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COLUMBIA UNIVERSITY MEDICAL CENTER

NewYork-Presbyterian

Implications of Detecting Carriers Through Newborn Screening:

Lessons Learned from Spinal Muscular Atrophy Newborn Screening in New York State

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

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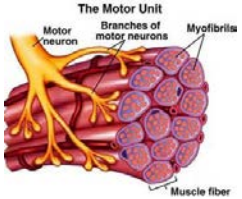
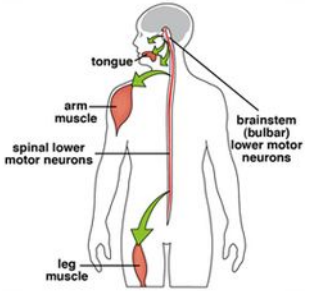
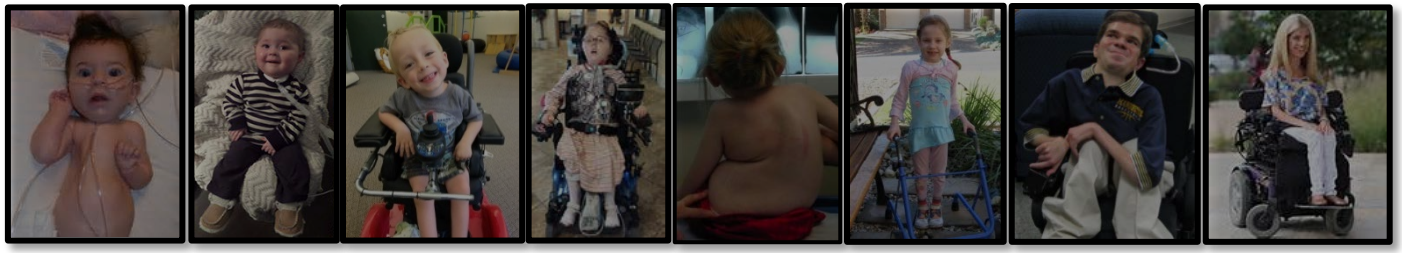
Spinal Muscular Atrophy (SMA)

- Progressive degeneration & loss of spinal cord & brainstem motor neurons
- Muscle weakness, atrophy
- Difficulty breathing, poor weight gain, pneumonia, scoliosis, joint contractures





Age at onset, symptoms, severity and survival vary – type 1 (most severe), 2, 3, 4



SMA (Chr. 5) Incidence and Genetics

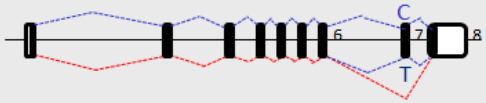
Most common genetic cause of infant & toddler death

- Incidence: 1 in 6,000 to 1 in 11,000
- Carriers: 1 in 50 to 1 in 60

95%–98% homozygous deletion of **S**urvival of **M**otor **N**euron **1** (*SMN1*) exon 7

SMN2 = *SMN1* homologue
(differ by few nucleotides | both code for SMN)

SMN1 full-length SMN (100%)



SMN2 truncated, non-functional SMN (~85-95%)
full-length SMN (~5-15%)

genomic copies of *SMN2* varies (0–5)
↑ *SMN2* ≈ less severe, later onset

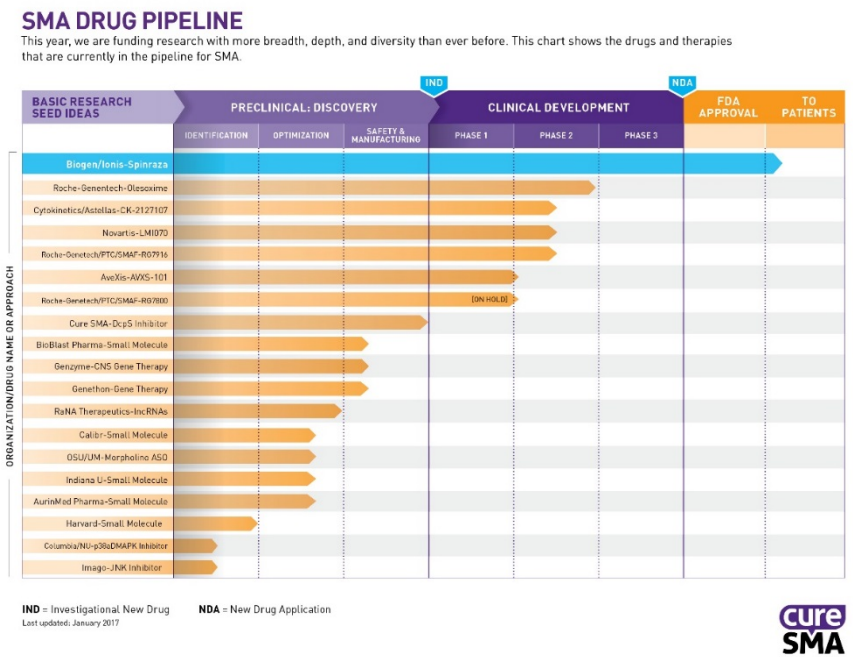
Treatment

≤ 2016 Supportive – respiratory, nutritional, gastrointestinal, orthopedic

Unsuccessful preclinical, clinical trials

2016 First FDA-approved treatment Spinraza™ (nusinersen) ASO to increase SMN from *SMN2*

201x Others in development, clinical trials



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SMA Newborn Screening

Should carrier status of newborns be reported to families?

- **It is not recommended to subject minors to carrier testing**
- **Newborn screening -- incidental finding**

photo: March of Dimes

Pilot SMA Newborn Screening

Columbia University Medical Center, NY Presbyterian Hospitals, NYS Newborn Screening Program

Major Goals:

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

NY Presbyterian, Morgan Stanley Children's Hospital
Manhattan
4,400 births/yr

Weill-Cornell Medical Center
Manhattan
5,800 births/yr

Allen Hospital
Upper Manhattan/ Bronx
2,000 births/yr

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Recruitment – Opt-in Model

Sites: 3 NYC hospitals, 12,000 births/year

Materials: video & brochure

Coordinators: describe study, answer questions, informed consent on tablet (REDCap), mark Guthrie card

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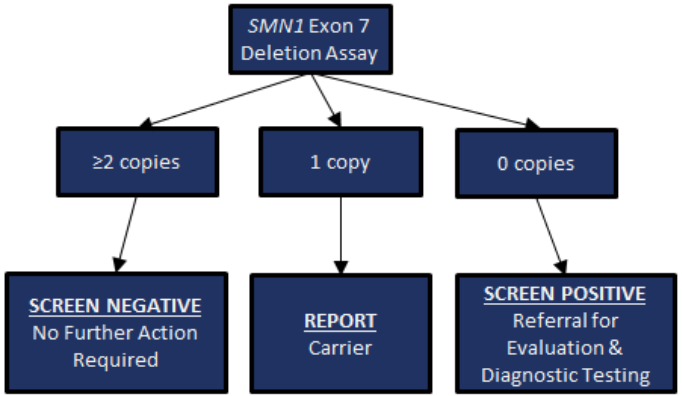
Screening – *SMN1* exon 7 deletion assay

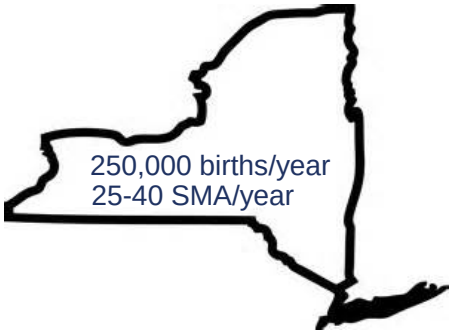
- First genomic DNA test
- DNA extracted from dried blood spot
- TaqMan real-time qPCR assay
  - *SMN1* exon 7
  - *RPPH1* (internal control gene)
- ABI 7900HT / QuantStudio 12K Flex
- ΔΔCt to calculate *SMN1* copy number



Anhuf, Eggermann, Rudnik-Schöneborn, Zerres (2003) Human Mutation;22(1):74-8.

Results

January 15, 2016 – October 6, 2017
8,167 infants screened
93% opt in rate



Hospital	# Screened	Carriers (freq)	SMA
NY Presbyterian, Morgan Stanley Children's Hospital	3,654	50 (1 in 73)	-
Weill-Cornell Medical Center	2,956	53 (1 in 56)	-
Allen Hospital	1,557	11 (1 in 142)	1
Overall	**8,167**	**114 (1 in 72)**	**1**

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Opt in rate: 93%

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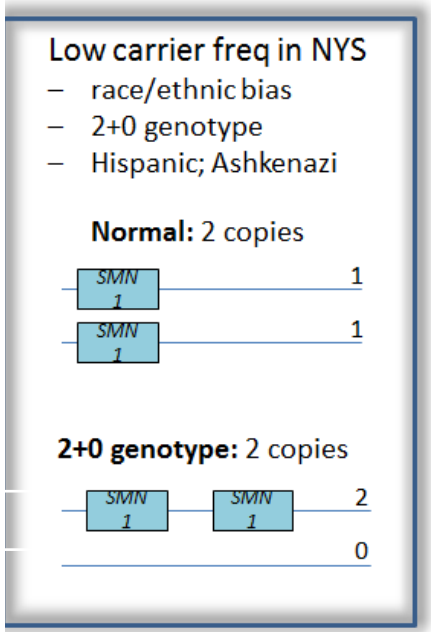


Follow-up – Carriers

14.1% (16/113) agreed to genetics referral
- **73.3% (11/15) made appointment**
- **72.7% (8/11) maintained appointment**

- **Most parents expressed concern**
- **After speaking with counselor, expressed understanding of "carrier" status versus "affected“**

- **46.9% (53/113) knew they were carriers**
  - **Less concerned, better understanding**

Results – Affected Infant

Genotype:

***SMN1*: homozygous Δ exon 7**
***SMN2*: 2 copies**

predicts
SMA type 1

SMA Type 1 Natural History– What is Expected

- **Onset: <6 months**
- **Survival: ≤2 years**
- **Major motor milestones reached: None; never sit unassisted.**
- **Symptoms: Profound hypotonia and flaccidity, no head control, poor suck & swallow; Respiratory and nutritional problems**

@ 21 months – tolerates medication, meeting milestones on time, walking, running, talking

Conclusions from Pilot Study

- SMA newborn screening is feasible
  - $0.20/baby if multiplexed*
- 93% of families opted in
- Carrier rate = 1 in 72
- 1 infant predicted to have type 1 infantile SMA identified (1 in 8,167 currently)
  - treated with nusinersen (Spinraza)
  - asymptomatic at 21 months

*$0.20 is lab cost only; with SCID multiplex

The Question of Carriers
Current Management of Carrier Results

Hemoglobinopathies

- Carriers by report
- No follow-up
- No further action required
- SCC not notified
- Letter/brochure to parents

Cystic Fibrosis*

- Carriers by report
- Follow-up req'd
- Screen positive
- Prompt action
- SCC notified
- Sweat test req'd

*When we begin FGA; will be handled like hemoglobin

Adrenoleukodystrophy

- Carriers by report
- Follow-up req'd
- Screen positive
- Prompt action
- SCC notified
- VLCFA req'd
- Plasmalogen levels may be req'd

Hemoglobinopathy Volumes by Births

	Births	AS	AC	A Other	SS	SC	CC	Other disease
2015	237,502	5,048	1,521	705	124	74	26	51
2016	234,107	5,070	1,547	753	102	59	24	47

NYS hemoglobin carrier frequency: ~1 in 32

Cystic Fibrosis Volumes by Births

	Births	Referrals	CF Confirmed*	Other	NY panel carriers
2015	237,502	840	29	22	600
2016	234,107	816	28	31	558

* Includes VHIRT
*** Includes CRMS, possible CF, 2 mut/negative sweat
\+ Includes all carriers

NYS CF carrier frequency: ~1 in 407
 # detected by NBS; we miss carriers; expect 1/35 based on incidence

Adrenoleukodystrophy Data

December 30, 2013 – October 5, 2017

891,185 babies screened
456,034 males
434,911 females
240 gender unknown/ambiguous

Adrenoleukodystrophy Data

69 total referrals (12/30/2013 – 10/5/2017)

54 are related to Adrenoleukodystrophy

- 28 boys with ALD (*includes possible)
- 25 carrier girls
- 1 carrier boy*

12 referrals without ABCD1 mutation:

- 7 Zellweger syndrome
- 1 Aicardi-Goutieres syndrome
- 2 likely PBD; 1 expired
- 1 neonatal lupus; elev. VLCFA
- 1 D-bifunctional protein deficiency

3 still pending

ALD by the Numbers

- Referral rate: 1 in 12,916 or 0.0077% of infants screened
- Incidence of ALD: 1 in 31,828 all births (n=28)
- Incidence of ALD: 1 in 16,287 males (n=28)
- Incidence of ALD*: 1 in 16,815 all births (n=53)
- Incidence of PBDs: 1 in 99,020 births (n=9)

* Assumption that all with mutations will become symptomatic (includes female carriers; excludes KS male).

Issues Related to Carrier Detection 1

Specialists generally feel this will introduce additional burden

- Calls from providers and families; dearth of counselors
- Family planning; interest in carrier screening of infant's siblings
- NBS mission creep
- Many providers interpret carrier or positive as 'affected—
- "Do I need to do anything"

- Professional community has not reached consensus on reporting carrier status in the context of newborn screening
- Hispanic carrier frequency is ~1/100; 2+0 carriers; not detected, health disparity?
- Ashkenazi Jewish 2+0 detectable with haplotype analysis (Luo et al, 2014)
- A proportion of families refused due to increased SMA prenatal screening
- 47% of carriers already knew carrier status when called

Issues Related to Carrier Detection 2

- With ACOG recommendation for carrier prenatal screening, uptake is high but variable depending on the hospital; that population doesn't come for NBS follow-up
- Based on the follow-up survey data from the pilot 4-5% of those asked don't recall carrier status of the newborn
- Prenatal carrier screening "feels different"; affects parent, not their baby
- Additional parent concern despite reassurance, "What should I look for"?
- Few parents request follow-up sequence analysis after a carrier newborn
- Phone counseling caveats (cannot read body language, distractions etc.).
- Each consult is about 15 minutes by phone
- Parents making appointments after a carrier newborn are offered carrier screening

Future Directions

SMA newborn screening

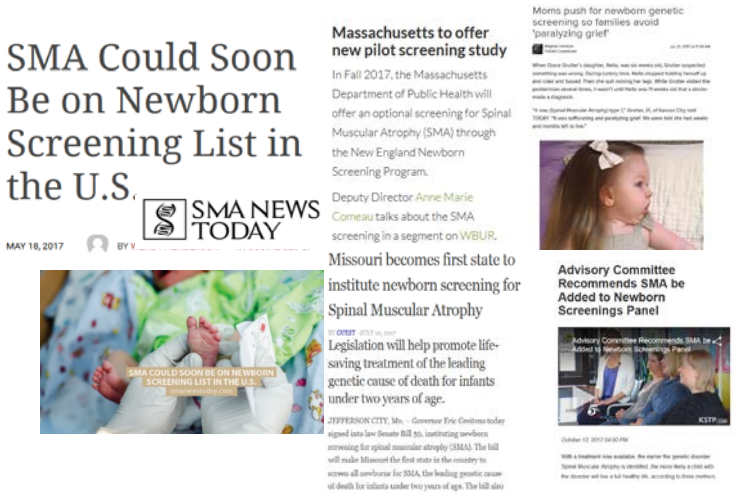
- Other states
- ACHDNC SMA evidence review & recommendation for/against addition to RUSP (Feb, 2018)

Population-wide screening in NYS

- State public health law / regulation
- Care center network, neuromuscular specialists
- Multiplex qPCR assay ($0.20/baby)
- Carrier reporting?

Other considerations

- Detection of late onset SMA
- False negatives (point mutations)
- Current treatment ($$$, when to initiate)
- Additional treatments



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