NBS Implementation for Conditions Added to the RUSP: Review of Prior Report

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

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Background

- Final report previously presented July 2019
- Summary of findings from review of NBS Implementation of SCID, CCHD, Pompe disease, MPS I, and X-ALD (SMA discussed in a separate report, but included here)
  - Primary Goal: Review implementation of conditions added to the RUSP between 2010-2018
  - Secondary Goal: Develop methods to evaluate screening implementation and outcomes after addition the RUSP

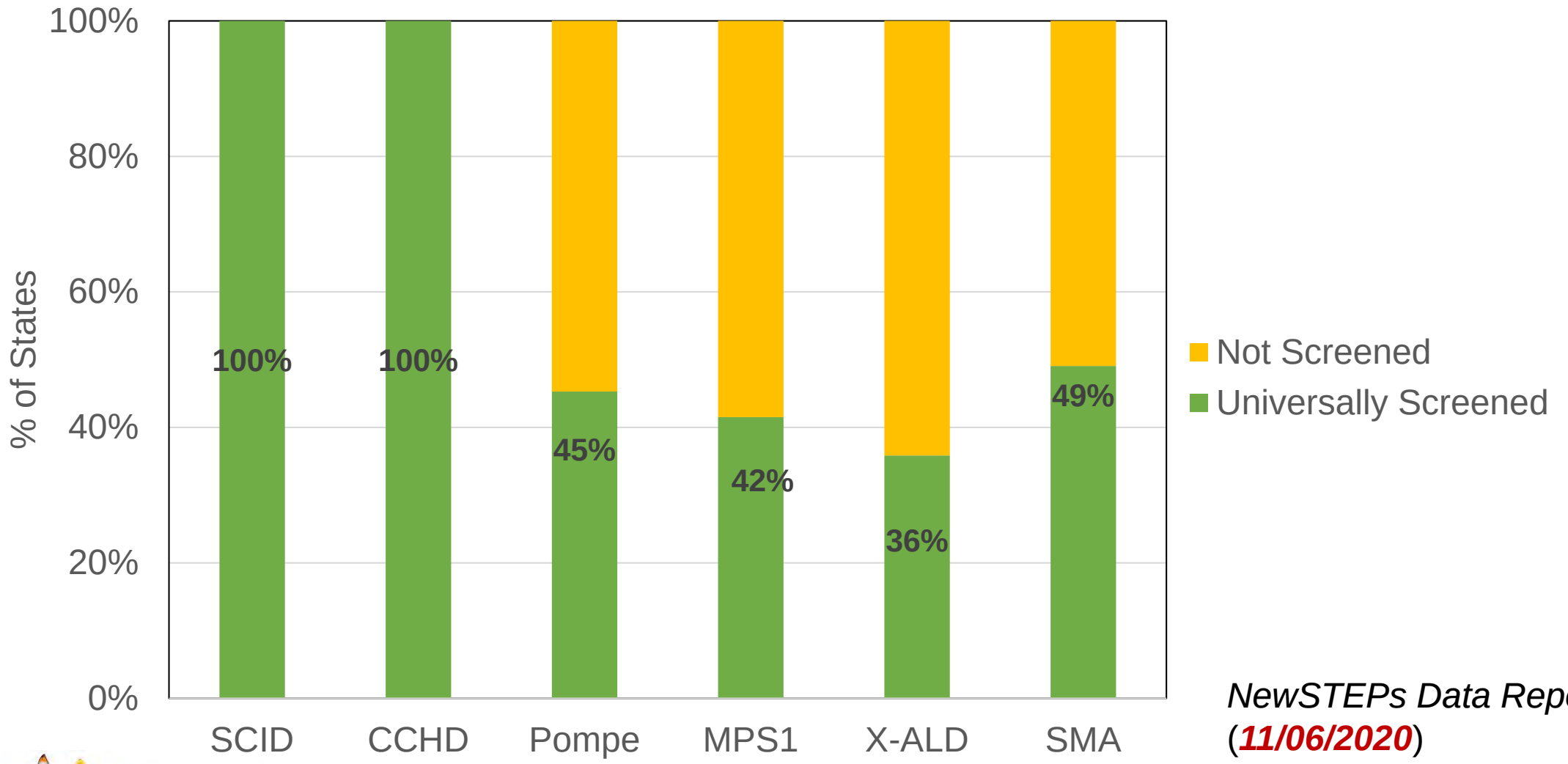
Timeline and Special Features of Added RUSP Conditions

Added RUSP Conditions	Date Added to RUSP	Special Features for Expanded NBS
Severe Combined Immunodeficiency	Feb 2010	1st targeted gene sequencing (non-MS/MS) method
Critical Congenital Heart Disease	Sept 2011	Point-of-care screening, non-DBS
Pompe Disease	March 2015	Late-onset phenotypes, pseudodeficiency, multiplex MS/MS
MPS I	Feb 2016	Late-onset phenotypes, multiplex MS/MS
X-linked Adrenoleukodystrophy	Feb 2016	X-linked, late-onset phenotypes; female 'carriers'/late-onset, multiplex MS/MS
Spinal Muscular Atrophy (5q)	July 2018	Can multiplex with SCID

Timeline: Nomination to Addition to RUSP

Added RUSP Conditions	Initial Nomination	Second Nomination	AC Vote to Recommend	Date Secretary HHS Added to RUSP
SCID	Sept 2007	Jan 2010	Jan 2010	May 2010
CCHD	Jan 2010	---	Sept 2010	Sept 2011
Pompe Disease	2006	May 2012	May 2013	March 2015
MPS I	May 2012	---	Feb 2015	Feb 2016
X-ALD	Sept 2012	Jan 2014	Aug 2015	Feb 2016
SMA	Nov 2008	May 2017	Feb 2018	July 2018

Percent (%) of states screening for each condition



NewSTEPs Data Repository
(***11/06/2020***)

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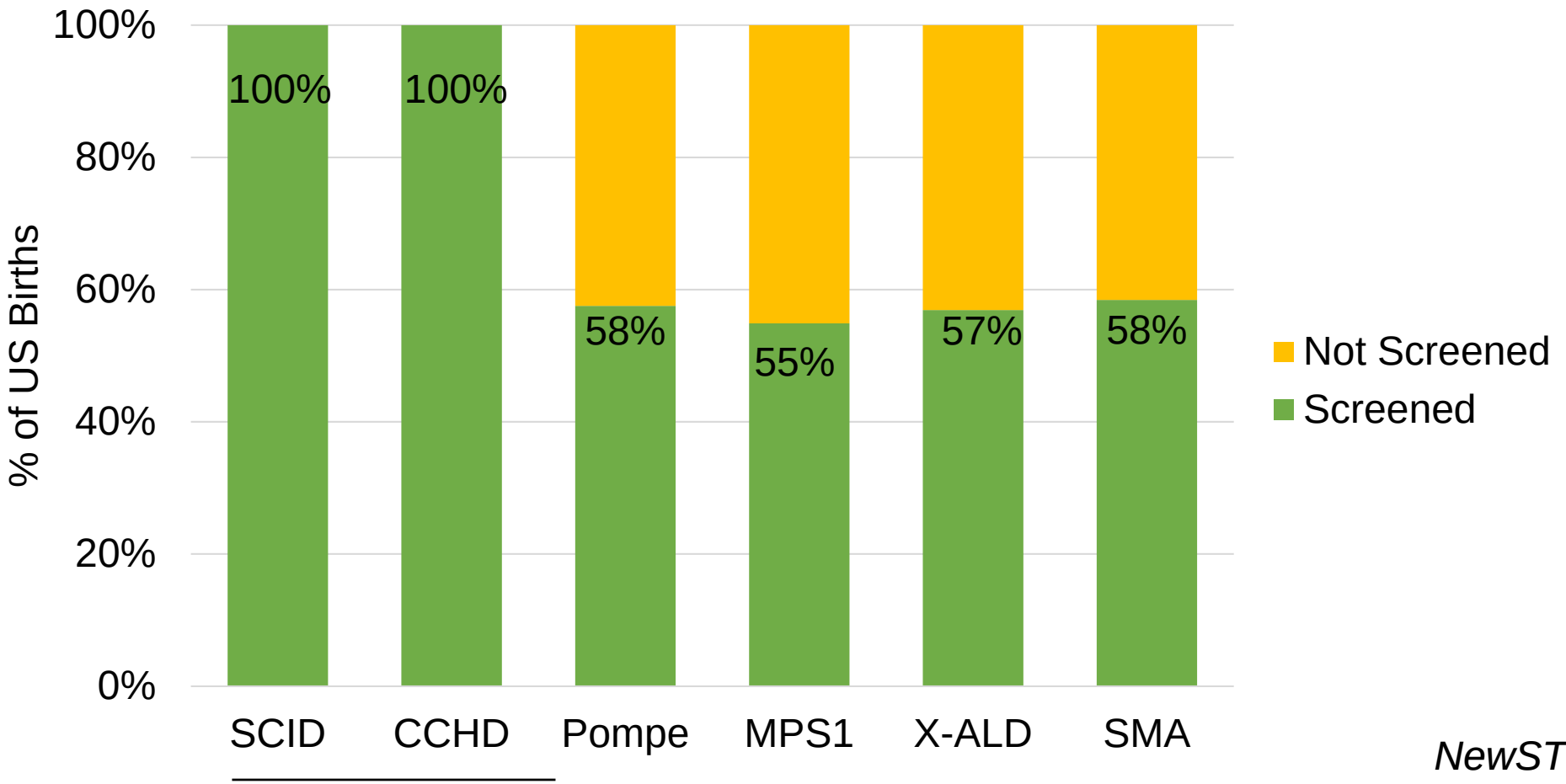
Percent (%) of U.S. births* screened annually for each condition



*Births based on 2018 annual birth data.

Source: https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_13-508.pdf

NewSTEPs Data Repository
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Challenges to new disorder implementation

- Hiring and training new personnel
- Delays in procurement and installation of equipment
- New screening approaches (e.g., point of care, new equipment)
- Refining screening algorithms (reduce false positives, improve presumptive positive screens)
- Updating Laboratory Information Management Systems
- Lack of shared genomic variant databases, unknown variants
- Developing follow-up programs and clinical management plans for infants with late-onset or unknown disease risk

Facilitators of new disorder implementation

- Peer Resource Networks
- Pilot and/or implementation funding
- Ability to integrate into NBS infrastructure or multiplex
- Patient advocacy groups – Collaborative nomination teams
- Working group for newborn screening and clinical follow-up and management, especially for disorders with later-onset forms
- Post-analytic tools and registry databases (e.g., CLIR, LPDR)
- Next-generation sequencing for second-tier testing
- Mandated state adoption of RUSP conditions

Newborn Screening Outcomes

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 lymphopenia**	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)
- 52 infants identified with SCID (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 - 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, congenital heart disease, and others)

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

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 *	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					*short follow-up	No ECG follow-up

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%	26%
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 *(confirmed diagnosis)*	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

MPS I – 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	5%	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

MPS I – 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 X-ALD

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 X-ALD

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SMA Outcomes

New York State Screening for SMA (published)

- 225,093 newborns screened in the first year
- 8 newborns identified with SMA (three with 2 copies of *SMN2*, three with three copies, and two with four or more copies).
- 7 of 8 infants with SMA received gene therapy
- Median days follow-up at specialty center: 7.5 days after birth.

NBSTRN/APHL informal reports

- Of over 1 million newborns screened for SMA, at least 111 identified with SMA (85 from universal newborn screening, 26 from pilot or validation activities)

Aggregated Summary of Published Screening Results*

*(*reported in final evidence review reports)*

	SCID	CCHD	Pompe	MPS I	X-ALD	SMA
Date	2008-2017	2013 - 2018	2013– 2017	2013– 2017	2017 – 2018	2018-2019
Total Infants Screened	3,946,037 (3 programs)	176,819 (6 programs)	594,979 (4 programs)	681,424 (5 programs)	120,136 (2 programs)	225,093 (1 program)
Positive Screens	1,165	145	308	318	26	8
True Positives	65	10	45	5	12 (males)	8
Positive Predictive Value	5.5%	6.9%	14.6%	1.6%	46.2%	100%
By Phenotype *(if applicable or provided)*	NR	NR	10-IOPD 33-LOPD (2 NR)	3 severe MPSI (1 NR)	NR	3 with 2 *SMN2* 3 with 3 *SMN2* 2 with ≥4 *SMN2*
Other Positive Screen Results	277 other T-cell lymphopenia 769 unaffected	NR†	56 carriers 49 pseudodeficiency 137 unaffected 13 undetermined	19 carriers 126 psuedodeficiency 133 unaffected 6 undetermined	7 carriers/heterozygote females 4 other disorders	0
State programs Source *(1st author and pub year)*	WI - Verbsky (2011) CA - Amatuni (2019) NY - Vogel (2014)	GA - Diller (2018) NJ – Garg (2013) TX – Guillory (2017) MA – Johnson (2014) MN – Kochilas (2013) CO – Wright (2014)	NY – Wasserstein (2018) KY – Minter Baerg (2018) IL – Burton (2017) MO – Hopkins (2018)	NC – Taylor (2019) NY – Wasserstein (2018) KY – Minter Baerg (2018) IL – Burton (2017) MO – Hopkins (2018)	NC – Taylor (2019) MN – Wiens (2019)	NY – Kay (2020)

†*Other conditions identified through POX, though not included here due to variability in reporting*

Questions?


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