Severe Combined Immunodeficiency Newborn Screening Implementation

In Person Meeting

July 30-31, 2015

NewSTEPs

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This meeting, and related SCID activities, are funded through a cooperative agreement (#UG5MC27837) to APHL by the Genetic Services Branch of the Health Resources and Services Administration (HRSA).

NewSTEPs Vision

Dynamic newborn screening systems have access to and utilize accurate, relevant information to achieve and maintain excellence through continuous quality improvement.

NewSTEPs Mission

To achieve the highest quality for newborn screening systems by providing relevant, accurate tools and resources and to facilitate collaboration between state programs and other newborn screening partners.

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Background

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The Foundation for SCID Newborn Screening

Immune deficiencies, infection, and systemic immune disorders

Development of a routine newborn screening protocol for severe combined immunodeficiency

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Background: Severe combined immunodeficiency (SCID) is characterized by the absence of functional T cells and B cells. Without early diagnosis and treatment, infants with SCID die from severe infections within the first year of life.
Objective: To determined the feasibility of detecting SCID in newborns by quantitating T-cell receptor excision circles (TRECs) from dried blood spots (DBSs) on newborn screening (NBS) cards.
Methods: DNA was extracted from DBSs on deidentified NBS cards, and real-time quantitative PCR (RT-qPCR) was used to determine the number of TRECs. Positive controls consisted of DBS from a 1-week-old $T^-B^-NK^+$ patient with SCID and whole blood specimens selectively depleted of naive T cells.
Results: The mean and median numbers of TRECs from 5766 deidentified DBSs were 827 and 708, respectively, per 3.2-mm punch (~3 μL whole blood). Ten samples failed to amplify TRECs on initial analysis; all but 1 demonstrated normal TRECs and β-actin amplification on retesting. No TRECs were detected in either the SCID or naive T-cell–depleted samples, despite the presence of normal levels of β-actin.
Conclusions: The use of RT-qPCR to quantitate TRECs from DNA extracted from newborn DBSs is a highly sensitive and specific screening test for SCID. This assay is currently being used in Wisconsin for routine screening infants for SCID.
(J Allergy Clin Immunol 2009;124:522-7.)

Key words: *Dried blood spots, hematopoietic stem cell transplantation, newborn screening, real-time quantitative PCR, severe combined immunodeficiency, T-cell receptor excision circles*

The goal of newborn screening (NBS) is to identify presymptomatic newborns with potentially serious or fatal disorders that can be successfully treated, leading to significant reductions in morbidity and mortality. The 45-year history of NBS demonstrates that it is an extremely successful and cost-efficient public health undertaking and provides useful information in the field of preventive medicine.[1,2] Routine NBS began in the1960s with a single disorder, phenylketonuria, and grew to a core panel of 29 disorders as recommended by the American College of Medical Genetics.[3] As knowledge of the causes of genetic disorders increases, detection technologies advance, and better treatment regimens emerge, more diseases will be added to the NBS panel.

Severe combined immunodeficiency (SCID) was recognized as a disorder that meets the criteria for inclusion in NBS in a Centers for Disease Control and Prevention 2004 conference entitled "Applying Public Health Strategies to Primary Immunodeficiency Diseases."[4] Criteria include infants who are asymptomatic at birth, serious medical consequences without treatment, availability of confirmatory tests and effective treatment, and improved outcomes with early intervention. The National Advisory Committee of Heritable Disorders in Newborns and Children has selected SCID as the focus of an evidentiary review regarding recommendations for NBS.[5]

J Inherit Metab Dis (2010) 33 (Suppl 2):S273–S281
DOI 10.1007/s10545-010-9103-9

NEWBORN SCREENING

Guidelines for implementation of population-based newborn screening for severe combined immunodeficiency

Anne Marie Comeau · Jaime E. Hale · Sung-Yun Pai · Francisco A. Bonilla · Luigi D. Notarangelo · Mark S. Pasternack · H. Cody Meissner · Ellen Rae Cooper · Alfred DeMaria · Inderneel Sahai · Roger B. Eaton

Received: 22 January 2010 / Revised: 26 March 2010 / Accepted: 1 April 2010 / Published online: 20 May 2010

Abstract Severe combined immunodeficiency (SCID) is a Primary Immune Deficiency that is under consideration for population-based newborn screening (NBS) by many NBS programs, and has recently been recommended for inclusion in the US uniform panel of newborn screening conditions. A marker of SCID, the T cell receptor excision circle (TREC), is detectable in the newborn dried blood spot using a unique molecular assay as a primary screen. The New England Newborn Screening Program developed and validated a multiplex TREC assay in which both the TREC analyte and an internal control are acquired from a single punch and run in the same reaction. Massachusetts then implemented a statewide pilot SCID NBS program. The authors describe the rationale for a pilot SCID NBS program, a comprehensive strategy for successful implementation, the screening test algorithm, the screening follow-up algorithm and preliminary experience based on statewide screening in the first year. The Massachusetts experience demonstrates that SCID NBS is a program that can be implemented on a population basis with reasonable rates of false positives.

Communicated by: Rodney Pollitt

Competing interest: None declared.

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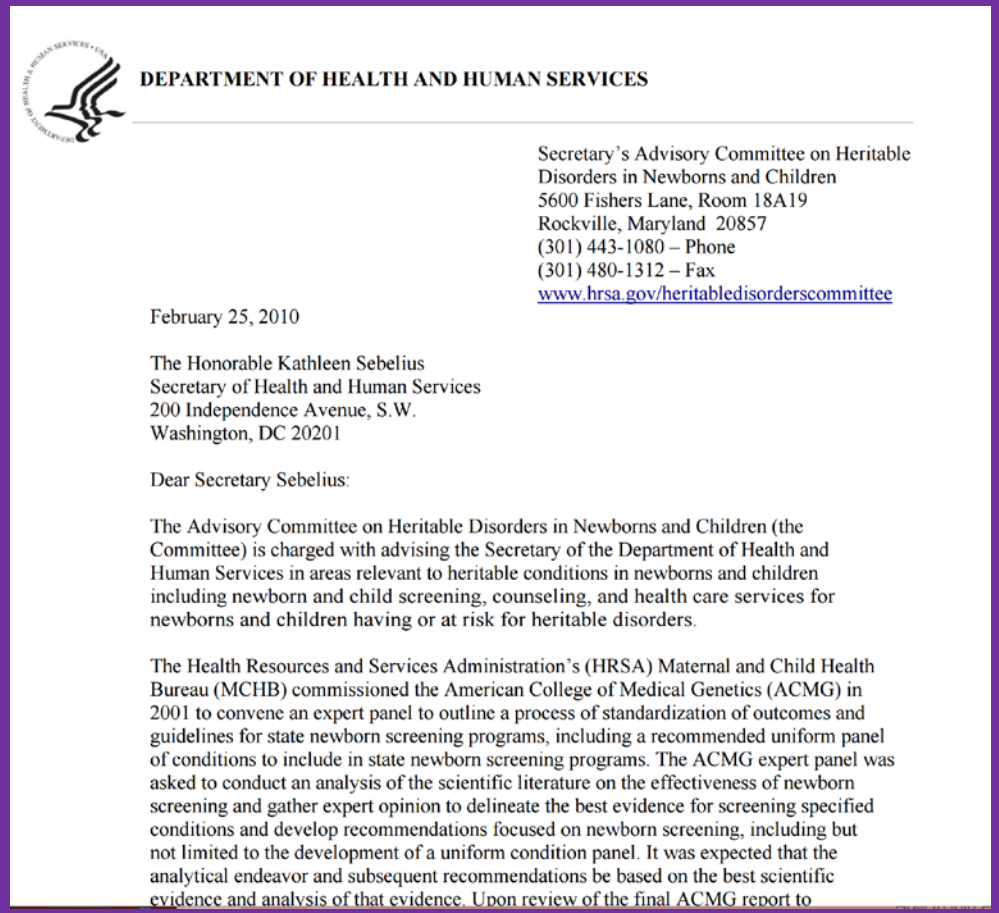
Introduction

Severe combined immunodeficiency (SCID) denotes a group of diseases in the spectrum of primary immunodeficiency (PID). SCID is particularly worthy of consideration for inclusion in the list of conditions subject to population-

Addition to the Recommended Uniform Screening Panel: February 2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Secretary's Advisory Committee on Heritable Disorders in Newborns and Children
5600 Fishers Lane, Room 18A19
Rockville, Maryland 20857
(301) 443-1080 – Phone
(301) 480-1312 – Fax
www.hrsa.gov/heritabledisorderscommittee

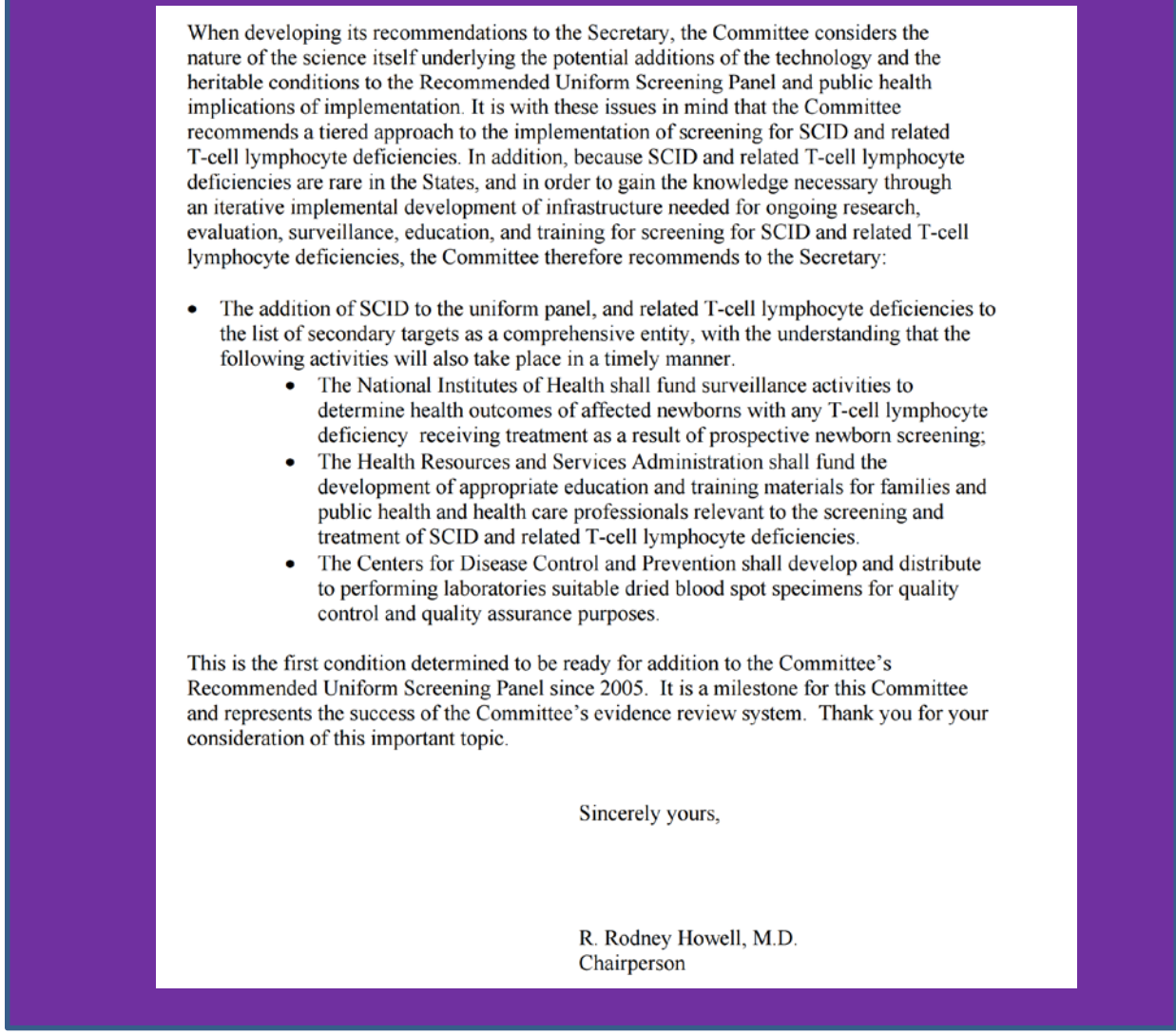
February 25, 2010

The Honorable Kathleen Sebelius
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Secretary Sebelius:

The Advisory Committee on Heritable Disorders in Newborns and Children (the Committee) is charged with advising the Secretary of the Department of Health and Human Services in areas relevant to heritable conditions in newborns and children including newborn and child screening, counseling, and health care services for newborns and children having or at risk for heritable disorders.

The Health Resources and Services Administration's (HRSA) Maternal and Child Health Bureau (MCHB) commissioned the American College of Medical Genetics (ACMG) in 2001 to convene an expert panel to outline a process of standardization of outcomes and guidelines for state newborn screening programs, including a recommended uniform panel of conditions to include in state newborn screening programs. The ACMG expert panel was asked to conduct an analysis of the scientific literature on the effectiveness of newborn screening and gather expert opinion to delineate the best evidence for screening specified conditions and develop recommendations focused on newborn screening, including but not limited to the development of a uniform condition panel. It was expected that the analytical endeavor and subsequent recommendations be based on the best scientific evidence and analysis of that evidence. Upon review of the final ACMG report to



When developing its recommendations to the Secretary, the Committee considers the nature of the science itself underlying the potential additions of the technology and the heritable conditions to the Recommended Uniform Screening Panel and public health implications of implementation. It is with these issues in mind that the Committee recommends a tiered approach to the implementation of screening for SCID and related T-cell lymphocyte deficiencies. In addition, because SCID and related T-cell lymphocyte deficiencies are rare in the States, and in order to gain the knowledge necessary through an iterative implemental development of infrastructure needed for ongoing research, evaluation, surveillance, education, and training for screening for SCID and related T-cell lymphocyte deficiencies, the Committee therefore recommends to the Secretary:

- The addition of SCID to the uniform panel, and related T-cell lymphocyte deficiencies to the list of secondary targets as a comprehensive entity, with the understanding that the following activities will also take place in a timely manner.
    - The National Institutes of Health shall fund surveillance activities to determine health outcomes of affected newborns with any T-cell lymphocyte deficiency receiving treatment as a result of prospective newborn screening;
    - The Health Resources and Services Administration shall fund the development of appropriate education and training materials for families and public health and health care professionals relevant to the screening and treatment of SCID and related T-cell lymphocyte deficiencies.
    - The Centers for Disease Control and Prevention shall develop and distribute to performing laboratories suitable dried blood spot specimens for quality control and quality assurance purposes.

This is the first condition determined to be ready for addition to the Committee's Recommended Uniform Screening Panel since 2005. It is a milestone for this Committee and represents the success of the Committee's evidence review system. Thank you for your consideration of this important topic.

Sincerely yours,

R. Rodney Howell, M.D.
Chairperson

Challenges in SCID NBS Implementation

- **Approval/Legislation**
  - Funding
  - Priorities
- **Laboratory**
  - Equipment/Work flow
  - Training
  - Technical Challenges and Analysis
- **Follow-up and Clinical**
  - Availability of Immunologists
  - Developing Relationships
- **Education**
  - Staff
  - Leadership
  - Clinicians
  - Community/Advocacy

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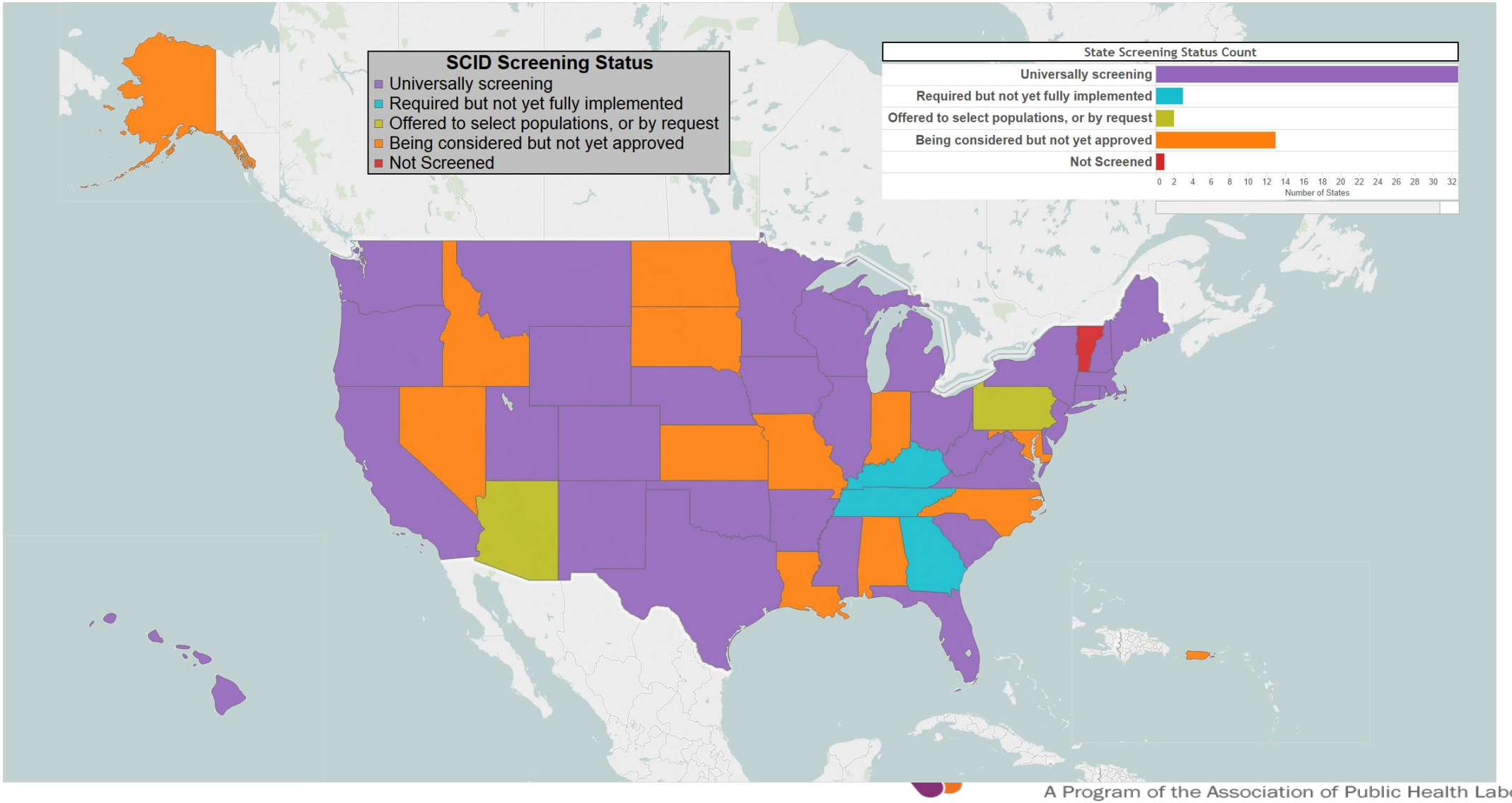
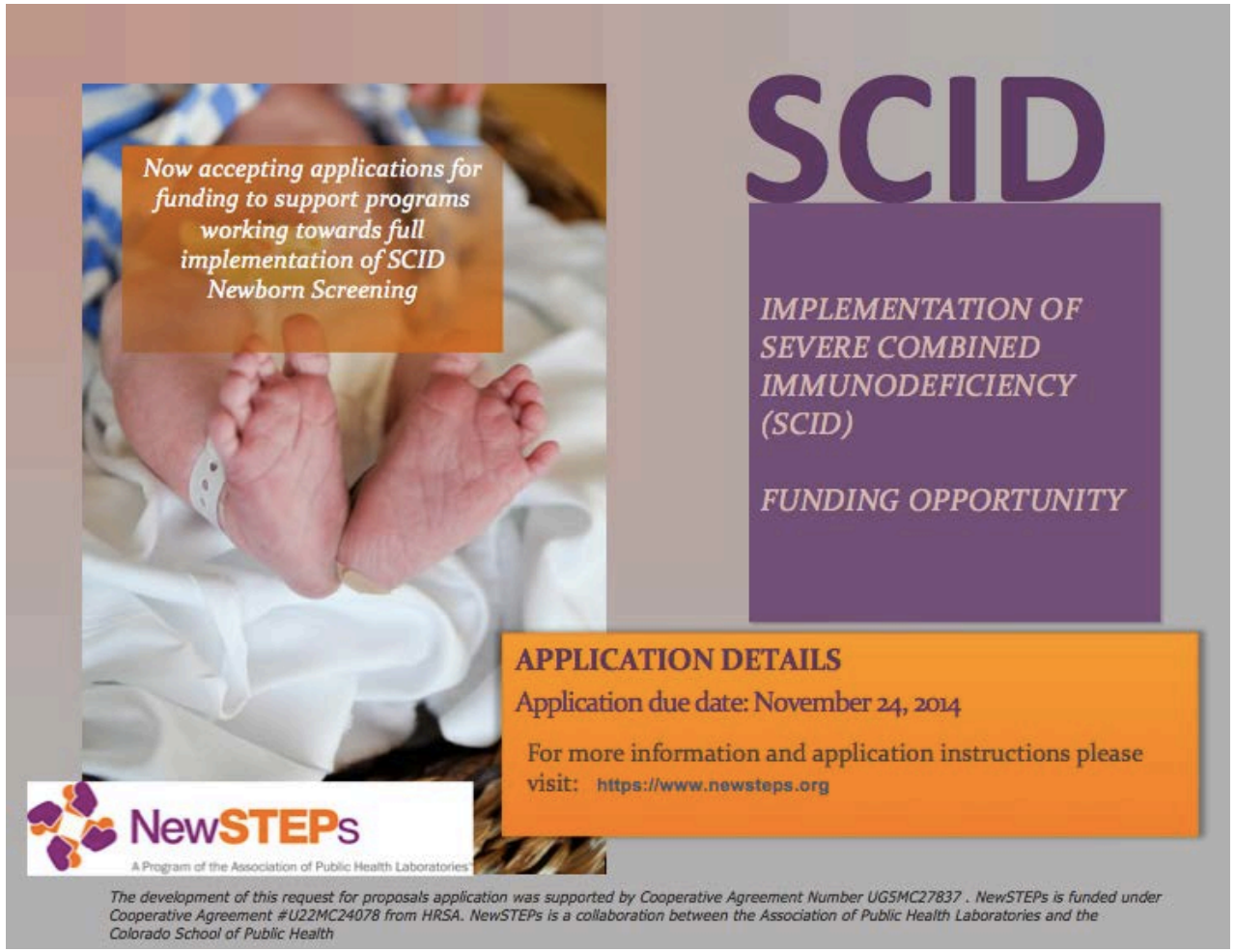
Current Status



NewSTEPs funding

- Funding opportunity to assist NBS programs in moving forward for SCID implementation
  - Legislative approval and funding
  - Laboratory technology
  - Follow-up
  - Clinical Referral Network
  - Education



The funding opportunity was supported by HRSA Cooperative Agreement UG5MC27837

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NewSTEPs SCID funded programs

- Alabama
- Arizona
- Hawaii
- Kansas
- Kentucky
- Maryland
- North Carolina
- North Dakota
- Puerto Rico
- Tennessee
- Utah
- Immune Deficiency Foundation

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Progress in SCID Implementation

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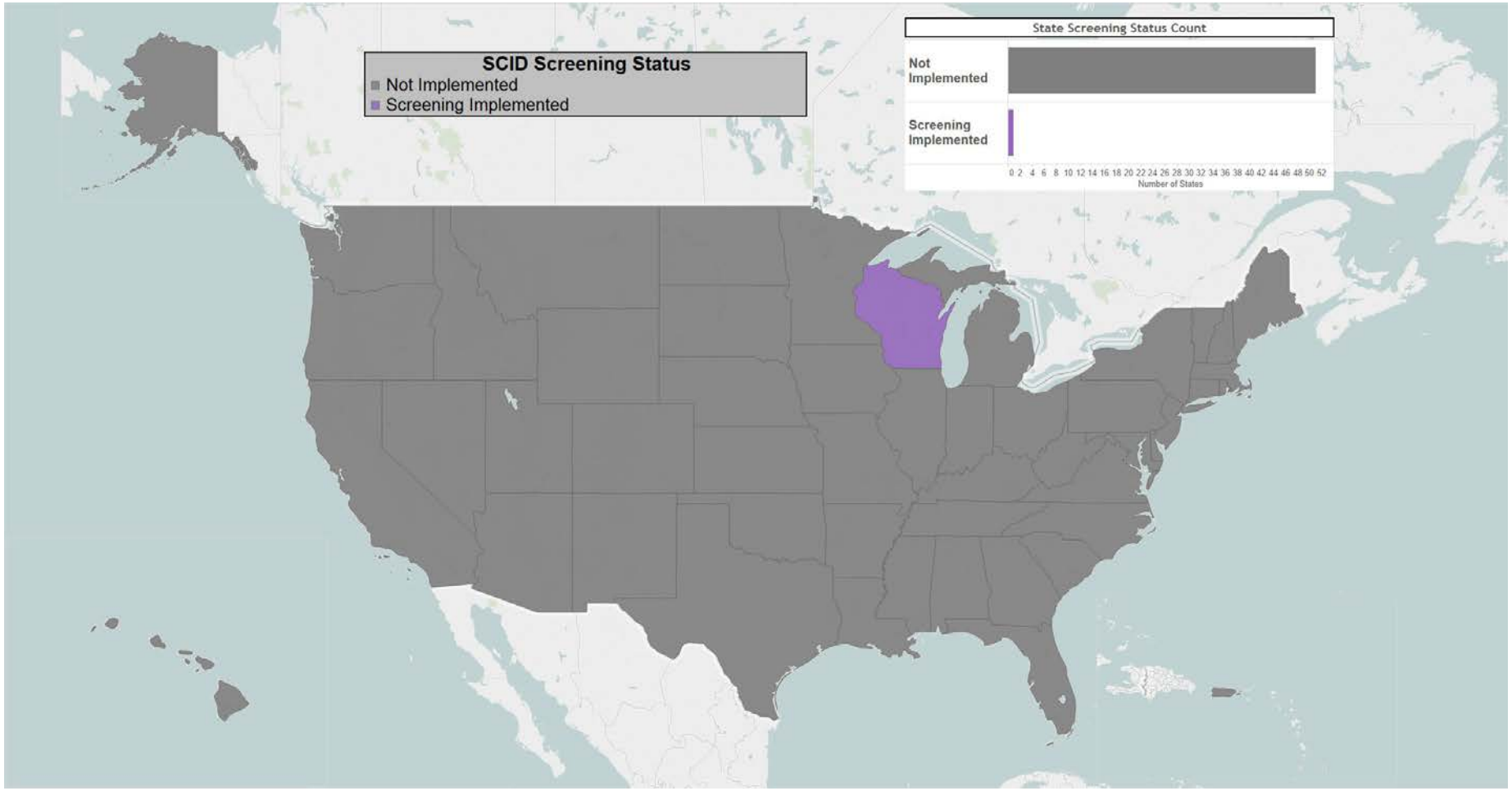
2008



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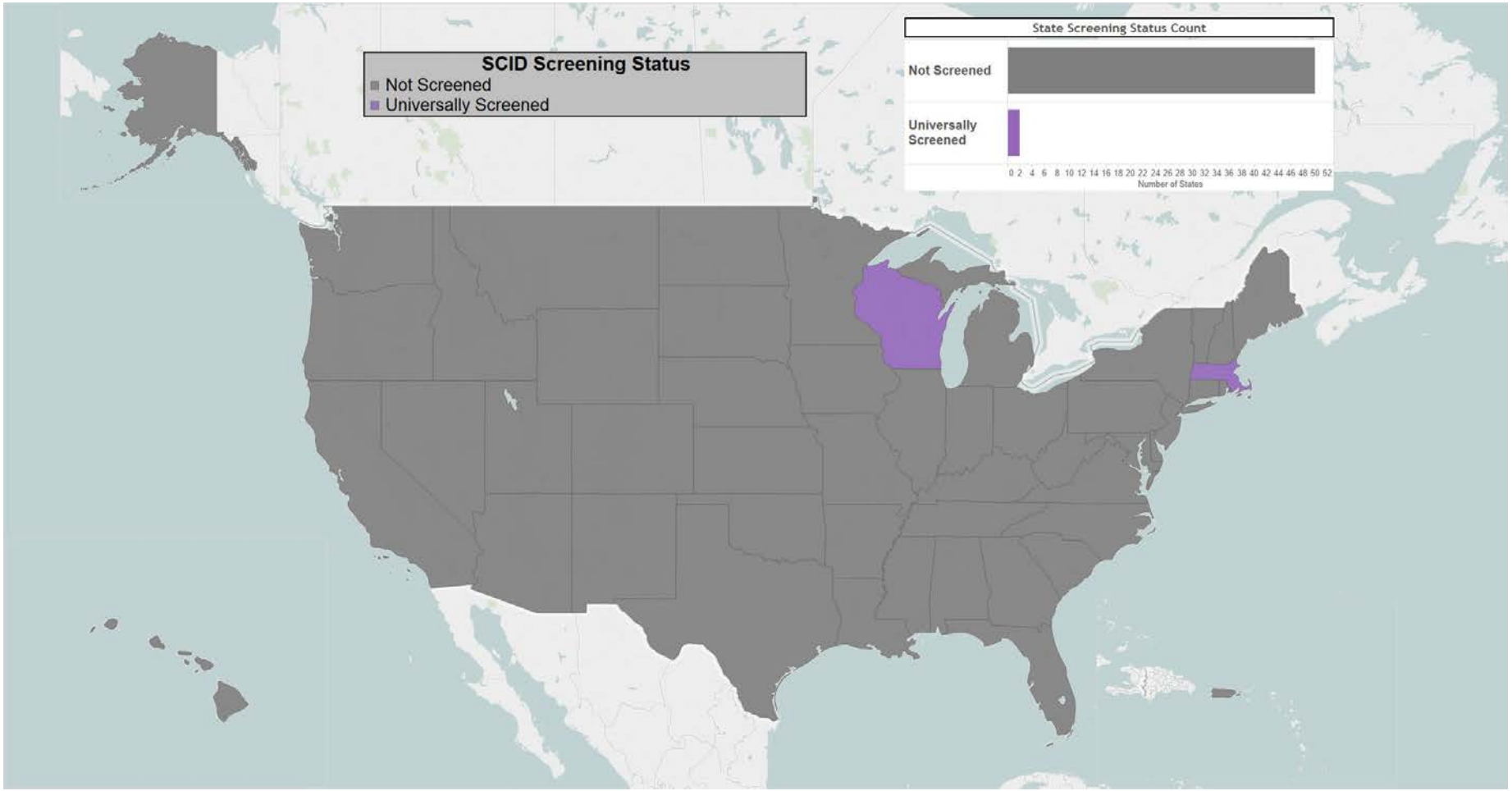
** Note map is not to scale (HI, AK, Caribbean Islands moved to fit onto slide)*

2009



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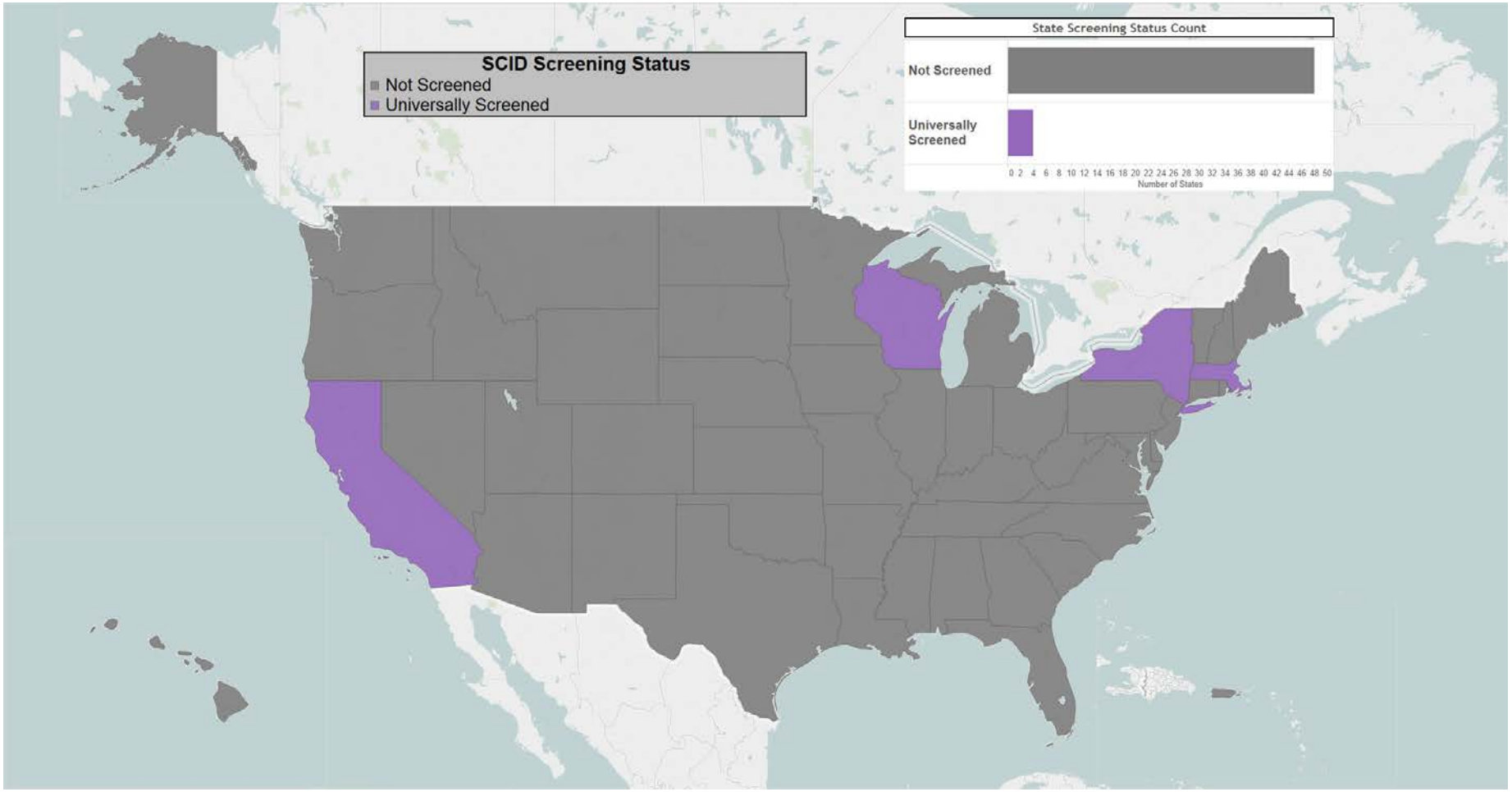
2010 – Added to RUSP



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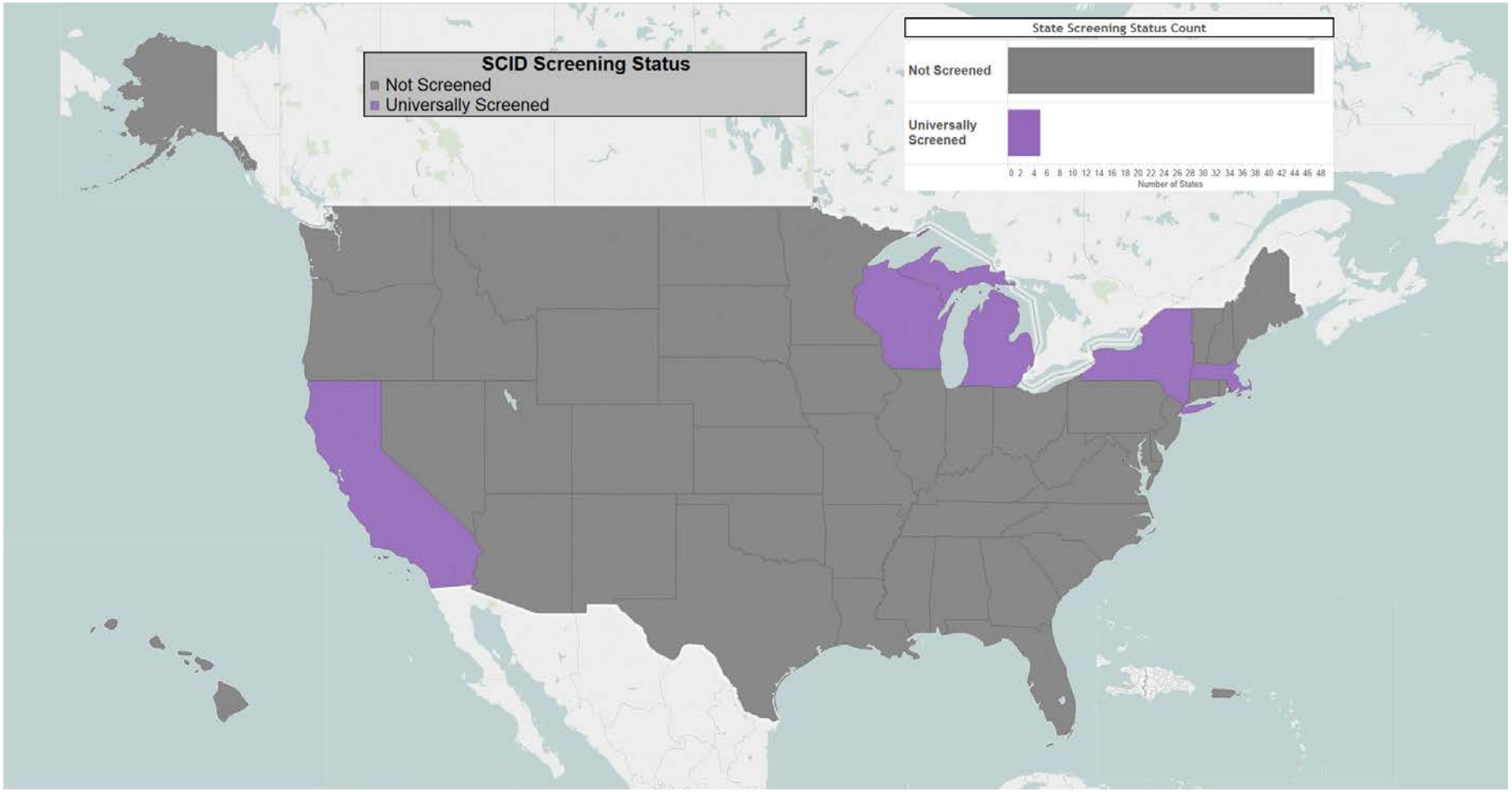
2011



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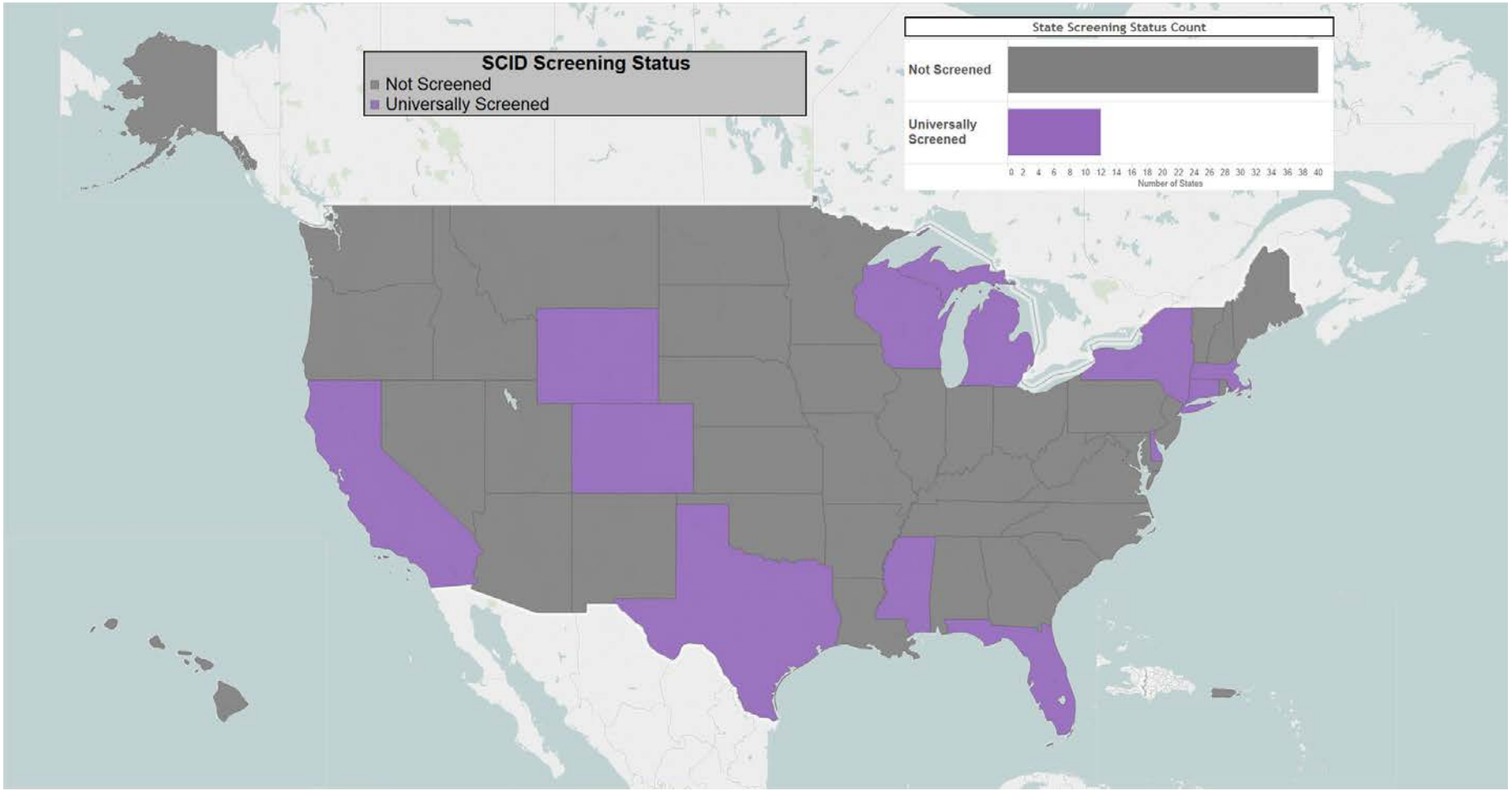
2012



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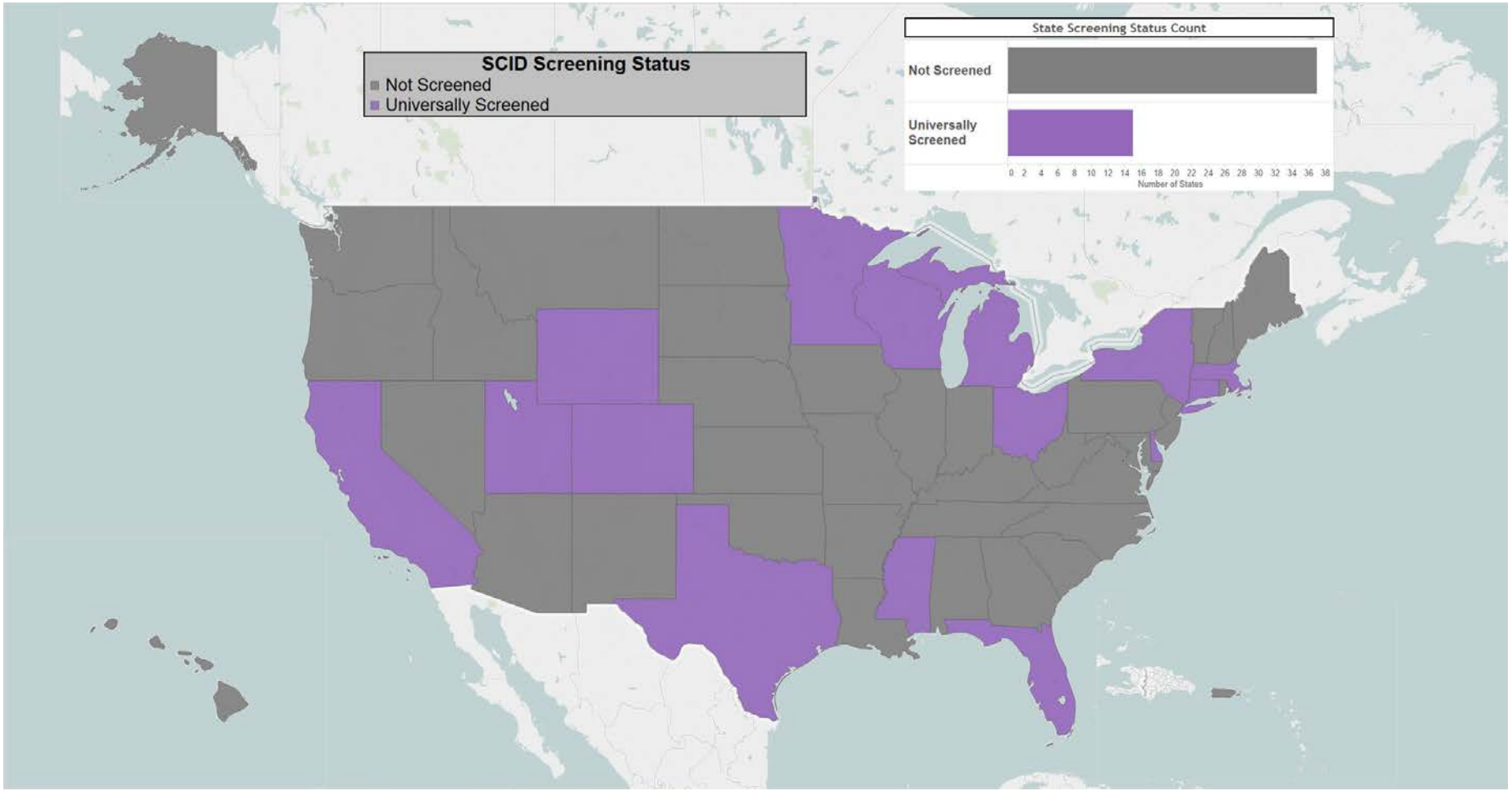
2013



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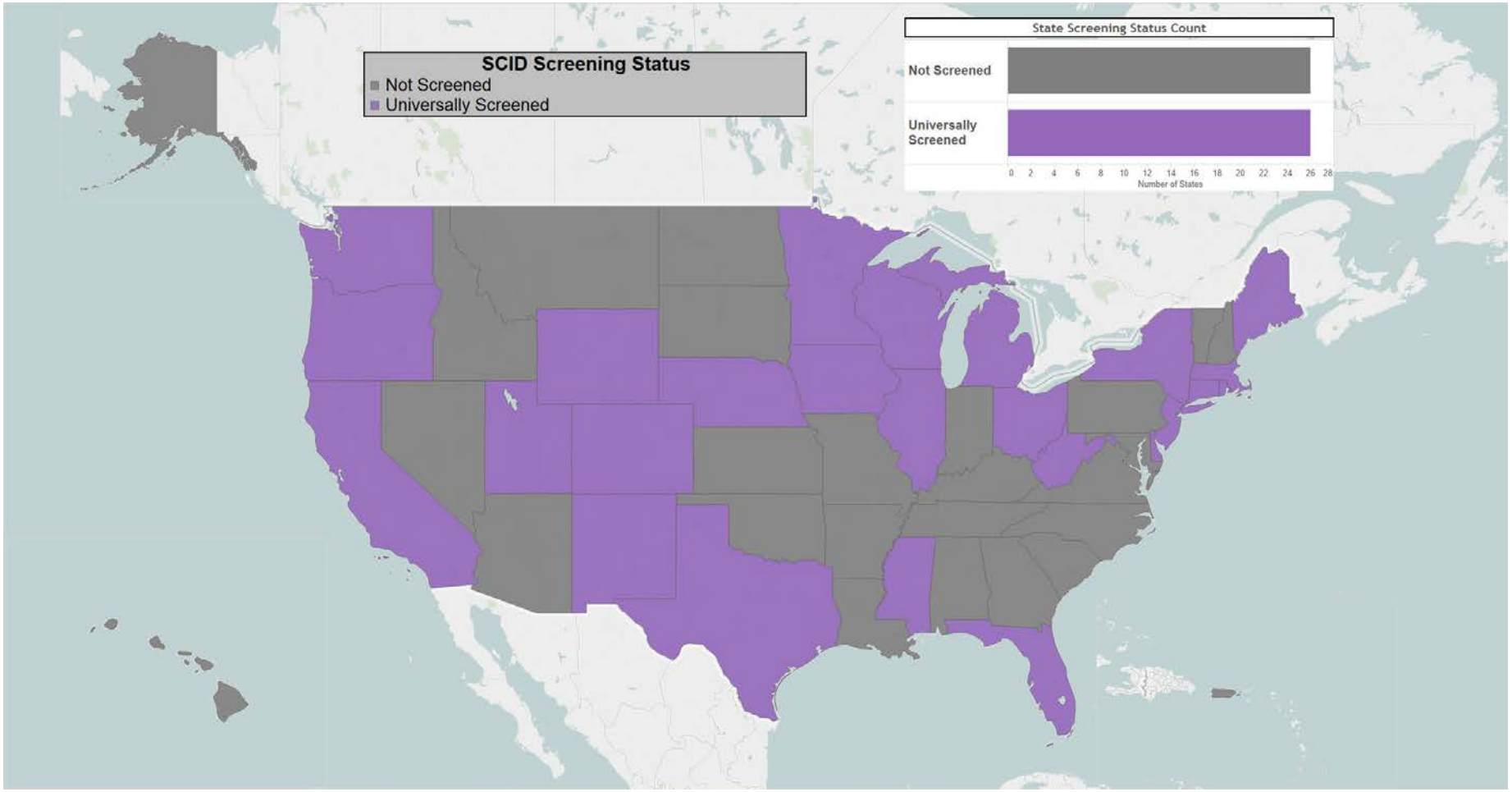
2014



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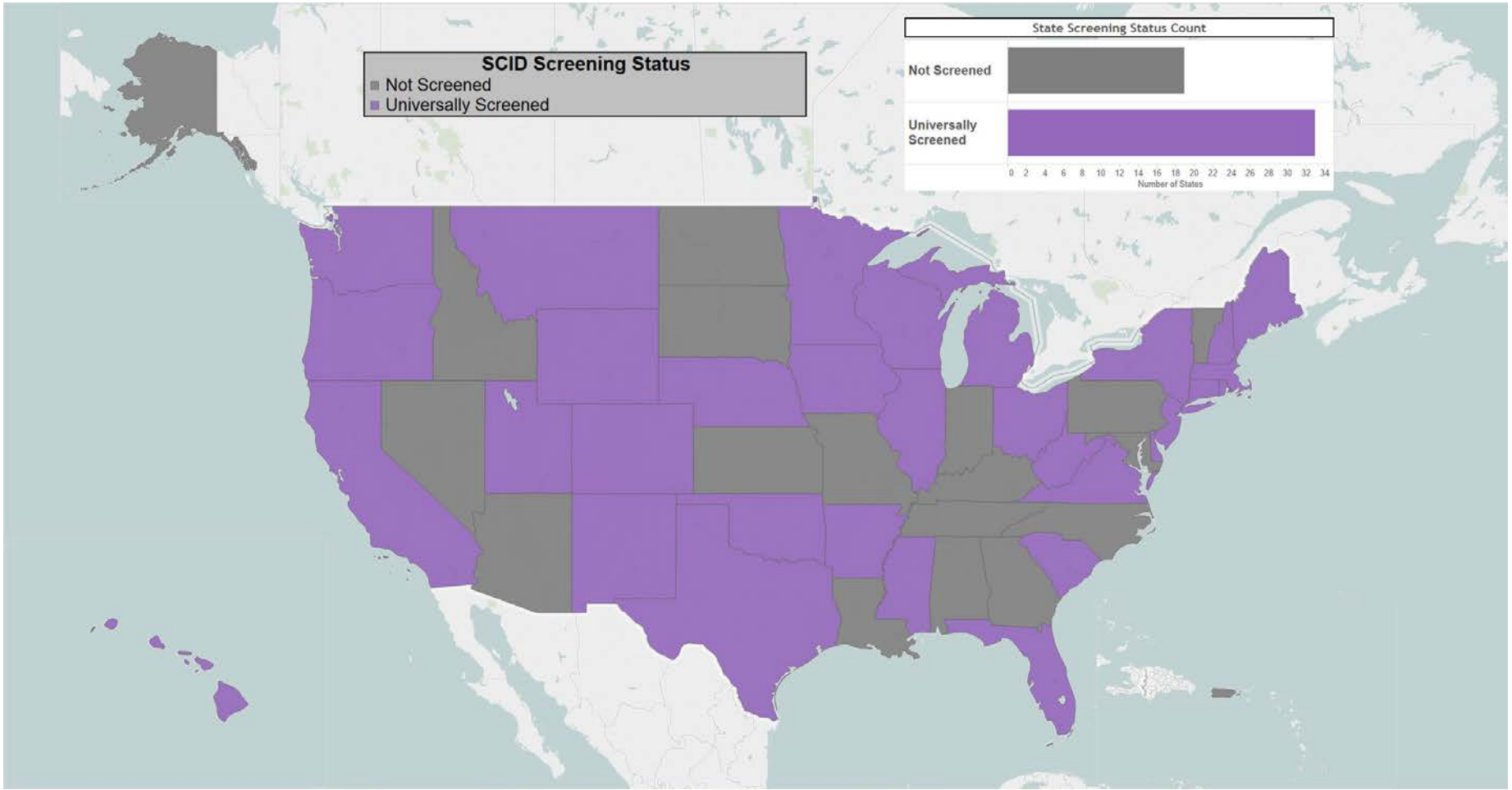
2015



71% of Newborns Screened

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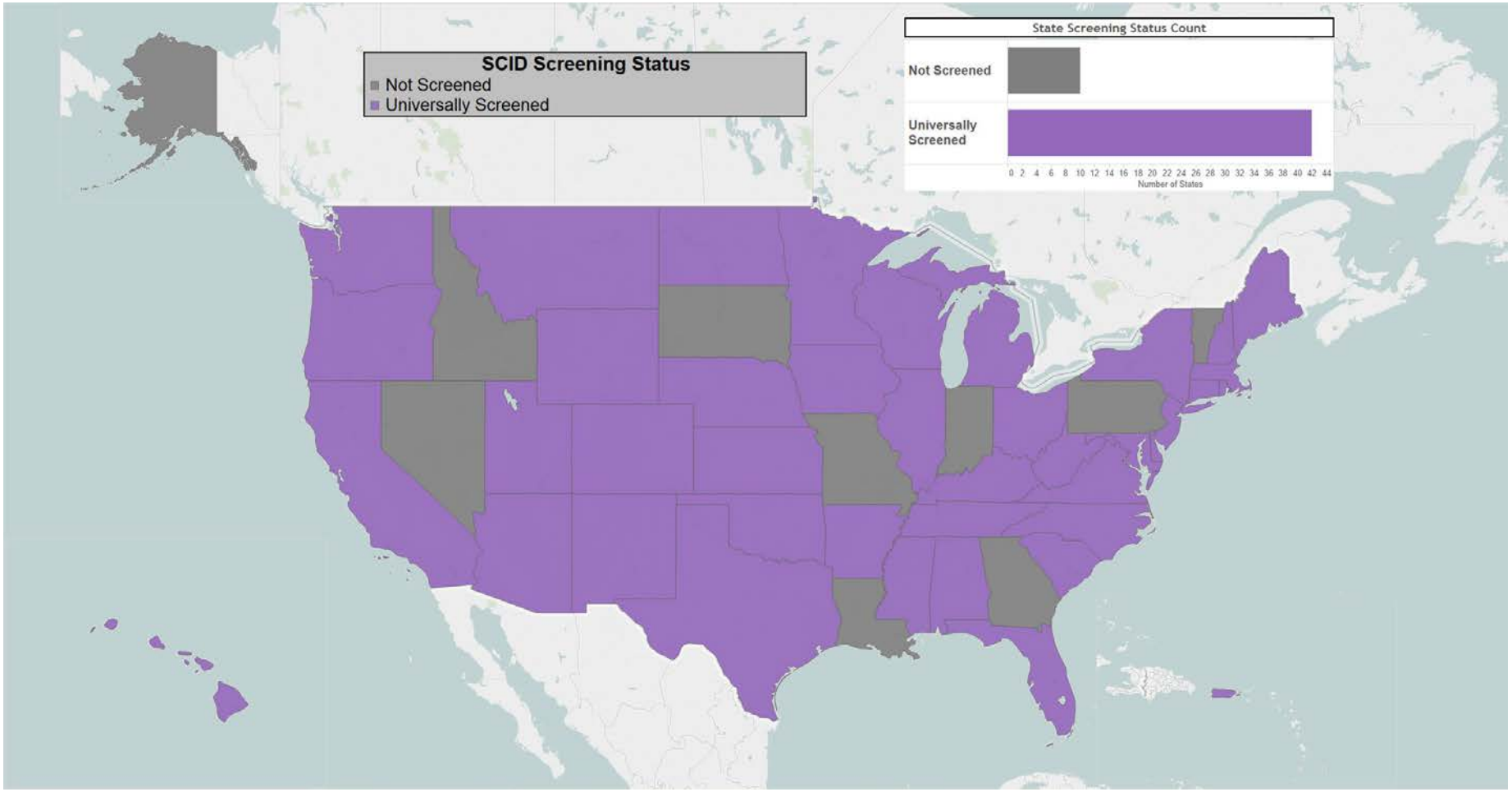
** Note map is not to scale (HI, AK, Caribbean Islands moved to fit onto slide)*

2016 – Projected

Updates based on NewSTEPs Grantees projections, other states likely to start in 2016



85% of Newborns Screened

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Comparison to CF

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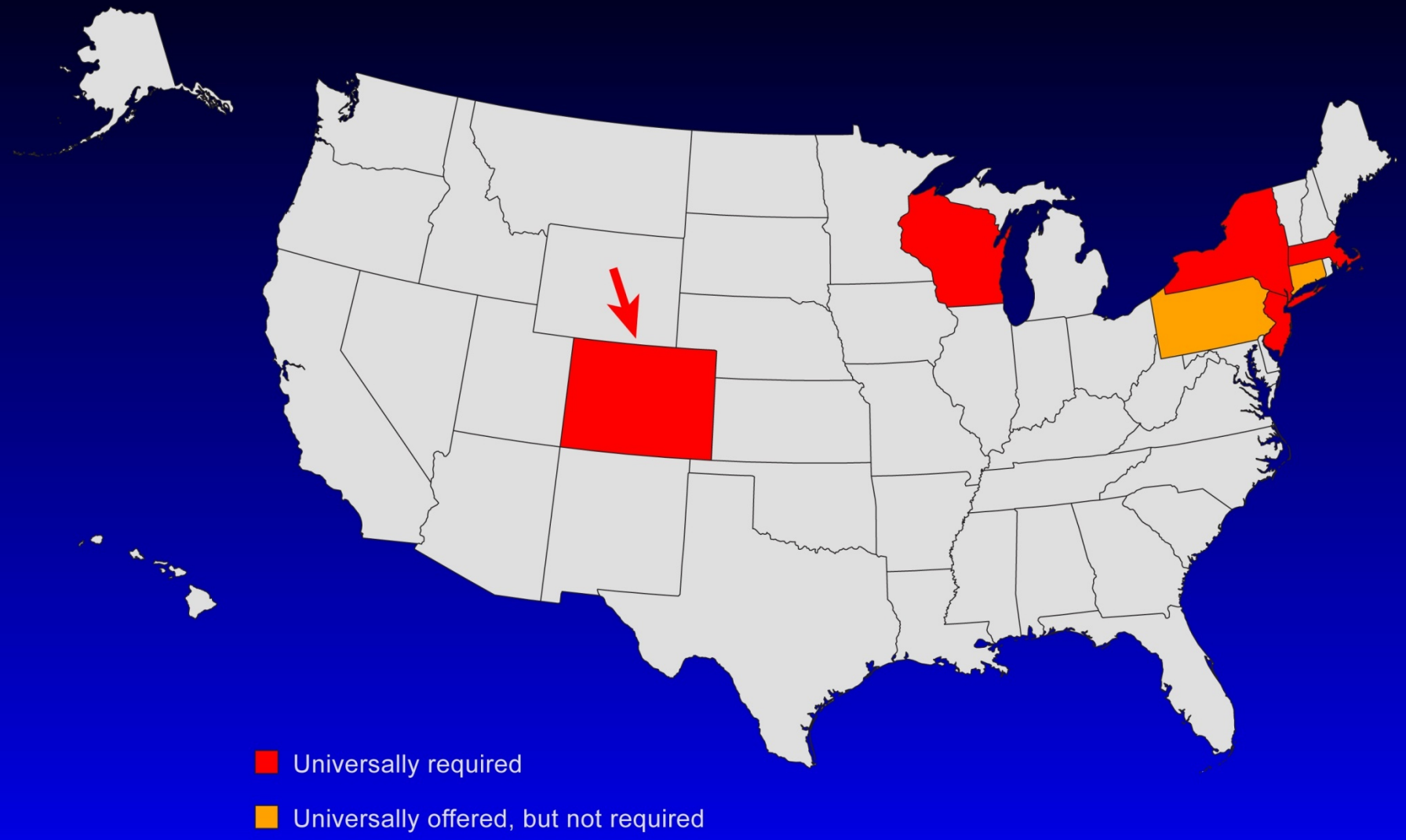
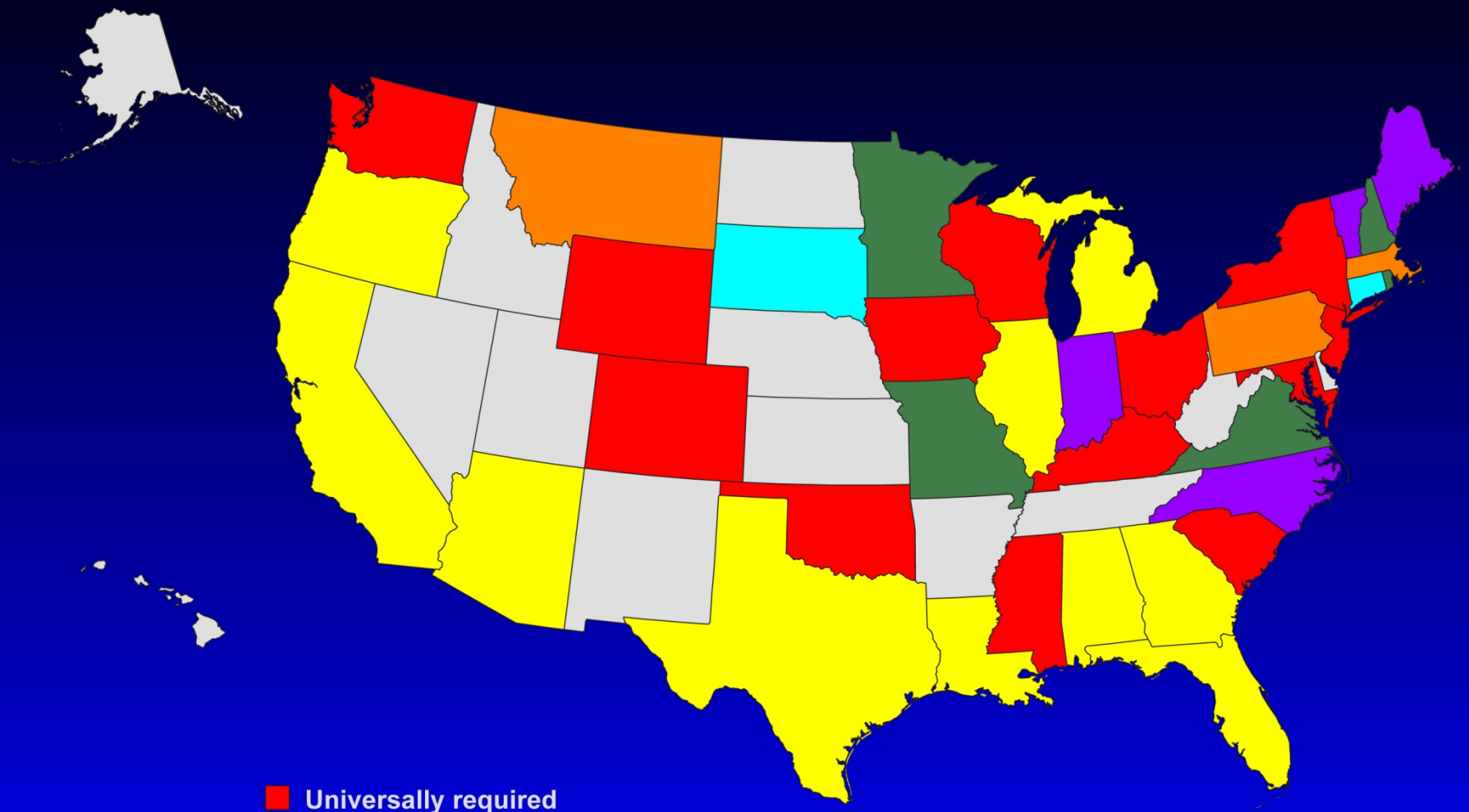
Status of CF NBS in 2004



Slide courtesy P. Farrell

Current Status of CF NBS (2006)

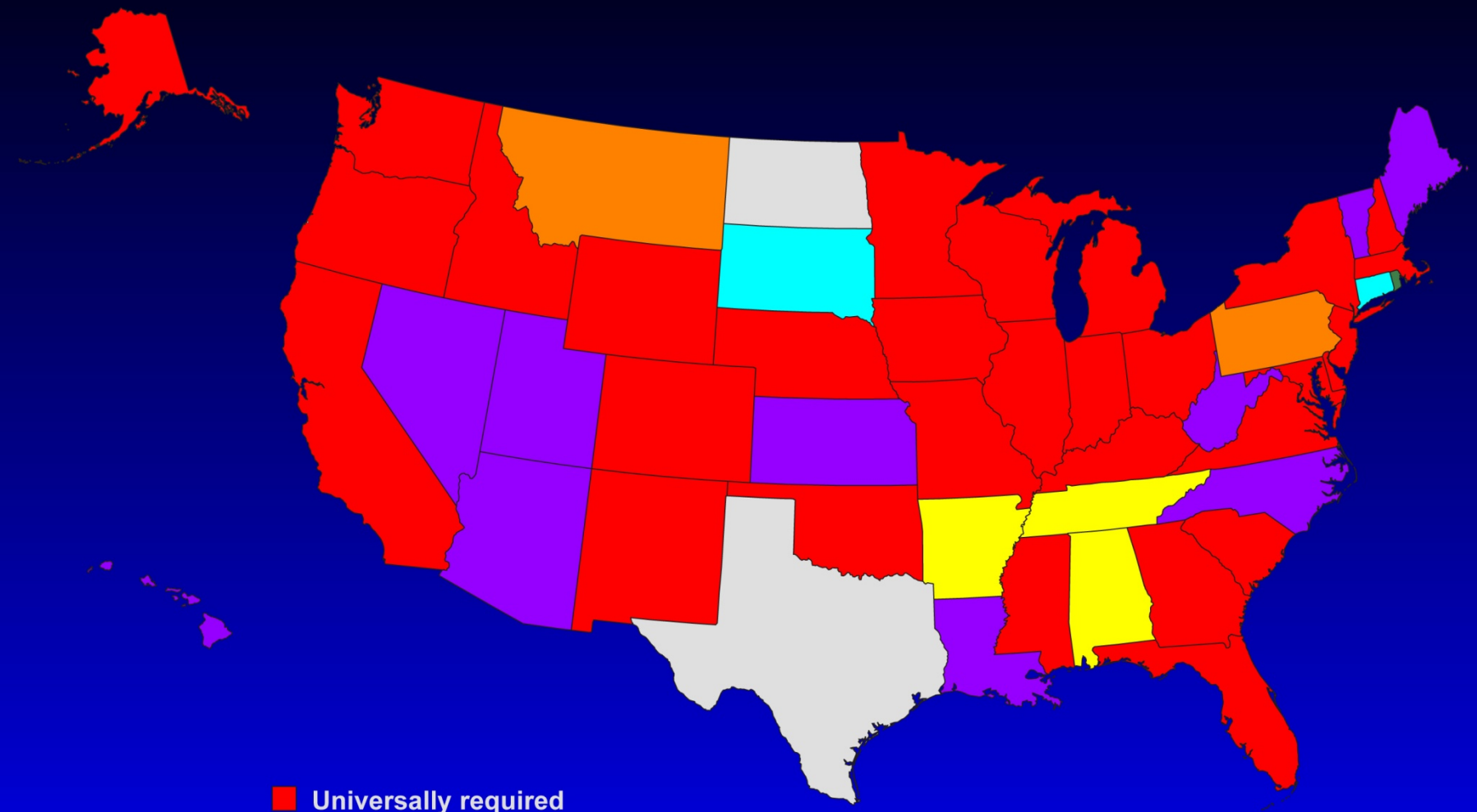


- Universally required
- Universally offered, but not required
- Offered to select populations or by request
- Required but not yet implemented
- Advanced planning stages
- Considering various options
- No information on current intentions

9/06

Slide courtesy P. Farrell

Current Status of CF NBS (2007)



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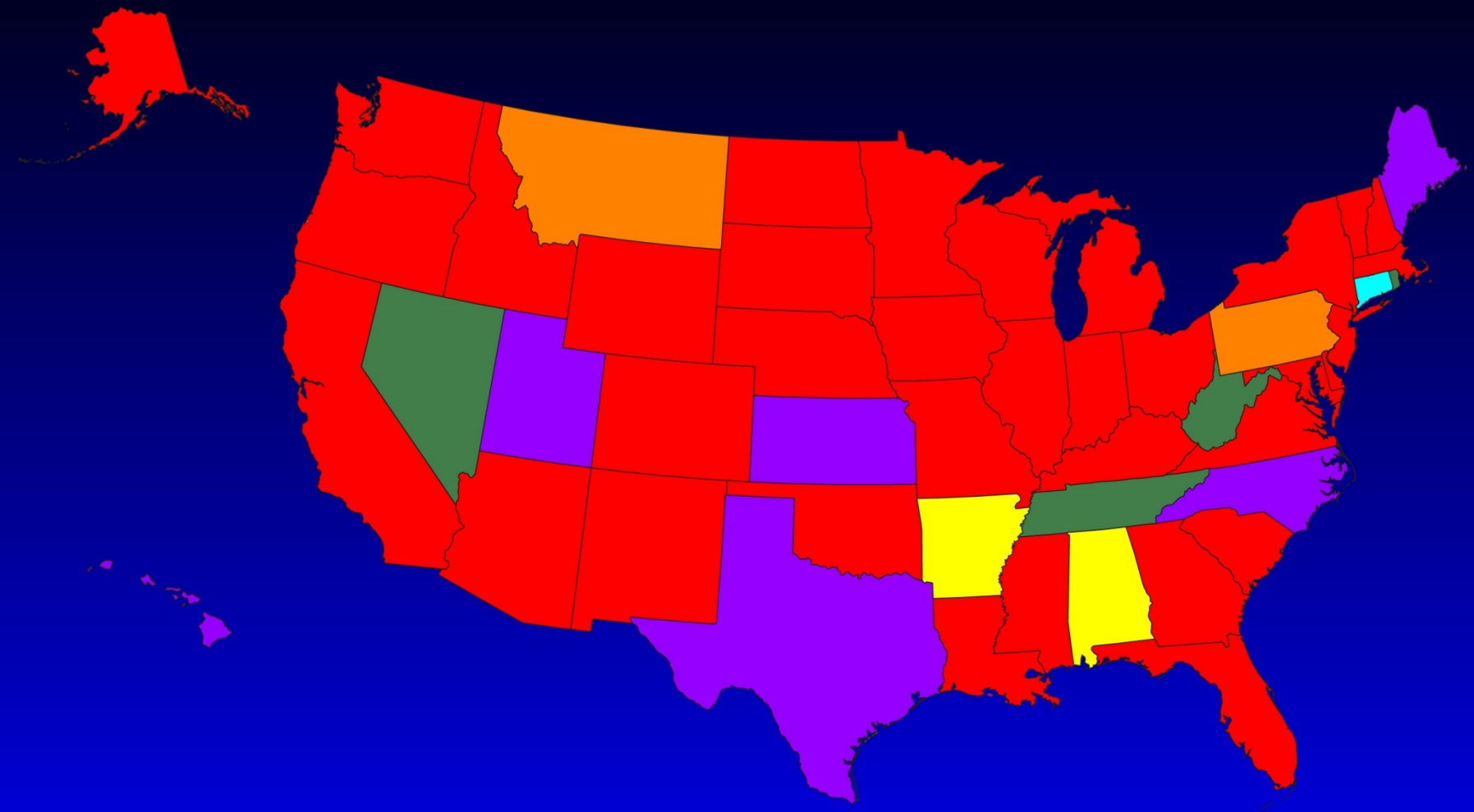
Current Status of CF NBS (2008)



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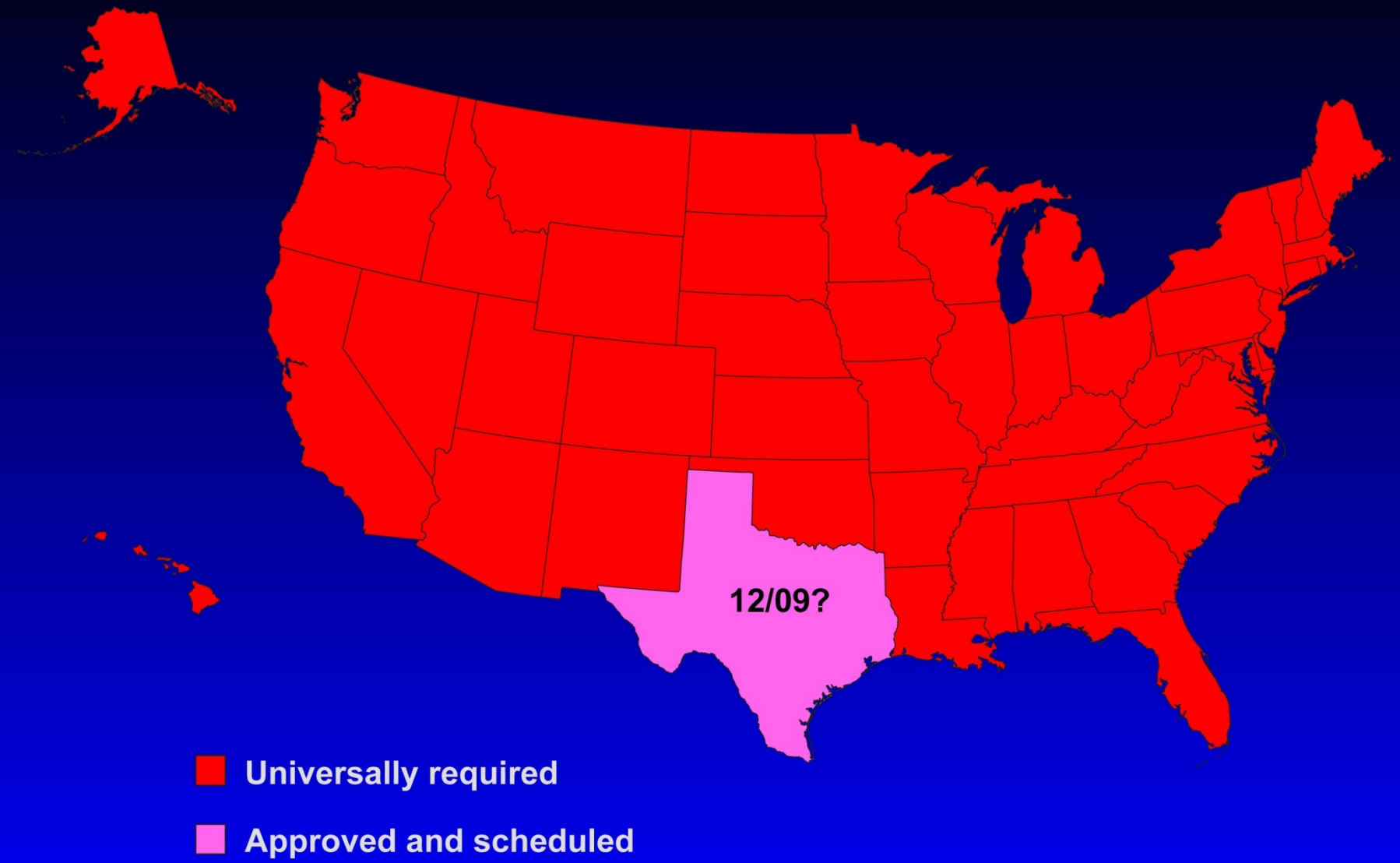
Current Status of CF NBS (2009)



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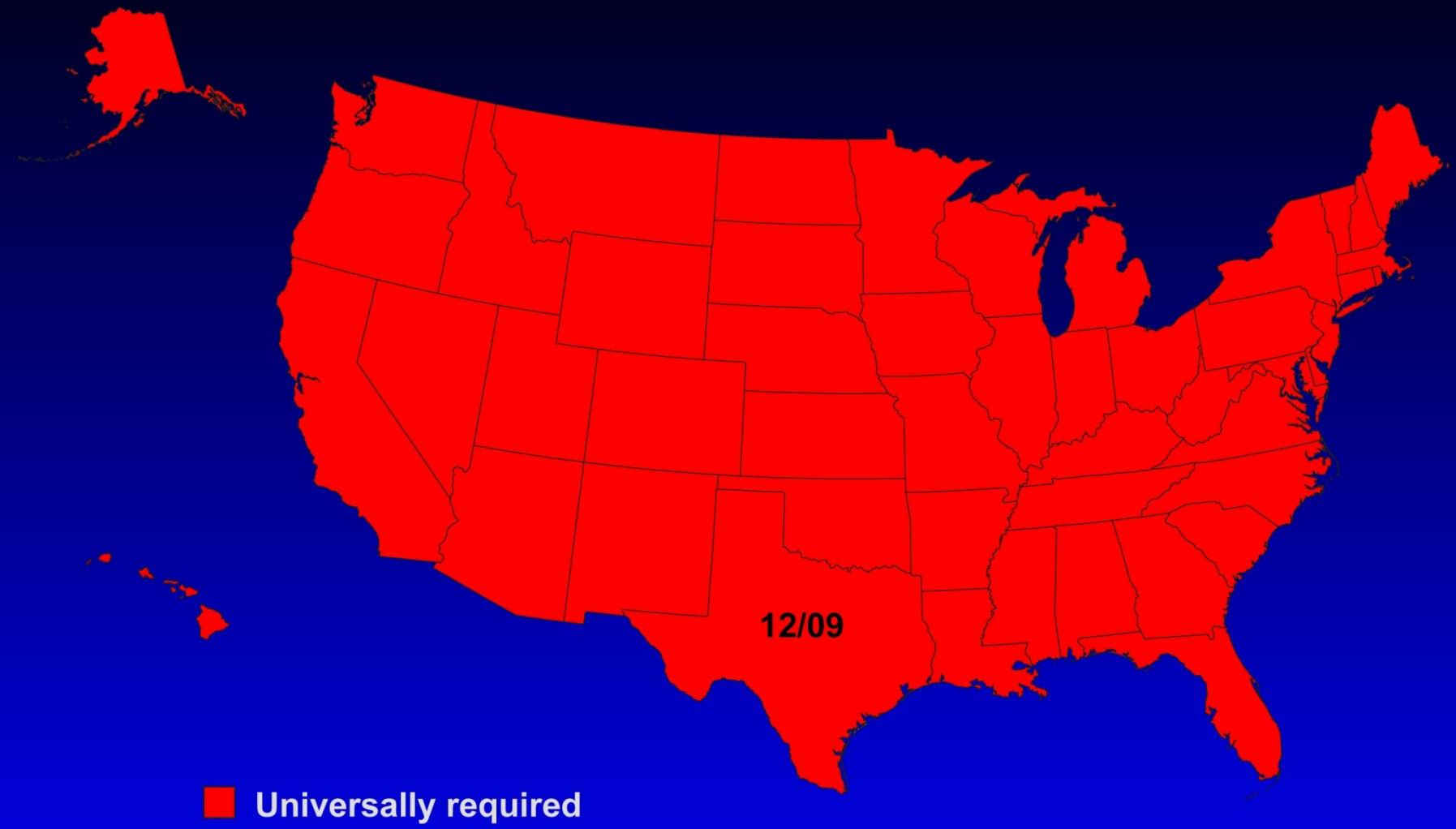
Current Status of CF NBS (2010)



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National Data Repository for NBS

Purpose: Provide tools to state newborn screening systems to adequately evaluate, analyze, and benchmark the performance of their tests and the quality of their newborn screening programs

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Colorado's Status

Severe Combined Immunodeficiencies - SCID

Universally required by Law or Rule and fully implemented

First Screen First Tier Method
Target:
TREC

Second Screen First Tier Method
Target:
TREC

Status Date:
2/2012

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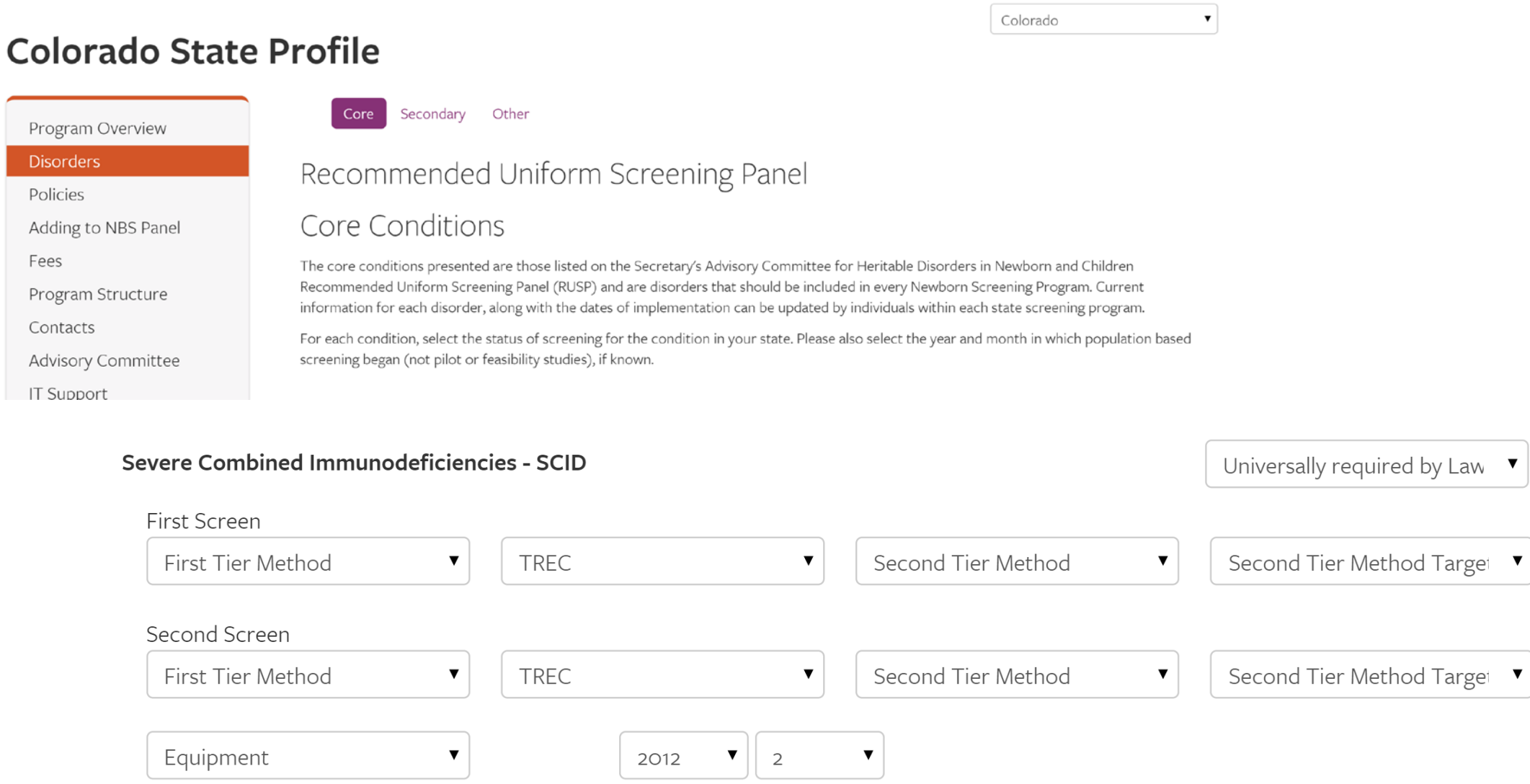
SCID Screening Status



From: **Newborn Screening for Severe Combined Immunodeficiency in 11 Screening Programs in the United States**

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

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]		

Abbreviations:
PHA, phytohemagglutinin;
SCID, severe combined immunodeficiency.

[a] As adopted by the Primary Immune Deficiency Treatment Consortium and R4S Laboratory Performance Database, SCID and leaky SCID were defined by laboratory criteria rather than infectious complications.

[b] On discovery of an etiology for low T cells, the affected individual was moved to the appropriate alternative category.

Table Title:

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

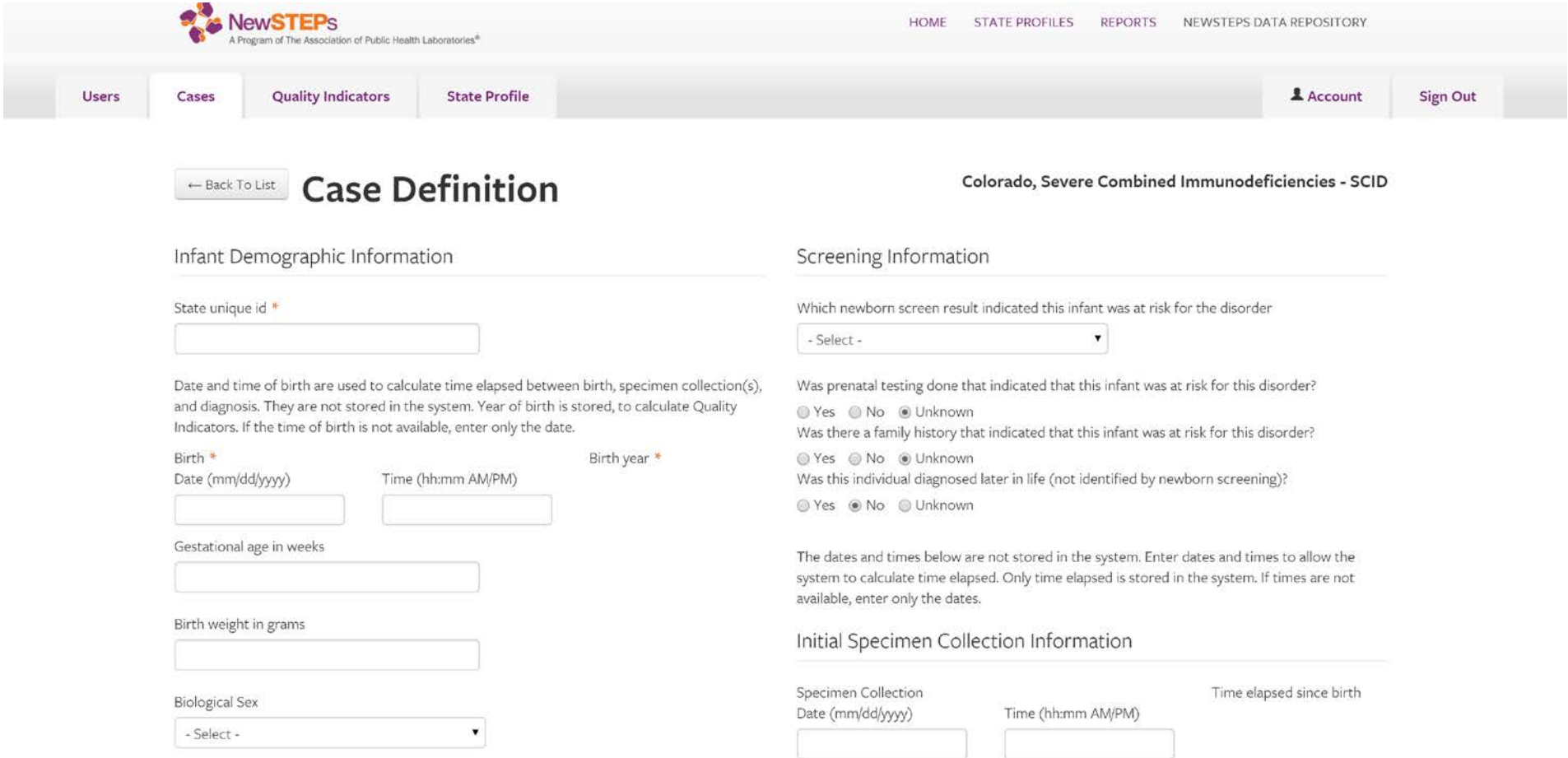
WHY Enter SCID Cases??

- Understand the frequency of the disorder – need population data
- Compare frequencies across states/regions
- Understand the burden of the different diagnoses

SCID Case Data Entry

- Primary targets of NBS
  - Classic SCID
  - Leaky SCID
  - Omenn Syndrome
- Secondary targets of NBS
  - Syndrome with low T-cell numbers
  - Secondary T-cell lymphopenia
  - Preterm birth alone
  - Idiopathic T-cell lymphopenia (Variant SCID)

SCID Cases



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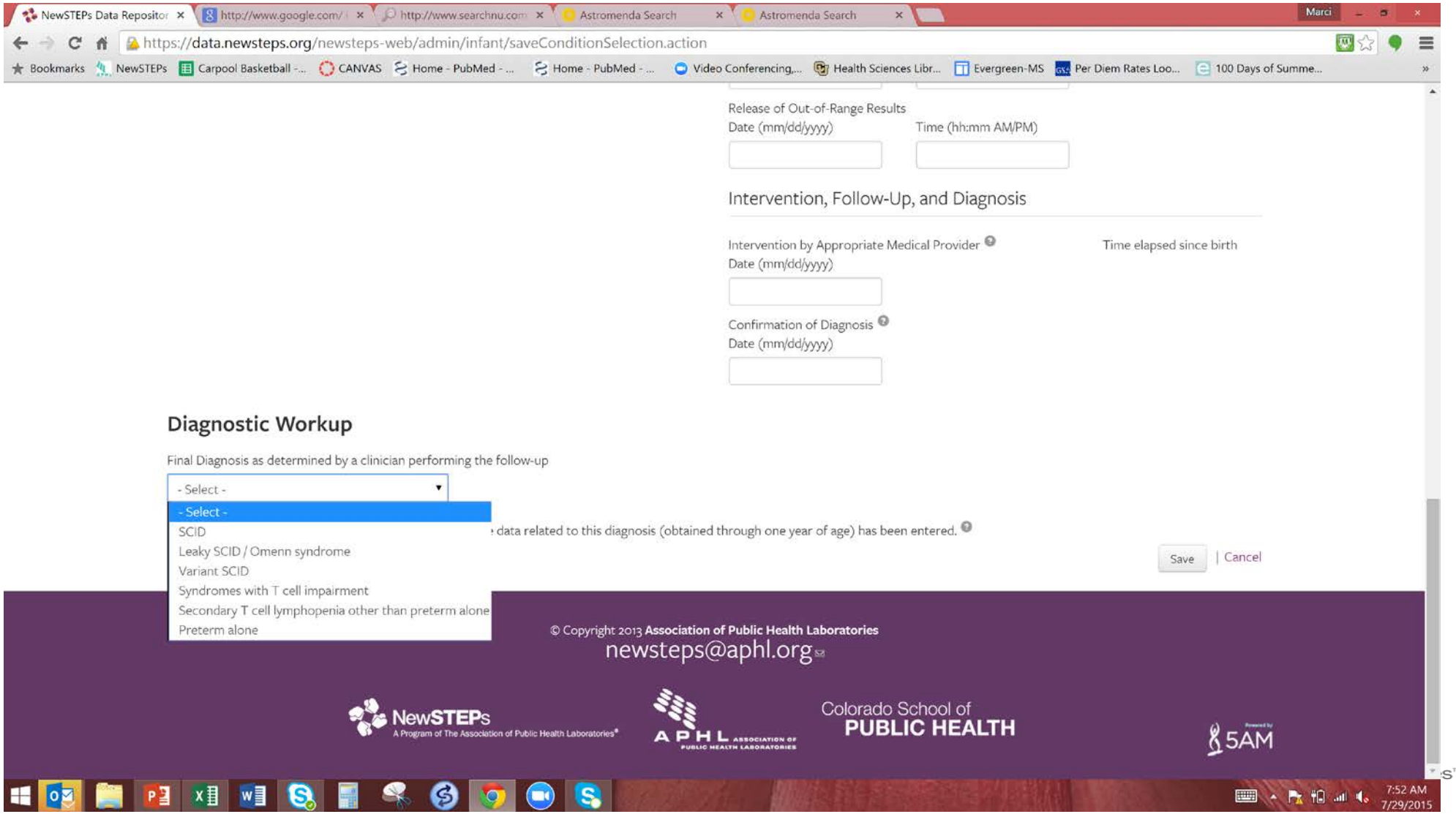
SCID Cases


NewSTEPs Data Repositor
https://data.newsteps.org/newsteps-web/admin/infant/saveConditionSelection.action
Release of Out-of-Range Results
Date (mm/dd/yyyy)
Time (hh:mm AM/PM)
Intervention, Follow-Up, and Diagnosis
Intervention by Appropriate Medical Provider
Time elapsed since birth
Date (mm/dd/yyyy)
Confirmation of Diagnosis
Date (mm/dd/yyyy)
Diagnostic Workup
Final Diagnosis as determined by a clinician performing the follow-up
- Select -
- Select -
SCID
Leaky SCID / Omenn syndrome
Variant SCID
Syndromes with T cell impairment
Secondary T cell lymphopenia other than preterm alone
Preterm alone
data related to this diagnosis (obtained through one year of age) has been entered.
Save
Cancel
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APHL
Colorado School of PUBLIC HEALTH
5AM
7:52 AM
7/29/2015

Overview of Meeting

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Format and expectations of the meeting

- Formal presentations
  - Legislation/authority/fees
  - Laboratory and follow-up efforts
  - Education and advocacy
  - Parental experiences
- Expectation:
  - Active listening
  - Turn off cell phones/email
  - Limit additional conversations
  - Staying on time

Network and Have fun!

- Small group work
  - Legislation/authority/fees
  - Laboratory and follow-up efforts
  - Education and advocacy
- Expectation:
  - Active participation
  - Contribute and listen
  - Grantees: Share progress/lessons
  - No need to ‘Echo’

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Severe Combined Immunodeficiency (SCID) In-Person Meeting

Meeting Day 1: July 29th, 2015		
8: 30 am - 9:00 am	Arrival and Continental Breakfast	Grand Foyer
9:00 am – 10:30 am	Full Group	Salons G & H
10:30 am – 11:15 am	Breakout Session 1	Groups 1 – 5 & 11: Salons G & H Groups 6 – 10: Linden Oak (Downstairs)
11:15 am – 12:00 pm	Full Group	Salons G & H
12:00 pm – 1:00 pm	Lunch	Salon F
1:00 pm – 2:30 pm	Full Group	Salons G & F
2:30 pm – 3:15 pm	Breakout Session 2	Groups 1 – 5: Salons G & H Groups 6 – 10: Linden Oak (Downstairs)
3:15 pm – 3:30 pm	Break	Grand Foyer
3:30 pm – 4:30 pm	Full Group	Salons G & F

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Meeting Day 2: July 30th, 2015		
8: 00 am – 8:30 am	Arrival and Continental Breakfast	Grand Foyer
8:30 am – 9:15 am	Full Group	Salons G & H
9:15 am – 10:00 am	Breakout Session 3	Groups 1 – 5: Salons G & H Groups 6 – 10: Linden Oak (Downstairs)
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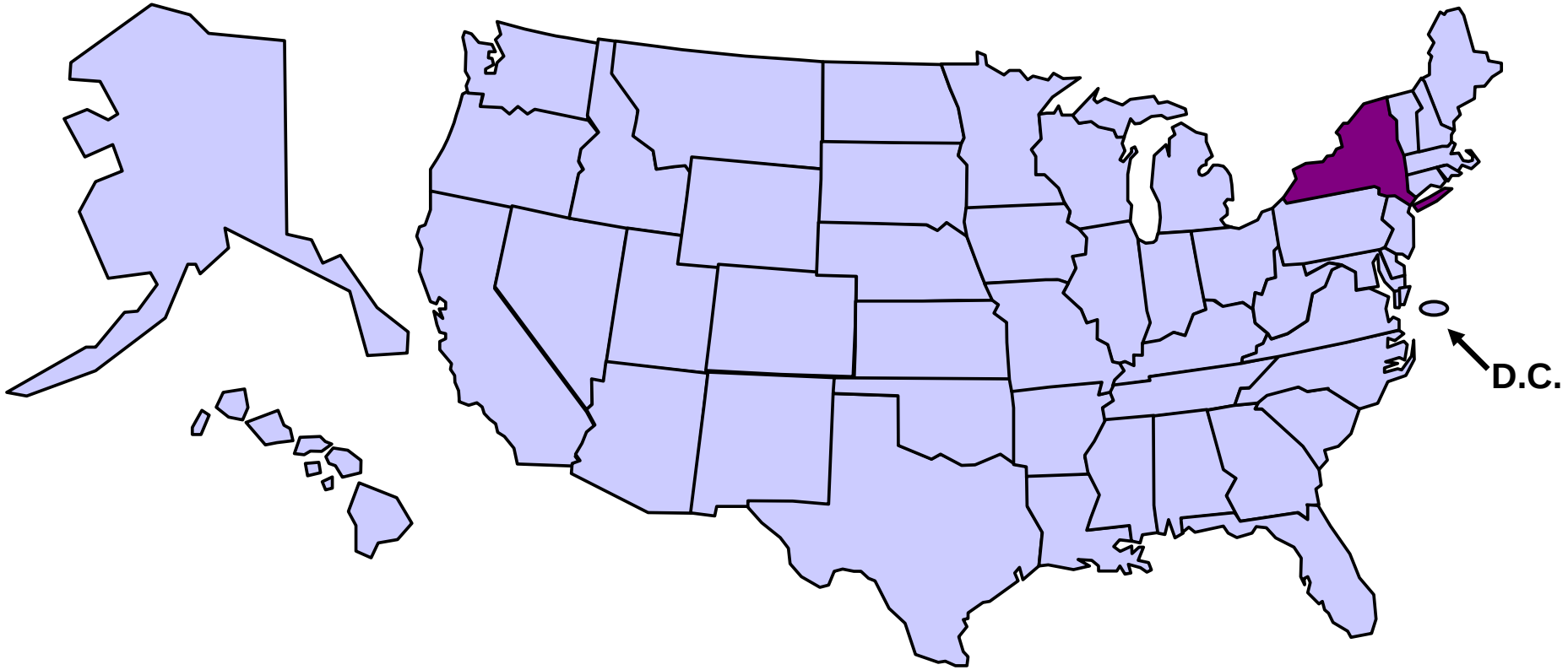

Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening April 1, 1975

National Newborn Screening and Genetics Resource Center
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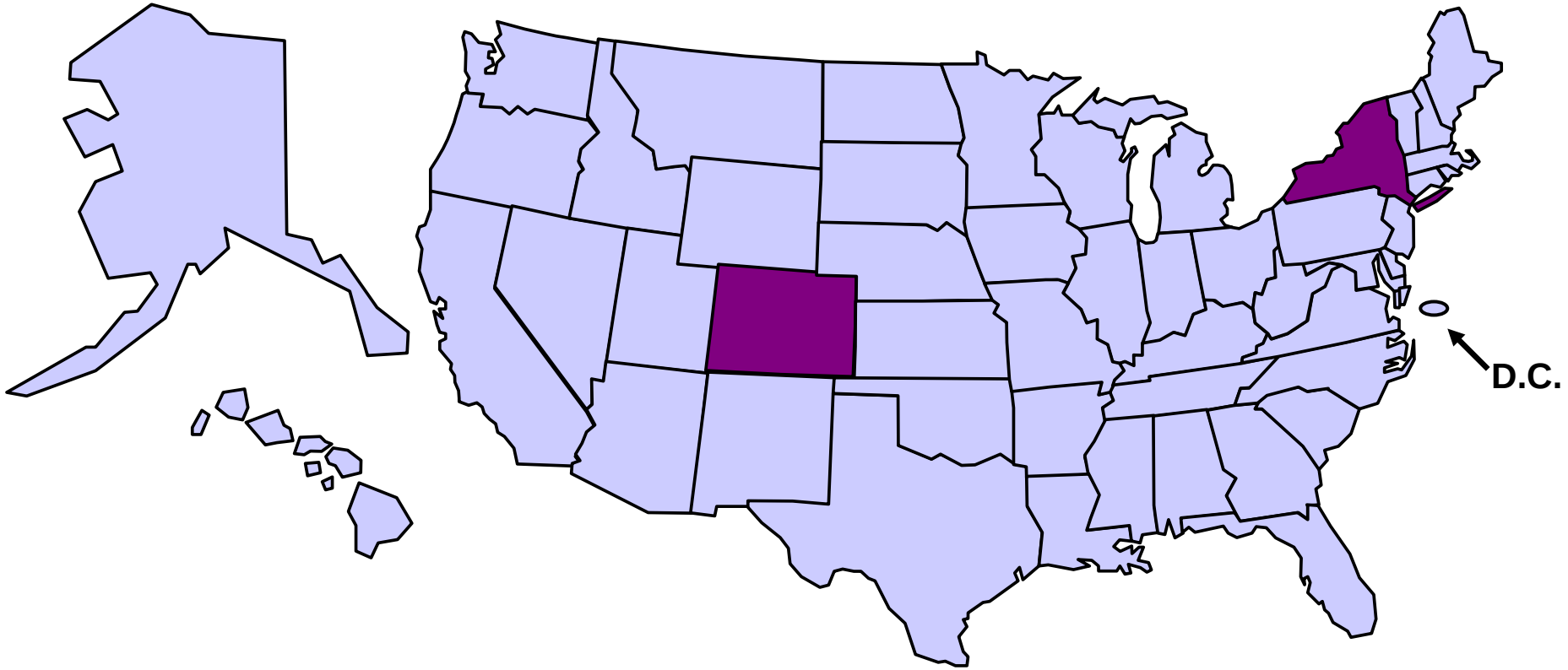
Benson and Therrell. Semin Perinatol 34:134-144 (2010).



Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening January 1, 1979

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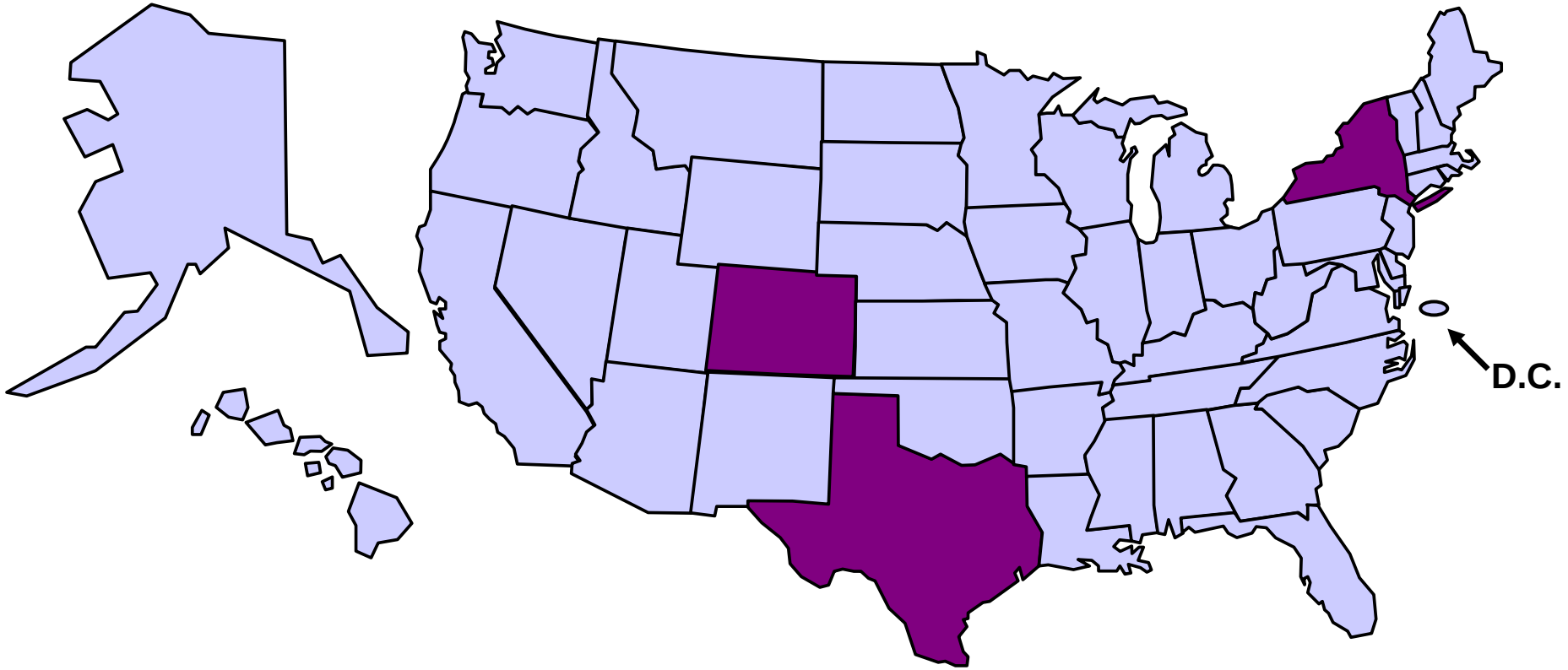
Benson and Therrell. Semin Perinatol 34:134-144 (2010).



Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening November 1, 1983

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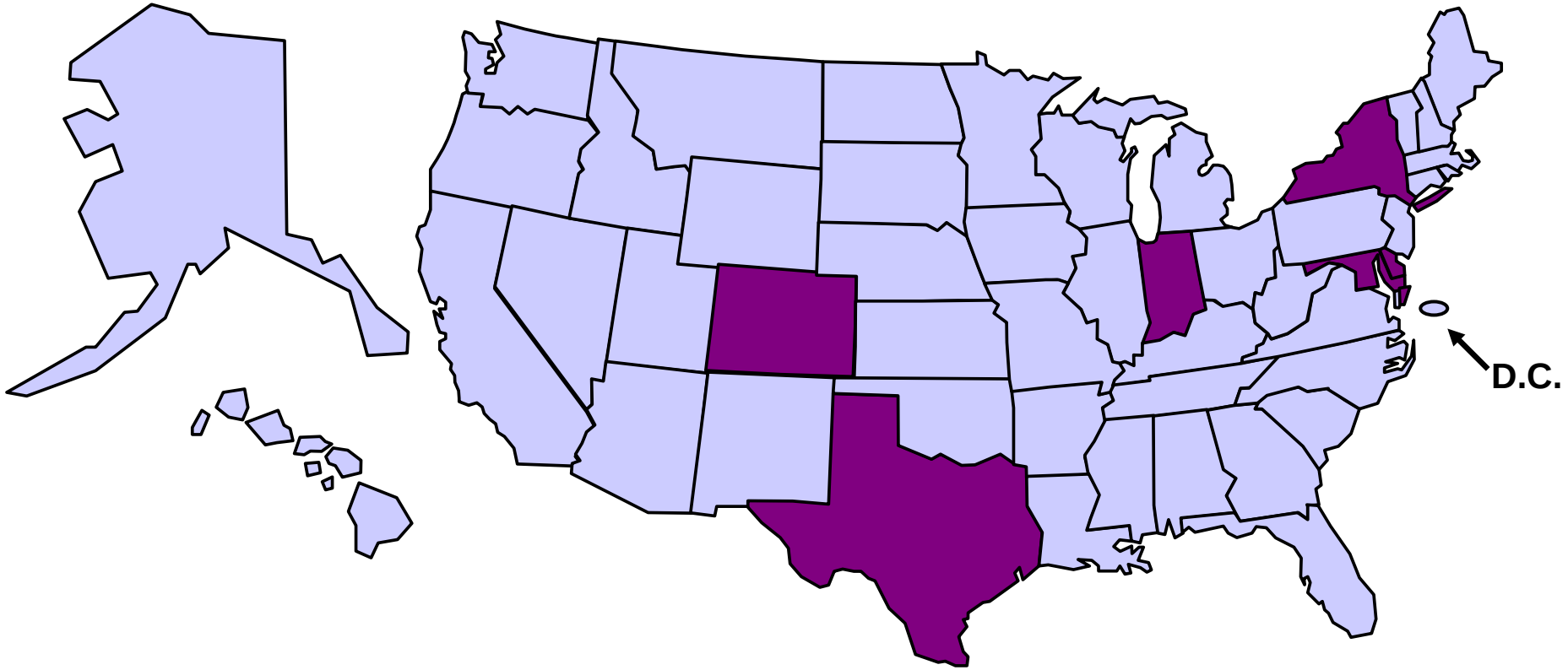

Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening July 1, 1985

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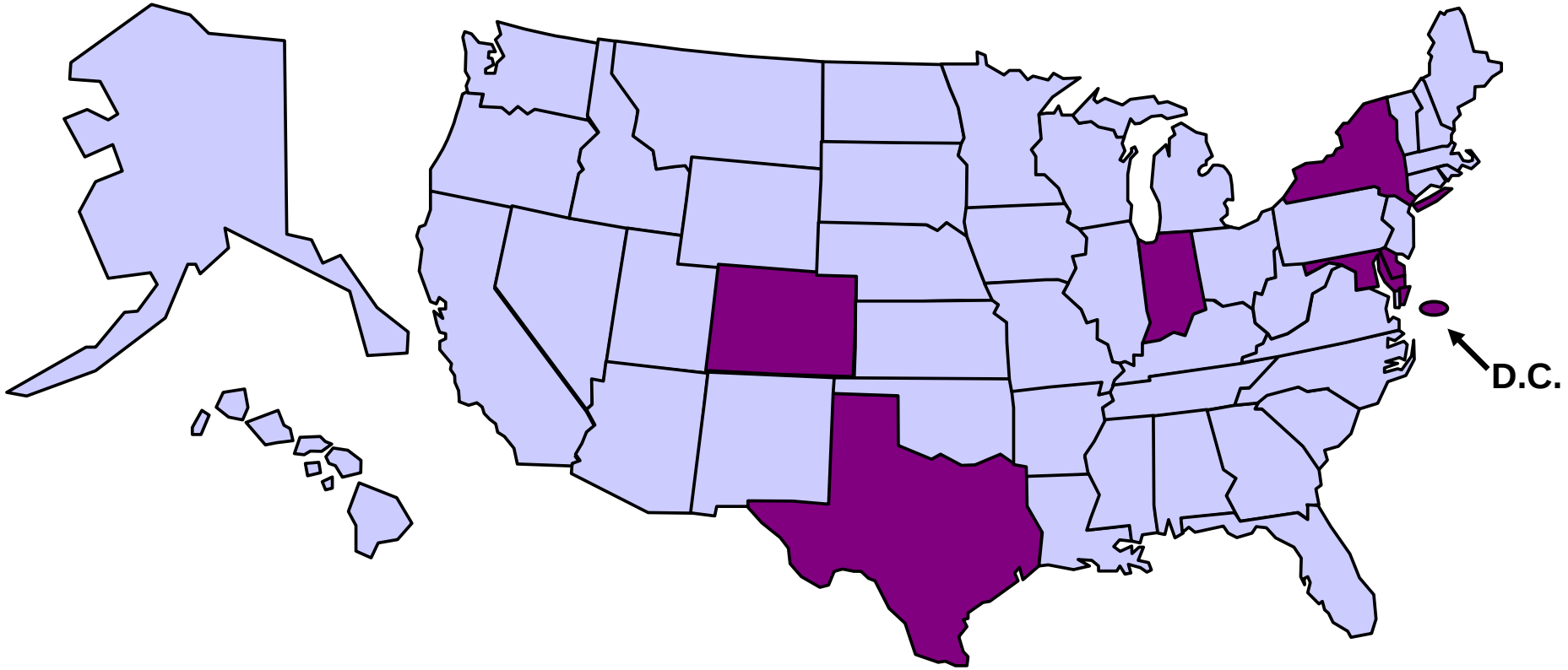

Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening January 1, 1986

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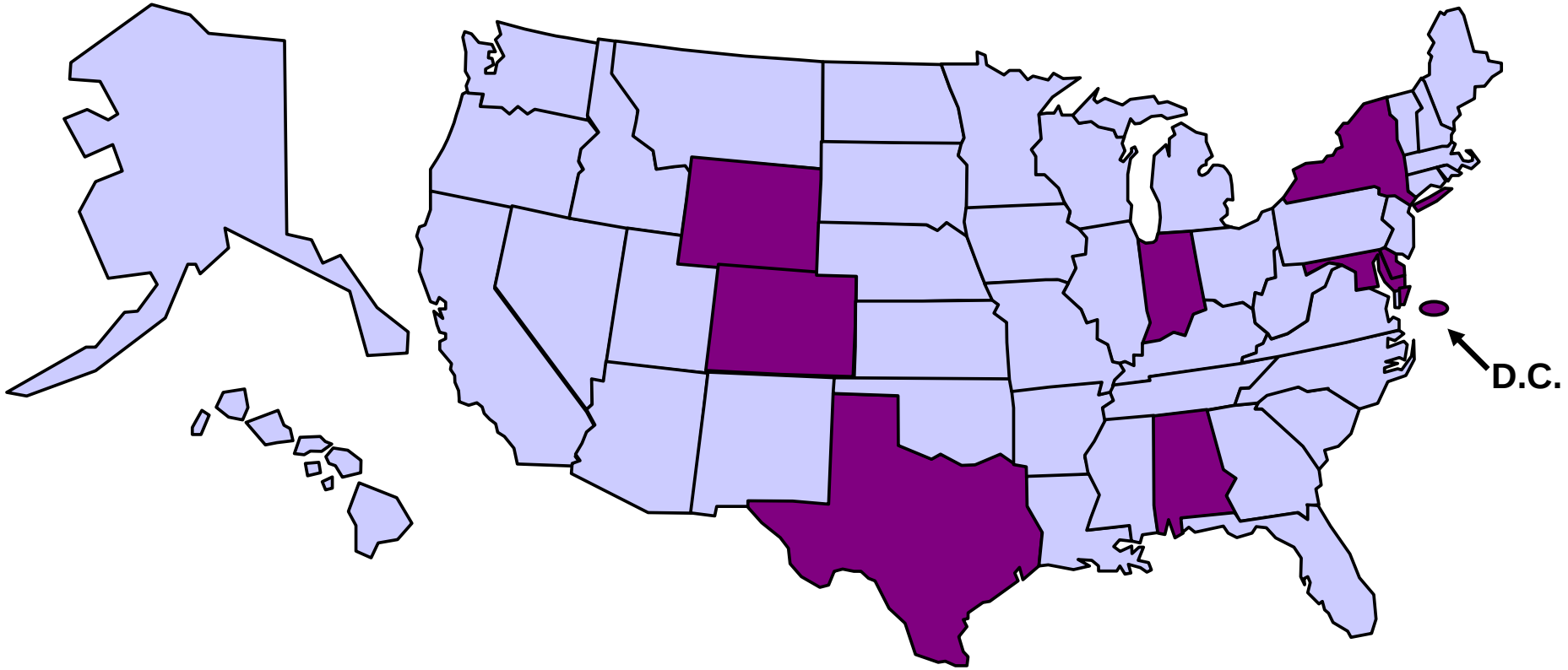

Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening January 1, 1987

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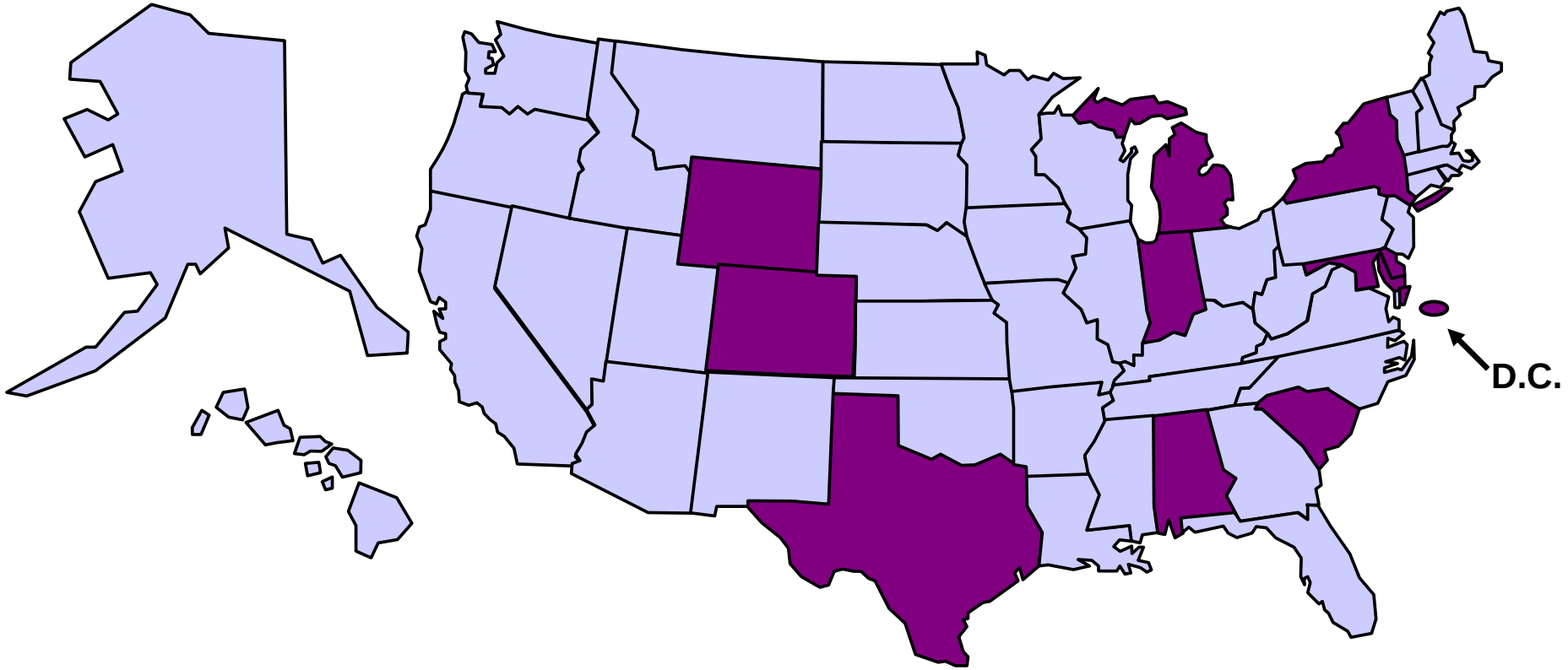

Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening July 1, 1987

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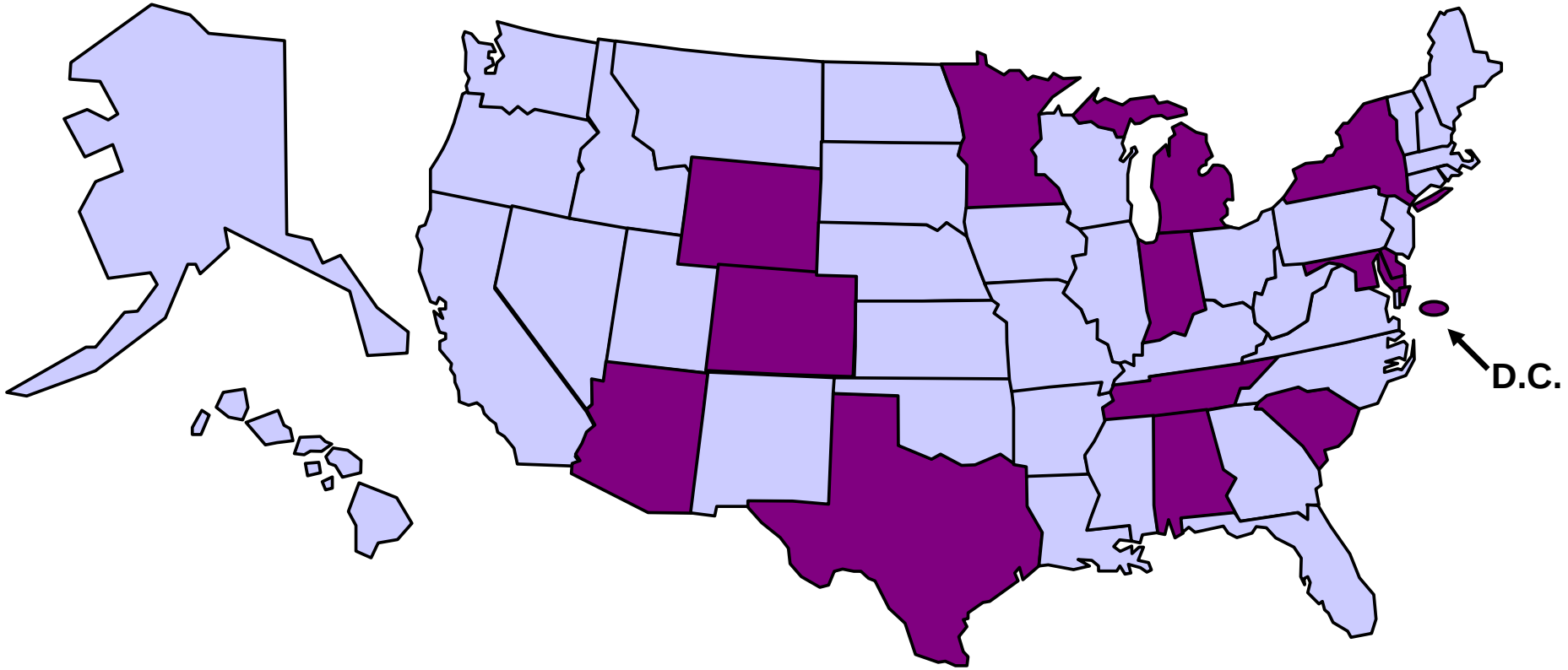
Benson and Therrell. Semin Perinatol 34:134-144 (2010).



Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening January 1, 1988

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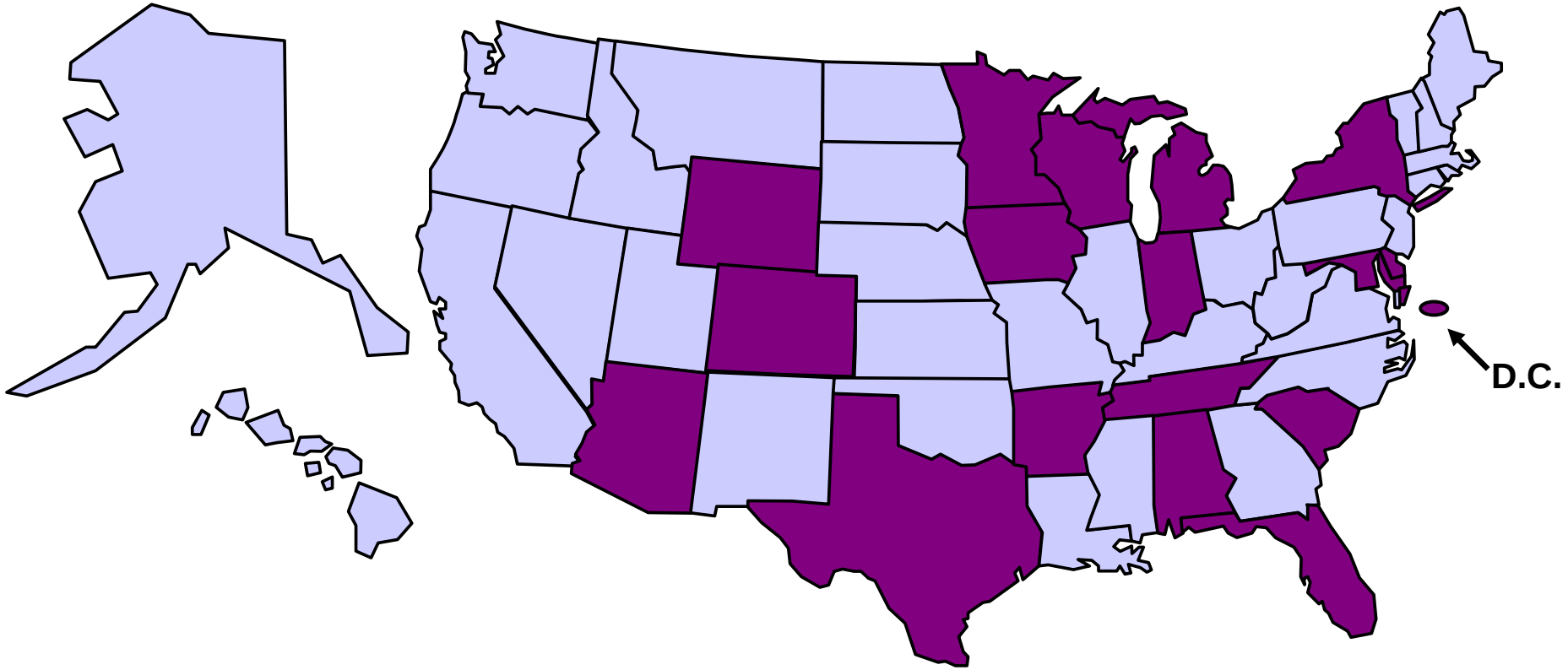

Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening By January 1, 1989

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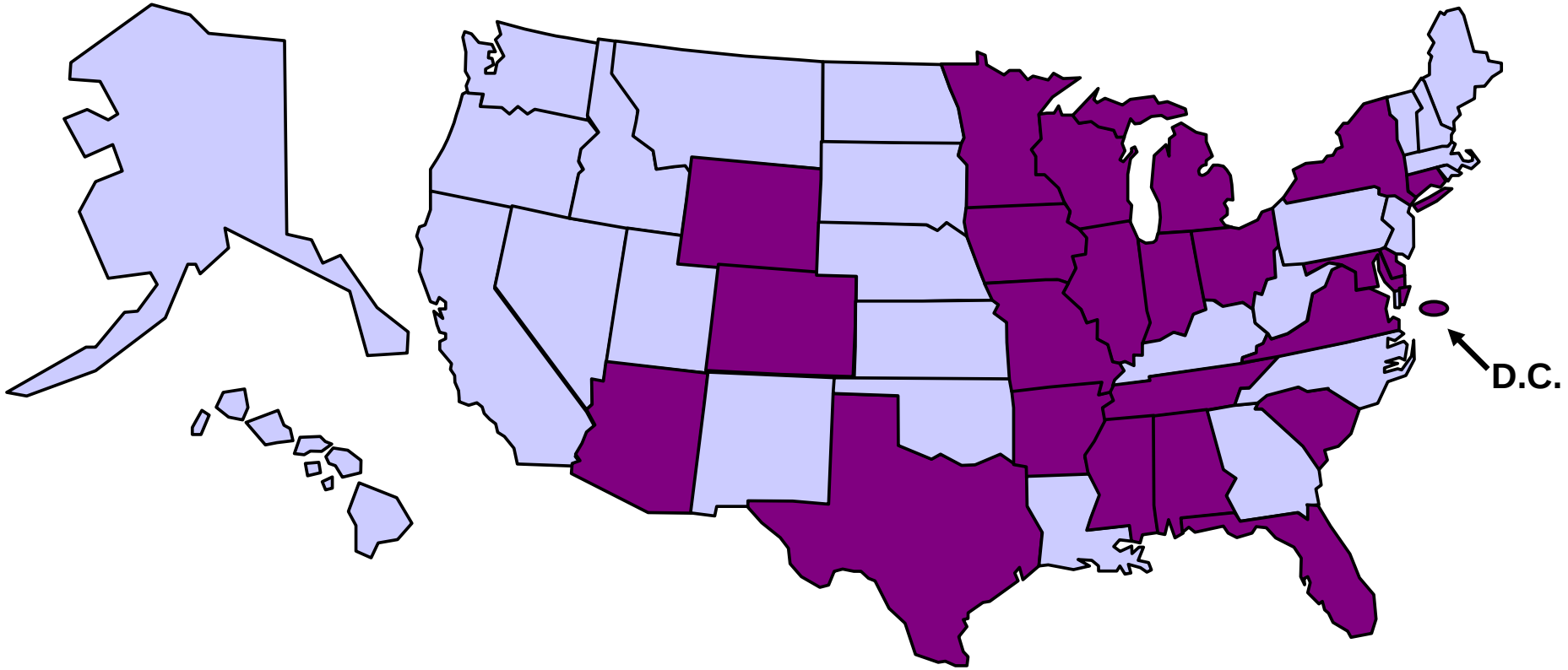

Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening By January 1, 1990

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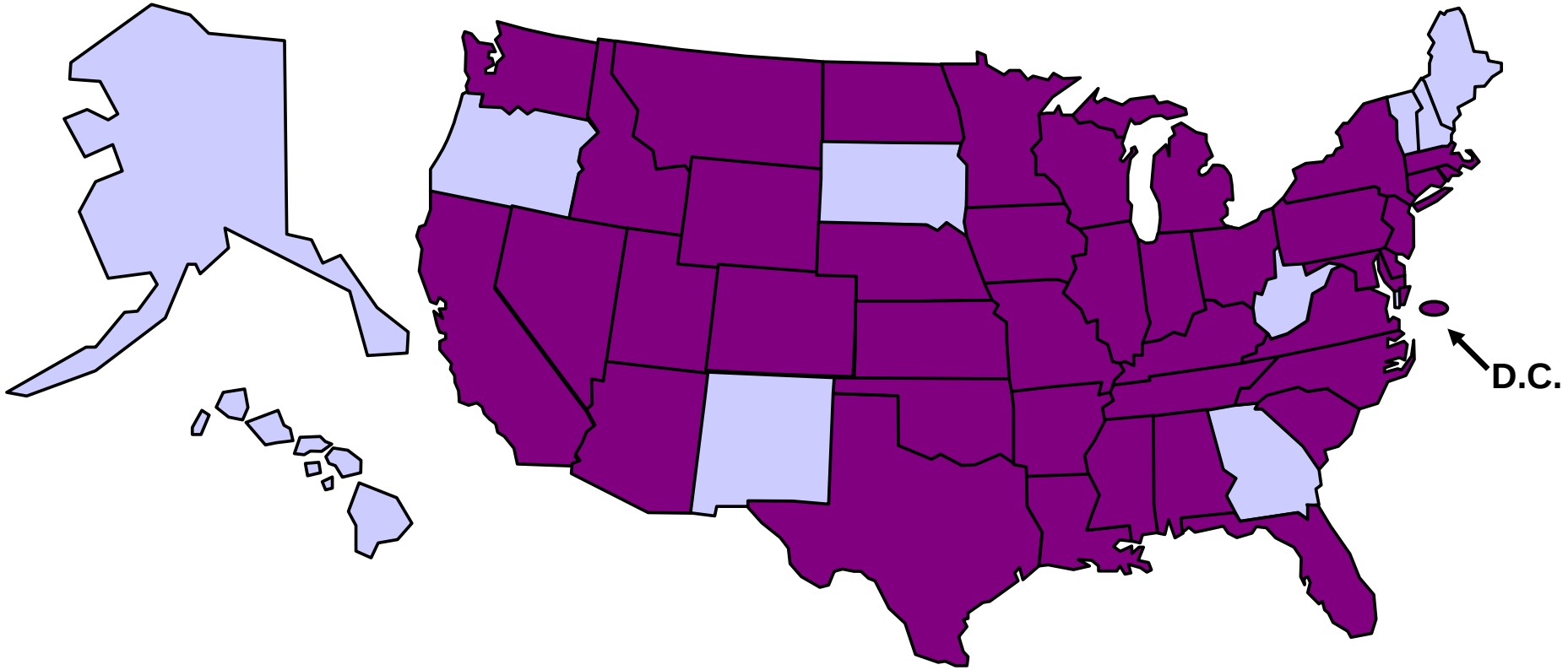

Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening By January 1, 1995

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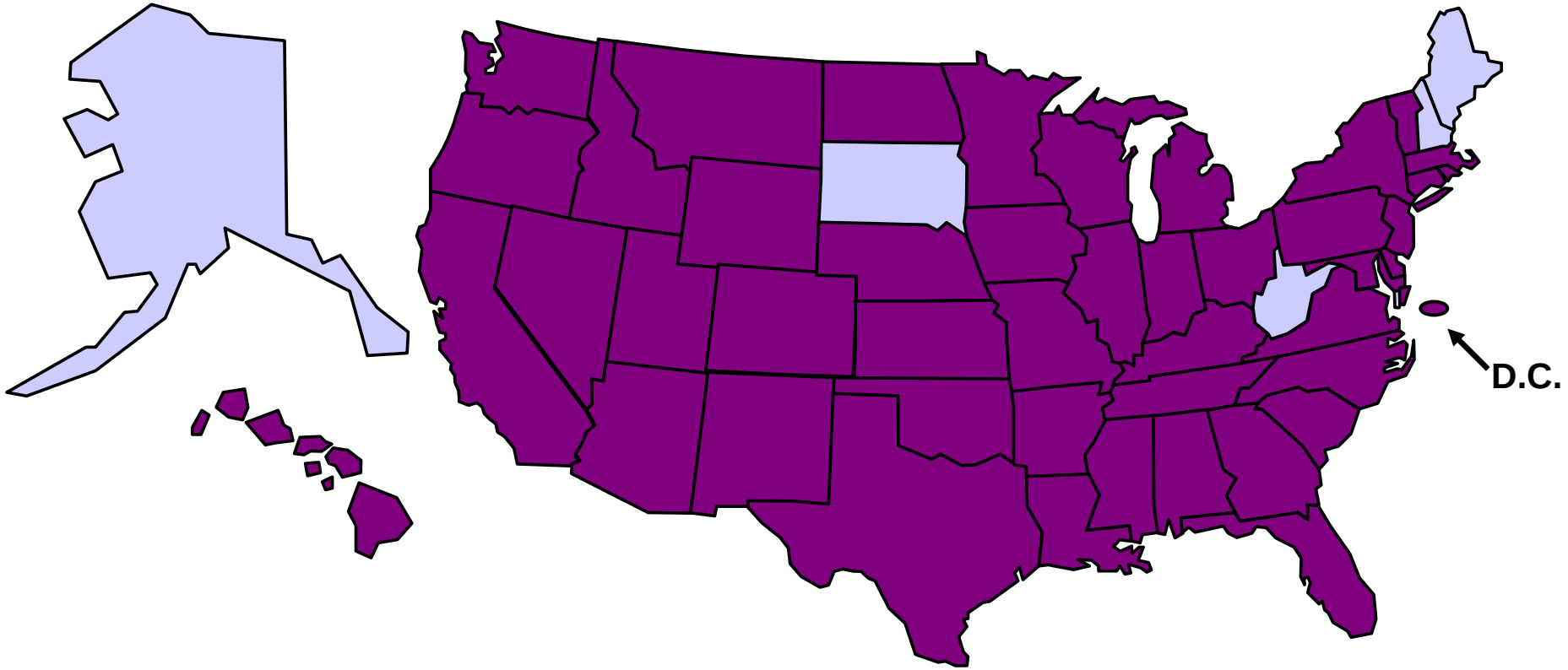

Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening By January 1, 2000

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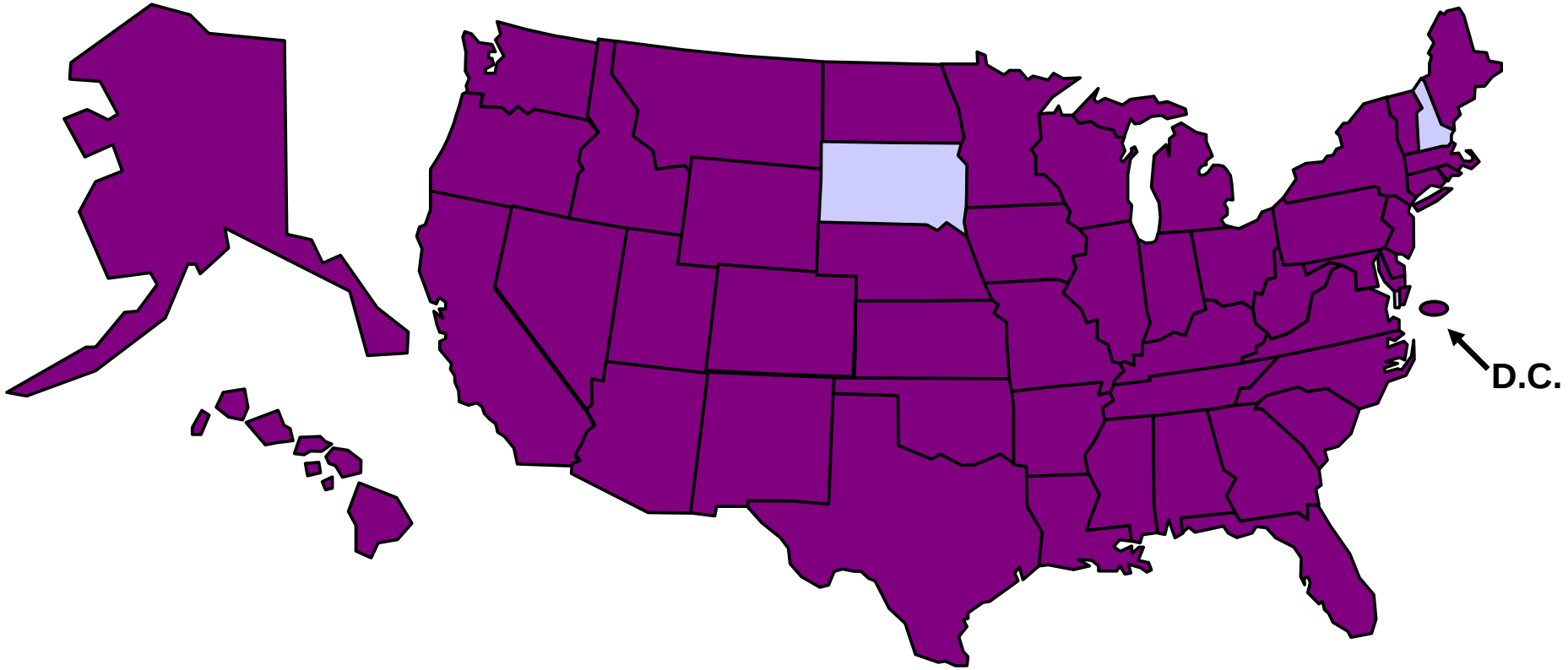

Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening By January 1, 2005

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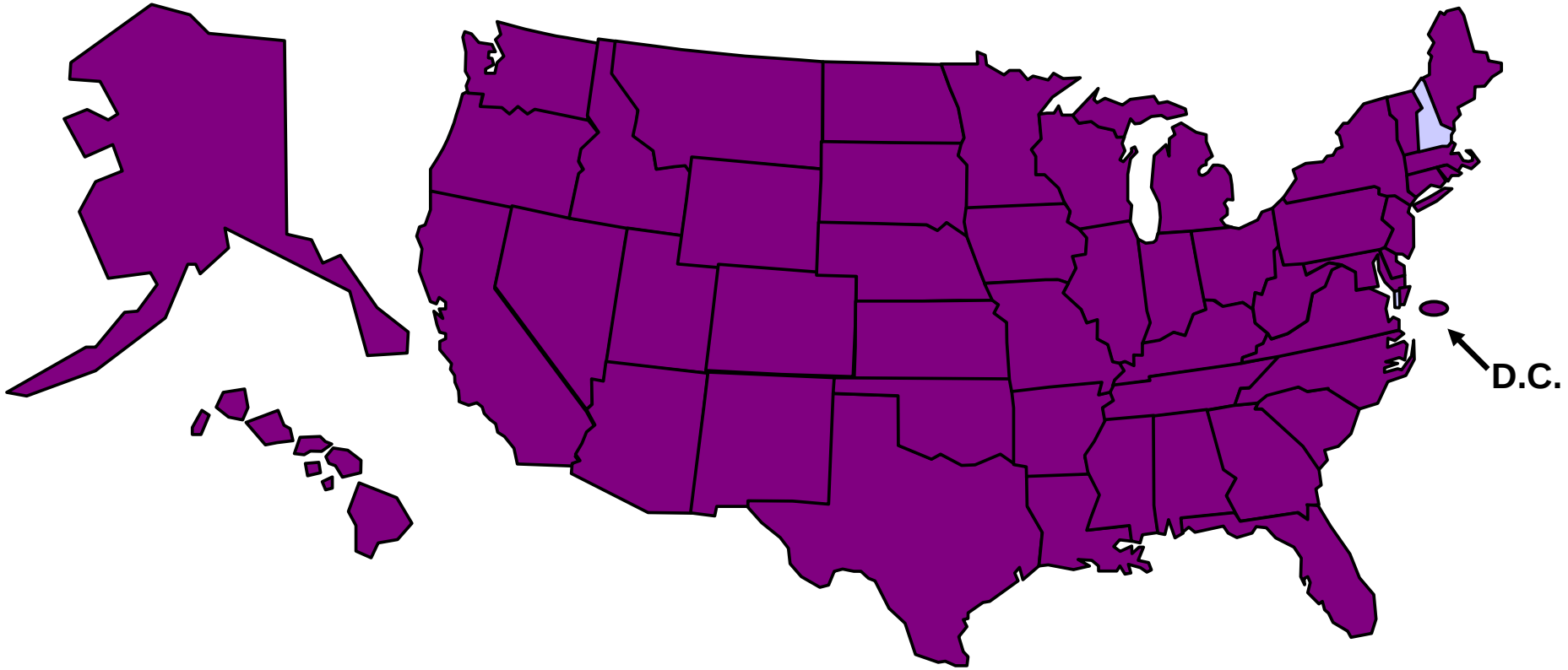

Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening By June 1, 2005

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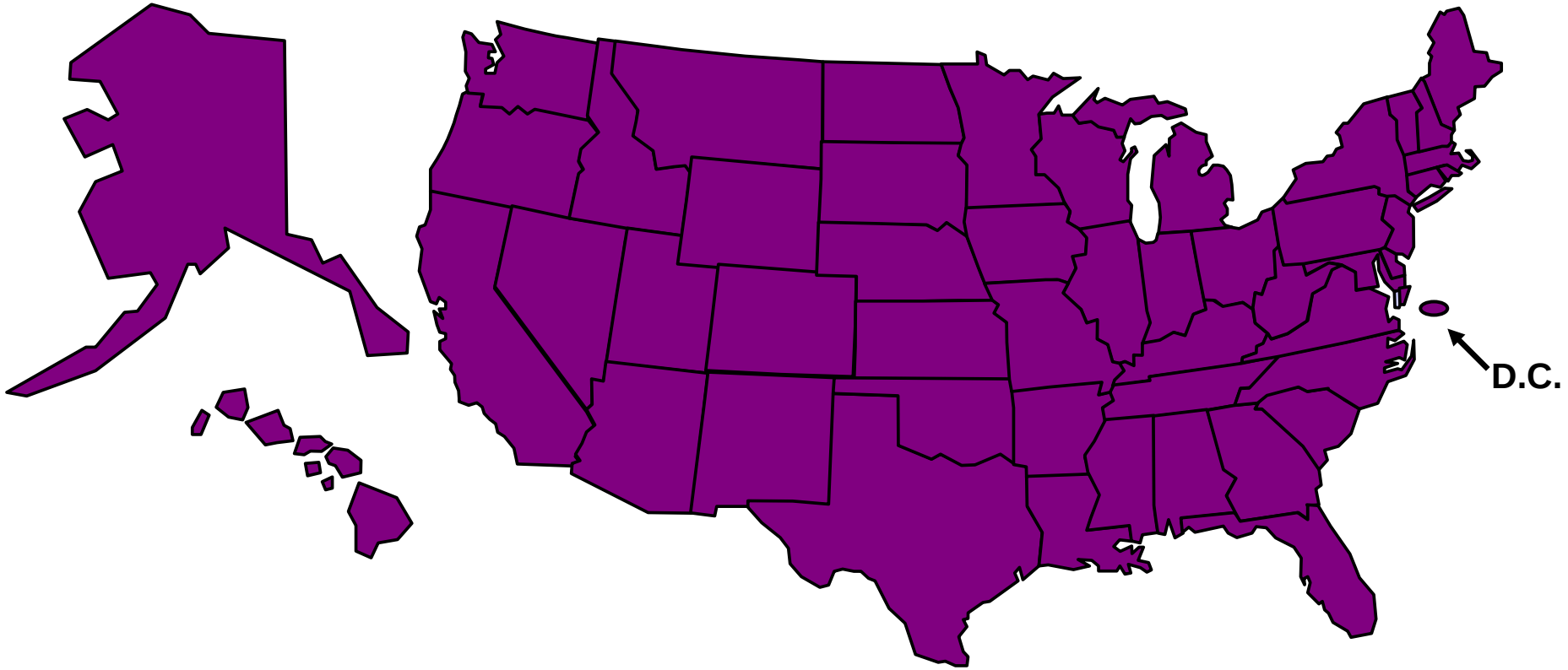

Universal Newborn Hemoglobinopathy Screening Mandated

Newborn Hemoglobinopathy Not Universally Mandated

U.S. History of Hemoglobinopathy Screening By May 1, 2006 All 51 Programs

Benson and Therrell. Semin Perinatol 34:134-144 (2010).