NBS Implementation for Conditions Added to the RUSP

Presented to the Advisory Committee on Heritable Disorders in Newborns and Children

August 1, 2019

Alex R. Kemper, MD, MPH, MS
Margie Ream, MD, PhD
K.K. Lam, PhD
Ashley Lennox, PhD

Nationwide Children's
When your child needs a hospital, everything matters.℠

Duke Clinical & Translational Science Institute

Background

- Review of SCID, CCHD, Pompe Disease, MPS I, X-ALD
  - Primary Goal: Review implementation conditions added to the RUSP between 2010-2017
  - Secondary Goal: Develop methods to evaluate screening implementation and outcomes after addition the RUSP

Presentation Outline

- Scope and methods
- Implementation characteristics of specific conditions
    - SCID (2010)
    - CCHD (2011)
    - Pompe Disease (2015)
    - MPSI (2016)
    - X-ALD (2016)
- Describe barriers and facilitators to new condition implementation
- Next Steps

Scope and Methods

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

Duke Clinical & Translational Science Institute

Project Scope

Topics

- State Implementation
- Public Health Implications
- Clinical outcomes and impact

Data sources

- Original evidence reviews, published literature, and grey literature
- NewSTEPs Data Repository and APHL New Disorders Project Funding Reports
- State program interviews (on-going)

Guiding issues

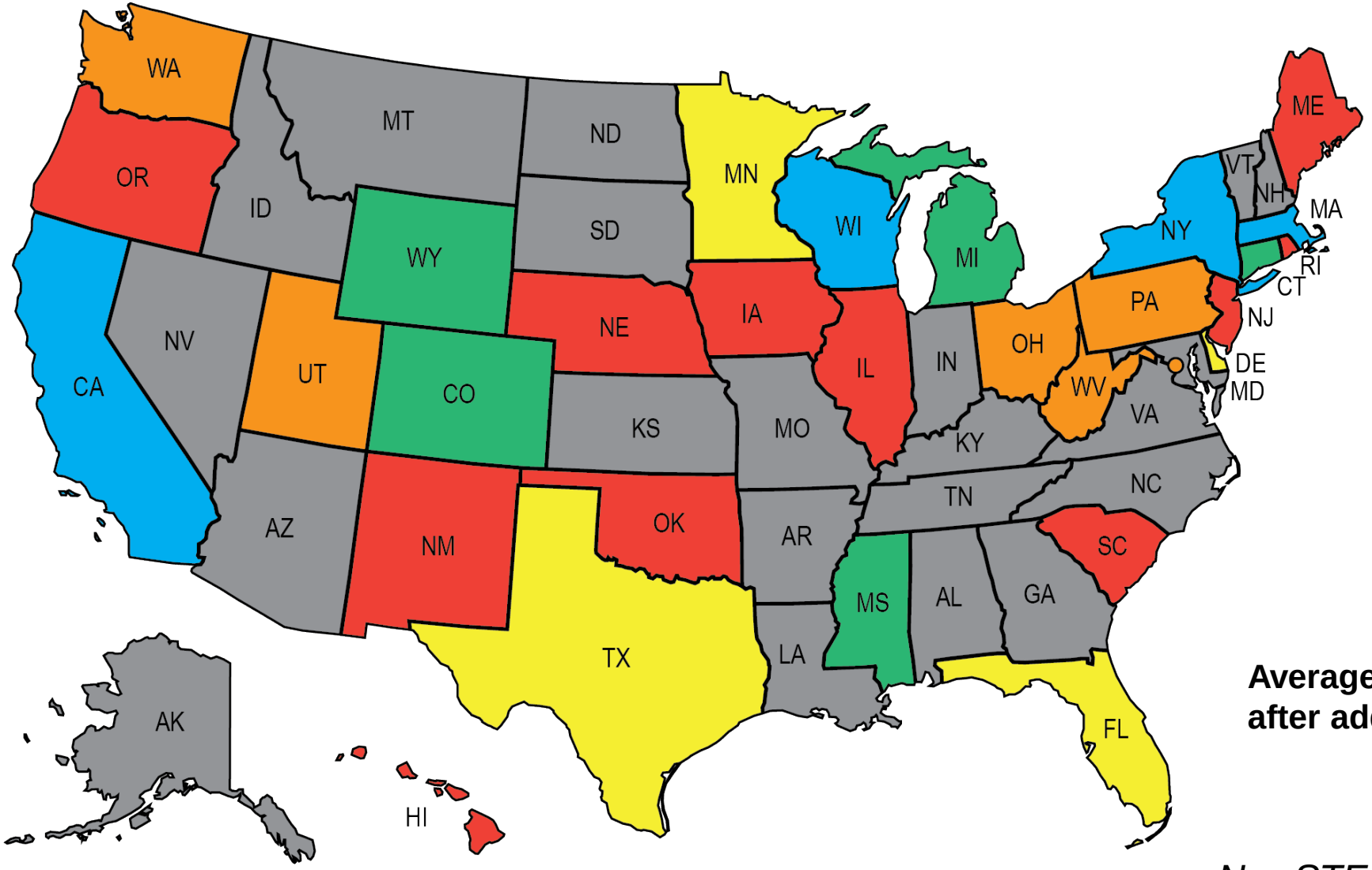
- Condition-specific factors
  - Gaps in knowledge about screening, diagnosis, and treatment
  - Long-term follow-up requirements and availability of services
- Newborn screening program
  - Screening challenges
  - Support
  - Advocacy

Specific conditions

Severe Combined Immunodeficiency (SCID)

- September 2007 – Initial nomination
  - Advisory Committee voted to conduct full evidence review
- February 2009 – Evidence review completion
  - Advisory Committee voted against recommending SCID for the RUSP
  - Encouraged additional studies (including prospective identification of ≥1 infant with SCID)
- January 2010 – Second nomination
  - Advisory Committee voted to recommend adding SCID to the RUSP
- May 2010 – Secretary adds SCID to the RUSP

SCID Full-Population Screening Implementation



Time to Implement after Addition to the RUSP

- <1 year 4/51 (8%)
- 1-2 years 5/51 (10%)
- 2-3 years 4/51 (8%)
- 3-4 years 6/51 (12%)
- 4-5 years 11/51 (22%)
- >5 years 21/51 (40%)

Average time to implement: 4.3 years after added to RUSP (rg -1.8 to 8.6)

NewSTEPs Data Repository, May 2019

Challenges to Implementing SCID Screening

- First use of molecular testing for first-tier screening
- Variations in targets of screening
- Preterm infants (<37 weeks of gestation) had a high retest rate compared to full-term infants
- Variation in incidence by race/ethnicity (e.g., Navajo Nation)

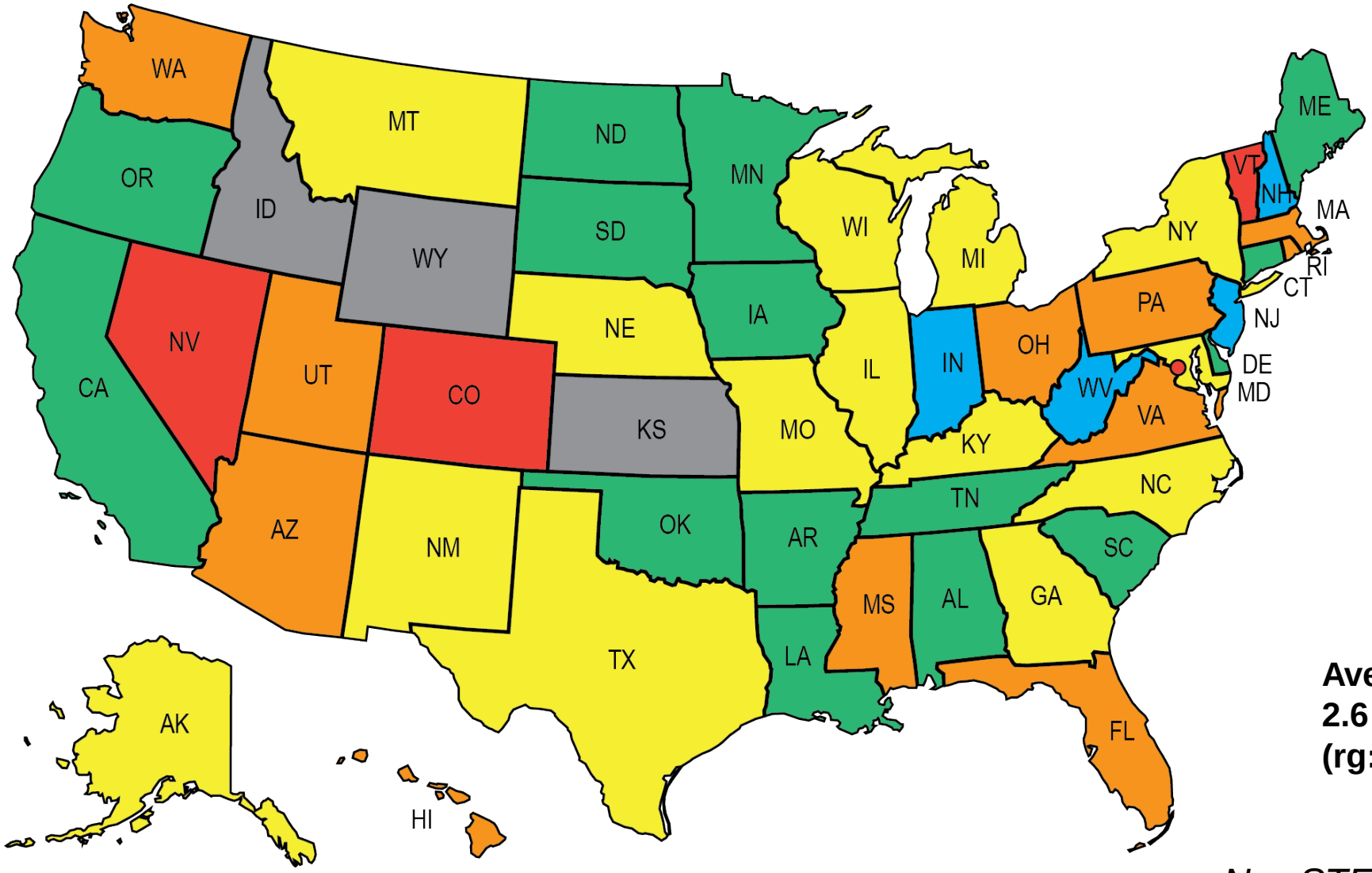
Facilitators to Implementing SCID Screening

- Collaborations and partnerships established among federal, state, non-profit organizations
- National technical assistance activities
- SCID newborn screening pilots
- Commercially available kits that were relatively straightforward to use and ensured uniformity

Critical Congenital Heart Disease (CCHD)

- January 2010 – Initial nomination
  - Advisory Committee voted to conduct full evidence review
- September 2010 – Evidence review completion
  - Advisory Committee voted to recommend CCHD
- April 2011 – Secretary requests additional information
- September 2011 – Secretary adds CCHD to the RUSP

CCHD Full-Population Screening Implementation



Time to Implement after Addition to the RUSP

- <1 year 4/51 (8%)
- 1-2 years 15/51 (29%)
- 2-3 years 14/51 (28%)
- 3-4 years 13/51 (25%)
- 4-5 years 2/51 (4%)
- >5 years 3/51 (6%)

Average time to implement: 2.6 years after added to RUSP (rg: 0 to 6.8)

NewSTEPs Data Repository, May 2019

Challenges to Implementing CCHD Screening

- Point-of-care test
- Variability in approach to requiring the screening
- Decentralized
  - Hospitals, birthing centers, home
  - Variable reporting requirements
  - Differences in screening algorithm
- Special settings
  - High altitude
  - NICU

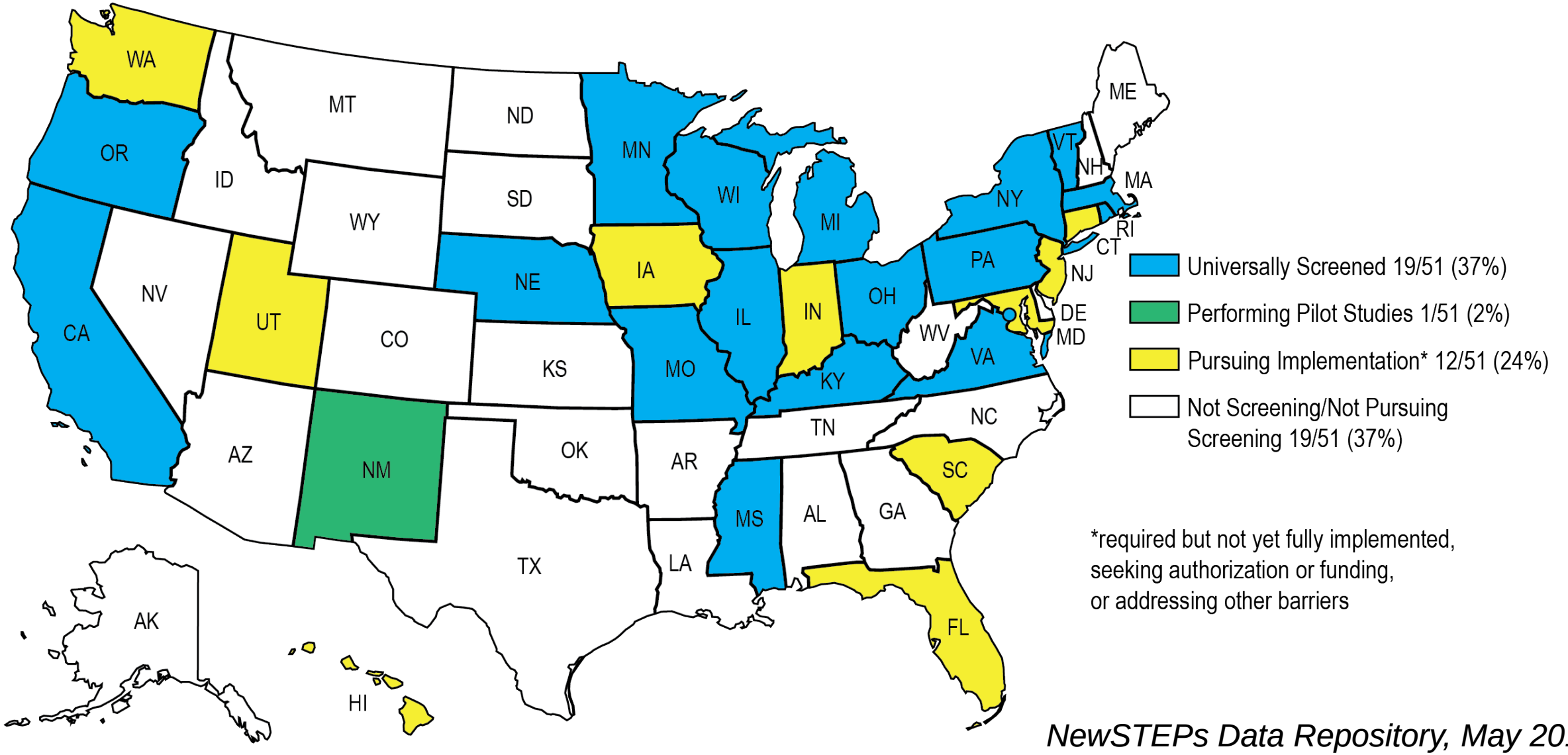
Facilitators to Implementing CCHD Screening

- Development of educational material
- Use of birth defect registries
- Telemedicine

Pompe Disease

- 2006 – Initial nomination
  - Advisory Committee voted to conduct full evidence review in January 2008
- October 2008 – Evidence review completion
  - Advisory Committee voted against recommending addition of Pompe to the RUSP
- May 2012 – Second nomination
  - Advisory Committee voted to conduct full evidence review
- May 2013 – Evidence review completion
  - Advisory Committee voted to recommend addition of Pompe to the RUSP
- January 2014 – Secretary requests additional information
- March 2015 – Secretary adds Pompe to the RUSP

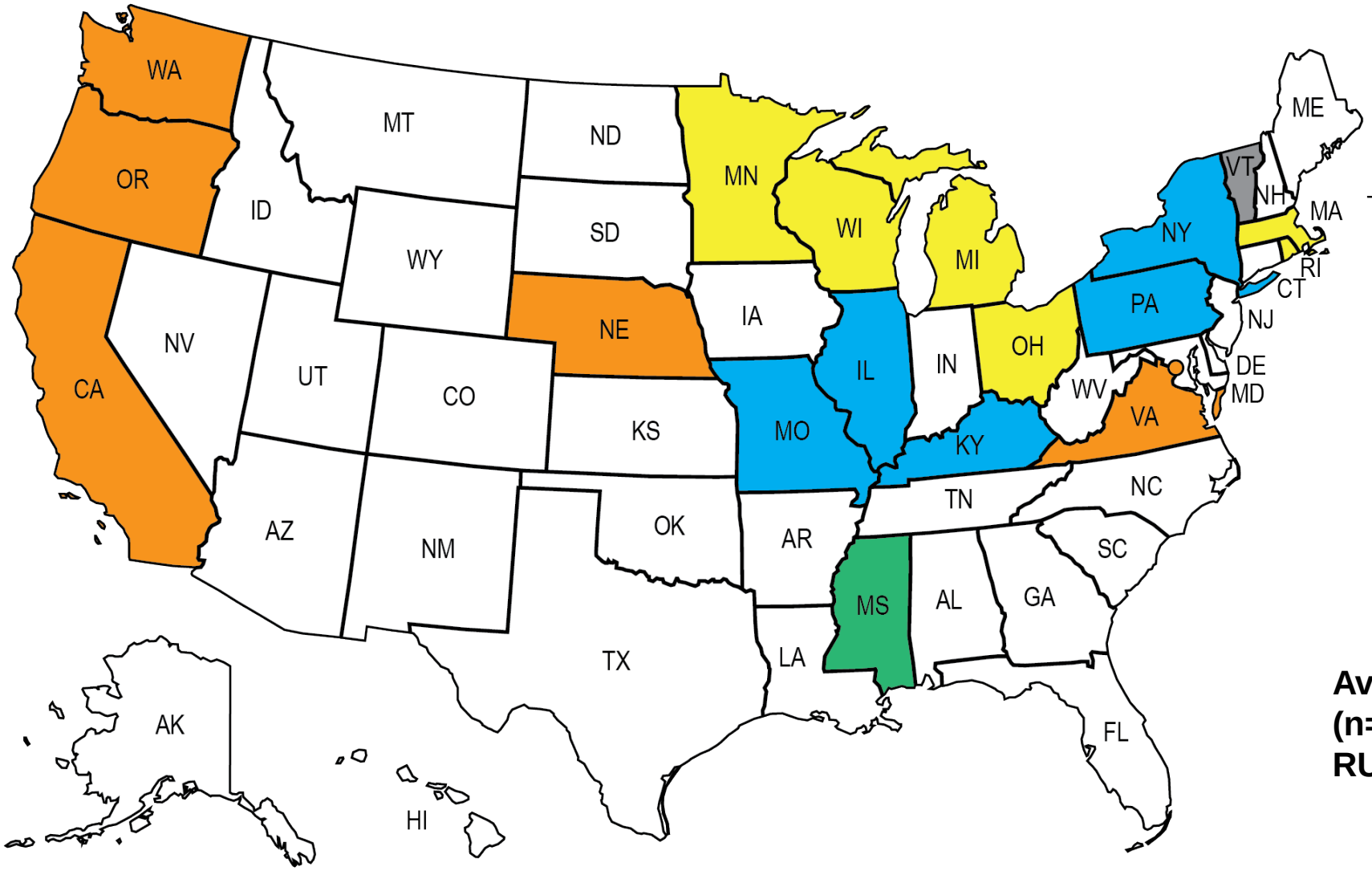
Pompe Disease Screening Status



*required but not yet fully implemented, seeking authorization or funding, or addressing other barriers

NewSTEPs Data Repository, May 2019

Pompe Disease Full-Population Screening Implementation



Time to Implement after Addition to the RUSP

- <1 year 5/51 (10%)
- 1-2 years 1/51 (2%)
- 2-3 years 7/51 (14%)
- 3-4 years 5/51 (10%)
- >4 years 1/51 (2%)
- Not Screening/Not Pursuing Screening 32/51 (62%)

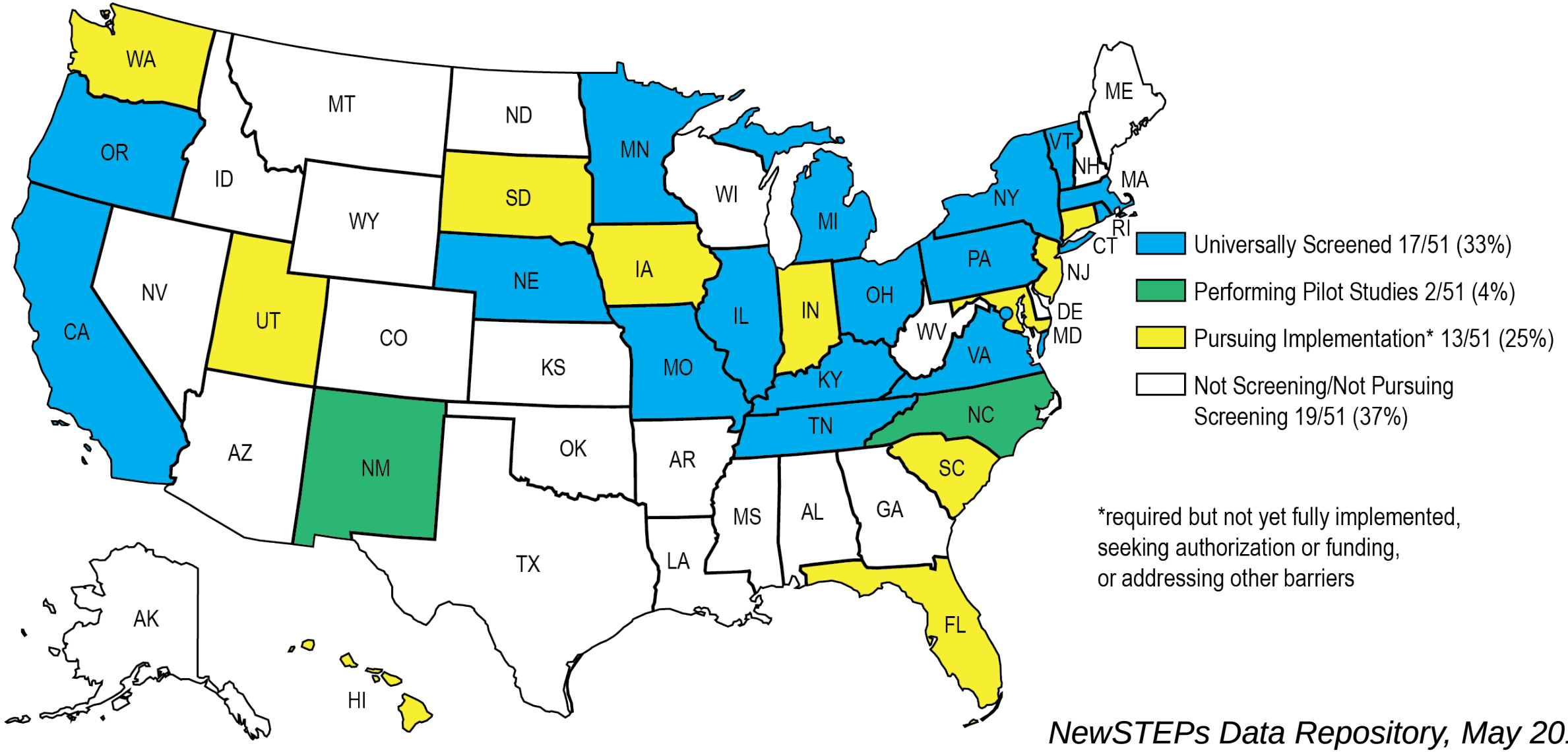
Average time to implement (n=19): 2.2 years after added to RUSP (rg: 0.4 to 4.2)

NewSTEPs Data Repository, May 2019

Mucopolysaccharidosis Type I (MPSI)

- May 2012 – Initial nomination
  - Advisory Committee voted to conduct full evidence review
  - Delayed review while formal Public Health Impact Assessment procedures were developed
- February 2015 – Evidence review completion
  - Advisory Committee voted to recommend MPSI to the RUSP (B3)
- February 2016 – Secretary adds MPSI to the RUSP

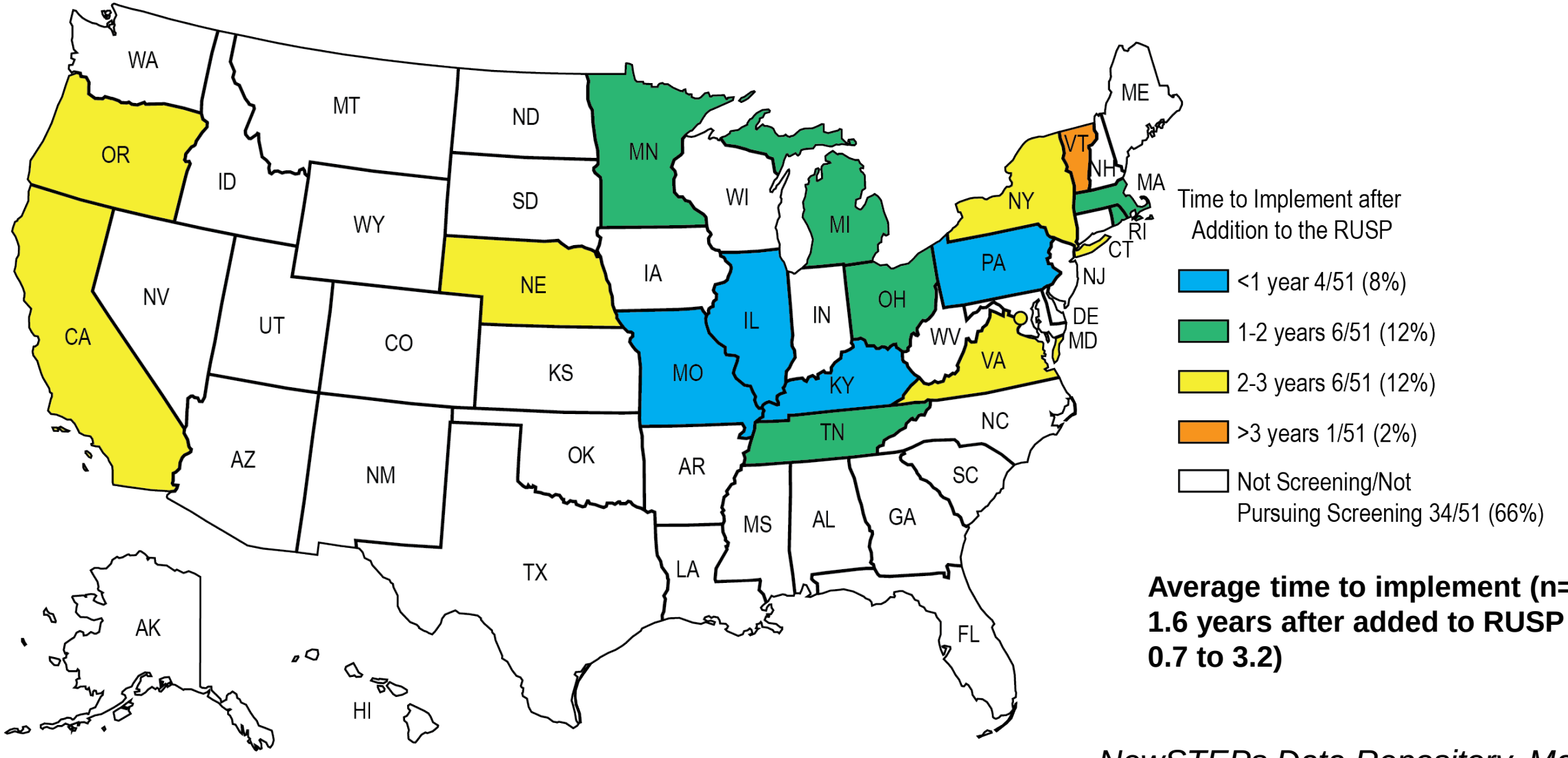
MPSI Screening Status



*required but not yet fully implemented, seeking authorization or funding, or addressing other barriers

NewSTEPs Data Repository, May 2019

MPSI Full-Population Screening Implementation



Average time to implement (n=17): 1.6 years after added to RUSP (rg 0.7 to 3.2)

NewSTEPs Data Repository, May 2019

Challenges to Implementing Pompe Disease and MPSI Screening

- Commercially available kits are labor and time intensive
- Reference testing samples challenging to obtain
- Pseudodeficiency
- Diagnostic uncertainty
- Identification of late-onset forms

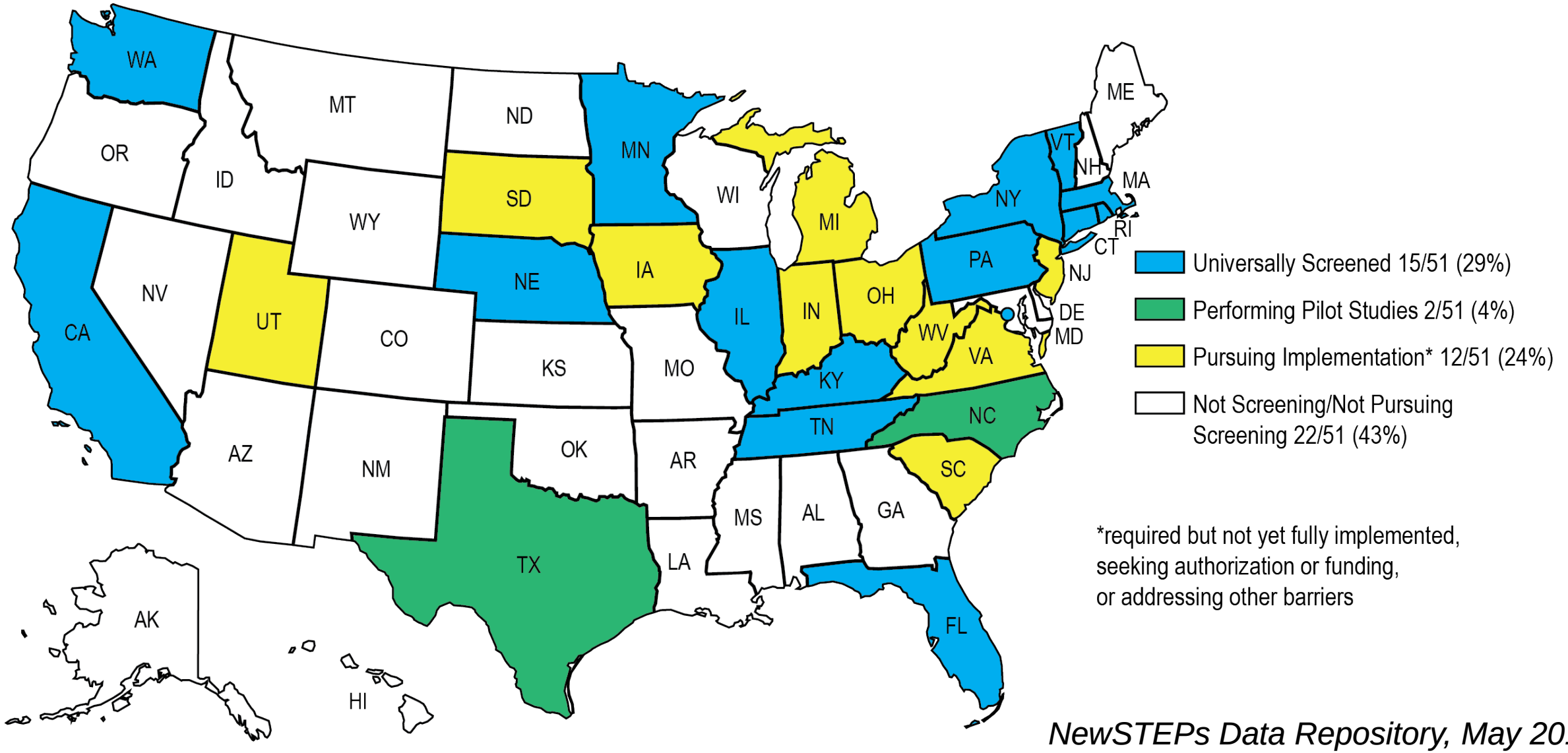
Facilitators to Implementing Pompe & MPSI Screening

- LSDs can be multiplexed
- Second-tier biochemical tests and post-analytical tools (e.g., CLIR) can reduce false positives
- Pilot studies to determine cut-offs
- Registry databases with mutations and expected clinical characteristics

X-linked Adrenoleukodystrophy (X-ALD)

- September 2012 – Initial nomination
  - Advisory Committee voted against conducting evidence review
- January 2014 – Second nomination
  - Advisory Committee voted to conduct evidence review
- August 2015 – Evidence review completion
  - Advisory Committee voted to recommend addition to the RUSP (A2)
- February 2016 – Secretary adds X-ALD to the RUSP

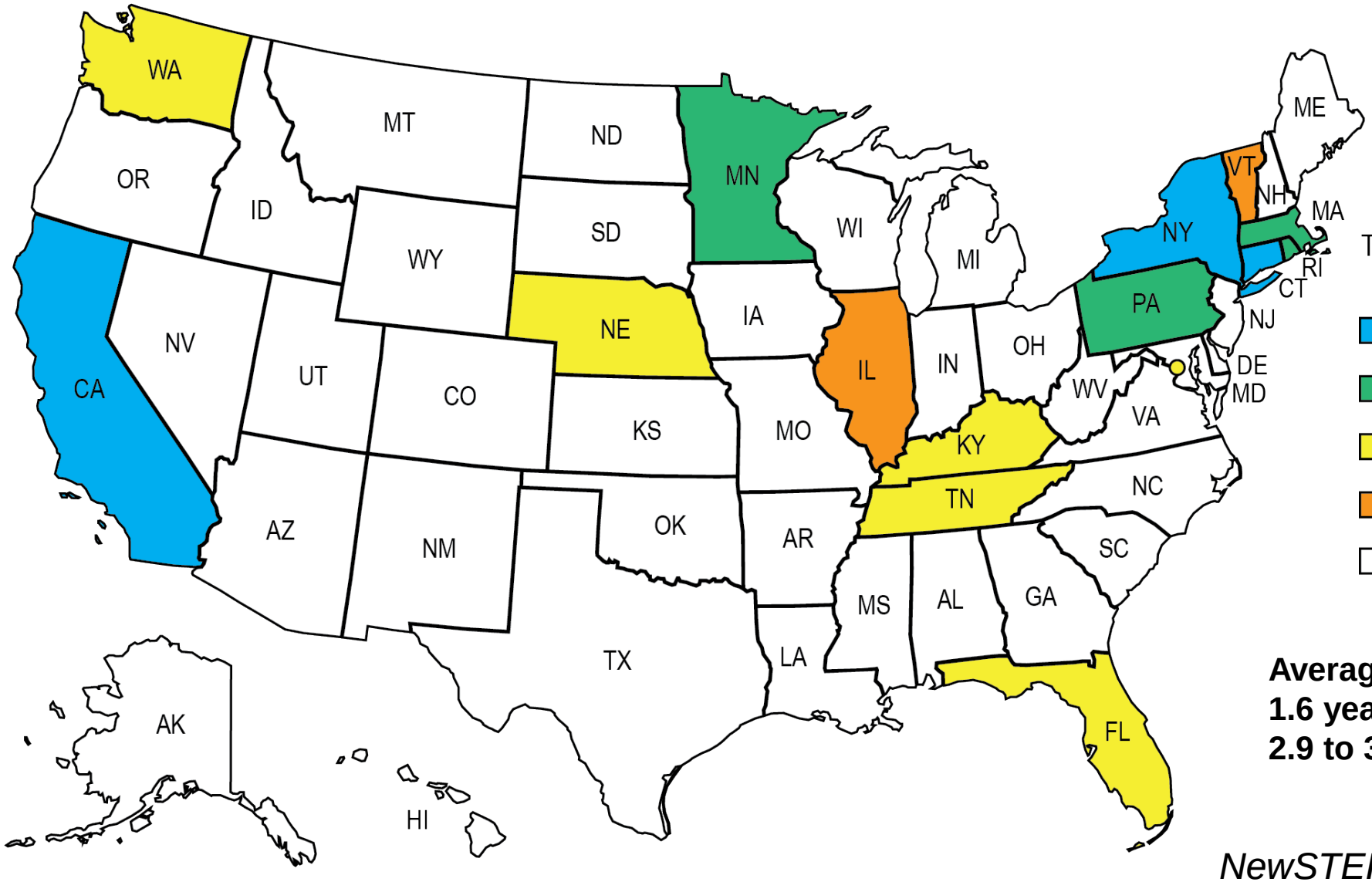
X-ALD Screening Status



*required but not yet fully implemented, seeking authorization or funding, or addressing other barriers

NewSTEPs Data Repository, May 2019

X-ALD Full-Population Screening Implementation



Time to Implement after Addition to the RUSP

- <1 year 3/51 (6%)
- 1-2 years 4/51 (8%)
- 2-3 years 6/51 (12%)
- >3 years 4/51 (4%)
- Not Screening 35/51 (70%)

Average time to implement (n=15): 1.6 years after added to RUSP (rg 2.9 to 3.3)

NewSTEPs Data Repository, May 2019

Challenges to Implementing X-ALD Screening

- Delays in FDA approval for commercially-available reagents and discontinuation of LC-MS/MS columns impeded screening optimization and implementation
- Diagnostic challenges (e.g., variants of unknown significance, lack of genotype-phenotype correlation)
- Long-term follow-up
- Cascade testing
- Higher incidence than expected (1:4845 in Minnesota vs. 1:16,900 from the evidence review)

Facilitators to Implementing X-ALD Screening

- Adjustments to follow-up algorithm to expedite confirmatory testing by immediately referring screen positives to genetic counselors and specialists (MN)
- Potential for multiplexing with Pompe Disease and MPSI
- Registry databases

Common barriers and facilitators to new condition implementation

Common challenges to new disorder implementation

- Hiring and training new personnel
- Delays in procurement and installation of equipment
- Updating Laboratory Information Management Systems
- Lack of shared genomic variant databases
- Developing follow-up programs and clinical management plans for infants with late-onset or unknown disease risk

Common facilitators of new disorder implementation

- Peer Resource Networks
- Pilot and/or implementation funding
- Working group for newborn screening and clinical follow-up and management, especially for disorders with later-onset forms
- Next-generation sequencing for second-tier testing
- Common legislative approaches

Legislation for NBS expansion

- Variations in the policy and legislative mechanisms for adopting new condition screening across states
  - New legislation to approve screening for each new condition
  - Separate legislation for funding
  - Screening expansion decided by Department of Health, with funds later appropriated by state (increased budget, fee increase)

“Blanket” Legislation as facilitator of NBS expansion

- California Senate Bill 1095 – September 2016
  - Screen for any disease(s) recommended by the federal RUSP with an implementation deadline of 2 years from RUSP addition
  - State required to outlay funding or appropriations for implementation
- Florida SB 1124 – June 2017
  - Florida Advisory Council must review any condition added to the RUSP within 1 year of its RUSP addition
  - Conditions approved by FL Advisory Council must be implemented within 18 months
- North Carolina SB 99/SL 2018-5 – 2018
  - Grants state Department of Health and Human Services discretion over newborn screening expansion

State Interviews *(underway)*

- Follow up with selected state programs re: implementation status, results
- Target “early adopters” and “late adopters” to understand factors that influence their implementation of new conditions

In the table:
X stands for full population screening and PI stands for pursuing implementation

State	SCID	CCHD	Pompe	MPSI	XALD
Massachusetts	X	X	X	X	X
Tennessee	X	X	X	X	X
Kentucky	X	X	X	X	X
Nebraska	X	X	X	X	X
Hawaii	X	X	PI	PI	
Iowa	X	X	PI	PI	PI
Washington	X	X	PI	PI	X
West Virginia	X	X	-	-	PI
Wisconsin	X	X	X	-	-
Idaho	X	X	-	-	-
Texas	X	X	-	-	Pilot
Colorado	X	X	-	-	-

Newborn Screening Outcomes & Diagnoses

SCID – Screening Outcomes *(published)*

Study	Verbsky et al., 2011	Kwan et al., 2013	Amatuni et al., 2019	Vogel et al., 2014.
STATE	WISCONSIN	CALIFORNIA	CALIFORNIA	NEW YORK
Date	Jan 1, 2008 – Dec 31, 2010	Aug 2010 – Aug 2012	Aug 15, 2010 – Mar 31, 2017	Sep 29, 2010 – Sep 28, 2012
Total Infants Screened	207,969	993,724	3,252,156	485,912
Negative Screen*	207,897 (99.96%)	993,563 (99.98%)	3,251,594 (99.98%)	485,381 (99.89%)
Repeat Rate	0.19%	0.08%	N/A	0.269%
Positive Screen	72 (0.037%)	161 (0.016%)	562 (0.017%)	531 (0.36%)
SCID True Positives	5 (0.002%)	21 (0.002%)	50 (0.0015%)	10 (0.002%)
Other T-Cell lymphopenias**	28 (0.013%)	29 (0.003%)	162 (0.005%)	87 (0.018%)
Unaffected	38 (0.0018%)	110 (0.011%)	350 (0.011%)	381 (0.078%)
False Negatives	0	0	2[2]	0
False Positive Rate***	0.018%	0.011%	0.011%	0.078%
Positive Predictive Value for SCID	6.94%	13.12%	8.90%	1.88%
Positive Predictive Value for SCID + TCLs	45.83%	31.25%	37.72%	18.27%
Full Term Repeat Rate	51/188,741 (0.027%)	132/2,959,462 (0.004%)	N/A	561
Pre-Term or NICU Repeat Rate[1]	241/18,955 (1.27%) pre-term	747/292,694 (0.25%) NICU	N/A	746 pre-term

SCID Clinical Outcomes (published)

- Combined NBS data from 11 screening programs or pilot projects (Kwan et al., 2014)
- Screening from 2010-2013, 3,030,083 infants (11 programs)
- Of 52 infants identified with SCID
  Diagnoses
  - 42 – typical SCID
  - 9 - leaky SCID
  - 1 – Omenn syndrome
- Treatments
  - 44 received HSCT
  - 4 received gene therapy
  - 2 received enzyme injection therapy for adenosine deaminase
- Survival
  - 7 died (perinatal complications, medical issues preventing HSCT, 4 post-transplant)
  - Overall survival of infants detected through NBS with SCID: 87% (45 of 52)
  - Overall survival of infants detected through NBS and receiving treatment: 92% (45 of 49)
- Incidental Findings: 411 infants diagnosed with non-SCID T-cell lymphonia (e.g., DeGeorge syndrome, trisomy 21, trisomy 18, congential heart disease, and others)

CCHD – Screening Outcomes *(published)*

Study	Diller et al., 2018.	Garg et al., 2013	Guillory et al., 2017	Johnson et al., 2014	Kochilas et al., 2013	Wright et al., 2014
Location	GEORGIA, LEVEL III NURSERY	NEW JERSEY	TEXAS	MASSACHUSETTS	MINNESOTA	COLORADO, MODERATE ALTITUDE
Date	Jan 2013 – Dec 2016	Aug 31, 2011 – May 31, 2012	Feb 1, 2013 – Jul 1, 2013	Jan 1, 2013 – Dec 31, 2013	Aug 2011 – Aug 2012	Jul 2012 – Oct 2012
Total Infants Screened	77,148	72,964	11,322	6,838	7,549	998
Passed/Negative POS	77,144 (99.96)	72,915 (99.93%)	11,311	6,803 (99.5%)	7,543 (99.92%)	997 (97.89%)
Failed/Positive POS	34 (0.044%)	49 (0.067%)	11 (0.097%)	34 (0.497%)	6 (0.079%)	11 (1.1%)
True Positives	1	7	1	0	1 (0.013%)	N/A
False Positives	33 (0.043%)	42 (0.057%)	0.088%	34 (0.497%)	5 (0.066%)	N/A
False Negatives	6 (0.008%)	N/A	0	1 (0.014%)	0 (short follow-up)	N/A
Positive Predictive Value	2.94%	14.28%	9.09%	0%	16.67%	N/A
Sensitivity	14.3%	-	100%	-	-	N/A
Specificity	99.96%	-	99.91%	-	-	N/A
Other notes	-	-	-	-	-	No ECG follow-up

CCHD Clinical Outcomes (published)

- Policy analysis – association between state screening policies and infant deaths, 2011 – 2013 (Abouk, Grosse et al., 2017)

- States with mandated CCHD screening policies:
  - 33.4% reduction in deaths due to CCHD following NBS implementation

Pompe Disease – Screening Outcomes *(published)*

Study	Wasserstein et al., 2018.	Minter Baerg et al., 2018.	Burton et al., 2017	Hopkins et al., 2018
Location	NEW YORK	KENTUCKY	ILLINOIS	MISSOURI
Date	May 2013 – Oct 2014	Feb 17, 2016 – Feb 18, 2017	Nov 1, 2014 – Aug 31, 2016	Jan 11, 2013 – Jan 10, 2017
Total Infants Screened	18,105	55,161	219,713	308,000
Negative Screen	18,099 (99.97%)	55,159 (99.99%)	219,574 (99.93%)	307,839 (99.95)
Repeat Rate	N/A	15 (0.027%)	527 (0.24%)[1]	
Positive Screen	6 (0.033%)	2 (0.0003%)	139 (0.063%)	161 (0.052%)
True Positives	1 (0.005%)	2 (0.0003%)	10 (0.004%)	32 (0.01%)
False Negatives	N/A	N/A	N/A	N/A
False Positive Rate*	0.027%	0.0%	0.055%	0.042%
Positive Predictive Value	16.67%	100%	7.19%	19.87%
Screening Method	MS/MS	MS/MS with post-analytic interpretation	MS/MS	Digital microfluidics

Pompe – Screening / Diagnoses *(published)*

Study	Wasserstein et al., 2018.	Minter Baerg et al., 2018.	Burton et al., 2017	Hopkins et al., 2018
Location	NEW YORK	KENTUCKY	ILLINOIS	MISSOURI
Date	May 2013 – Oct 2014	Feb 17, 2016 – Feb 18, 2017	Nov 1, 2014 – Aug 31, 2016	Jan 11, 2013 – Jan 10, 2017
Total Infants Screened	18,105	55,161	219,713	308,000
Positive Screen	6 (0.033%)	2 (0.0003%)	139 (0.063%)	161 (0.052%)
True Positives	1 (0.005%)	2 (0.0003%)	10 (0.004%)	32 (0.01%)
IOPD	0	NR	2	8
LOPD	1	NR	8	24
Carriers	2 (0.011%)	0	15 (0.007)	39 (0.013%)
Pseudodeficiencies	3 (0.016%)	0	15 (0.007%)	31 (0.010%)
Unaffected	0	0	87 (0.039%)	50 (0.016%)
Undetermined	0	0	4 (0.002%)	9 (0.003%)
Screening Method	MS/MS	MS/MS with post-analytic interpretation	MS/MS	Digital microfluidics

MPSI – Screening Outcomes *(published)*

Study	Taylor et al., 2019	Wasserstein et al., 2018.	Minter Baerg et al., 2018.	Burton et al., 2017	Hopkins et al., 2018
Location	NORTH CAROLINA	NEW YORK	KENTUCKY	ILLINOIS	MISSOURI
Date	Aug 15, 2016 – Mar 10, 2017	May 2015 -	Feb 17, 2016 – Feb 18, 2017	Nov 1, 2014 – Aug 31, 2016	Jan 11, 2013 – Jan 10, 2017
Total Infants Screened	62,734	35,816	55,161	219,713	308,000
Negative Screen	62,718 (99.97%)	35,803 (99.96%)	55,159 (99.99%)	219,562 (99.93%)	307,867 (99.95%)
Repeat Rate	1,289 (2.05%)	N/A	57 (0.10%)	527 (0.24%)[2]	N/A
Positive Screen	19 (0.030%)	13 (0.036%)	2 (0.0036%)	151 (0.069%)	133 (0.043%)
True Positives	1 (0.0016%)	0 (0.00%)	1	1 (0.00046%)	2 (0.0006%)
False Negatives	N/A	N/A	N/A	N/A	0
False Positive Rate*	0.027%	0.036%	0.002%	0.068%	0.04%
Positive Predictive Value	33.3%	0%	50%	0.66%	1.5%
Screening Method	MS/MS with post-analytic interpretation	MS/MS	MS/MS with post-analytic interpretation	MS/MS	Digital microfluidics

MPSI – Screening / Diagnosis *(published)*

Study	Taylor et al., 2019	Wasserstein et al., 2018.	Minter Baerg et al., 2018.	Burton et al., 2017	Hopkins et al., 2018
Location	NORTH CAROLINA	NEW YORK	KENTUCKY	ILLINOIS	MISSOURI
Date	Aug 15, 2016 – Mar 10, 2017	May 2013 – Oct 2014	Feb 17, 2016 – Feb 18, 2017	Nov 1, 2014 – Aug 31, 2016	Jan 11, 2013 – Jan 10, 2017
Total Infants Screened	62,734	35,816	55,161	219,713	308,000
Positive Screen	19 (0.030%)	13 (0.036%)	2 (0.0036%)	151 (0.069%)	133 (0.043%)
True Positives	1 (0.0016%)	0 (0.00%)	1	1 (0.00046%)	2 (0.0006%)
Severe MPSI	1	0	1 (BMT @ 6 mos)	1 (HSCT @ 2.5 mos)	NR
Carriers	2 (0.003%)	4	0	5 (0.0023%)	8 (0.0026%)
Pseudodeficiencies	17[1]	8	0	30 (0.014%)	71 (0.023%)
Unaffected	-	0	1	87 (0.04%)	45 (0.014%)
Undetermined	0	1	0	4 (0.0018%)	2
Method	MS/MS with post-analytic interpretation	MS/MS	MS/MS with post-analytic interpretation	MS/MS	Digital microfluidics

X-ALD – Screening Outcomes *(published)*

Study	Taylor and Lee, 2019	Wiens et al., 2019
Location	NORTH CAROLINA	MINNESOTA
Date	Mar 5 2018 – Dec 2018	Feb 2017 – Feb 2018
Total Infants Screened	52,301	67,835 (34,903 m, 32,392 f)
Negative Screen	52,289 (99.98%)	67,821 (99.98%)
Repeat Rate	N/A	44 (0.0648%)
Positive Screen	12 (0.023%)	14 (9 m, 5 f) (0.021%)
False Negatives	N/A	0
Positive Predictive Value	25% for X-ALD; 83.3% for X-ALD, carriers, and other disorders*	100%
Other notes	m/f breakdown not available	17 male, 24 female relatives of affected infants subsequently diagnosed with XALD

X-ALD – Screening / Diagnosis *(published)*

Study	Taylor and Lee, 2019	Wiens et al., 2019
Location	NORTH CAROLINA	MINNESOTA
Date	Mar 5 2018 – Dec 2018	Feb 2017 – Feb 2018
Total Infants Screened	52,301	67,835 (34,903 m, 32,392 f)
Positive Screen	12 (0.023%)	14 (9 m, 5 f) (0.021%)
True Positives (males)	3 (0.0057%)	9 (0.0258%)
Carriers or Heterozygous Females	2 (0.0038%)	5 (0.015%)
Other Disorders	4 (0.0076%)	0
False Positives	3 (0.004%)	0
Positive Predictive Value	25% for X-ALD; 83.3% for X-ALD, carriers, and other disorders*	100%
Other notes	m/f breakdown not available	17 male, 24 female relatives of affected infants subsequently diagnosed with XALD

Questions?

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

Duke Clinical & Translational Science Institute