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Newborn Screening for Spinal Muscular Atrophy (SMA)

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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

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SMA

Phenotype	Age of Onset	Life Span	Motor Milestones	Other Findings
SMA 0	Prenatal	<6 months	None achieved	Severe neonatal hypotonia Severe weakness Early respiratory failure Facial diplegia
SMA I Werdnig-Hoffman	<6 months	Most often ≤2 years, but may live longer	Sit with support only	Mild joint contractures Normal or minimal facial weakness Variable suck & swallow difficulties
SMA II **Dubowitz**	6-18 months	70% alive at age 25 years	Independent sitting when placed	Postural tremor of fingers
SMA III **Kugelberg-Welander**	>18 months	Normal	Independent ambulation	
SMA IV	Adulthood	Normal	Normal	

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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

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SMN2 Copy Number	Normal	In SMA I	In SMA III	Total (SMA I + SMA III)
0	14.4%	**0**	0	
1	32%	**7** (13.5%)	0 (0%)	**7** (4.9%)
2	51%	**43** (82.7%)	0 (0%)	**43** (30.3%)
3	4%	**2** (3.9%)	**70** (77.8%)	**72** (50.7%)
4		**0** (0%)	**20** (22.2%)	**20** (14.1%)
Total		**52**	**90**	**142**

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 +

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Kemper et al ACHDNC evidence review group 8/3/2017

Mechanism of Action

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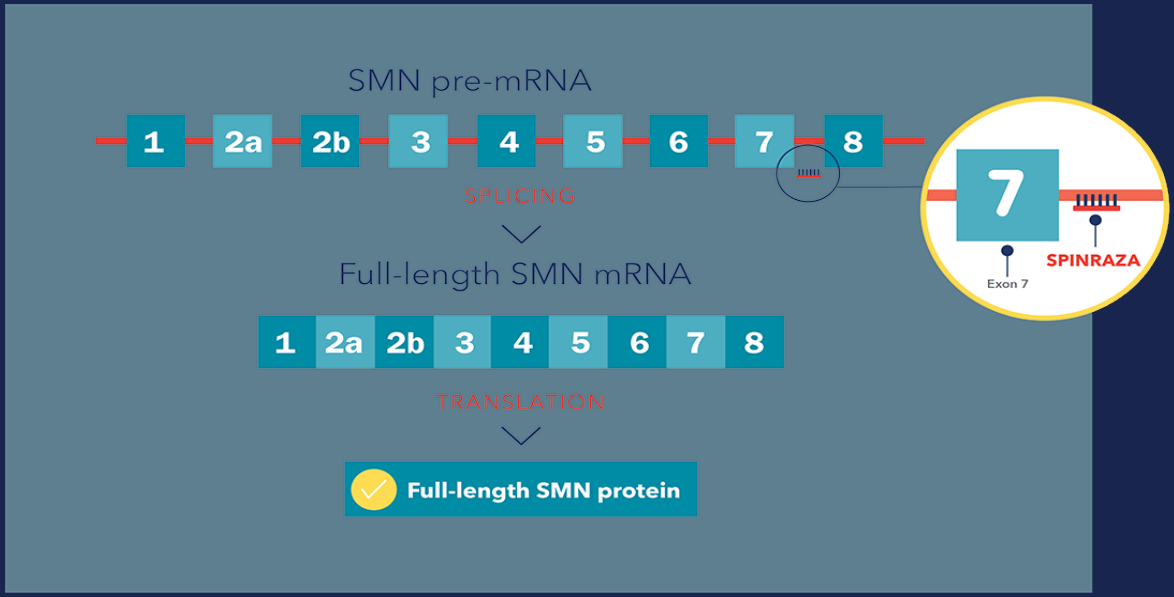

SPINRAZA binds to a specific sequence in the intron downstream of exon 7 of the *SMN2* transcript

From Sprinraza Manufacturer
https://www.spinraza-hcp.com/en_us/home/about/mechanism-of-action.html

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

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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.

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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

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Thank you