programs included infants with higher T-cell numbers (see Table 4).[b] | | |

*JAMA*. 2014;312(7):729-738. doi:10.1001/jama.2014.9132

**Table 2. Infants Screened and Incidence of SCID (Including Leaky SCID) in 11 Contributing Programs**

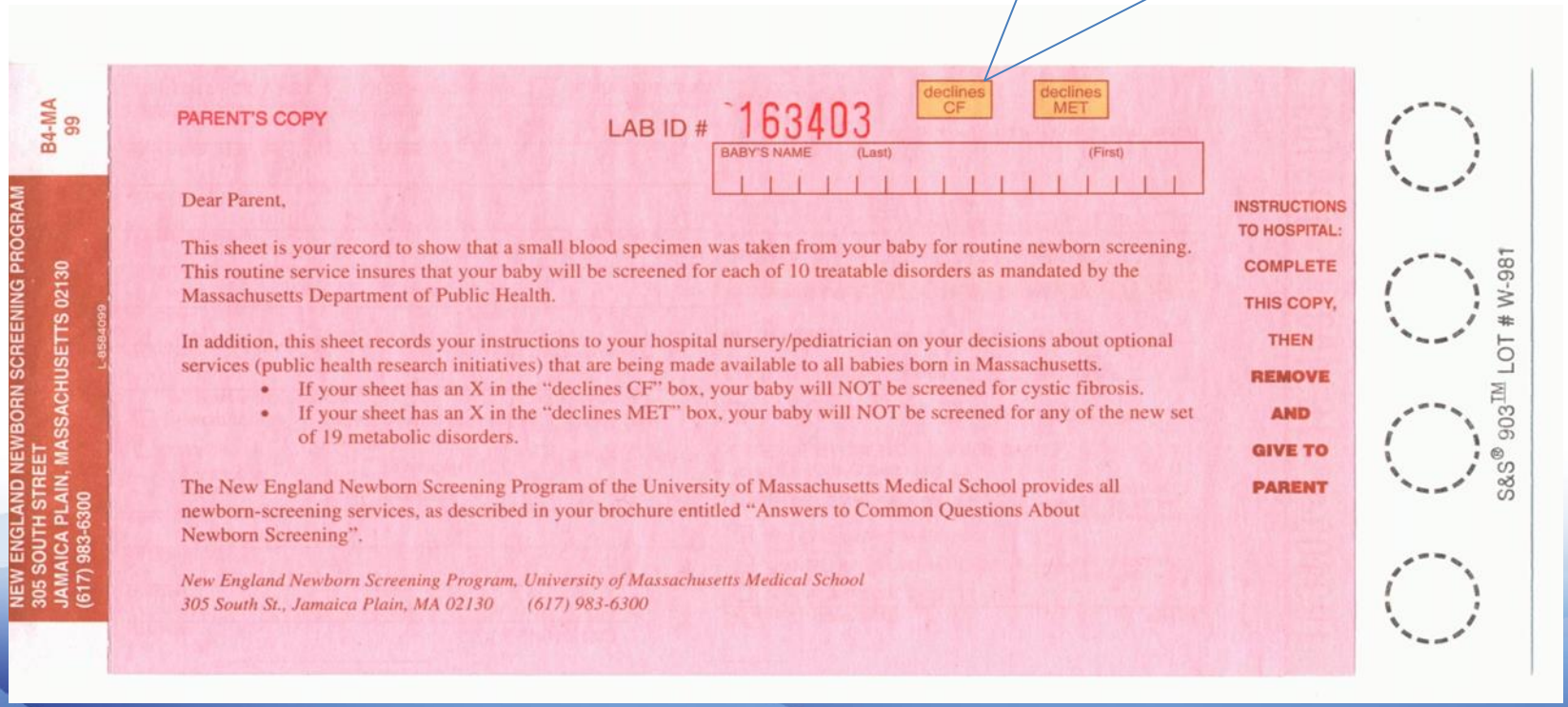
| | California | Colorado | Connecticut | Delaware | Massachusetts | Michigan | Mississippi | Navajo Nation | New York | Texas | Wisconsin | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Duration of screening included, mo | 34 | 13 | 19 | 12 | 48 | 18 | 12 | 17 | 24 | 6 | 60 | |
| Infants screened, No.[a] | 1 384 606 | 70 989 | 57 136 | 11 202 | 293 371 | 162 528 | 37 613 | 3498 | 485 912 | 183 191 | 340 037 | 3 030 083 |
| Flow cytometry referrals,[b] No. (%) [95% CI][c] | 206 (14.9) [12-17] | 10 (14.1) [5.4-23] | 22 (38.5) [22-55] | 9 (80.3) [28-133] | 63 (21.5) [16-27] | 114 (70.1) [57-83] | 5 (13.3) [1.6-25] | 1 (28.6) | 478 (98.4) [90-107] | 249 (135.9) [119-153] | 108 (31.8) [26-38] | 1265 (41.8) [39-44] |
| SCID cases | 23 | 1 | 3 | 1 | 4 | 2 | 1 | 1 | 10 | 2 | 4 | 52 |
| SCID incidence | 1/60 000 | 1/71 000 | 1/19 000[d] | 1/11 000[d] | 1/73 000 | 1/81 000 | 1/38 000 | 1/3500[d] | 1/49 000 | 1/92 000 | 1/85 000 | 1/58 000 [1/46 000-1/80 000] |
| SCID cases per 100 000 screened, No. [95% CI][c] | 1.7 [1.0-2.3] | 1.4 [0.3-5.2] | 5.2 [1.9-15] | 8.9 [2.2-49] | 1.4 [0.4-3.5] | 1.2 [0.4-4.4] | 2.7 [0.6-5] | 29 [6.9-159] | 2.0 [0.8-3.3] | 1.1 [0.3-3.9] | 1.2 [0.3-3.0] | 1.72 [1.3-2.2] |
| SCID infant survival, No./Total No. (%) [95% CI][c,e] | 21/23 (91) [83-100] | 1/1 (100) | 3/3 (100) | 1/1 (100) | 4/4 (100) | 1/2 (50) | 0/1 | 1/1 (100) | 9/10 (90) [70-100] | 0/2 | 4/4 (100) | 45/52[f] (86) [79-98] |

# Data retrieval and analyses - essential

# Informed consent protocol: Proposed change to documentation

- Education via brochure
- Ask each infant's parent
- Provide parent with record of their decision

**ACCEPTS PILOT**



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PARENT'S COPY

LAB ID # 163403

declines CF | declines MET

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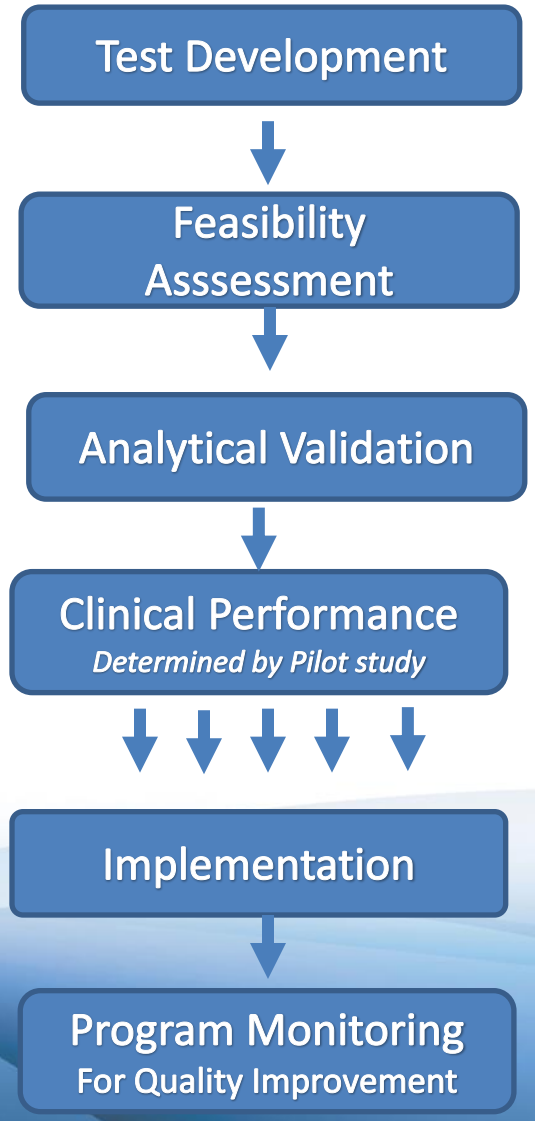
# Ethical Compliance and Comfort




## ***Intent of These Activities***

Implement a test that has been shown to have appropriate analytical and clinical performance characteristics.

# More challenges

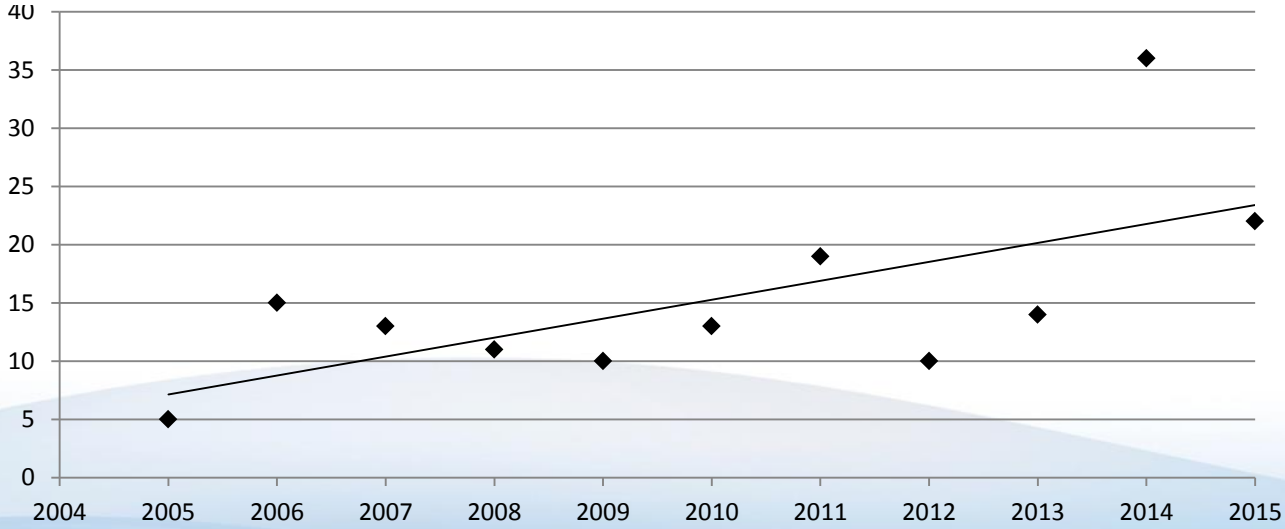
Many conditions being nominated for screening are not like SCID –

- Clinical utility of screening may be questionable
- Treatments may be experimental, requiring enrollment in clinical trial.

# More challenges

Technologies may greatly expand list of conditions at the same time as expanding questionable outcomes–

# Massachusetts Parents who are refusing all newborn screening services

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# What happens when newborn screening programs cannot do research (due to policy or lack of funds)?

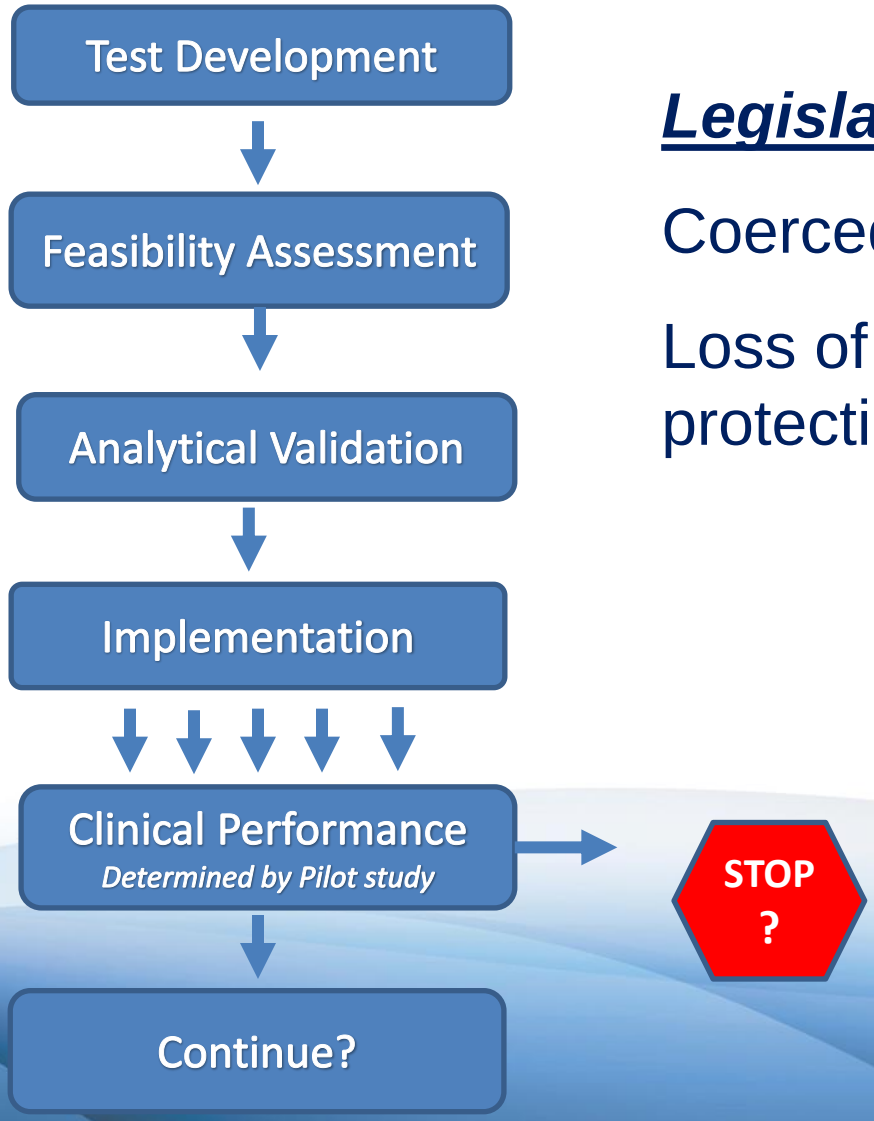
- Loss of transparency
  - Loss of distinction between conditions that meet criteria for screening and those that do not

  or
- Lost opportunity to offer services with potential for benefit

# What happens when newborn screening programs cannot do research
## (due to policy or lack of funds)?

- Increased use of legislative mandates rather than evidence-review process.
- Risk false starts by researchers who do not have public health perspective.
- Risk replacement by commercial ventures.

# Ethical Dilemma




***Legislative Mandates:***

Coerced performance of research

Loss of human subjects protection.

# Newborn Screening Program Research Priorities

- To advance newborn screening activities
- To advance diagnostic/treatment developments for newborns and young infants
- To advance understanding of disease in newborns and young infants
- To advance understanding for general medical knowledge

# Advancing Newborn Screening Program Research Agenda

- Expectations–recognizing the necessity for research emerging from service programs

- Trust – educate the public about the population-based research that benefits individuals and society

# Thank you