Newborn Screening for Spinal Muscular Atrophy (SMA)

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• Autosomal Recessive Condition
• Progressive muscle weakness and atrophy resulting from progressive degeneration and loss of lower motor neurons (anterior horn cells)
• Incidence of ~1/10,000
• Etiology is:
  • homozygous deletion/gene conversion of exon 7 in the SMN1 (survival motor neuron gene) located on 5q
    95% - 98% of cases
  • compound heterozygotes (point mutations)
    2 - 5% of cases
  • 2% of affected individuals de novo deletion
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Age of Onset</th>
<th>Life Span</th>
<th>Motor Milestones</th>
<th>Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA 0</td>
<td>Prenatal</td>
<td>&lt;6 months</td>
<td>None achieved</td>
<td>Severe neonatal hypotonia</td>
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<td>Severe weakness</td>
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<td></td>
<td>Early respiratory failure</td>
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<td></td>
<td>Facial diplegia</td>
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<tr>
<td>SMA I Werdnig-Hoffman</td>
<td>&lt;6 months</td>
<td>Most often ≤2 years, but may live longer</td>
<td>Sit with support only</td>
<td>Mild joint contractures</td>
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<td>Normal or minimal facial weakness</td>
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<td>Variable suck &amp; swallow difficulties</td>
</tr>
<tr>
<td>SMA II Dubowitz</td>
<td>6-18 months</td>
<td>70% alive at age 25 years</td>
<td>Independent sitting when placed</td>
<td>Postural tremor of fingers</td>
</tr>
<tr>
<td>SMA III Kugelberg-Welander</td>
<td>&gt;18 months</td>
<td>Normal</td>
<td>Independent ambulation</td>
<td></td>
</tr>
<tr>
<td>SMA IV</td>
<td>Adulthood</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
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</tbody>
</table>
SMA Clinical Variability

- SMN2 gene is located adjacent to the SMN1 gene
- Gene differs from SMN1 by only 5 bases, none of which are predicted to change the amino sequence of the protein
- SMN2 has a single base change intronic to Exon 7 (C to T transition) which disrupts a modulator of splicing leading to exclusion of Exon 7 from 90% of the mRNA transcript
- Clinical severity depends on the copy number of SMN2 genes
<table>
<thead>
<tr>
<th>SMN2 Copy Number</th>
<th>Normal</th>
<th>In SMA I</th>
<th>In SMA III</th>
<th>Total (SMA I + SMA III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14.4%</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>32%</td>
<td>7 (13.5%)</td>
<td>0 (0%)</td>
<td>7 (4.9%)</td>
</tr>
<tr>
<td>2</td>
<td>51%</td>
<td>43 (82.7%)</td>
<td>0 (0%)</td>
<td>43 (30.3%)</td>
</tr>
<tr>
<td>3</td>
<td>4%</td>
<td>2 (3.9%)</td>
<td>70 (77.8%)</td>
<td>72 (50.7%)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0%)</td>
<td>20 (22.2%)</td>
<td>20 (14.1%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>90</td>
<td>142</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from [Mailman et al. 2002]
NBS for SMA

**New York State Pilot**
- Real time qPCR to detect homozygous SMN1 exon 7 deletion
- Second tier to detect SMN2 copy number by targeted Sanger SMN1 gene or digital droplet PCR

**Perkin Elmer (in Development)**
Multiplexed single tier assay with SCID combines detection of SMN1 exon 7 deletion, SMN2 copy number, TREC(SCID) and KREC (XLA)

**Taiwan Pilot**
- Real Time PCR
- Digital droplet PCR for SMN2 copy number and false +
Mechanism of Action

From Sprinraza Manufacturer
Treatment of SMA

• Anti sense oligonucleotide that binds to C6T in SMN2 (Spinraza-nusinersen)
• Allows increased production of full length SMN 2 gene product to increase SMN protein
• Approved by the FDA 12/23/2016
• Intra thecal administration
• Cost estimates:
  • $750,000 for first year
  • $350,000 subsequent years
• Gene Therapy in development
Newborn Screening Method

- First tier screen entails using real-time qPCR to detect SMN1 deletion of exon 7.
  - ≥ 2 copies = normal
  - 1 copy = carrier
  - 0 copies = positive screen
- First tier can be multiplexed with current SCID screening.
- Second tier screen entails using real-time PCR or digital droplet PCR to determine SMN2 copy number.
NY Pilot Results

- 3 NYC hospitals, 12,000 births a year
- Informed consent using an opt-in model
- Infant screened = 7,317
- SMA Type I = 1
- Carriers = 100 (1 in 73)
- False positives = 0
- False negatives = expected ~5-7%
  - Other point mutations possible
  - 5% SMA cases - compound heterozygous for exon 7 deletion and other point mutations would currently be reported as carriers in NYS

From Denise Kay, PhD, New York State Department of Health
SMA Screening in Texas?

• ACHDNC–SMA evidence review & recommendation (Feb, 2018)
• Funding and resources
Thank you