Implications of Detecting Carriers Through Newborn Screening: Lessons Learned from Spinal Muscular Atrophy Newborn Screening in New York State

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Michele Caggana, Sc.D., FACMG
Director, Newborn Screening Program
Wadsworth Center, NYS Department of Health
Disclosures

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Biogen, Idec had no role in data analysis, interpretation, or decisions regarding patient counseling or care.

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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 Survival of Motor Neuron 1 (SMN1) exon 7
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
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
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
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
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

Results

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

<table>
<thead>
<tr>
<th>Hospital</th>
<th># Screened</th>
<th>Carriers (freq)</th>
<th>SMA</th>
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<tbody>
<tr>
<td>NY Presby, Morgan Stanley Children’s Hospital</td>
<td>3,654</td>
<td>50 (1 in 73)</td>
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</tr>
<tr>
<td>Weill-Cornell Medical Center</td>
<td>2,956</td>
<td>53 (1 in 56)</td>
<td>-</td>
</tr>
<tr>
<td>Allen Hospital</td>
<td>1,557</td>
<td>11 (1 in 142)</td>
<td>1</td>
</tr>
<tr>
<td>Overall</td>
<td>8,167</td>
<td>114 (1 in 72)</td>
<td>1</td>
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250,000 births/year
25-40 SMA/year
Results

January 15, 2016 – October 6, 2017

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Opt in rate: 93%

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Low carrier freq in NYS
- race/ethnic bias
- 2+0 genotype
- Hispanic; Ashkenazi

Normal: 2 copies
- SMN1
  - 1
- SMN1
  - 1

2+0 genotype: 2 copies
- SMN1
  - 1
  - SMN1
  - 2

0
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:

predicts

$SMN_1$: homozygous $\Delta$ exon 7  
$SMN_2$: 2 copies

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 multiple:
### The Question of Carriers
#### Current Management of Carrier Results

<table>
<thead>
<tr>
<th>Hemoglobinopathies</th>
<th>Cystic Fibrosis*</th>
<th>Adrenoleukodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>carriers by report</td>
<td>carriers by report</td>
<td>carriers by report</td>
</tr>
<tr>
<td>no follow-up</td>
<td>follow-up req’d</td>
<td>follow-up req’d</td>
</tr>
<tr>
<td>no further action required</td>
<td>screen positive</td>
<td>screen positive</td>
</tr>
<tr>
<td>SCC not notified</td>
<td>prompt action</td>
<td>prompt action</td>
</tr>
<tr>
<td>letter/brochure to parents</td>
<td>SCC notified</td>
<td>SCC notified</td>
</tr>
<tr>
<td></td>
<td>sweat test req’d</td>
<td>VLCFA req’d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>plasmalogen levels may be req’d</td>
</tr>
</tbody>
</table>

*When we begin FGA; will be handled like hemoglobin
# Hemoglobinopathy Volumes by Births

<table>
<thead>
<tr>
<th>Year</th>
<th>Births</th>
<th>AS</th>
<th>AC</th>
<th>A Other</th>
<th>SS</th>
<th>SC</th>
<th>CC</th>
<th>Other disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>237,502</td>
<td>5,048</td>
<td>1,521</td>
<td>705</td>
<td>124</td>
<td>74</td>
<td>26</td>
<td>51</td>
</tr>
<tr>
<td>2016</td>
<td>234,107</td>
<td>5,070</td>
<td>1,547</td>
<td>753</td>
<td>102</td>
<td>59</td>
<td>24</td>
<td>47</td>
</tr>
</tbody>
</table>

**NYS hemoglobin carrier frequency:** ~1 in 32
# Cystic Fibrosis Volumes by Births

<table>
<thead>
<tr>
<th></th>
<th>Births</th>
<th>Referrals</th>
<th>CF Confirmed*</th>
<th>Other</th>
<th>NY panel carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>237,502</td>
<td>840</td>
<td>29</td>
<td>22</td>
<td>600</td>
</tr>
<tr>
<td>2016</td>
<td>234,107</td>
<td>816</td>
<td>28</td>
<td>31</td>
<td>558</td>
</tr>
</tbody>
</table>

* 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

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

- 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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