Spinal Muscular Atrophy

The Disease and New Treatments

United Healthcare®

Spinal Muscular Atrophy (SMA)

Disclaimer

I have no actual or potential conflict of interest in relation to any product or service mentioned in this presentation.

Spinal Muscular Atrophy (SMA)
Objectives

1. Know what Spinal Muscular Atrophy is.
2. Be familiar with the clinical presentations of the different types of spinal muscular atrophy (SMA).
3. Know lab tests that are used to identify spinal muscular atrophy (SMA).
4. Understand how spinal muscular atrophy (SMA) is treated.
5. Have a basic understanding that will enable you to support families with children with SMA.

Spinal Muscular Atrophy
Questions We Will Address

1. What is Spinal Muscular Atrophy?
2. What is the prevalence of spinal muscular atrophy (SMA) in the US?
3. Which clinical history findings are characteristic of spinal muscular atrophy (SMA)?
4. Which lab test results are characteristic of spinal muscular atrophy (SMA)?
5. How is spinal muscular atrophy (SMA) treated?

(Answers available in the handout)

Spinal Muscular Atrophy
The Disease

- SMA is a group of inherited neuromuscular disorders
- The incidence is 1 in 10,000 infants born each year
- Causes a loss of nerve cells in the spinal cord and the brainstem that go to skeletal muscles (voluntary/striated muscles)
- May affect other tissues in the body

Spinal Muscular Atrophy
The Disease

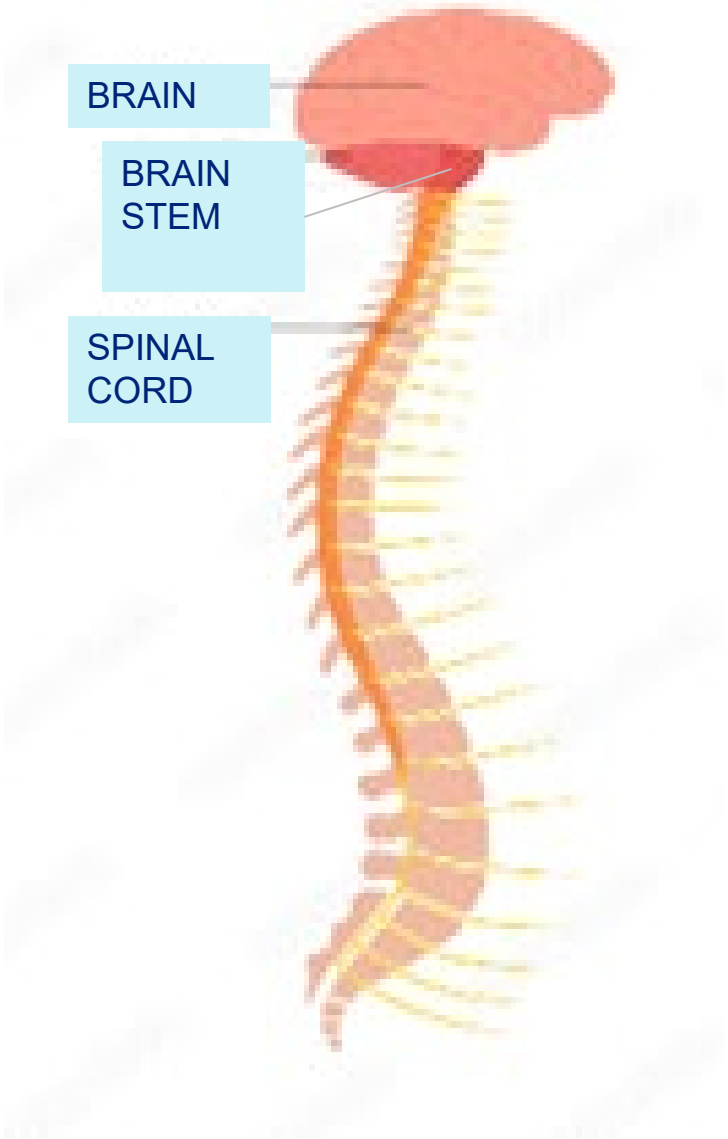
Laboratory Tests

The only laboratory tests that are helpful are genetic tests for Spinal Muscular Atrophy

Tests are commercially available for patients and pregnant women for prenatal diagnosis

Spinal Muscular Atrophy

- Brain
- Brain Stem
- Spinal Cord



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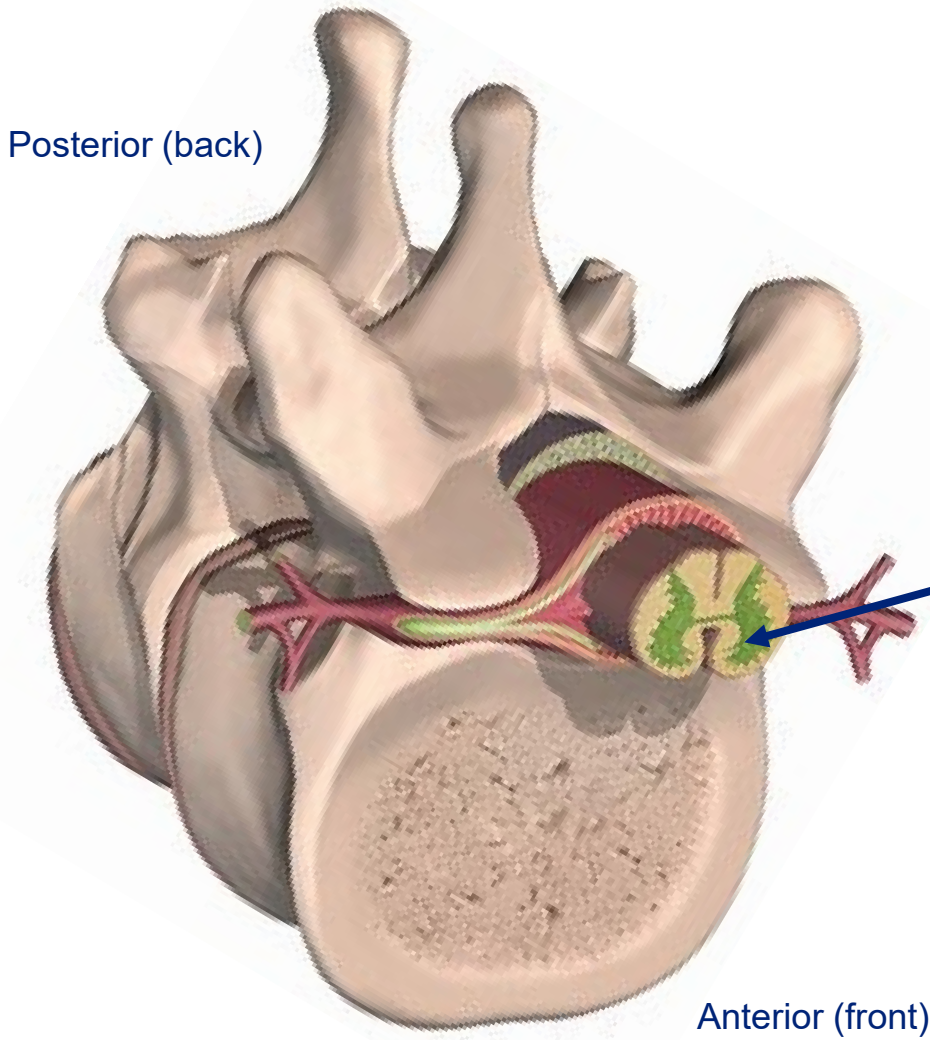
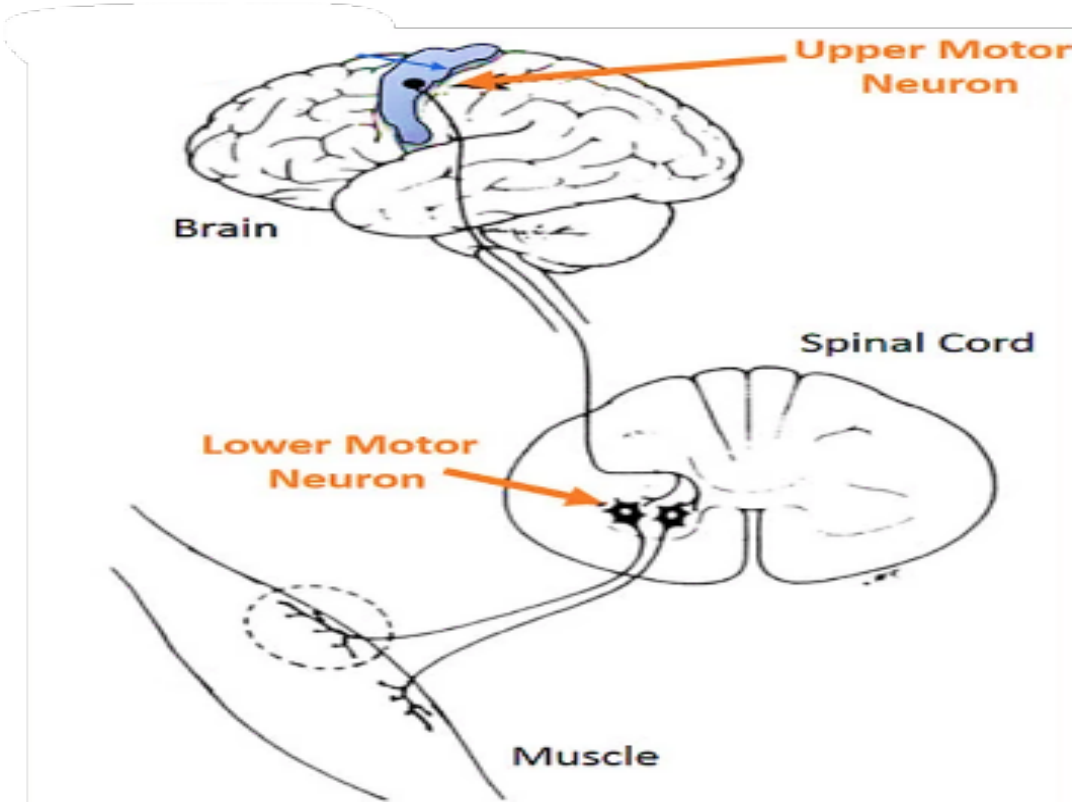
Spinal Muscular Atrophy
The Disease

The affected nerve cells are called **LOWER MOTOR NEURONS** or **ANTERIOR HORN CELLS**.

Spinal Muscular Atrophy
The Disease



Spinal Muscular Atrophy
The Disease

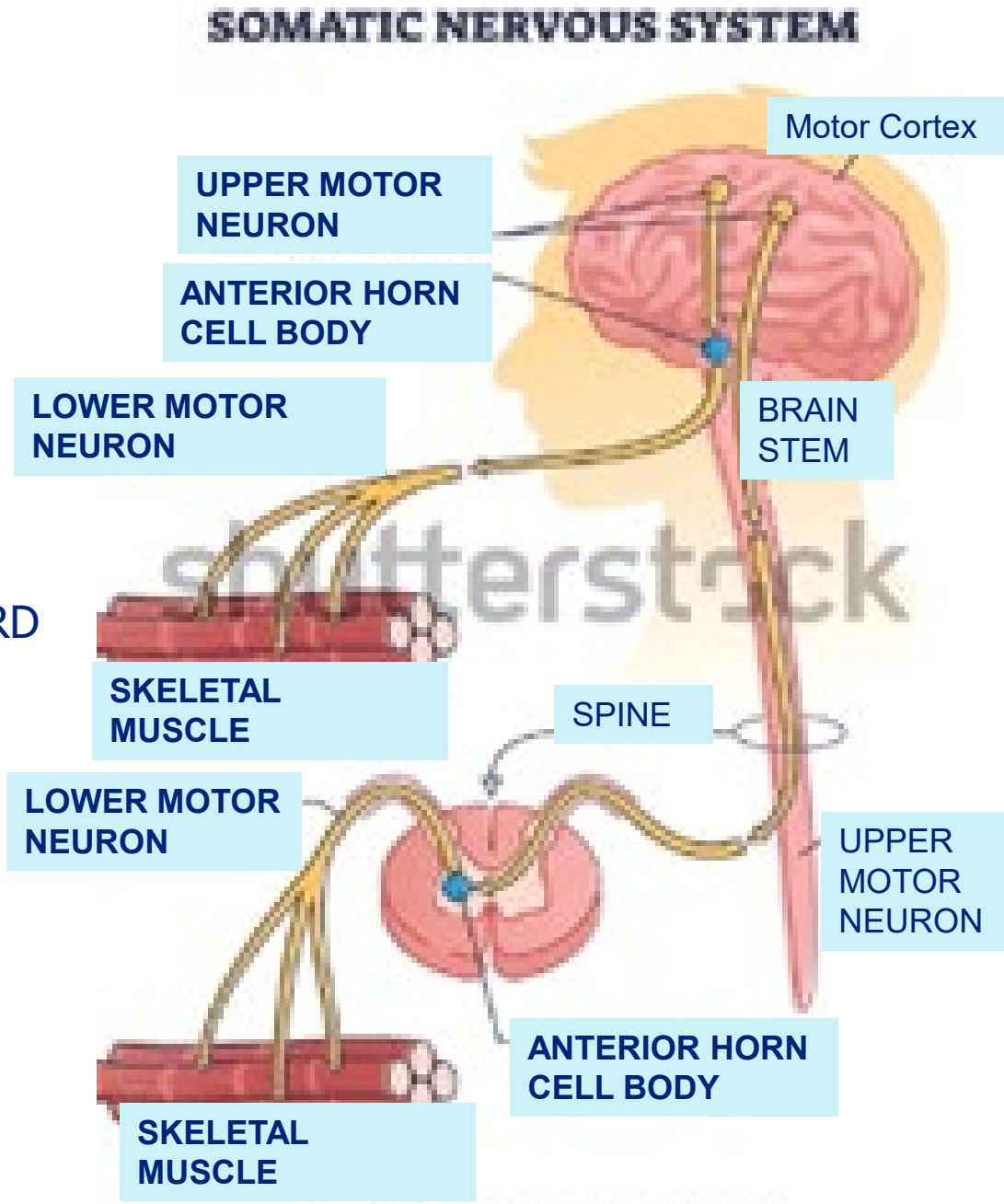


Spinal Muscular Atrophy
The Disease

Lower Motor Neurons relay nerve impulses from upper motor neurons, located in the brain, to the muscles they control

Spinal Muscular Atrophy

- BRAIN (Motor Cortex)
- UPPER MOTOR NEURON
- BRAIN STEM
- SPINE
- ANTERIOR HORN OF SPINAL CORD CELL BODY
  -(cross section)
- SPINAL CORD
- LOWER MOTOR NEURON
- SKELETAL MUSCLE



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Spinal Muscular Atrophy
The Disease

- The loss of lower motor neurons leads to:
  -progressive muscle WEAKNESS
  -muscle wasting: ATROPHY
  -low muscle tone: HYPOTONIA

Spinal Muscular Atrophy
The Disease

- More pronounced in muscles closest to the trunk of the body:

proximal muscles

-shoulders,

-hips

-back.

Spinal Muscular Atrophy
The Disease

- Neurons controlling any voluntary muscle can be affected,
  - Including muscles for:
    - feeding
    - swallowing
    - breathing
    - vision

Spinal Muscular Atrophy
The Disease

- Most common form of SMA
  - -Caused by a mutated or missing gene
  - -Name of the gene:
  - -SURVIVAL MOTOR NEURON 1 GENE

SMN 1

  - -Responsible for production of the

SURVIVAL MOTOR NEURON PROTEIN

  - -This protein is necessary for normal neuron growth and function

Spinal Muscular Atrophy
The Disease

- SMA is divided into 5 types

- 5 SMA types are labelled 0 to 4
  - based on:
    - -age of symptoms onset
    - -maximum motor function achieved

Spinal Muscular Atrophy
The Disease

SMA Type 0

- Occurs before birth
- Move less in the uterus
- Joint deformities: CONTRACTURES
- Weak muscle tone: HYPOTONIA
- Respiratory muscles are weak
- Often do not live past infancy

Spinal Muscular Atrophy
The Disease

SMA Type 0

- Have respiratory failure
- Some have heart defects
  - Heart defects are related to the severe deficiency of SMN Protein
- This type is rare

Spinal Muscular Atrophy
The Disease

SMA Type I

- WERDNIG-HOFFMAN disease or
  INFANTILE-ONSET SMA
- More severely affected children have:
  - reduced movement
  - shortening of muscles or tendons: CONTRACTURES
- Evident before 6 months of age
  - sometimes in utero or at birth

Spinal Muscular Atrophy
The Disease

SMA Type I

- Other symptoms
  - -Weak muscle tone, HYPOTONIA
  - -lack of tendon reflexes
  - -twitching
  - -skeletal abnormalities,
  - -problems swallowing or feeding.

Spinal Muscular Atrophy
The Disease

SMA Type I

- Bell-shaped chest that inhibits breathing
- This is the most common type
- Without supportive treatment, many affected children die before age 2 years

Spinal Muscular Atrophy
The Disease

SMA Type ll

- DUBOWITZ DISEASE
- Onset between 6 and 12 months of age
- Children can sit without support
- Unable to stand or walk without help
- Children may have respiratory problems
- Develop tremors in their fingers

Spinal Muscular Atrophy
The Disease

SMA Type ll

- DUBOWITZ DISEASE
- Have scoliosis (spine curves side-to-side)
- Life expectancy is reduced
- Most live into adolescence or young adulthood.

Spinal Muscular Atrophy
The Disease

SMA Type lll

- KUGELBERG-WELANDER disease
- Appears after age 18 months
- Children can walk independently with difficulty
- Have trouble:
  - running
  - rising from a chair
  - climbing stairs

Spinal Muscular Atrophy
The Disease

SMA Type III

- Other complications:
  - -curvature of the spine: scoliosis (spine curves side-to-side)
  - -contractures
  - -respiratory infections.
- With supportive treatment, most individuals can have an average lifespan.

Spinal Muscular Atrophy
The Disease

SMA Type IV

- SMA Type IV develops after 21 years of age
- This type is rare
- Mild to moderate leg muscle weakness
- Tremors
- Mild breathing problems
- Normal life expectancy

Spinal Muscular Atrophy
The Disease

Inheritance

- SMA is inherited as an autosomal recessive trait on chromosome 5
- Both parents must carry the abnormal SMN1 gene for SMA to occur
- Based upon classical Mendelian Genetics, ¼ of the infants from these parents will have SMA

Spinal Muscular Atrophy
The Disease

Variable Presentations

- Normal SMN1 genes produce a fully functional SMN protein.

When the **SMN1** gene is **dysfunctional** because it has mutations or it has been deleted, **insufficient** amounts of **SMN protein** is produced.

Spinal Muscular Atrophy
The Disease

Variable Presentations

- SMN2 is a neighboring gene on chromosome 5
- Also produces SMN protein.
- Only a small percentage is functional
- Around 10% to 20%

Spinal Muscular Atrophy
The Disease

Variable Presentations

- A person can have multiple copies of the SMN2 gene.
- The number varies between zero and eight copies.
- The more SMN2 gene copies present, the greater the amount of functional SMN protein that is produced.
- This results in a milder disease
- Three or more copies of the SMN2 gene is associated with less severe disease

Spinal Muscular Atrophy
The Disease

Variable Presentations

- Disease modifiers can affect (modify) onset and severity
- Levels of both *plastin 3 protein* and *ZPR1 protein* have been identified as modifiers of SMN1-related SMA
- These proteins are not related to the SMN protein
- Their absence does not cause SMA

Spinal Muscular Atrophy
The Disease

Variable Presentations

- SMA from a defect or deleted SMN 1 gene is the most common
- Less common SMA forms are caused by changes in other genes including:
  - VAPB gene on chromosome 20.
  - DYNC1H1 gene on chromosome 14.
  - BICD2 gene on chromosome 9.
  - UBA1 gene on the X chromosome.

Spinal Muscular Atrophy
The Disease

Variable Presentations

- The less common genetic forms of SMA will not be included in today's presentation.

Spinal Muscular Atrophy
The Disease

- Treatment:

To understand the treatment options, it will be necessary to have a brief review of the genetics and pathogenesis of SMA

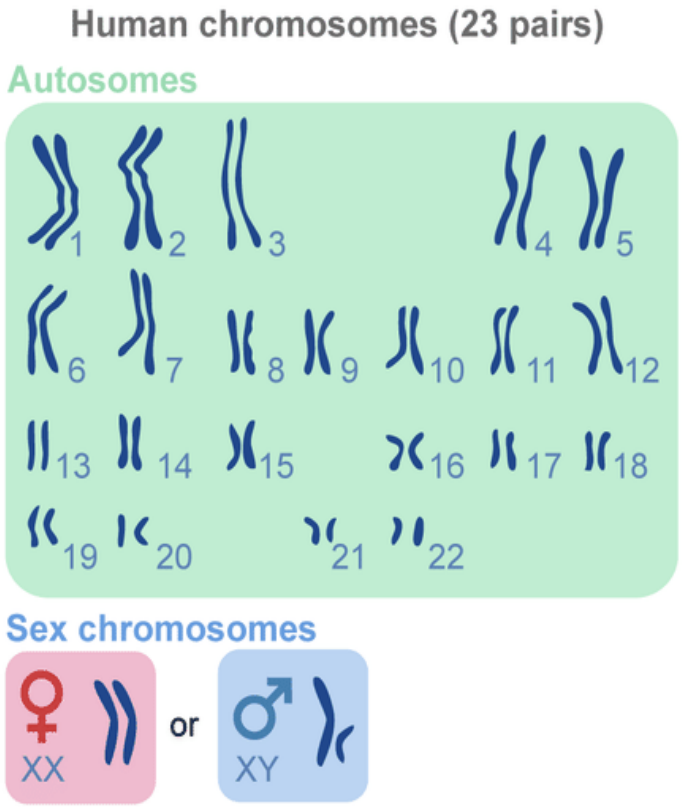
Spinal Muscular Atrophy Genetics

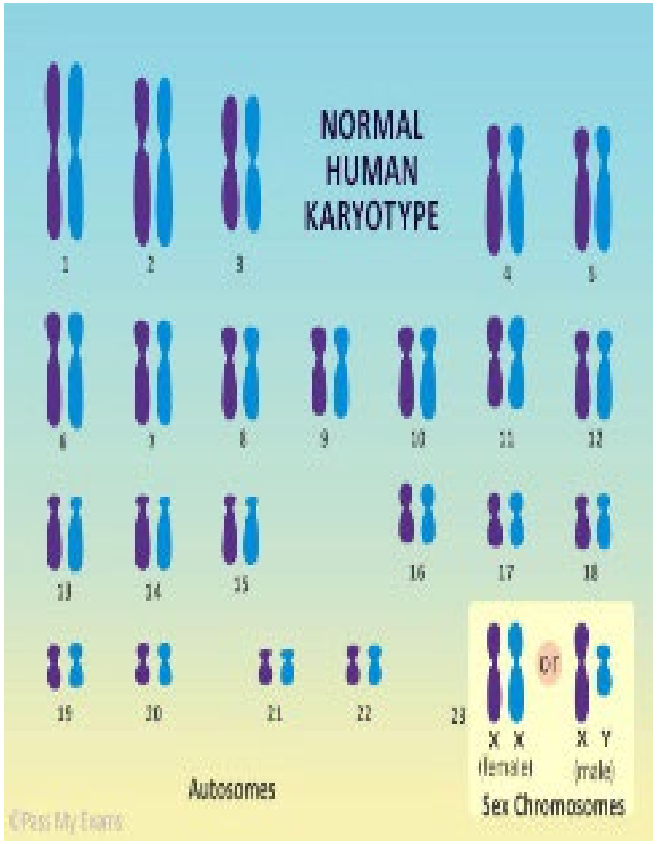
The next group of slides will be an abbreviated course in genetics.

Spinal Muscular Atrophy
Genetics

- **Chromosome**
- The structure that caries the genetic information in the nucleus of each cell
- 46 chromosomes in the human genome (the **KARIOTYPE**)
  - 22 pairs
  - 1 pair sex chromosomes
    - 2 X chromosomes or 1 X and 1 Y

Spinal Muscular Atrophy Genetics



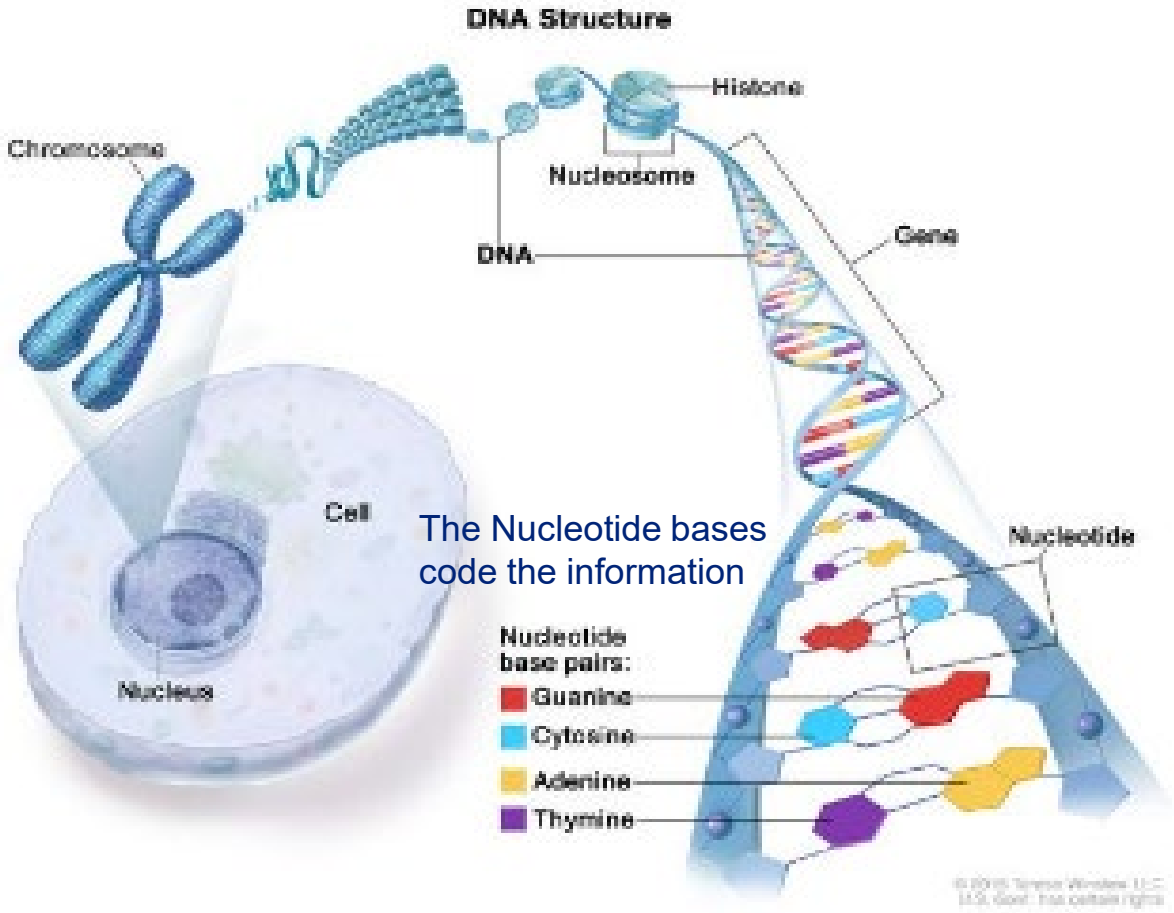


Each Chromosome has a matched partner except the male sex chromosomes (XY).

Spinal Muscular Atrophy
Genetics

- **Gene**
- Hereditary factor that determines (or influences) a particular trait
- A SPECIFIC DNA SEQUENCE
- Located on a SPECIFIC REGION
- On a SPECIFIC CHROMOSOME
- Specific location is a **genetic locus.**

Spinal Muscular Atrophy Genetics



The Nucleotide bases code the information

Spinal Muscular Atrophy Genetics

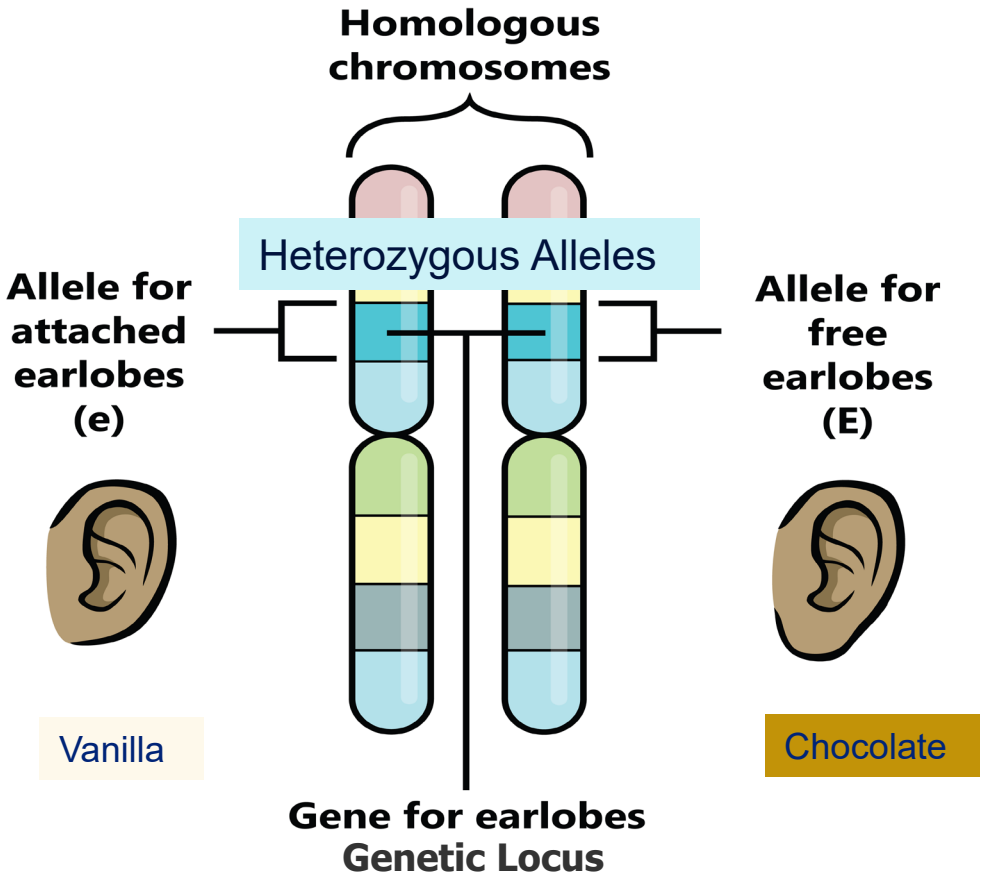
- **Allele**

- A variation of a gene
  - in the same way that chocolate and vanilla are variations of ice cream.

Spinal Muscular Atrophy
Genetics

- **Genotype**
- The collection of alleles found in the DNA
- **Homologous** chromosomes are a matched pair
  - -E.G., 2 of Chromosome #5
    - -(SMA Chromosome)
- If both chromones have same alleles for a particular gene = **homozygous**
- Two different alleles for a particular gene = **heterozygous** at that **genetic locus.**

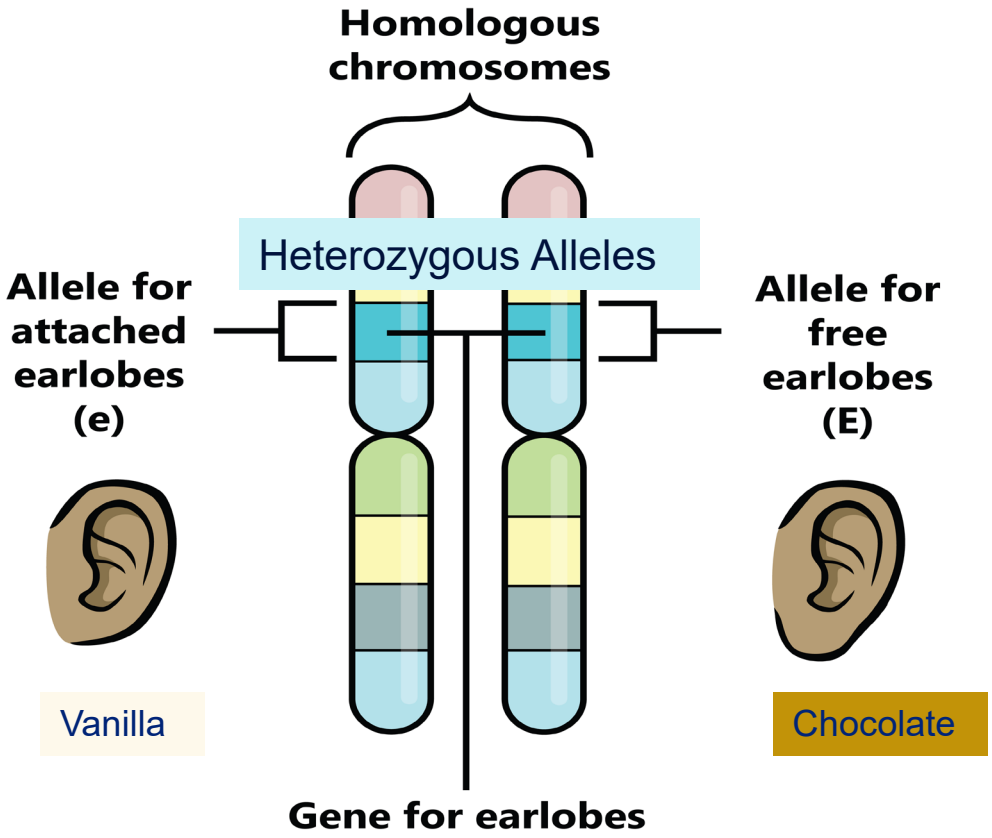
Spinal Muscular Atrophy Genetics



Spinal Muscular Atrophy
Genetics

- **Phenotype**
- Observable traits.
- **Genes** may be Homozygous or heterozygous at a particular locus
- The **Phenotype** expresses just one of them.
- One allele masks the appearance of the other
- **One is dominant, one is recessive**

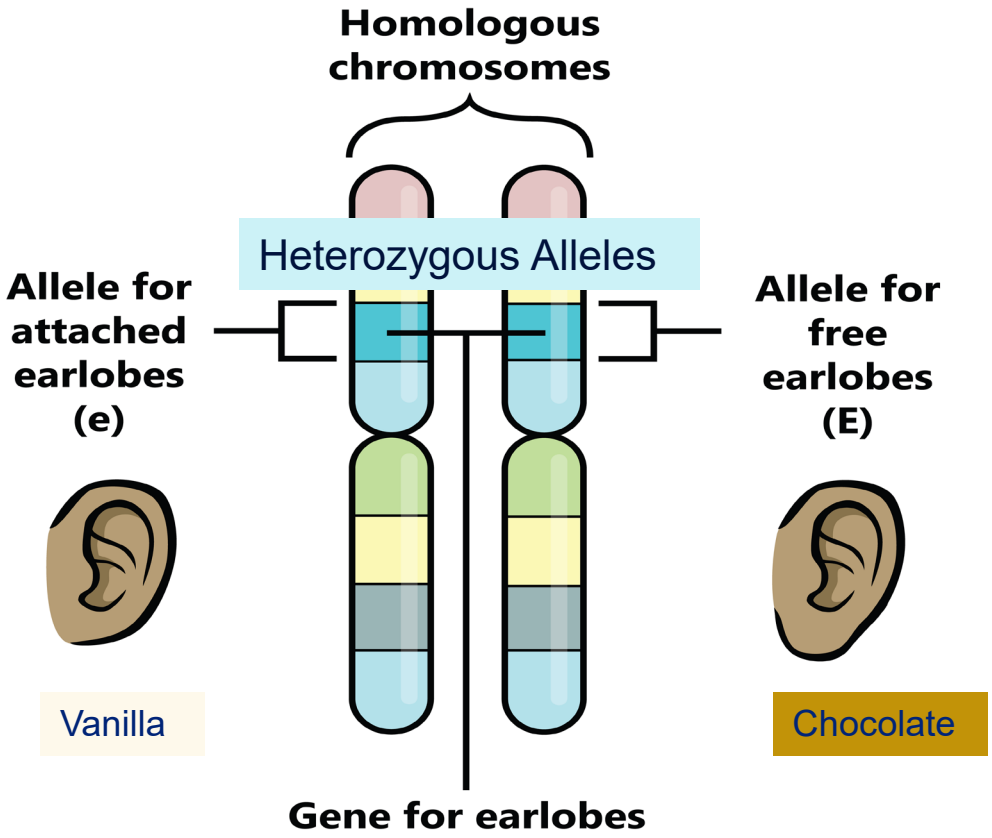
Spinal Muscular Atrophy Genetics



Spinal Muscular Atrophy
The Disease

- A **Dominant** allele produces its phenotype whether the organism is homozygous or heterozygous at that locus
- Chocolate dominates Vanilla even though they are both present
- A **Recessive** allele produces its phenotype only when homozygous at the locus (2 vanillas)

Spinal Muscular Atrophy Genetics



Spinal Muscular Atrophy Genetics

- Some **Recessive** alleles are associated with diseases.
- A heterozygous person will be phenotypically normal
- They carry the recessive disease-associated allele
- This person is a **carrier** and can pass on the disease allele to the offspring
- It takes 2 carriers to have a child with the disease

Spinal Muscular Atrophy Genetics

A is a **Dominan**t trait
Free earlobes/Chocolate

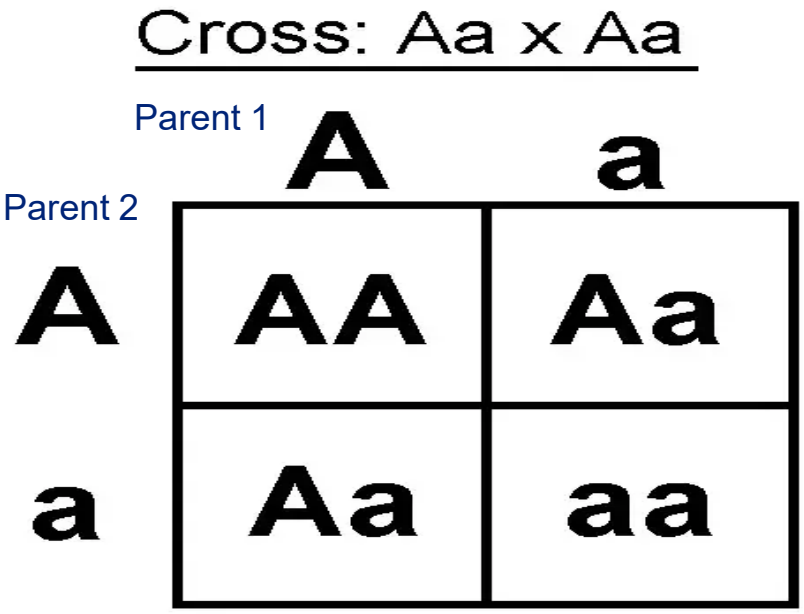
a is a **Recessive** trait
Attached earlobes/Vanilla

AA and **Aa** **Phenotype** will have **Free** earlobes

aa Phenotype will have **Attached** earlobes

Both parents are **Heterozygous Aa**

PUNNETT SQUARE



Spinal Muscular Atrophy Genetics

"Address" of a gene on a chromosome

- The address for the SMN1 gene

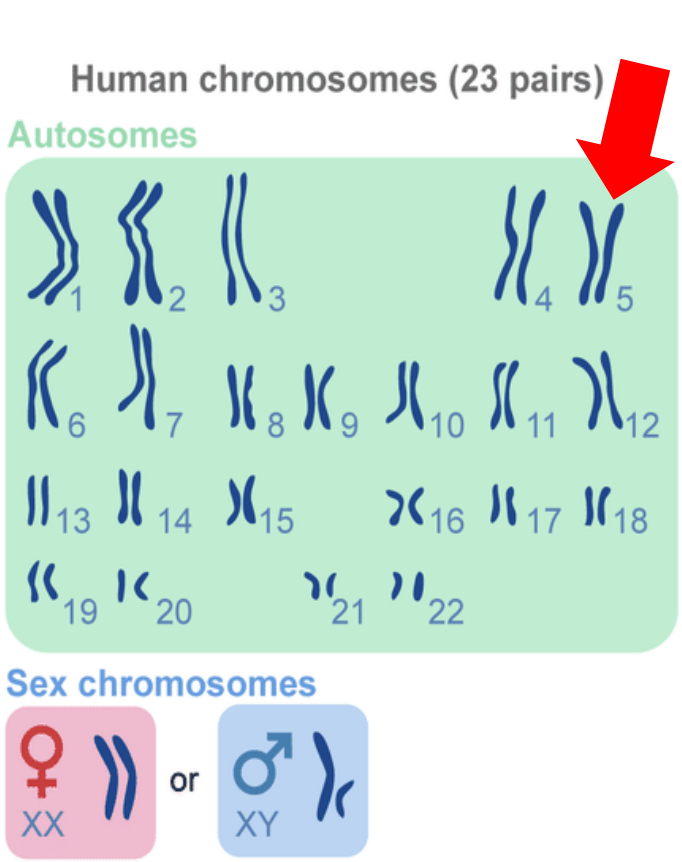
  5q13.2 region

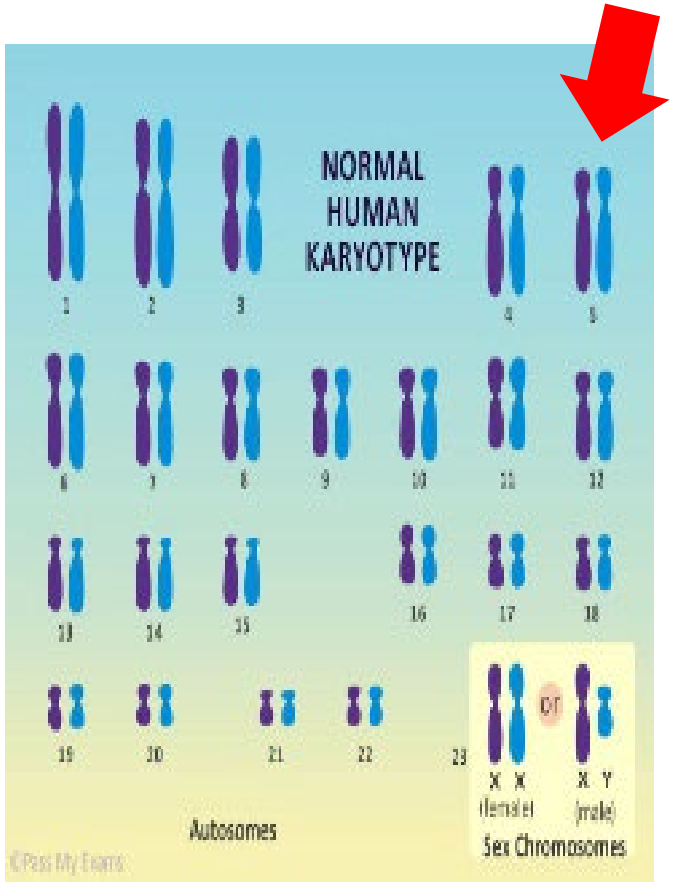
Chromosome 5

q is the short arm of Chromosome 5

13.2 band number on Chromosome 5

Spinal Muscular Atrophy Genetics



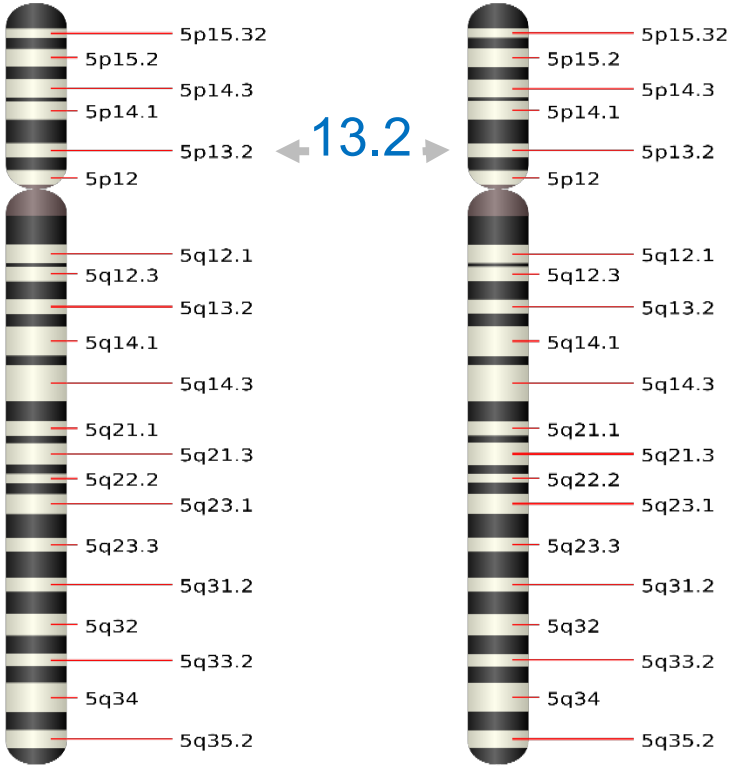


Each Chromosome has a matched partner except the male sex chromosomes (XY).

Spinal Muscular Atrophy Genetics

CHROMOSOME 5
Homogous Alleles

SHORT ARM

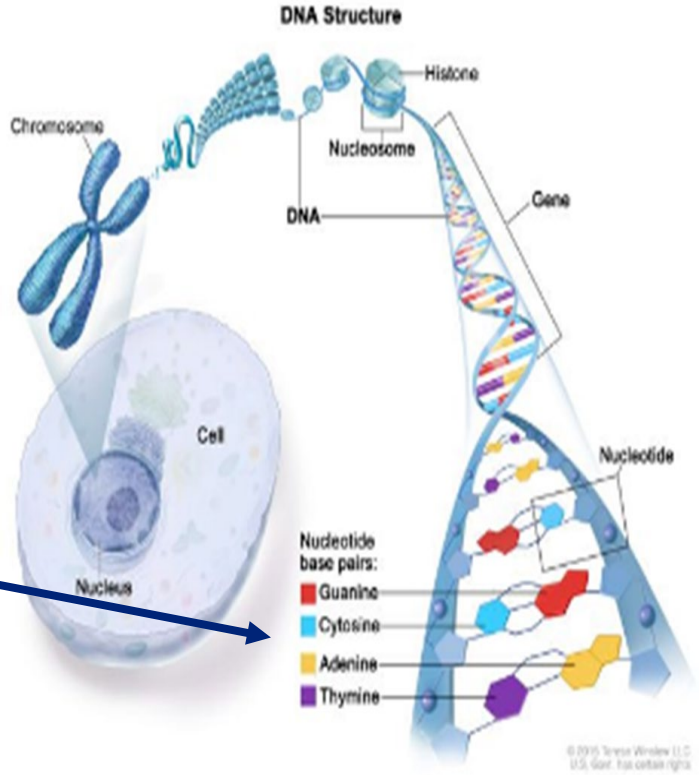


BOTH CHROMOSOMES HAVE TO HAVE THE ABNORMAL SMN1 GENE AT THE GENE LOCUS 13.2 FOR SMA TO OCCUR

Spinal Muscular Atrophy
Genetics

Subdivisions of a Chromosome

Genes are made up of a series of connected chemical bases.

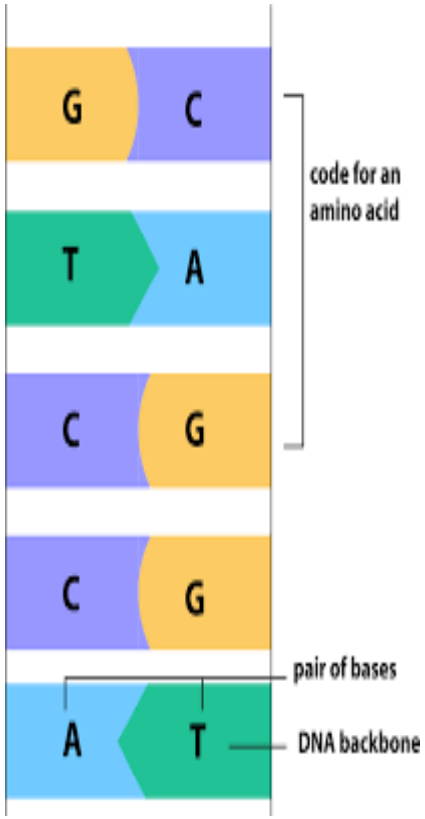


Spinal Muscular Atrophy Genetics

Subdivisions of a Gene

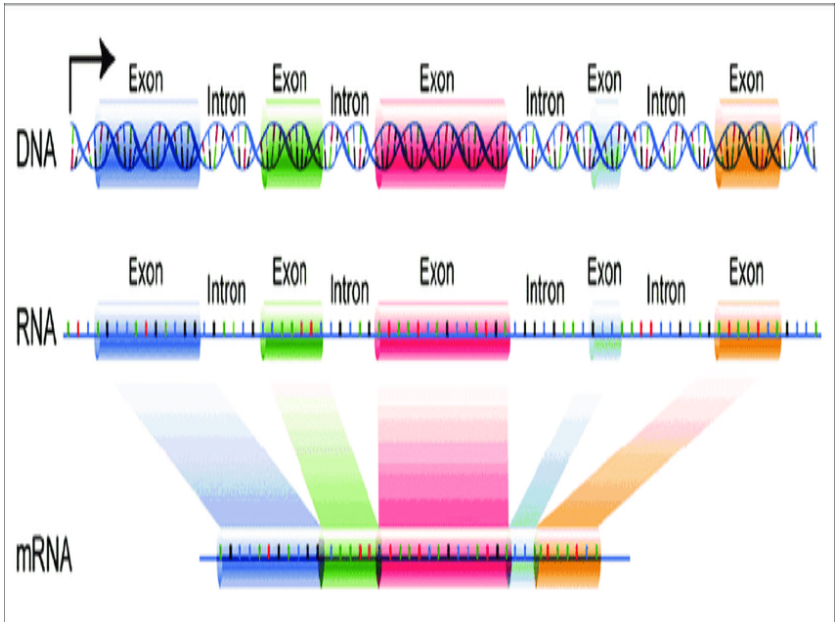
Each combination of 3 bases codes for an **Amino Acid.**

Amino Acids are the building blocks of **Proteins**



Spinal Muscular Atrophy Genetics

Several of these threesomes are grouped together to form an **EXON.** These code for a piece of a protein.



Others grouped together are separators- **INTRON**

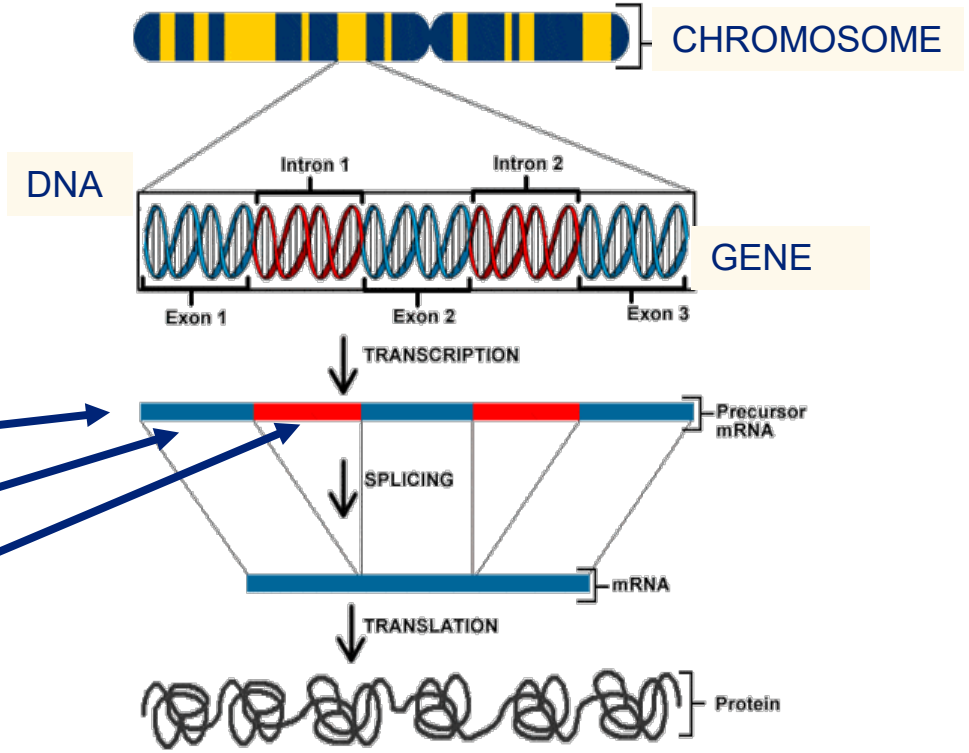
INTRONS separate the **EXONS**

INTRONS have other functions

Spinal Muscular Atrophy Genetics

How To Make A Protein

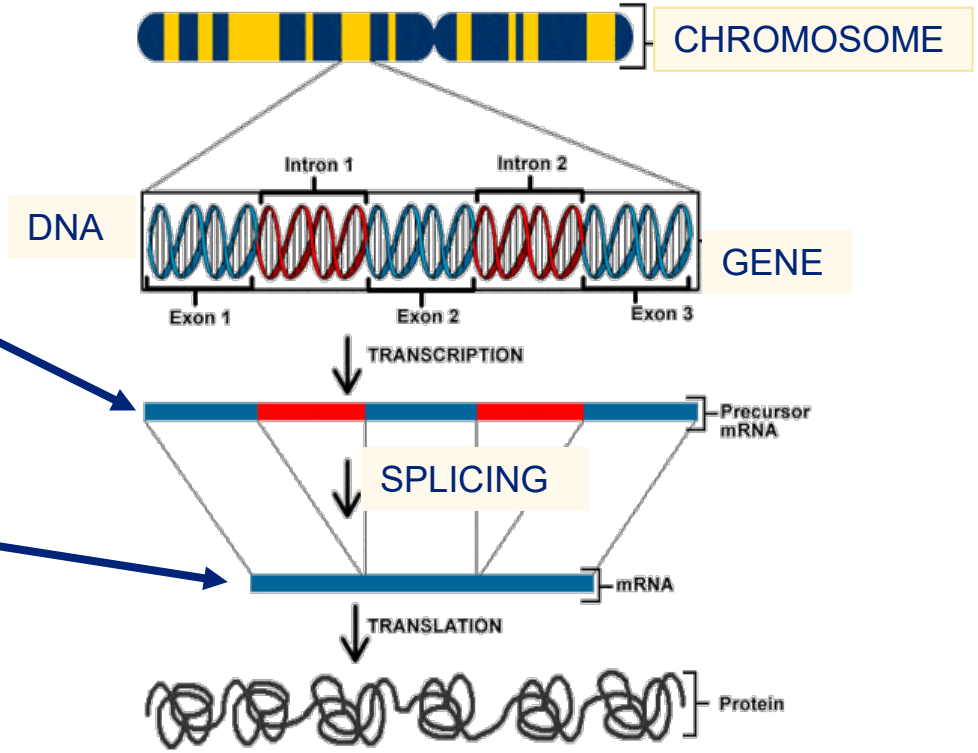
1. Transcription: Copy the DNA to RNA; this is the rough draft
Both the EXON
And INTRON
are copied



Spinal Muscular Atrophy Genetics

How To Make A Protein

2. The rough draft Precursor m-RNA is spliced to form the m-RNA



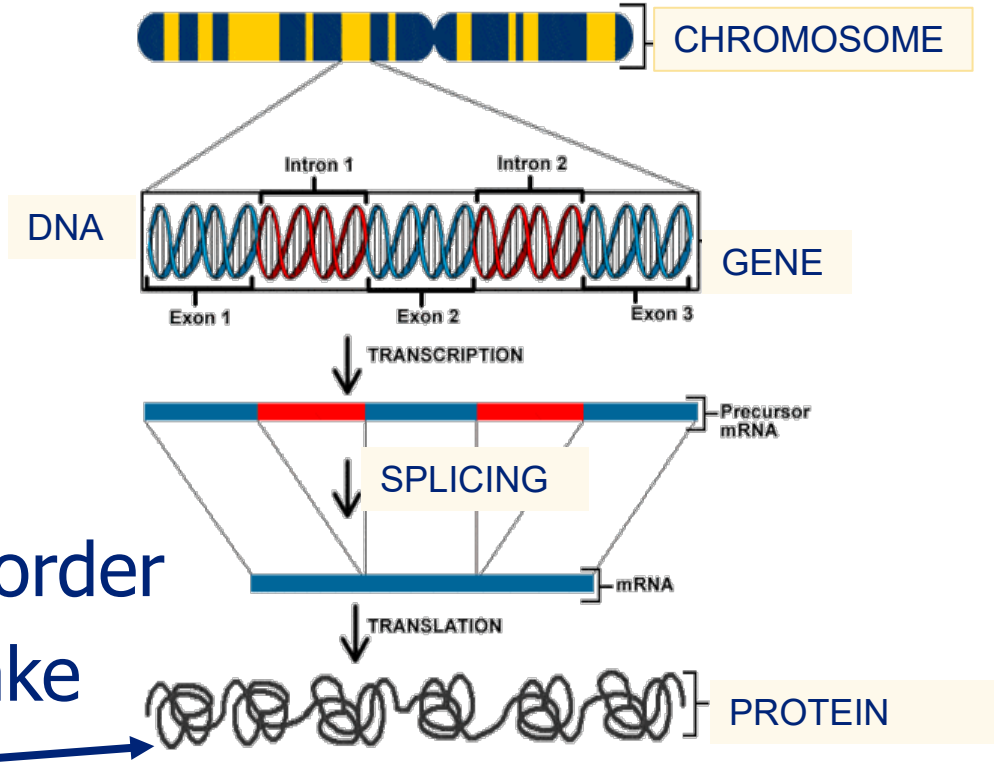
Spinal Muscular Atrophy Genetics

How To Make A Protein

3. Translation:

Each 3-base unit in a sequence identifies the Amino Acids.

They are lined up in order and connected to make the Protein

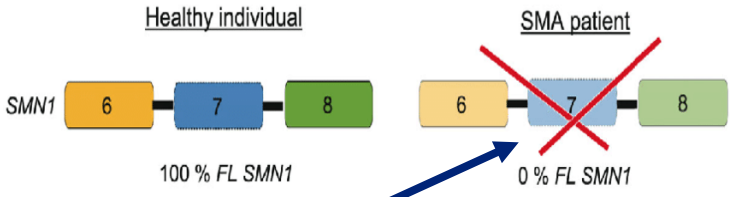


Spinal Muscular Atrophy Genetics

The Problem of SMA

Why do I need to know all this stuff?

In SMA there is
a defective process of
Transcription of
the SMN1 gene to the
Percussor m-RNA.
EXON 7 is lost



The defective SMN1 gene
codes for a SMN Protein that does not work

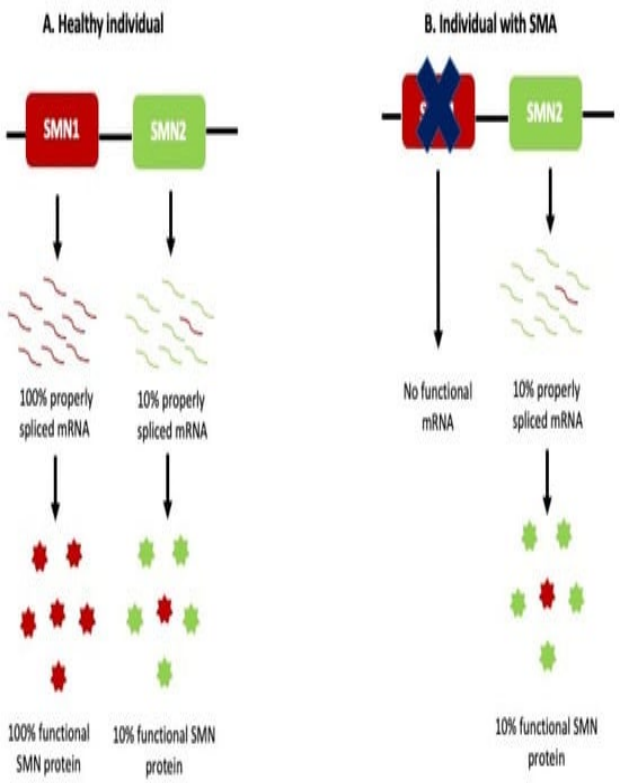
Spinal Muscular Atrophy Genetics

Sometimes the SMN1 gene has been deleted.

In both cases the SMN2 gene produces some SMN Protein.

10-20% of normal.

Motor Neurons Die



Spinal Muscular Atrophy Treatment

- Gene therapy has been shown to halt motor neuron destruction and slow disease progression in individuals with SMA.
- There are 3 medications available:
  - Spinraza (nusinersen)
  - Zolgensma (onasemnogene abeparvovec)
  - Evrysdi (risdiplam)

Spinal Muscular Atrophy Treatment

Spinraza (nusinersen)

- Antisense oligonucleotide(ASO)
- A single-stranded deoxyribonucleotide (a piece of DNA)
- Complementary to the DNA target (m-RNA)
- It fits the target RNA like a jigsaw puzzle part

Spinal Muscular Atrophy Treatment

Spinraza (nusinersen)

- Approved in 2016 for the treatment of any subtype of SMA
- Targets SMN2 gene to create more of the functional SMN protein
- Administered via intrathecal injection with 4 loading doses
- Maintenance doses every 4 months thereafter

Spinal Muscular Atrophy Treatment

Zolgensma (onasemnogene abeparvovec)

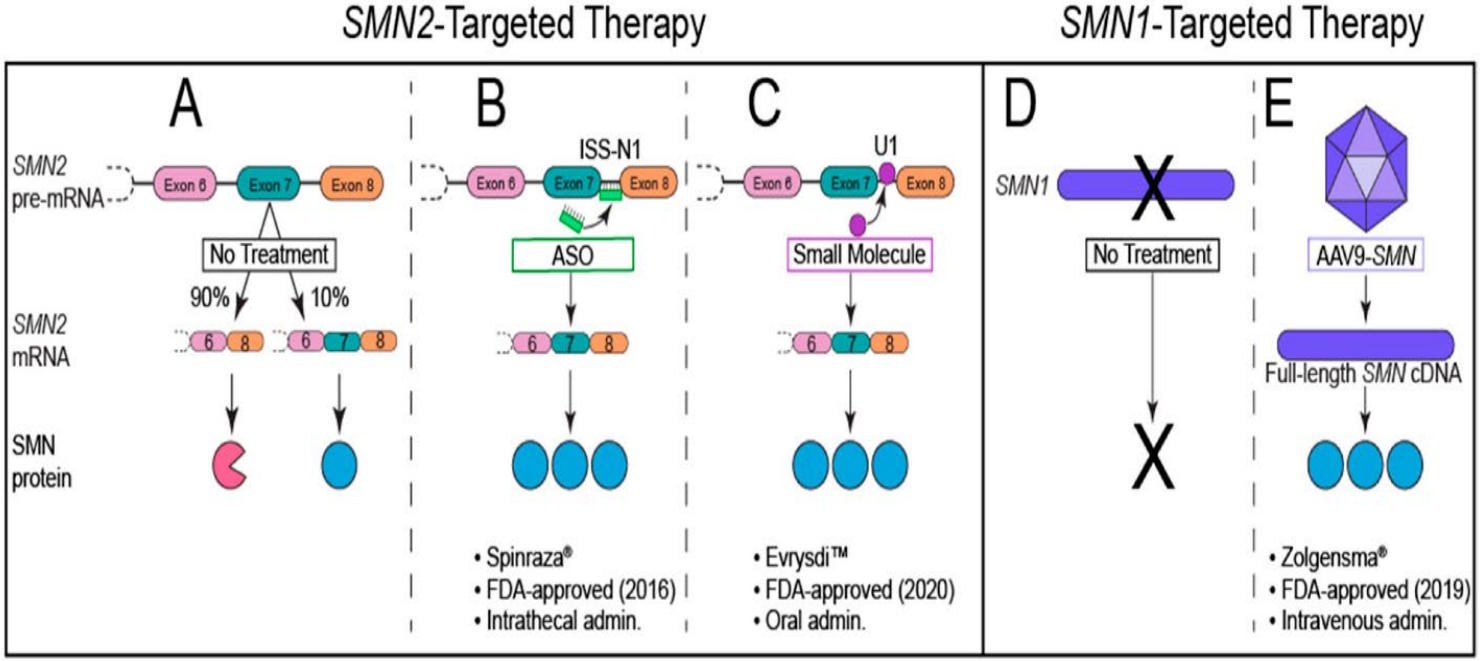
- A gene therapy
- Uses the adeno-associated virus serotype 9 vector (AAV9)
- Delivers a normal copy of the SMN1 gene to replace the defective or absent gene
- Approved on May 24, 2019
- Administered in a single intravenous dose
- Treat patients aged less than 2 years with any subtype of SMA.

Spinal Muscular Atrophy Treatment

Evrysdi™ (risdiplam)

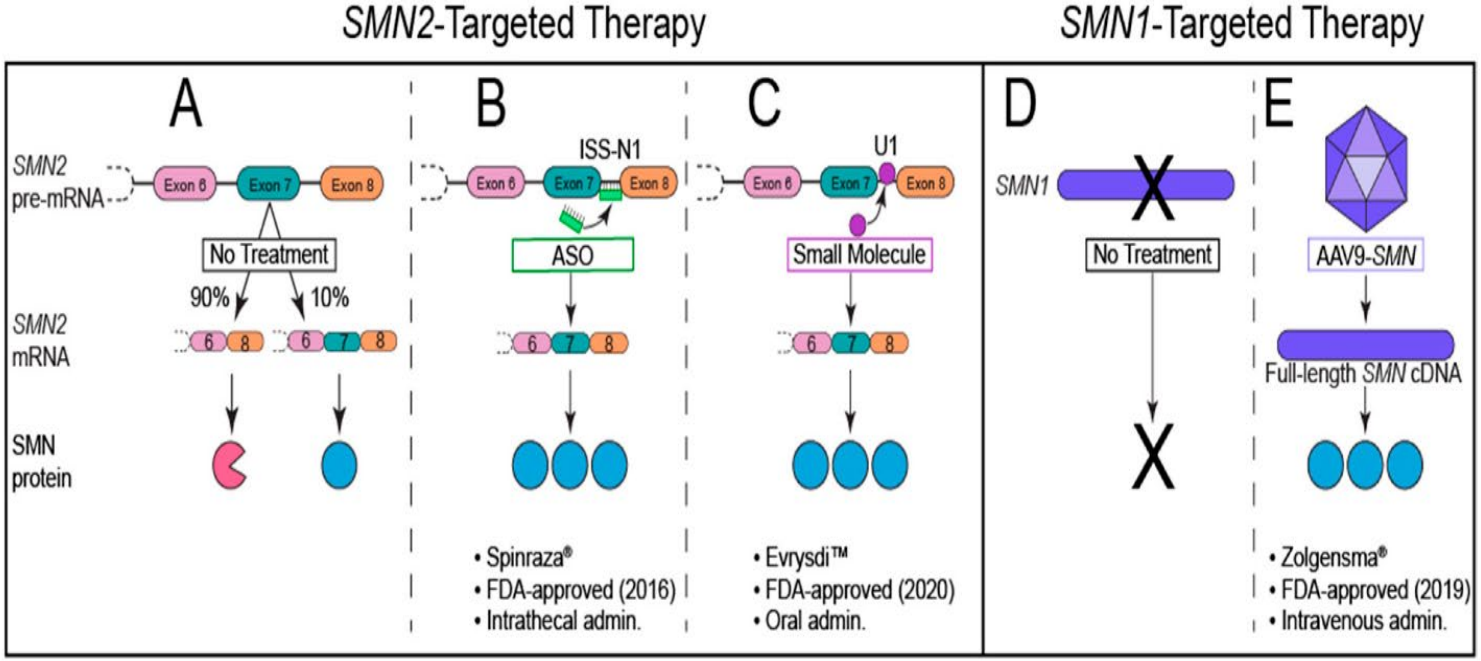
- Affects the Survival Motor Neuron 2 gene (SMN2)
  - A directed **RNA splicing modifier**
- Increases exon 7 inclusion in SMN2 m-RNA transcripts
- Produces full-length SMN protein
- Approved August 7, 2020
- Dosed orally once daily
- For patients 2 months of age and older

Spinal Muscular Atrophy Treatment



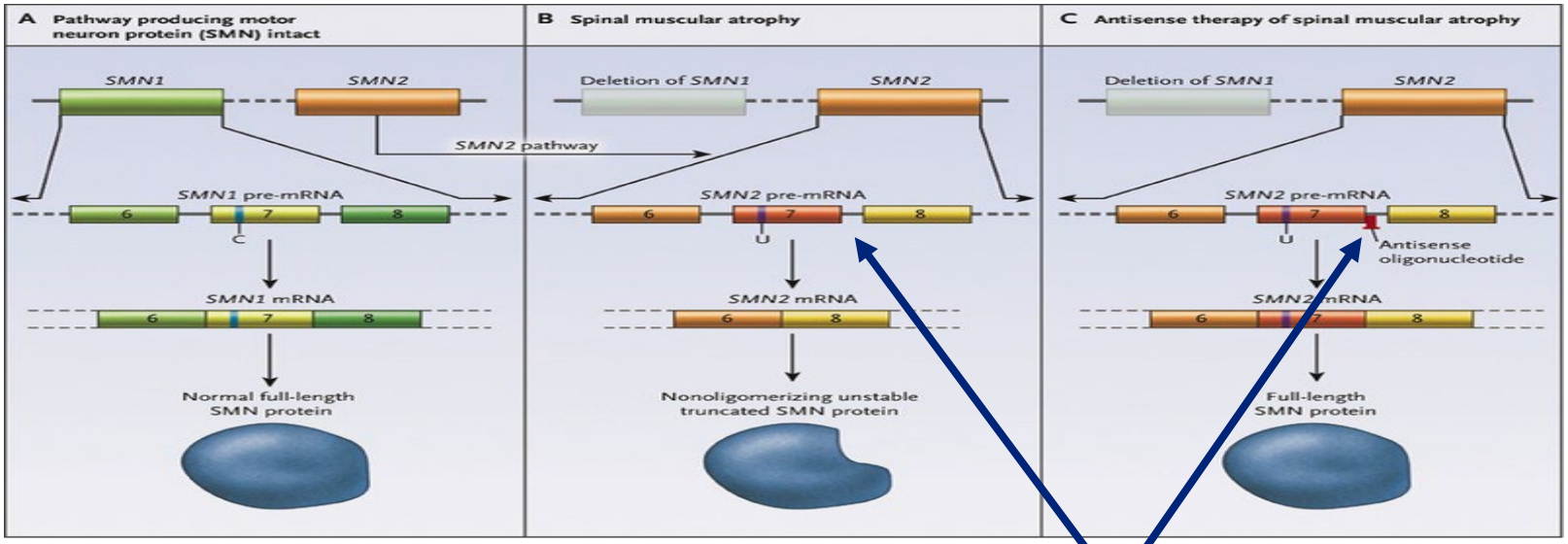
A and D SMA: no treatment; SMN 2 makes 10-20% of normal amounts of SMN protein.

Spinal Muscular Atrophy Treatment



B. Spinraza treatment; targets the SMN 2 gene inhibiter-of-inclusion of EXON 7 in pre-m-RNA/m-RNA (located in the INTRON)

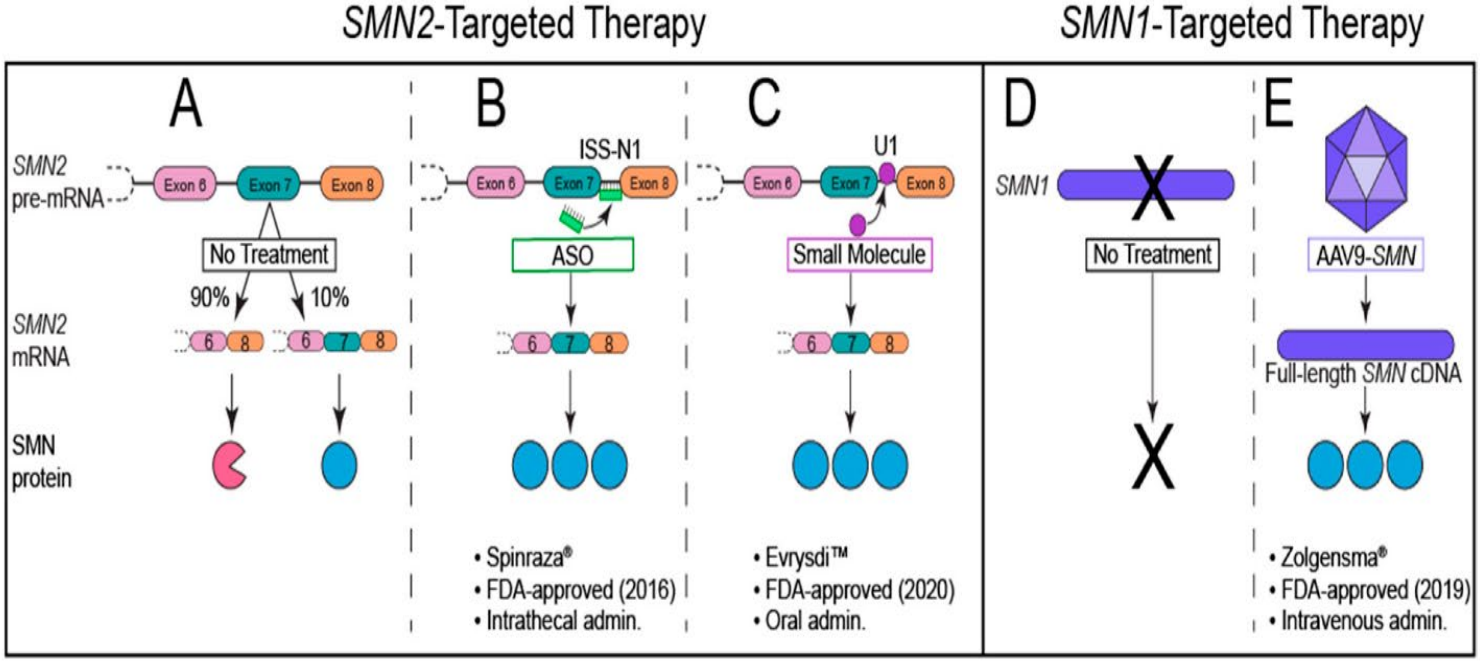
Spinal Muscular Atrophy Treatment



Spinraza modifies the splicing function
Enables the EXON 7 inclusion in the m-RNA

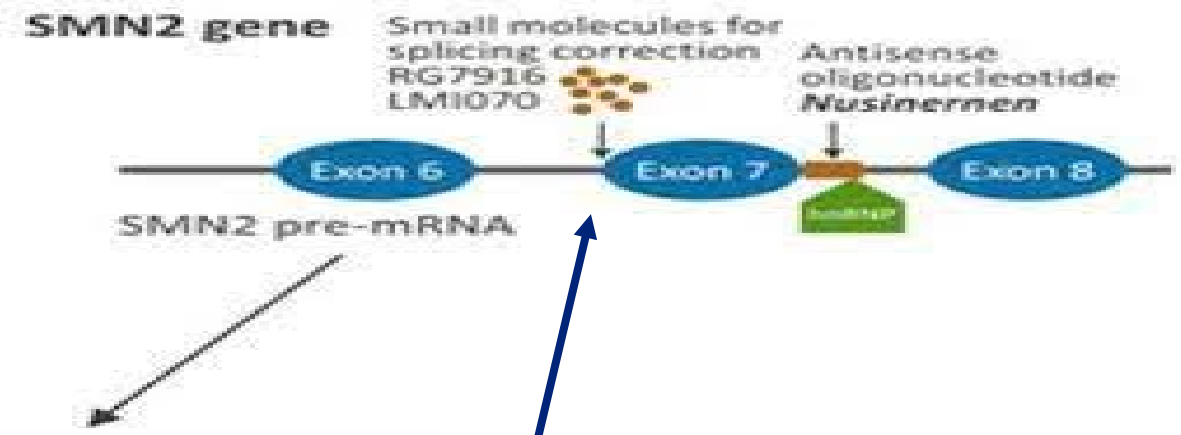
Allows translation to create an active SMN Protein from SMN2 gene (~100%)

Spinal Muscular Atrophy Treatment



C. Evrysdi is a small molecule splicing editor modifier. Modifies the splicer to include the EXON 7 in the m-RNA

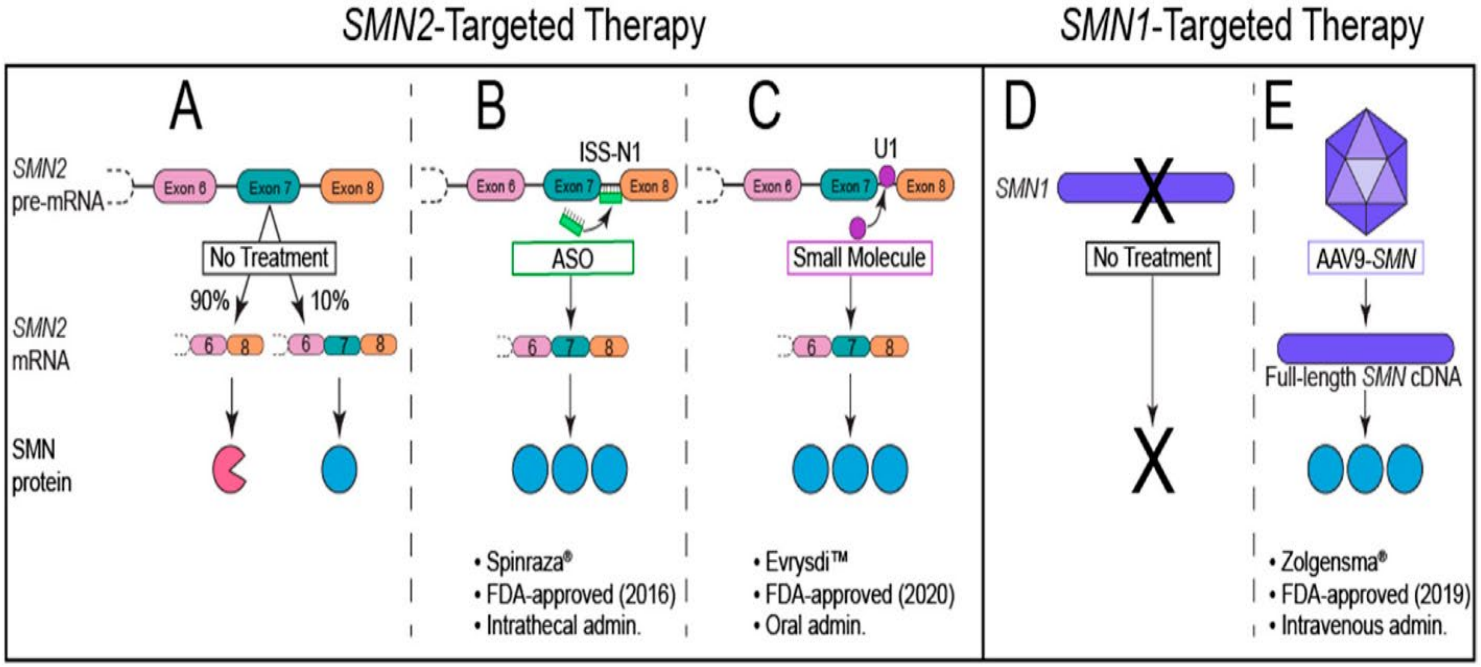
Spinal Muscular Atrophy Treatment



Evrysdi works at a different site than Spinraza. It corrects the splicer before it gets to the EXON 7

Corrects the SMN2 defect; increases SMN Protein from the SMN2 gene

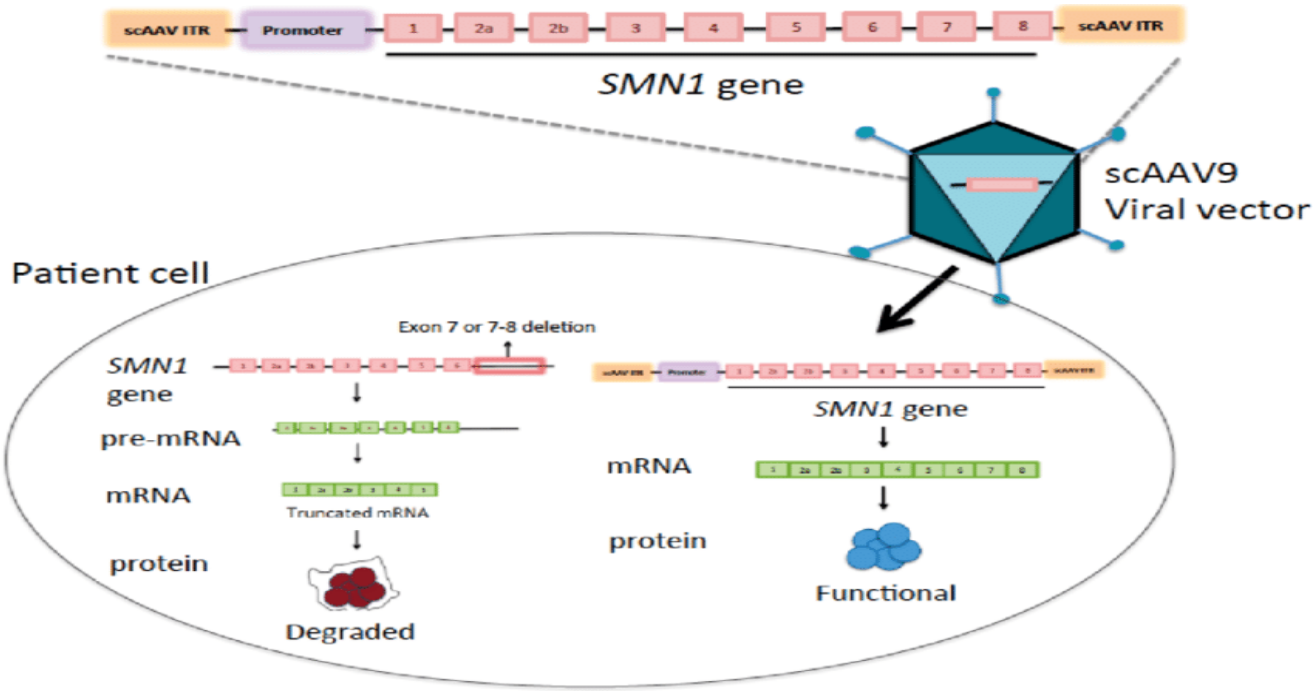
Spinal Muscular Atrophy Treatment



E. Zolgensma is a complete SMN1 gene (DNA) attached to an Adenovirus.

The virus infects the patient .

Spinal Muscular Atrophy Treatment



Delivers the gene to all the cells of the body.

Results in production of the normal SMN1 protein

Spinal Muscular Atrophy
Side Effects

- Spinraza
  - lower respiratory infection
  - upper respiratory infection
  - constipation
  - teething
  - congestion
  - ear infection
  - scoliosis

Spinal Muscular Atrophy
Side Effects

- Zolgensma
  - Most common is elevated liver enzymes
  - Vomiting.
  - Zolgensma has a boxed warning that acute serious liver injury can occur.

Spinal Muscular Atrophy
Side Effects

- Evrysdi
  - For later-onset SMA:
    - fever
    - diarrhea
    - rash.

Spinal Muscular Atrophy
Side Effects

Evrysdi

For infantile-onset SMA

- fever
- diarrhea
- rash
- runny nose
- sneezing
- sore throat (upper respiratory infection)
- lung infection (lower respiratory infection)
- constipation
- vomiting
- cough.

Spinal Muscular Atrophy Treatment
Cost

Spinraza
- Year 1: $750,000
- Subsequent years: $375,000
- Administration is intrathecal

- Zolgensma
  - $2,125,000 (one time, one dose)
  - Administration is by IV infusion
- Evrysdi
  - $340,000 per year
  - Administration is by mouth
- Reimbursement is by direct payment from patients/families; sometimes covered by government agencies, some insurances, and some special programs from the pharmacy company.

Spinal Muscular Atrophy Treatment

Addenda

There have been reports of Zolgensma failures where patients have opted for Spinraza

There have been reports of side effects so severe from Spinraza that some doses have been missed.

Evrysdi is so new on the market that no unanticipated problems have appeared yet.

Spinal Muscular Atrophy
Our Impact

What can we do to make a difference in the lives of these patients and their families?

- Ensure that available services are being engaged
  - -Encourage Caregivers to make a timely Social Security Income (SSI) application
  - -This allows for a STARKids status request
  - -Apply for the Medically Dependent Children Program (MDCP) Waiver

Spinal Muscular Atrophy
Our Impact

- These programs enable requests for
  - -Durable Medical Equipment (DME-think robotic feeding aids) not covered by regular Medicaid
  - -Private Duty Nursing beyond that available on regular Medicaid
  - -Personal Care Services
  - -Respite care
  - -Home and vehicle modifications

Spinal Muscular Atrophy
Our Impact

- These programs enable requests for
  - -Medicaid transportation services
  - -Referral to Early Childhood Intervention (ECI)
  - -Referral to schools for home-bound services
  - -Requests for additional help from community agencies

Spinal Muscular Atrophy
Our Impact

- Our role is
  - -to anticipate care needs and guide the families to improve the quality of life of these children and their caregivers
  - -reach out to less educated and recalcitrant caregivers to assist them in utilizing resources

Spinal Muscular Atrophy
Our Impact

I can't think of any better example of where our corporate commitment applies

Integrity, Compassion, Relationships, Innovation, Performance

Spinal Muscular Atrophy Conclusion

- SMA is a devastating genetic condition
- It has a high mortality rate
- 1 in 10,000 infants are born with this disease each year
- Until recently there has been little to offer beside genetic counseling
- Research is ongoing
- There are 3 genetic treatments currently available; all are extraordinarily expensive
- This information will enable you to assist affected patients and their families
- It remains to be seen how the patent holders and we as a nation come together to treat all those in need of the medications

QUESTIONS?