Lessons learned from coordination between research, public health and newborn screening programs

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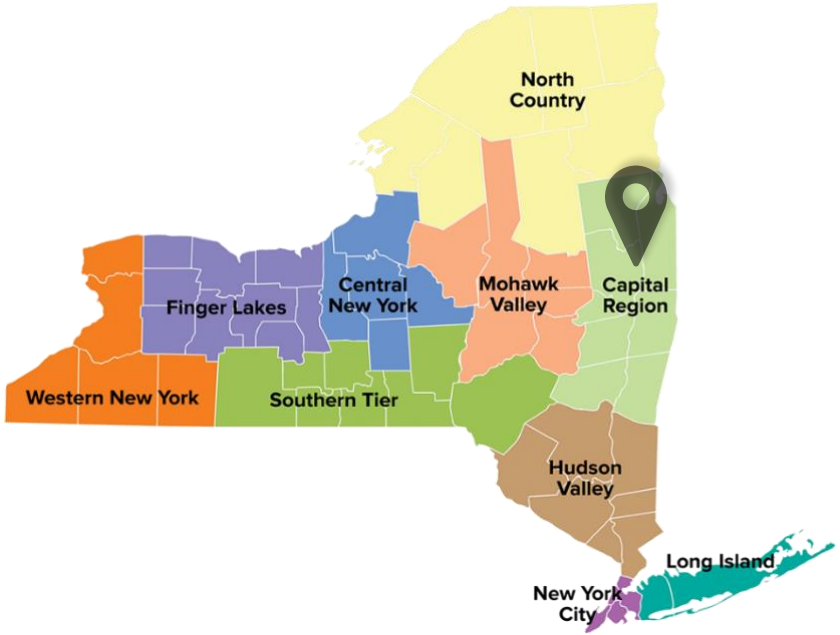
Disclosures

Funding to New York State Newborn Screening Program for pilot studies

- **Spinal Muscular Atrophy (SMA)** – Biogen, Idec
- **ScreenPlus** - *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), Abeona Therapeutics, Alexion Pharmaceuticals, the Michael, Marcia and Christa Parseghian Endowment for Excellence in Niemann Pick Type C Research, BioMarin Pharmaceutical, Cure Sanfilippo Foundation, Dana's Angels Research Trust, Firefly Fund, Genzyme Corporation, Noah's Hope - Hope4Bridget Foundation, Orchard Therapeutics, Passage Bio, Sio Gene Therapies, Takeda Pharmaceuticals, Travere Therapeutics, and Ultragenyx Pharmaceutical
- **GUARDIAN** – Sanofi, GeneDx, Illumina, Columbia Precision Medicine Initiative
- **Duchenne Muscular Dystrophy (DMD)** – Sarepta Therapeutics, PTC Therapeutics, Solid Biosciences, Wave Life Sciences, Pfizer, Inc., Parent Project Muscular Dystrophy, Revvity
- **Lysosomal disorders** – NICHD
- **Congenital Cytomegalovirus (cCMV)** – NICHD

New York State (NYS) Newborn Screening (NBS) Program



- Central lab in Albany
- 113 birth hospitals
- >50 conditions (plus pilots)
- 204,722 babies screened (2023; 5.9% of births in United States)

Photo: March of Dimes

Newborn screening “research”

- Assay development and validation
- Quality improvement (QI)
- Research
- **Prospective pilot studies**

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NYS NBS Program – Prospective pilot studies

Pilot Study	Study period	Hospital Sites	Screening Methods	# Infants Screened	# Confirmed Cases	Enrollment (Rates[1])	Pilot Study Outcomes
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Congenital Cyto-megalovirus (cCMV)	2023 – present	Universal	Molecular	101,644	98	Opt-out (0.13%)	Ongoing

[1]Rate based on proportion approached; [2]All predicted late onset; [3]Genetic testing performed via send-out.

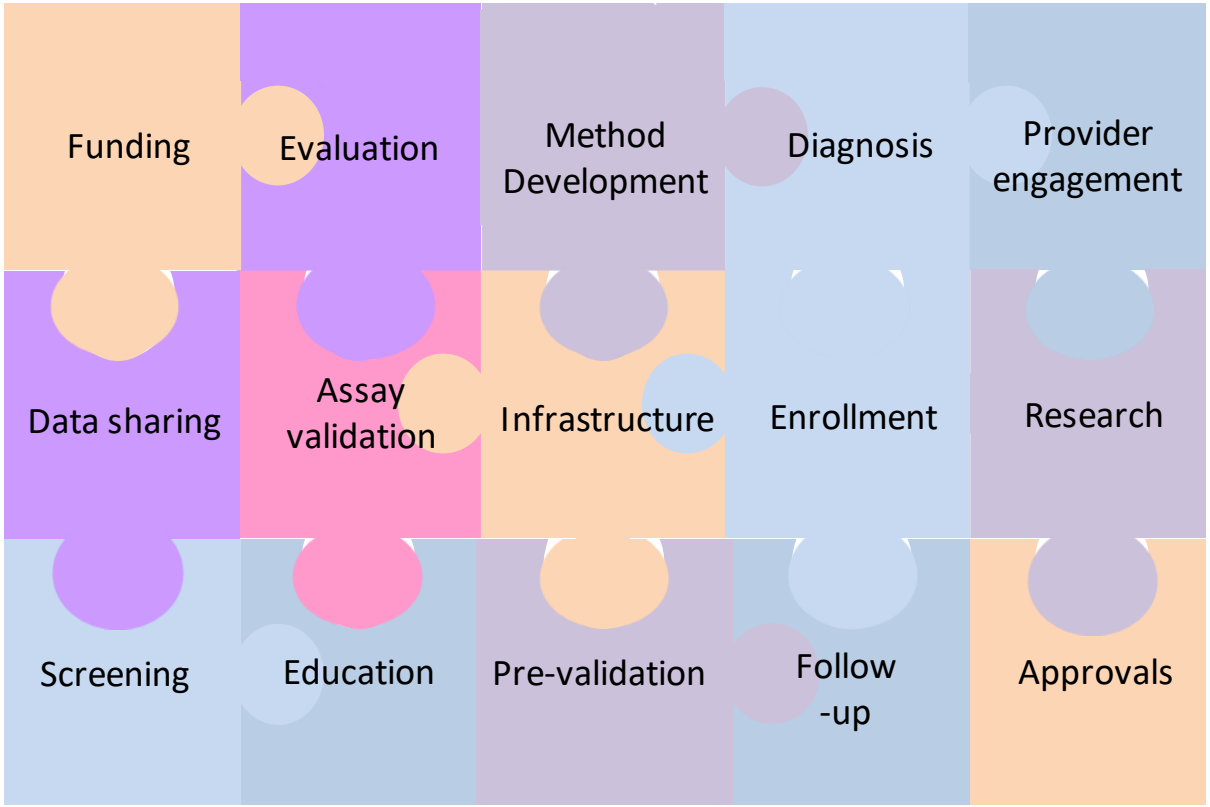
NYC=New York City; **MS/MS**=Mass spectrometry; **CTX**=Cerebrotendinous xanthomatosis; **MPS I**=Mucopolysaccharidosis Type I

Photo: March of Dimes

Should Spinal Muscular Atrophy (SMA) be screened?

- ☑ Important health problem
- ☑ Natural history known
- ☑ Recognizable latent stage
- ☑ Biomarker and test (2000's)
- ☑ Demonstrated benefit of early detection, intervention and treatment* (2016)
- ☑ Screening feasibility demonstrated in public health lab* (2016-2018)

Screening criteria adapted from Wilson and Jungner (1968) Principles and practice of screening for disease.
*Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) recommendations following nomination of SMA to Recommended Uniform Screening Panel (RUSP) in 2008.



Prospective NBS pilot studies – Logistics

- More than assay validation
- Many moving parts
- Many partners

*Most elements apply to pilots and implementing universal screening for new conditions

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Prospective NBS pilot studies – SMA

Actions		NYS SMA Pilot Study
Research	Stay abreast of literature, technology, tests, platforms, treatments	2000's: *SMN1* screening assays published 2008: SMA nominated for addition to RUSP 2008: Evidence review not completed 2010's: Clinical trials for novel therapies
Method development	Test kits or lab-developed tests (LDTs); Identify and test positive controls; adapt to dried blood spots; scale to high-throughput	2010-2011: Assessment of *SMN1* and *SMN2* assays by NBS lab staff, summer students
Pre-validation	Optimize assay; set preliminary reference ranges; set quality control/quality assurance metrics and processes	2012: Small retrospective study using deidentified dried blood spots

RUSP=Recommended uniform screening panel; ***SMN1***=Survival of motor neuron 1 gene; ***SMN2***=Survival of motor neuron 2 gene

Prospective NBS pilot studies – SMA

Actions		NYS SMA Pilot Study
Funding	Identify collaborations and funding source; submit proposal with budget for equipment, reagents, staff	2014: Discussions with collaborators 2014: Proposal submitted 2015: Proposal funded
Infrastructure	Set-up platforms, contracts for reagents, consumables, laboratory information management system (LIMS); train staff	2015: Hired 1 research assistant (100%)
Approvals	Obtain program, institution, NBS advisory board, funding agency, IRB, CLIA, CLEP, FDA approvals	2015: IRB protocol 2015: Regulatory approval (CLEP)

IRB=Institutional Review Board ; **CLIA**=Clinical Laboratory Improvement Amendments; **CLEP**=NYS Clinical Laboratory Evaluation Program; **FDA**=US Food and Drug Administration

Prospective NBS pilot studies – SMA

Actions		NYS SMA Pilot Study
Validation	Assess feasibility; perform retrospective population-based screen; finalize cutoffs; refine algorithms; formalize standard operating procedures (SOPs)	2015: Validation study
Education	Inform and educate birth hospitals and families	2015: Columbia clinical team
Follow-up	Establish referral, diagnostic, short- and long-term follow-up algorithms; certify care centers	2015: Columbia clinical team

Prospective NBS pilot studies – SMA

Actions		NYS SMA Pilot Study
Enrollment	Formalize mechanism (opt-in, opt-out, universal); recruit families; provide informed consent	2015: Columbia recruitment team (opt-in with informed consent)
Screen	Prospectively screen, report and refer to follow-up	2016-2018: Prospective screening
Diagnose	Diagnose, treat, and follow	2016-2018: Columbia clinical team

Prospective NBS pilot studies – SMA

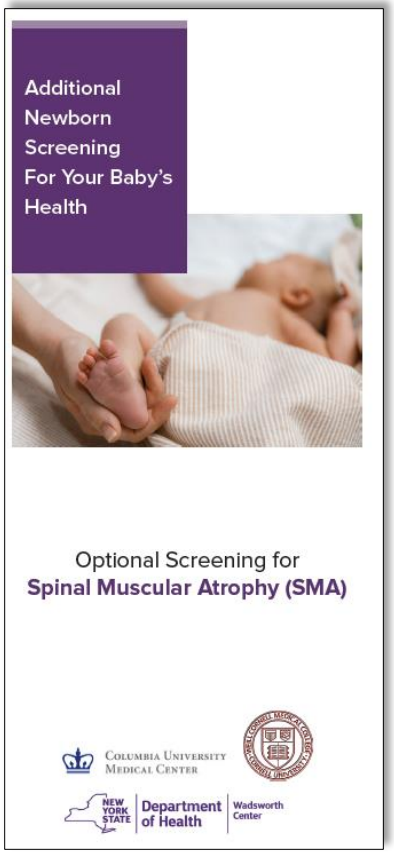
Actions		NYS SMA Pilot Study
Condition evaluation	Consider addition to mandated state panel: analytical validity, clinical validity, clinical utility, infant outcomes, impact on NBS program, healthcare system, families; cost, turnaround time, ethical, legal, social, policy, and financial issues	2016-2018: Ongoing during pilot
Dissemination	Share methods and results with community	2017: APHL public health system impact assessment 2017: ACHDNC review of SMA nomination 2018: NYS SMA pilot results published[1]

APHL=Association of Public Health Laboratories; **ACHDNC**= Advisory Committee on Heritable Disorders in Newborns and Children; [1]Kraszewski et al. 2018, PMID: 29758563

NYS SMA pilot study

Major goals

- Develop *SMN1* assay
- Demonstrate feasibility of high-throughput newborn SMA screening
- Offer screening, assess uptake and outcomes



Methods

- 01/15/2016–09/30/2018
- 4 NYC hospitals
- Opt-in model (informed consent)
- Carriers detected and reported

Results

Infants screened	16,712 (93% opted in)
SMA carriers	249 (1 in 67)
SMA cases	1 (1 in 16,712)

SMN1=Survival of motor neuron 1 gene

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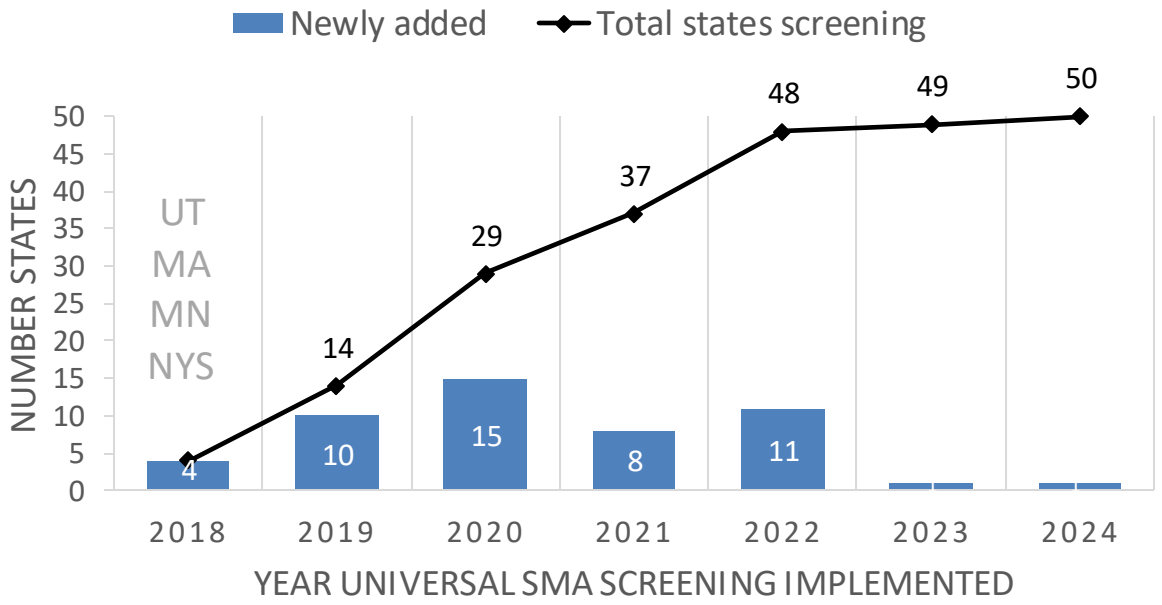
Implementation of SMA NBS in the US

2017: SMA re-nominated
2018: SMA added to RUSP

New York (2018-2024)
- 1.1 million screened
- 51 confirmed SMA

United States (2018-2022)*
- 6.1 million screened
- 402 confirmed SMA



*Data source: CureSMA, 2022

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Factors facilitating implementation of pilot SMA NBS in NYS

- Research – assay development
- Wadsworth Center – research-based public health laboratory
- Ability to screen using lab-developed tests (LDTs)
- Ability to add new conditions, designated by Commissioner of Health
- Implementation of DNA-first universal screen for severe combined immunodeficiency (SCID)
- Funding for dedicated lab staff member and test reagents
- Collaboration; key for recruitment

Factors facilitating implementation of universal SMA NBS in NYS

- NYS SMA pilot study – infrastructure, logistics; some changes
- Ability to plan for universal screening during pilot (e.g., assay revalidation; establishment of Care Centers)
- Ability to multiplex with severe combined immunodeficiency (SCID) assay (multiplexing not always simple!)
- ACHDNC recommendation to define "Spinal Muscular Atrophy due to homozygous deletion of exon 7 in *SMN1*" as the core condition on the RUSP

ACHDNC= Advisory Committee on Heritable Disorders in Newborns and Children;
RUSP=Recommended uniform screening panel

Upcoming challenge

NBS programs must be prepared to quickly implement screening for new conditions as methods are validated and novel treatments are approved

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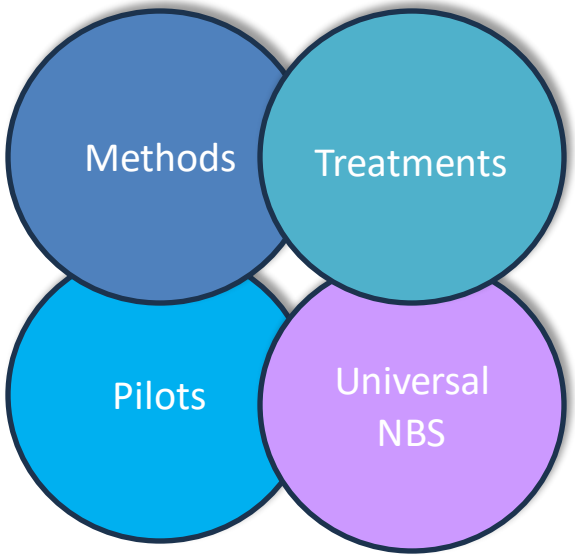
Collaborations between research and public health labs

- Novel methods developed by research labs
- Research methods adapted to scalable, cost-efficient assays by public health labs
- Population (NBS) + recruitment (research/clinical)
- “N of 1 rule” (ACHDNC)
- Complementary clinical, scientific, technical and policy expertise from public health, academia, industry, clinical sector, advocacy
- Well-rounded, competitive proposals for funding



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- NYS follow-up staff

Pilot studies

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- Melissa Wasserstein, MD
- Dorota Gruber, DHSc, MS, CGC

Funding for NYS pilot studies

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