Genetic Testing and Clinical Drug Development for Spinal Muscular Atrophy

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Disclosures

- I am an employee and stockholder of Biogen, Inc.
Spinal muscular atrophy (SMA):
Leading monogenic cause of mortality in infants and toddlers

Progressive, autosomal recessive disorder of alpha motor neurons of the spinal cord caused by loss of function of the survival motor neuron 1 (SMN1) gene

**Incidence** ~ 1/10,000 live births across all geographies

**Disease manifestations include:**
- Muscle weakness and atrophy
- Gastrointestinal and swallowing dysfunction
- Respiratory failure and susceptibility to infections

**Treatment:**
- Managed primarily through supportive care measures widely adopted across geographies
- **Spinraza (nusinersen) approved by FDA 12/23/16:** antisense oligonucleotide (ASO) that promotes proper splicing of backup SMN2 gene copies
SMA disease classification is based on highest motor function achieved

<table>
<thead>
<tr>
<th>Type</th>
<th>Age at Onset</th>
<th>Lifespan</th>
<th>Highest Function Achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA I (~60%)</td>
<td>0-6 months</td>
<td>≤ 2 years (median ~10.5 mos)</td>
<td>Never sit independently</td>
</tr>
<tr>
<td>SMA II (~25%)</td>
<td>7-18 months</td>
<td>2 years to the third decade of life</td>
<td>Sit independently, never walk independently</td>
</tr>
<tr>
<td>SMA III (~15%)</td>
<td>&gt;18 months</td>
<td>Often normal</td>
<td>Walk independently</td>
</tr>
</tbody>
</table>
Identification of SMN1 is a milestone in human genetics

~3.3 billion bp
in human genome

~11 million-bp interval

Genetic mapping of chronic childhood-onset spinal muscular atrophy to chromosome 5q11.2–13.3

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Identification and Characterization of a Spinal Muscular Atrophy–Determining Gene

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The SMN locus

• **SMN1** and **SMN2** reside within an inverted repeat region that covers ~ 2.0 MB on 5q13.

• **SMN2** arose from duplication and subsequent mutation of **SMN1**, in humans only.

• **SMN1** and **SMN2** have 5 nucleotide differences (intronic and exonic) over ~20 kb of each gene.
In SMA, backup SMN2 copies are insufficient for normal motor neuron function.

**Normal**

- **Gene/ pre-mRNA**
  - SMN1: C
  - SMN2: T

- **mRNA / protein**
  - ~100% full-length SMN
  - ~20% unstable SMNΔ7
  - ~80% unstable SMNΔ7

**SMA**

- **Gene/ pre-mRNA**
  - SMN2: ISS

- **mRNA / protein**
  - ~20% full-length SMN
  - ~80% unstable SMNΔ7
SMA severity is inversely correlated with SMN2 copy number

Disease severity

<table>
<thead>
<tr>
<th>SMA type</th>
<th>0 or I</th>
<th>I or II</th>
<th>II or III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>mouse model</td>
<td>Smn^-/-</td>
<td>Smn^-/-;</td>
<td>Smn^-/-;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 copies SMN2</td>
<td>4 copies SMN2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mouse lifespan</td>
<td>E3</td>
<td>~ 1 week</td>
<td>&gt;1.5 yrs</td>
<td></td>
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</tbody>
</table>
Molecular pathogenesis of SMA is correctable by promoting exon 7 inclusion in SMN2 transcripts.

Nusinersen sequence:

\[ 5'-\text{Me}_{\text{Me}}\text{CA}_{\text{Me}}\text{C}_{\text{Me}}\text{U}_{\text{Me}}\text{U}_{\text{Me}}\text{U}_{\text{Me}}\text{CA}_{\text{Me}}\text{UAA}_{\text{Me}}\text{UG}_{\text{Me}}\text{C}_{\text{Me}}\text{UGG}-3' \]

Backbone modifications:

- HnRNP A1/2
- Nusinersen
- ISS-N1

>80% unstable SMNΔ7

<20% full-length SMN

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Earlier treatment of an induced mouse model of SMA improves phenotype and rescue of gene expression profile

Staropoli JF et al., Genomics 104: 220-228 (2015)
Spinraza trials show improved outcomes with presymptomatic intervention

Data shown for subjects with SMN2 copy number = 2

- Presymptomatic neonates, open-label (1/2016 cut)
- Early-onset, randomized to Rx (6/2016 cut)
- Early-onset, open-label (1/2016 cut)
- Early-onset, randomized to sham (6/2016 cut)
Preclinical and clinical data support case for newborn screening

Pilot results support inclusion of SMA on federal newborn screening panel

- As of June 2016, ~100,000 newborns screened in Taiwan, 6 of whom were found to have SMA

- As of June 2016, ~2,000 newborns screened in New York, 1 of whom was found to have SMA

- No known false-negatives reported to date

- Validated assays and clinical data supported recent nomination of SMA for inclusion on the US Recommended Uniform Screening Panel; application submitted to HHS by CureSMA and Muscular Dystrophy Association