SCID Report to the Secretary and Committee Discussion

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Presentation Overview

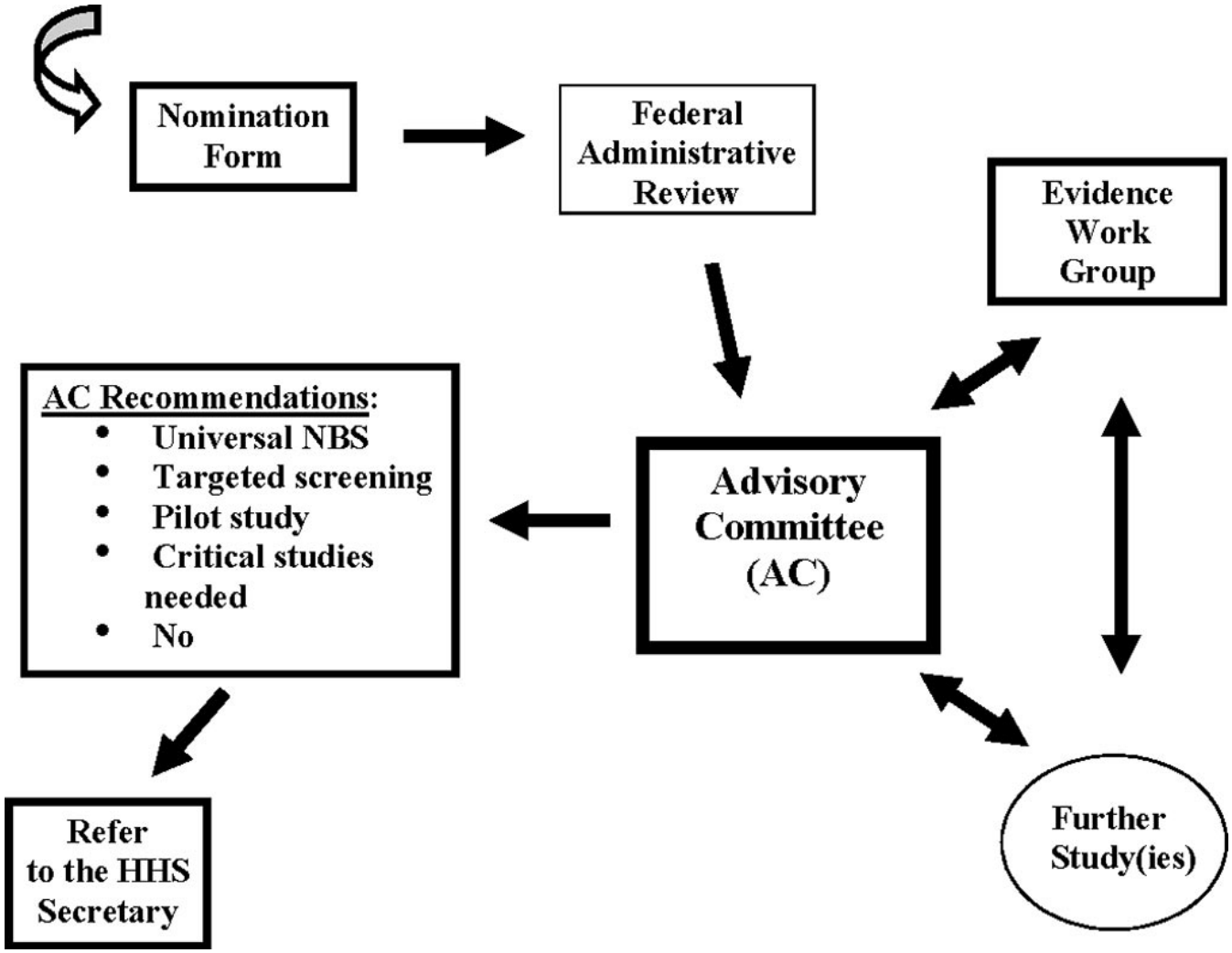
- Background
- Report to the Secretary
  - Background
  - Expansion of SCID Newborn Screening Pilot
  - Education Materials
  - Lessons Learned
  - Next Steps
- Committee Discussion

Background

- SCID and related T-cell lymphocyte deficiencies are a group of disorders
- Characterized by lack of functioning immune system
- Classic SCID is universally fatal in the first two years without immune reconstitution*
- Over 13 different genes cause SCID
- Babies born with SCID appear healthy
- Early diagnosis is essential for lifesaving treatment
- Recognized candidate for newborn bloodspot screening for many years

* Railey MD, Lokhnygina Y, Buckley RH. J Pediatr 2009;155:834-40

SACHDNC Nomination and Review Process



SCID Nomination and Review Summary

Step	Date(s)	Outcome
SCID Nomination	Sep 2007	• Approved for Evidence Review
Evidence Review	Jan 2008 to Feb 2009	• Preliminary Report Nov 08 • Final Report Feb 09
SACHDNC Vote	Feb 2009	• Recommended not adding condition • Recommended additional studies
SACHDNC Vote	Jan 2010	• Report on additional studies recommended in Feb 09 • Recommended addition and outlined activities take place
Secretary's Recommendation	May 2010	• The Secretary adopted the recommendation • Requested SACHDNC report in May 2011
SACHDNC Report	May 2011	• Draft report review and discussion

Report on Additional Studies Recommended in Feb 2009

"The major weakness of the nomination is whether there are sufficient population-based data to evaluate the clinical validity of the TREC-based screening test."

Identified Gap (Feb '09)	Update (Jan '10)
Prospective identification of at least one confirmed case of SCID through a population based newborn screening program	• Nomination included SCID and related T-cell lymphocyte deficiencies • All of these disorders have very low TRECs • Wisconsin pilot identified three cases of related T-cell lymphocyte deficiency between Feb '09 and Jan '10
Demonstrated willingness and capacity of additional states to implement newborns screening for SCID	• Massachusetts state-wide pilot initiated • Pilot in Navajo reservation initiated • New England Newborn Screening Program training of three additional states
Reproducibility of the screening test and continuance of a false positive rate of <0.1%	• Reproducibility of screening test validated in Massachusetts and Navajo pilots • False positive rate <0.1% maintained
Creation of a laboratory proficiency testing program through the Centers for Disease Control & Prevention's national Quality Assurance Program	• CDC-generated QC materials available • Proficiency Testing Program pilot completed in Wisconsin and Massachusetts and available to all programs in April 2010

Committee Recommendation

- Recommendation to add SCID in January 2010
- Outlined the following activities
  - Expanded Pilots - The National Institutes of Health [NIH]
  - Education and Training Materials - The Health Resources and Services Administration [HRSA]
  - Quality Assurance - The Centers for Disease Control and Prevention [CDC]

The Secretary's Adoption

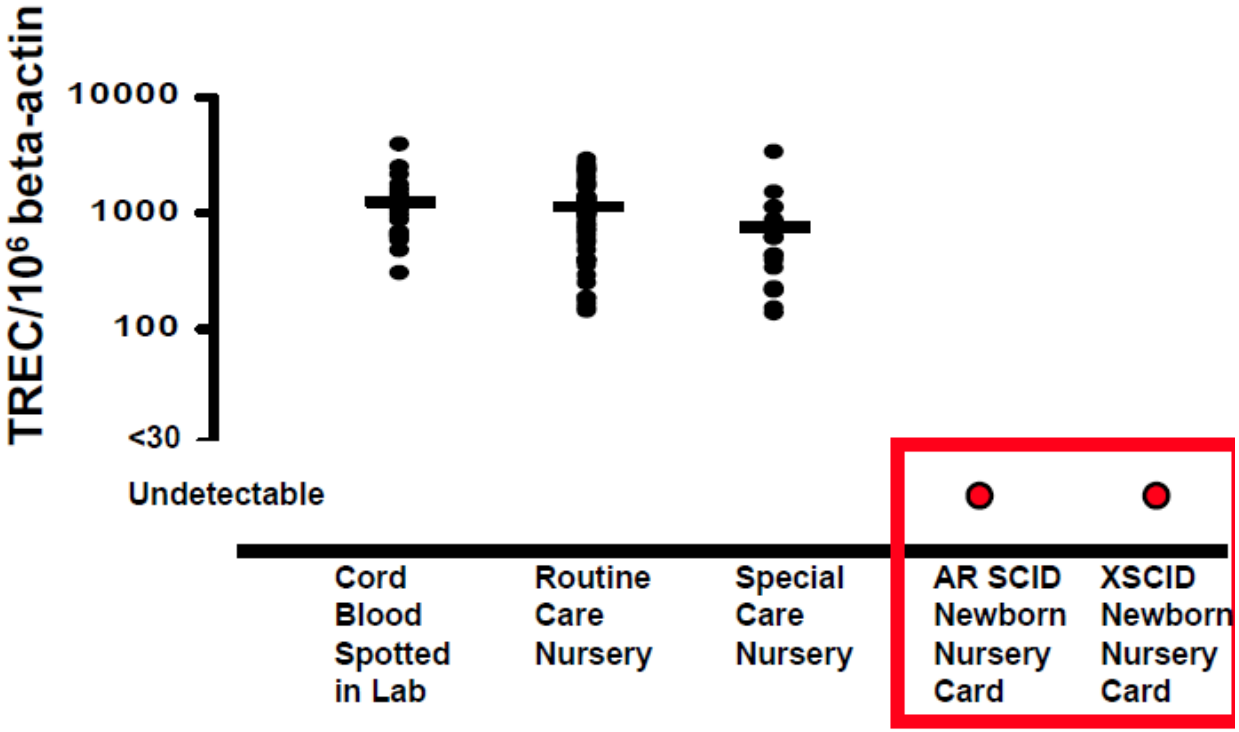
- Adoption of recommendation to add SCID in May 2010
  - "…as a national standard and affirms SACHDNC's updated Recommended Uniform Screening Panel to screen for 30 core conditions and report 26 secondary conditions."
- Requested report from SACHDNC in May 2011
  - Status of states' implementation of recommendation

Report to the Secretary

- Background
- Initial SCID Newborn Screening Pilots
- NIH-funded Expansion of SCID Newborn Screening Pilots
- Interim Pilot Study Results
- Efforts in Non-Pilot Sates
- Education Activities
- Lessons Learned and Next Steps

Background - Newborn Screening Assay Discovery

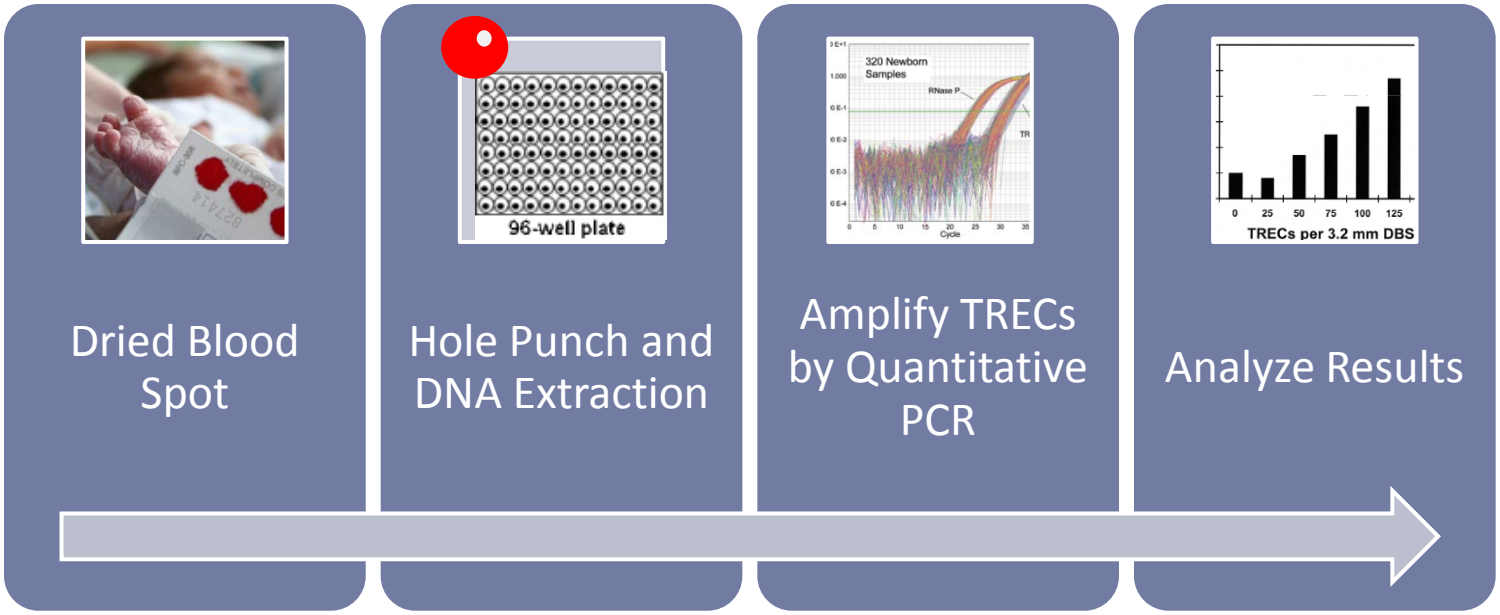
- Screening assay developed and validated by NIH in 2005
- Detects the presence of TREC, by-product of T-cell development



Chan K, Puck JM. Development of population-based newborn screening for severe combined immunodeficiency. *J Allergy Clin Immunol* 2005:Feb;115(2):391-8.

Newborn Screening Assay Development

- Assay development and validation by state newborn screening programs began in 2007
- Evidence of low screening positive rate and feasibility of state wide SCID screening using TREC assay



Initial SCID Newborn Screening Pilots

- State-wide screening – Wisconsin and Massachusetts
  - Wisconsin began in January 2008
  - Massachusetts began in February 2009
- High-Risk Population – Navajo Nation
  - Multi-state project to screen 2000 births began in 2009
  - New Mexico, Arizona, University of California

Initial SCID Newborn Screening Pilots

- Development and implementation of multiplex assay (Massachusetts)
- Development and implementation of high-throughput assay with automation (Massachusetts, Wisconsin)
- Generated screening and follow-up algorithms (All)
- Partnered with CDC in the development and validation of proficiency materials (Massachusetts, Wisconsin)
- Hosted multiple state programs for training (Massachusetts, Wisconsin)
- Created educational materials for families and health care providers (All)

Initial SCID Newborn Screening Pilots

- Successful response to SACHDNC call for additional studies
  - Prospective identification of confirmed case
  - Expansion of screening to additional states/populations
  - Replication of low false positive rate
  - Creation of laboratory proficiency test
- Source of evidence for SACHDNC reconsideration of SCID recommendation
- Over 200,000 newborns screened and several related T-cell lymphocyte deficiencies identified but no classic SCID by January 2010
  - First classic SCID case in April 2010

Expansion of SCID Newborn Screening Pilots

- NIH initiated project to enable additional states to pilot screening
- Key Features
  - Initiates pilots in high number birth states (New York, California)
  - High capacity assay development (New York, California)
  - Regionalization model
    - Puerto Rico → Massachusetts
    - Louisiana → Wisconsin
  - CDC quality assurance program
  - SCID data portal
  - Monthly conference calls to share expertise

SCID Data Portal

- Goal was to collect, aggregate and analyze de-identified screening data generated during the pilot
- Enables real-time laboratory performance quality improvement
- Stores laboratory protocols
- Facilitates tracking of emerging findings
- Provides disease definitions
- Available to any newborn screening program and or researcher

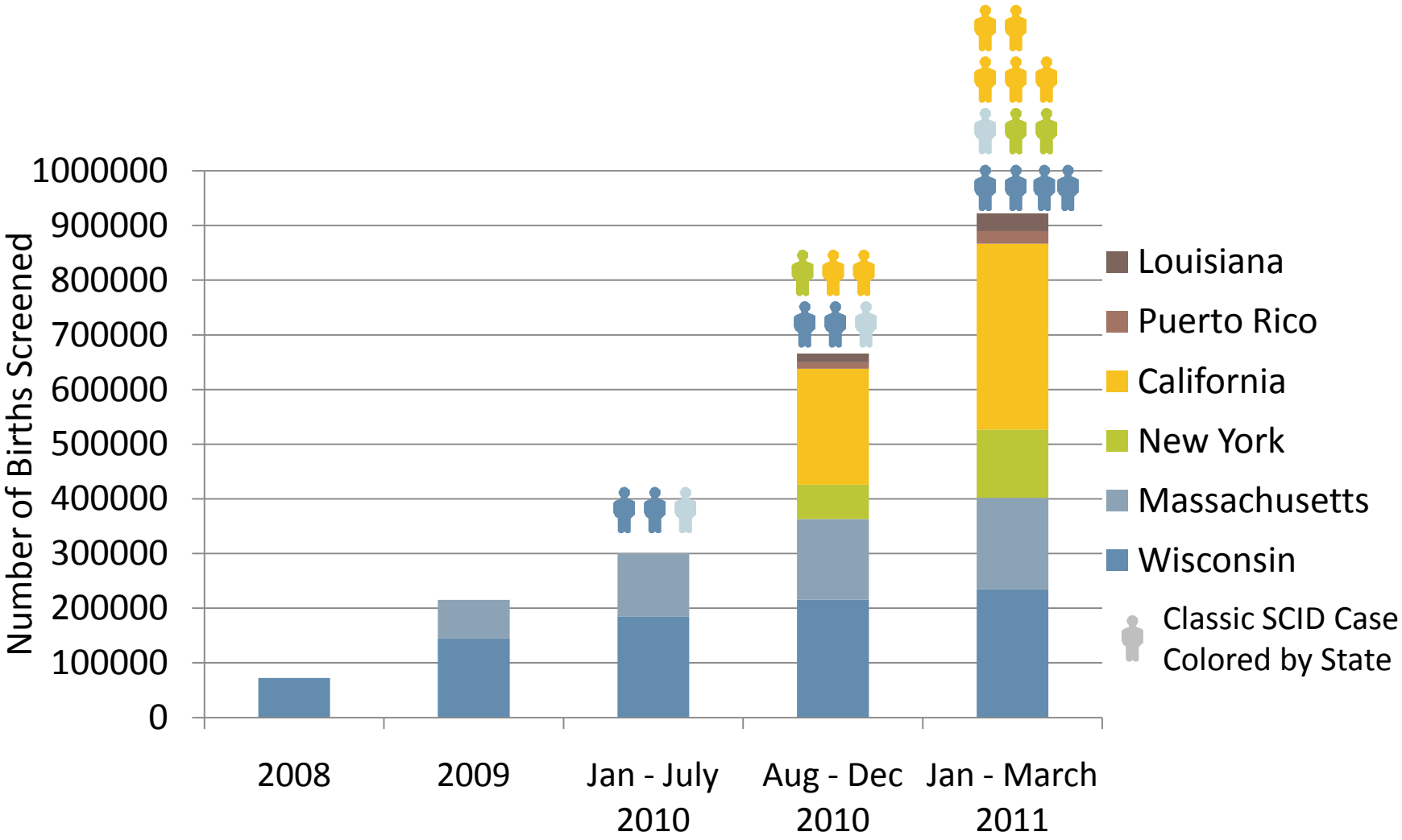
Disease Categories

Category	Working Definition
SCID	• **Deleterious** mutation in one of several genes • **Total failure** of normal function of the protein encoded by that gene • Significant problem with immune function
SCID Variant	• Variation in DNA of one of several genes • **Partial failure** of normal function of the protein encoded by that gene • Also known as “leaky SCID”, Combined Immunodeficiency (CID) or Omenn syndrome
Non SCID	• Loss or gain of a section of DNA in one of several genes/regions • **Multisystem syndromes** associated with variable severity of significant impairment in immune function

Interim Pilot Study Results

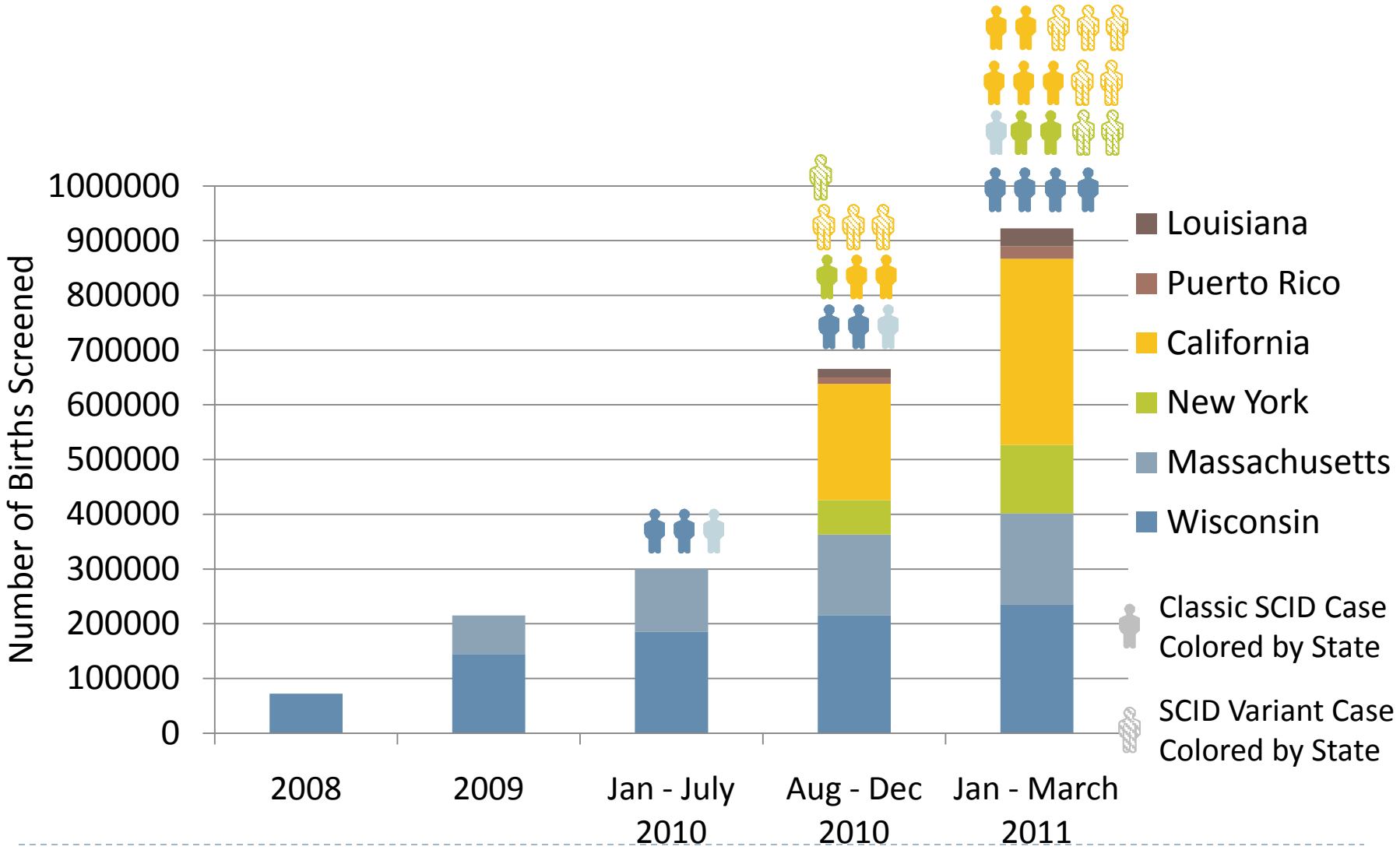
Pilot	Annual Births/Pilot Target	Start of Screening	Months Screening	Number of Infants Screened as of March 31, 2011	SCID	SCID Variant	Non SCID
Wisconsin	69,232	1/1/2008	39	225,004	4	0	5
Massachusetts	77,022	2/1/2009	26	166,881	1	0	12
Navajo Nation	2,000	2/1/2009	26	1,297	0	0	0
California	510,000	8/1/2010	8	340,000	5	5	5
Puerto Rico	45,620	8/1/2010	8	30,413	0	0	3
New York	236,656	9/30/2010	6	118,328	2	2	9
Louisiana	65,268	10/1/2010	6	32,634	0	0	1
		Total	119	914,557	12	7	35

State-wide Screening Pilots – Cumulative Classic SCID Cases



*Wisconsin total includes additional SCID case identified in April, 2011

State-wide Screening Pilots – Cumulative Classic SCID and SCID Variant



*Wisconsin total includes additional SCID case identified in April, 2011

Emerging Findings

- Incidence is generally higher than previously reported

Diagnosis	Incidence	State*			
		CA	NY	MA	WI
SCID		1 in 68,000	1 in 59,164	1 in 166,881	1 in 56,251**
SCID Variant		1 in 68,000	1 in 59,164	NA	NA
SCID + SCID Variant		1 in 34,000	1 in 29,582	1 in 166,881	1 in 56,982**

*LA and PR have not had a case

**Rate calculated with an additional SCID case identified in April, 2011

Incidence Rates – California Early Experience

Population	Incidence Rate	95% Confidence Intervals	
		Lower	Upper
All Classic SCID	1/33,000	1/20,000	1/65,000
Hispanic Classic SCID	1/22,000	1/9,000	1/40,000
All Related T-cell lymphocyte deficiencies	1/22,000	1/13,300	1/35,000

Emerging Findings

- Zero TREC with normal copy number for genomic PCR control consistently means the infant is at risk for profound T-cell lymphocyte deficiency
- Majority of classic SCID cases have zero TREC
- Molecular etiology of low TREC cases is varied
- Relatively low number of X-linked SCID in California

Incidence Caveats

- Definitions are still being refined between experts
- Large phenotypic variability both within SCID and SCID variant cases
- Cases are sometimes not finally diagnosed for many months
- Pilots are in progress

Tools and Resources Developed

QA Program

- Dried blood spot reference materials
- Available to any laboratory
- 11 labs – 100% sensitivity, >99% specificity

Data Portal

- Clinical validation through data sharing and analysis
- Available to any interested stakeholder
- Novel disease categories – SCID, SCID Variant, Non SCID

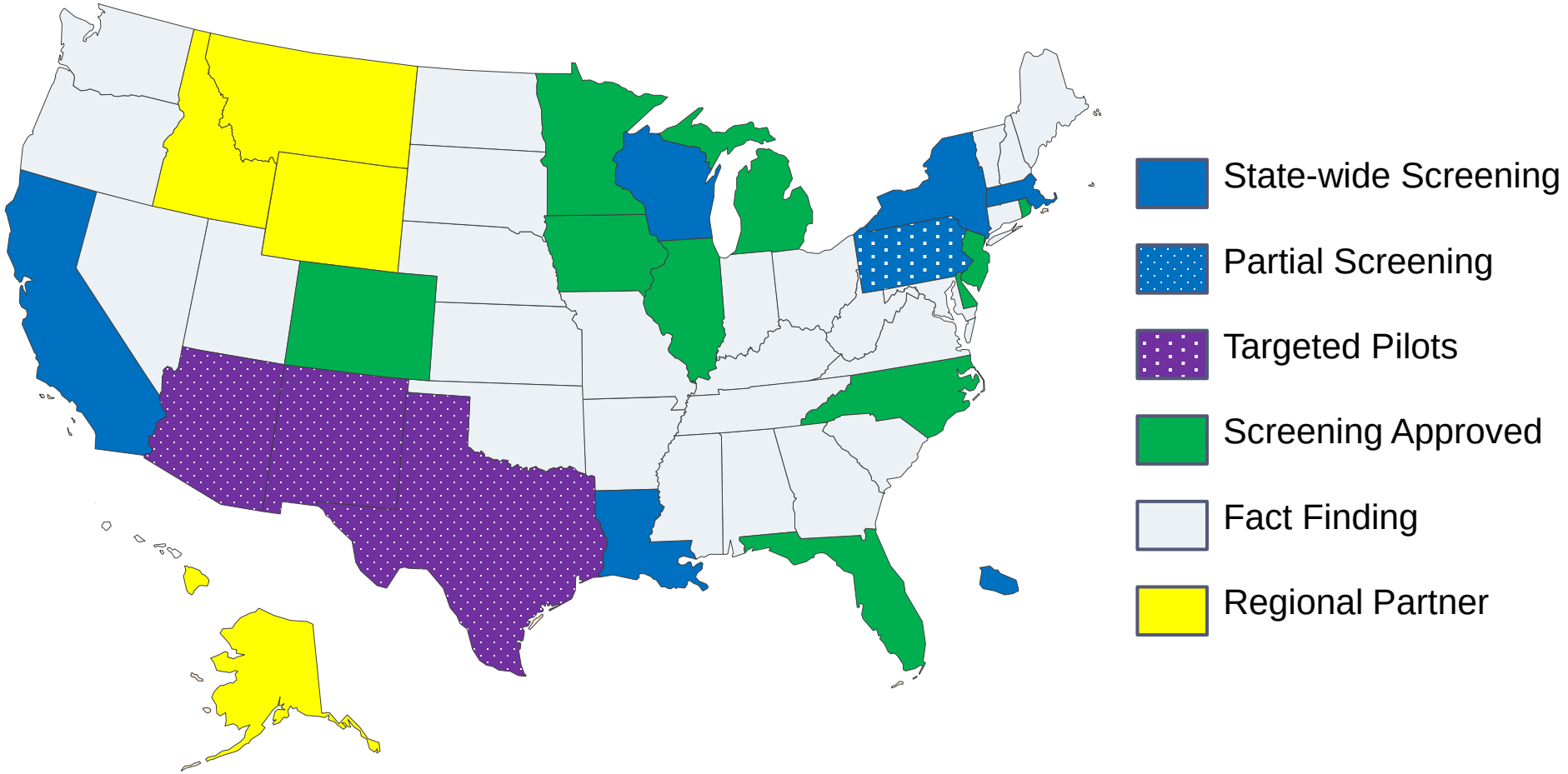
Laboratory Protocols

- Pilot state instruction manuals for implementing SCID newborn screening
- Available to any interested stakeholder
- Four independently validated laboratory developed tests

Information Sharing Resource

- Monthly conference calls to share expertise and discuss issues
- Available to any interested stakeholder
- 16 states, families, researchers, industry, advocates, foundations

Status of Nationwide Implementation



Status of State Implementation

Key Points

- All states surveyed have actively considered SCID newborn screening
- Twenty states have presented SCID newborn screening to their state advisory boards and all have recommended implementation
- Over 35% of states participate in a monthly conference call to share expertise and information
- Pilot states have played a key role in educating interested states and stakeholders
- Nine states rely on regional partners to adopt SCID newborn screening
- Three states report a requirement for an FDA cleared or approved kit

Education Activities

Pilot States

- R4S SCID Data Portal
- Laboratory Workshops
- Protocol Development and Distribution
- Parent Educational Materials

CDC, HRSA, NNSGRC, and APHL

- Meeting of State Newborn Screening Programs
- 48 states, 3 countries attended
- Laboratory Workshop with 28 states in attendance

HRSA, ACMG

- Clinical Decision Support Materials
- ACT Sheets
- Available online

Immune Deficiency Foundation

- SCID Newborn Screening Toolkit for Advocates
- Rotavirus Vaccine Pamphlet
- Parent Education Materials

CDC, APHL, and Jeffrey Modell Foundation

- Two-year fellowship for post-doctoral candidates
- Newborn screening research including immune deficiencies

Lessons Learned

- SACHDNC recommendations trigger state newborn screening programs to act
  - 100% of programs surveyed acted on SCID recommendation
- Discovery that biomarker identifies two different clinically relevant populations
  - “No TRECs” and “Low TRECs”
- Development, validation and piloting of novel screening technologies is possible in state newborn screening laboratories
  - No known missed cases using TREC assay
- Initiation of newborn screening for a new disorder does contribute to clinical and scientific understanding, and facilitates new research questions
  - Emerging evidence regarding molecular etiology, incidence

Lessons Learned

- Issues that delay implementation
  - Lack of cost benefit information
  - Lack of financial resources
  - Lack of personnel and expertise
  - Prior commitment of state resources to legislative mandate to screen other disorder(s)
  - Lack of FDA approved or cleared kit impacts some states

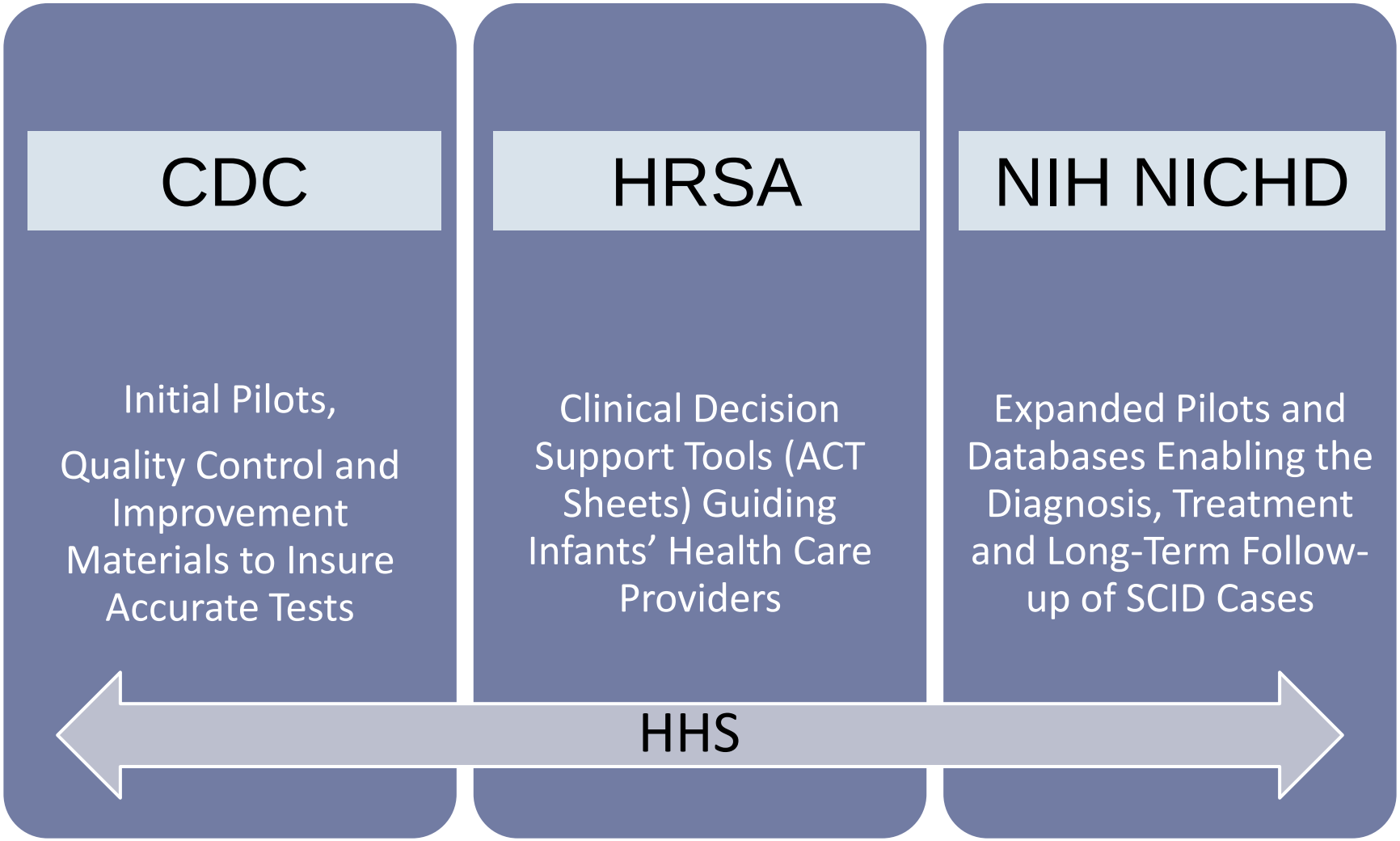
Next Steps

- Conclude pilots in June and October 2011
- Continued support of implementation
  - Publication of pilot findings
  - Dissemination of screening and follow-up protocols
  - Monthly conference calls
  - Ongoing R4S SCID data portal development
- New efforts
  - Creation of long-term follow-up data sets
  - Convene expert workgroup to continue to refine screening, diagnosis, and treatment protocols and guidelines
  - New funding opportunity through CDC for up to two newborn screening programs

Primary Immune Deficiency Treatment Consortium (PIDTC)

- Part of NIH Rare Diseases Clinical Research Network (RDCRN)
- Fourteen major centers in North America
- Goals
  - Identify factors that influence outcome, including newborn screening
  - Determine optimal treatments by natural history studies and multicenter clinical trials
- Open studies
  - Prospective natural history study of diagnosis, treatment and outcomes
  - Retrospective and cross-sectional study of SCID patients

Model of Collaboration Across HHS Agencies



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- National Library of Medicine
- Association of Public Health Laboratories
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- Newborn Screening Translational Research Network
- Newborn Screening Regional Collaborative Groups and National Coordinating Center

Committee Discussion