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**

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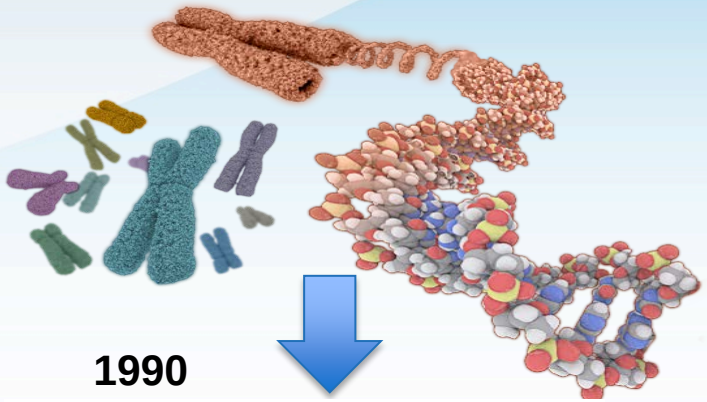
SMA disease classification is based on highest motor function achieved

Type (% live births)	Age at Onset	Lifespan	Highest Function Achieved
SMA I (~60%)	0-6 months	≤ 2 years (median ~10.5 mos)	Never sit independently
SMA II (~25%)	7-18 months	2 years to the third decade of life	Sit independently, never walk independently
SMA III (~15%)	>18 months	Often normal	Walk independently

Identification of *SMN1* is a milestone in human genetics



1990

~3.3 billion bp in human genome

1995

LETTERS TO NATURE

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

~11 million-bp interval

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Identification and Characterization of a Spinal Muscular Atrophy–Determining Gene

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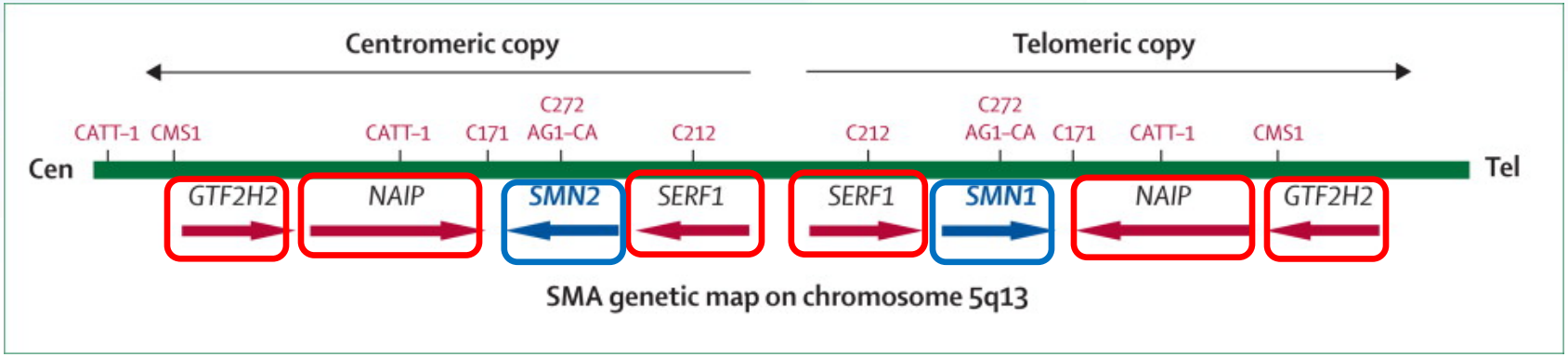
The SMN locus

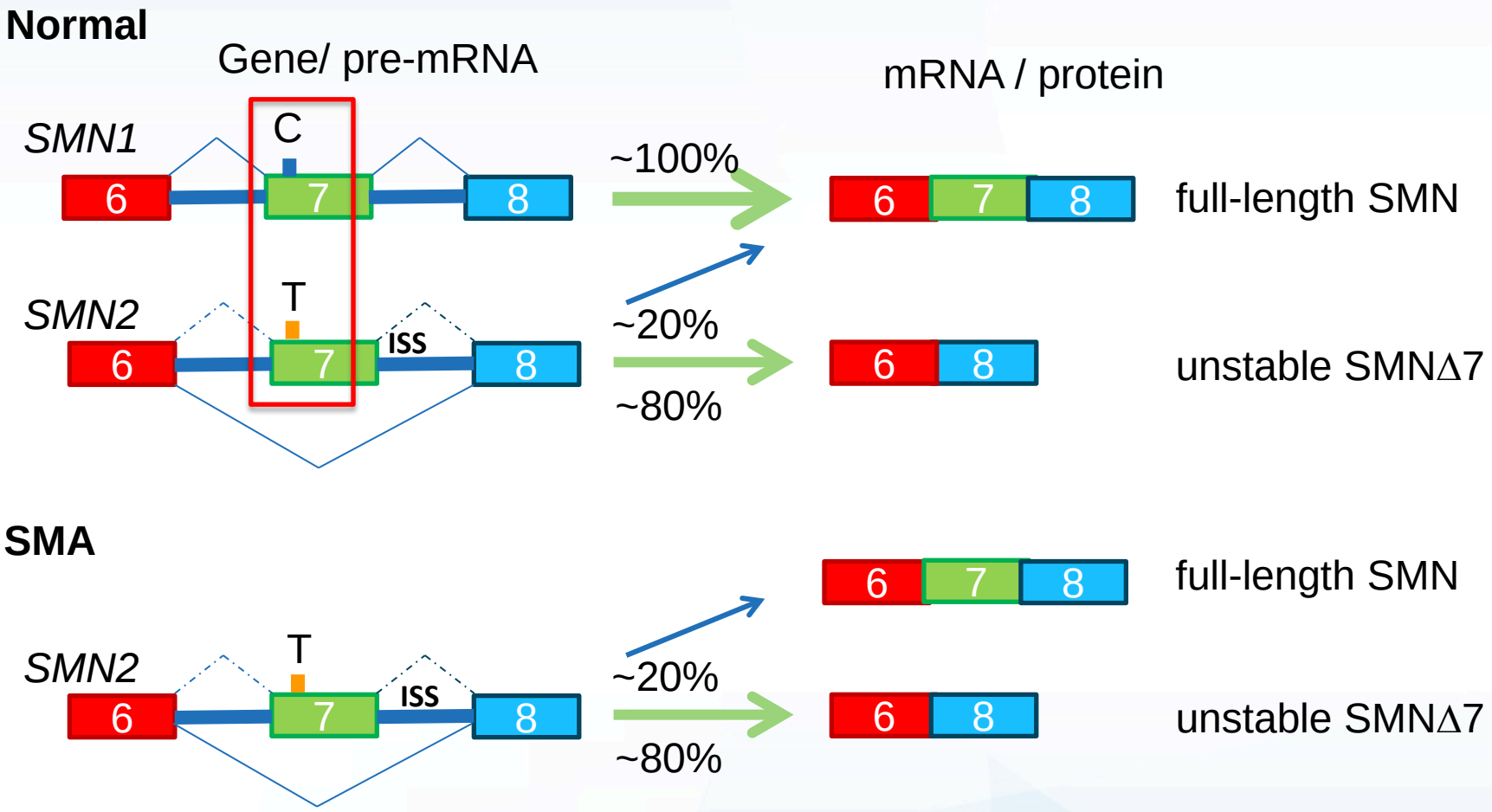


- *SMN1* and *SMN2* reside within an inverted repeat region that covers ~ 2.0 MB on 5q13.

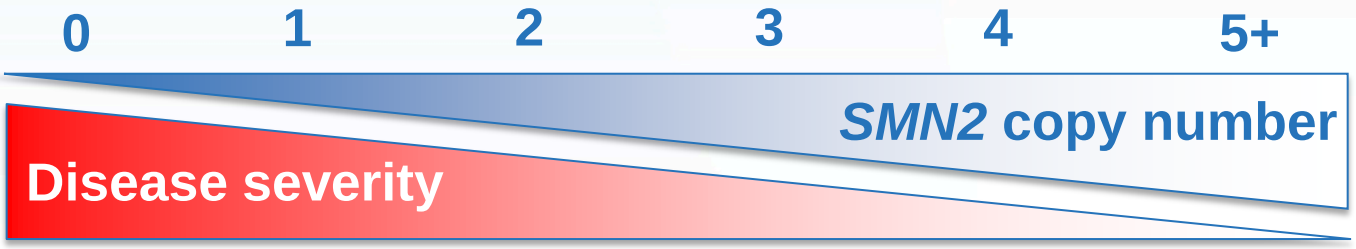
- *SMN2* arose from duplication and subsequent mutation of *SMN1*, in humans only.

- *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

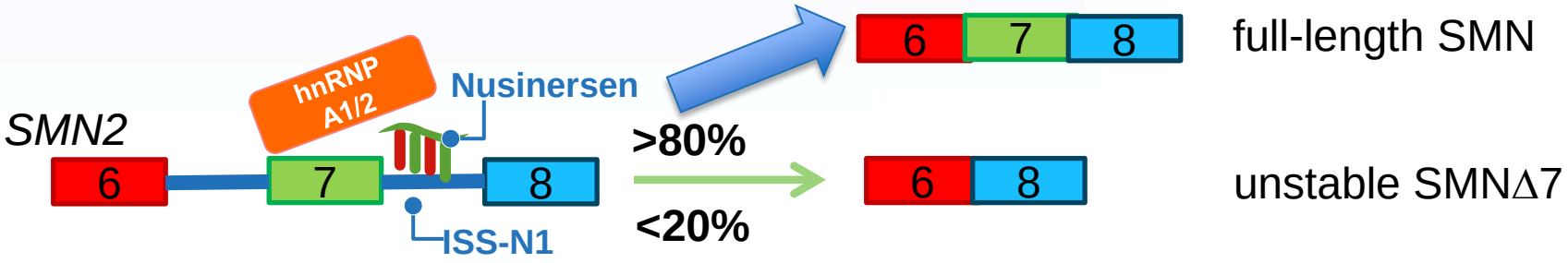


SMA severity is inversely correlated with *SMN2* copy number



SMA type	0 or I	I or II	II or III	IV
mouse model	*Smn*$^{-/-}$	*Smn*$^{-/-}$; 2 copies *SMN2*		*Smn*$^{-/-}$; 4 copies *SMN2*
mouse lifespan	E3	~ 1 week		>1.5 yrs

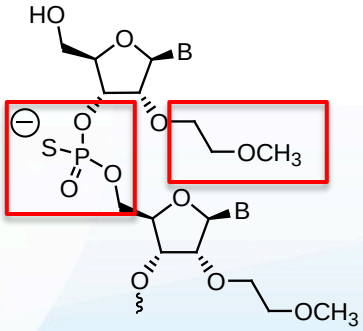
Molecular pathogenesis of SMA is correctable by promoting exon 7 inclusion in *SMN2* transcripts



Nusinersen sequence

5′-^{Me}U^{Me}CA^{Me}C^{Me}U^{Me}U^{Me}U^{Me}CA^{Me}UAA^{Me}UG^{Me}C^{Me}UGG-3′

Backbone modifications



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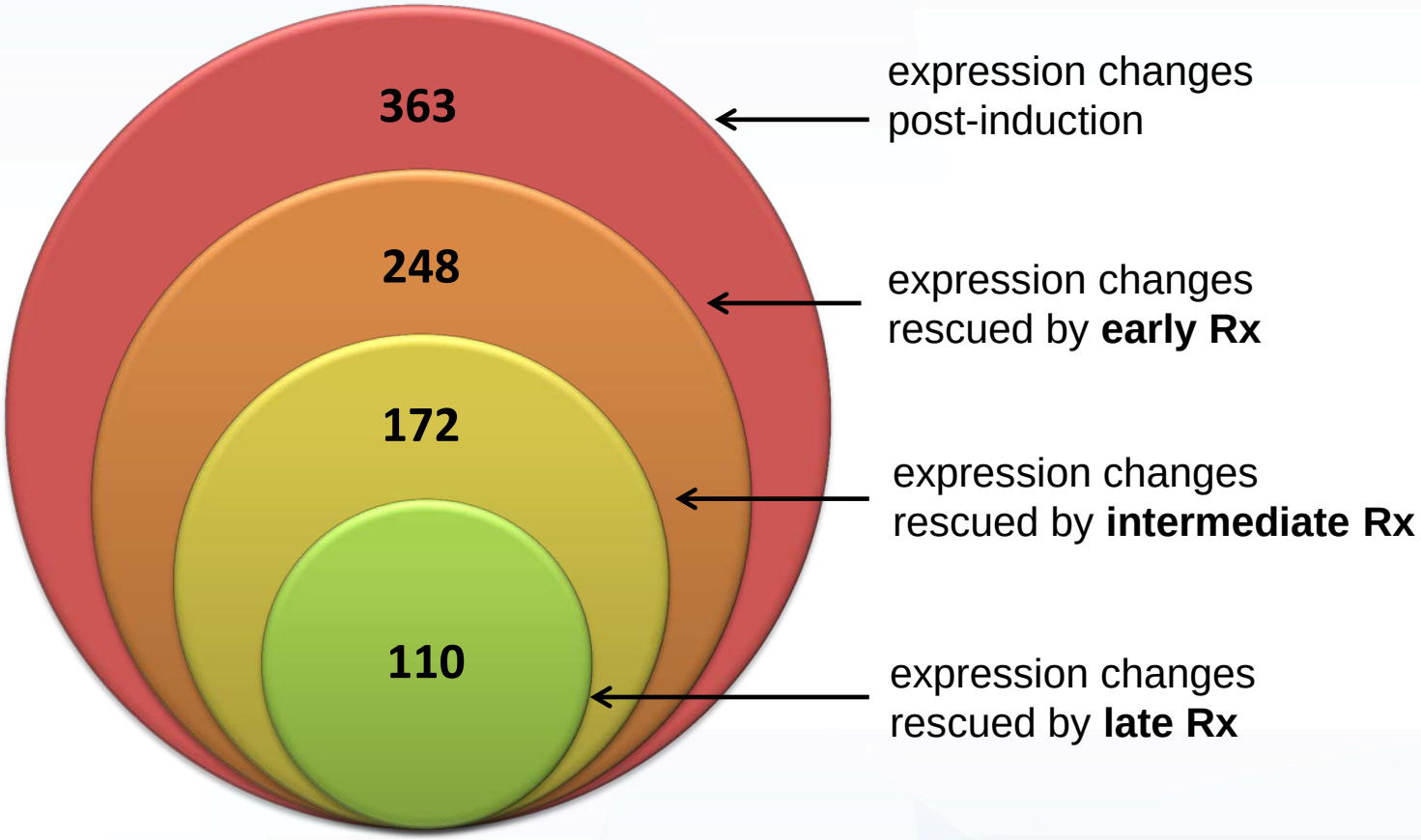
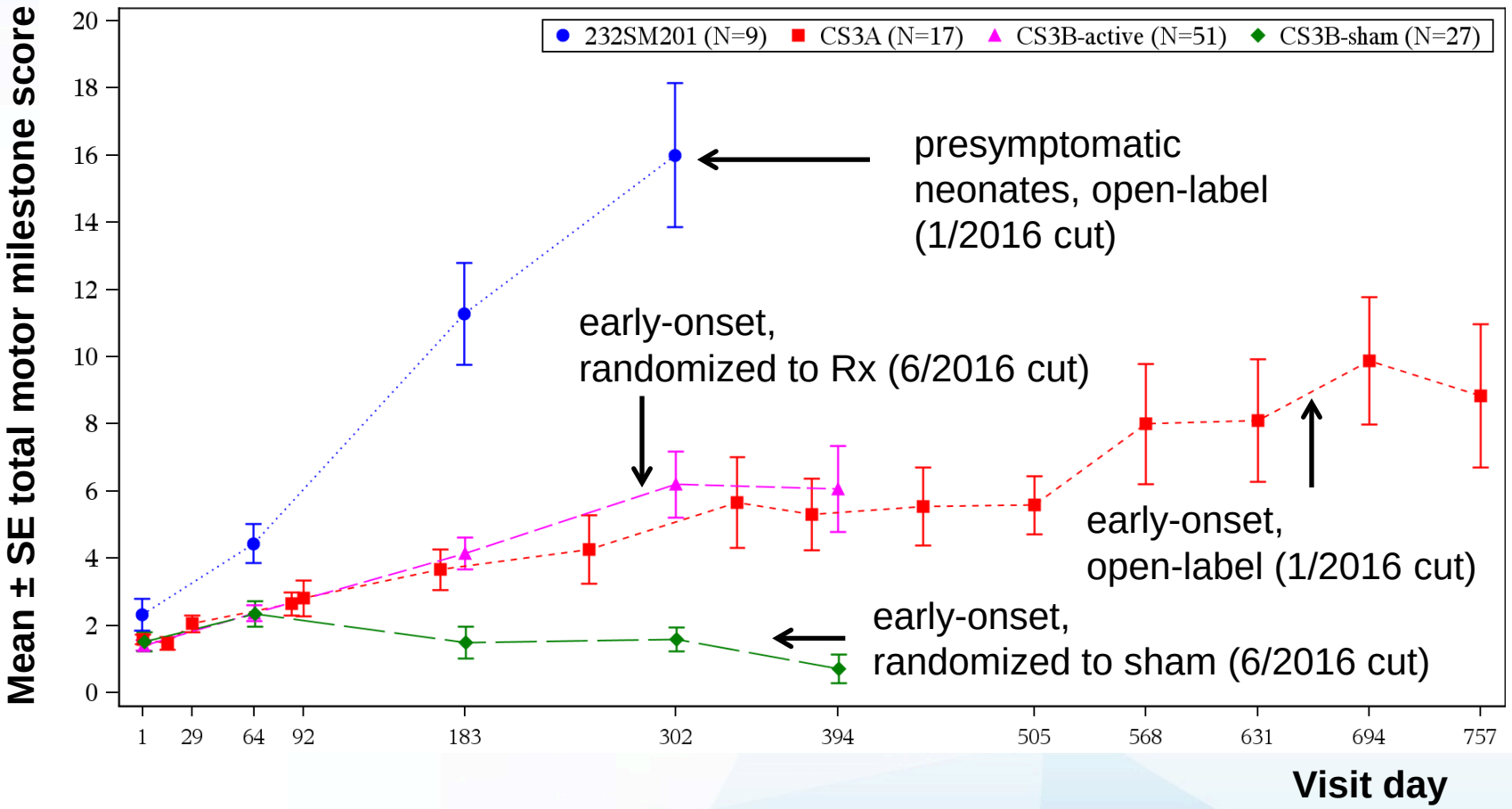
Earlier treatment of an induced mouse model of SMA improves phenotype and rescue of gene expression profile



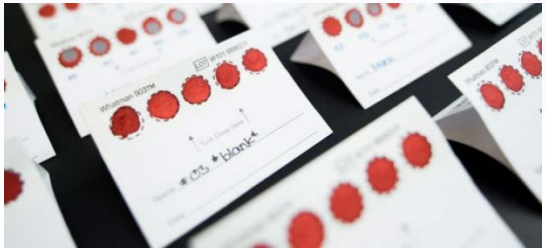
Staropoli JF et al., Genomics 104: 220-228 (2015)

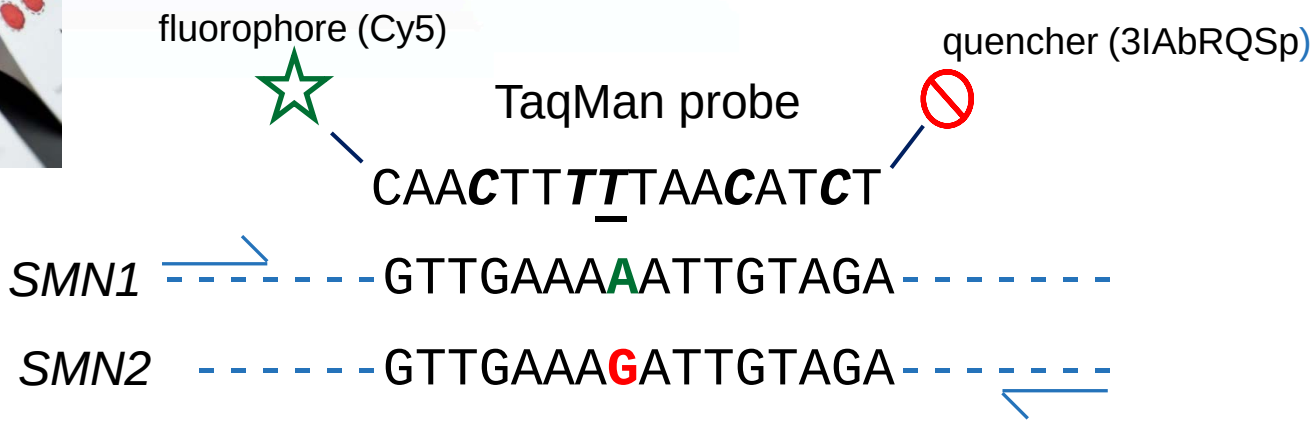
Spinraza trials show improved outcomes with presymptomatic intervention

Data shown for subjects with *SMN2* copy number = 2



Preclinical and clinical data support case for newborn screening





Bold italic indicates positions of locked nucleic acids in probe

Taylor J . et al. A newborn bloodspot screening test using multiplexed real-time PCR to simultaneously screen for spinal muscular atrophy and severe combined immunodeficiency. *Clinical Chemistry* [2015] 61:412-419.

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

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