

# Center for Clinical Genetics and Genomics Newsletter

October 2017



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## Carrier Screening: Spinal Muscular Atrophy (SMA)

<http://pittgenomics.org/>

**MESSAGE FROM THE DIRECTOR:** American College of Obstetrics and Gynecology recently updated their recommendations on carrier screening. In addition to cystic fibrosis, ACOG now recommends universal screening for spinal muscular atrophy (SMA). The public knowledge of SMA lags behind cystic fibrosis, yet it can be a devastating condition with early death due to respiratory failure. Recent breakthroughs in drug discovery, have made this condition responsive to drug therapy, if instituted before 7 months of age. It is therefore recommended that all of our patients be offered screening for SMA, in addition to cystic fibrosis. If there are any question or concerns regarding carrier screening in general, please do not hesitate to contact our prenatal genetics team at Magee. Aleksandar Rajkovic, MD, PHD

### *Spinal Muscular Atrophy (SMA)*

#### SMA FACTS:

- The leading genetic cause of infant death
- Muscle weakness and atrophy due to progressive degeneration and loss of the anterior horn cells in the spinal cord and the brain stem nuclei
- Autosomal recessive disorder
- Incidence: approximately 1 in 6,000-10,000 live births
- Carrier frequencies: 1 in 40-60 individuals in most populations (1 in 117 in Hispanic population)

*Screening for spinal muscular atrophy should be offered to all women who are considering pregnancy or are currently pregnant.*

*American College of Obstetricians and Gynecologists (ACOG) Committee Opinion 691, March 2017.*

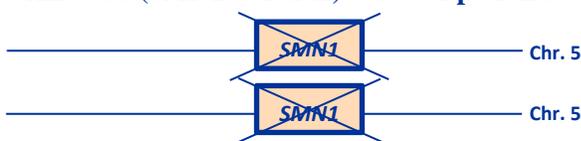
#### SMA Clinical Subtypes:

- **Type 0:** Prenatal onset; usually fatal at birth.
- **Type I (Werdnig–Hoffman):** The most severe and most common; onset within 6 months of age; death from respiratory failure in less than 2 years
- **Type II:** Onset within the first 6-18 months, intermediate severity with longer lifespan.
- **Type III:** Onset after 18 months of age; variable symptoms with normal lifespan.
- **Type IV:** Adulthood onset.

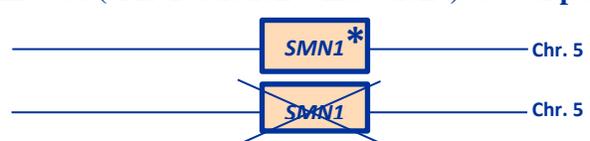
#### Molecular Genetics of SMA:

Survival motor neuron gene 1 (*SMN1*) has one copy per each chromosome 5. In >98% of SMA patients, both *SMN1* copies are altered due to gene deletions (95% of cases) or gene conversion events which are detected by loss of exon 7. Affected SMA patients have a loss of both *SMN1* alleles or a loss of *SMN1* on one allele and a pathogenic variant in the other *SMN1* copy. DNA analysis to diagnose affected SMA patients has sensitivity of 95% and specificity of 100%.

**Affected (*SMN1* deletion): 95% of patients**



**Affected (*SMN1* deletion + mutation\*): 5% of patients**



A second survival motor neuron gene (*SMN2*) is also present in humans. *SMN2* is identical to *SMN1* except for exon 7. A small difference in exon 7 of *SMN2* leads to a splicing problem. Consequently, *SMN2* produces only a small amount of functional SMN protein. Unlike *SMN1*, there can be 0-2 copies of *SMN2* per chromosome. A higher number of *SMN2* copies correlates with generally milder clinical phenotypes.

## Treatment:

Nusinersen (Spinraza) is the first FDA-approved drug for SMA. Spinraza works by increasing SMN protein levels through *SMN2* exon 7 splicing correction. Clinical trials showed a promising response in most treated infants with achievement of motor milestones and motor function, improvement of neuromuscular electrophysiology and ventilation independence with no safety concern.

More information on the new SMA treatment are found on FDA website:

<https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm534611.htm>

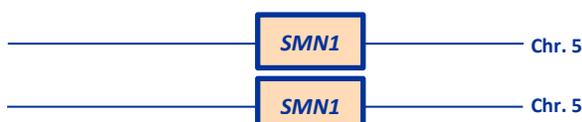
## Why SMA Screening Is Important?

- SMA is the most common genetic cause of childhood mortality.
- SMA has a well-defined early onset phenotype, and causes physical impairment with a detrimental effect on quality of life.
- Carrier frequencies are high in most populations.
- Carrier Detection rate in most populations: 90-95% (African Americans: 71%).
- New treatment is available BUT is only most effective if administered early in life. This narrow therapeutic window highlights the importance of carrier screening to identify affected newborns as early as possible.

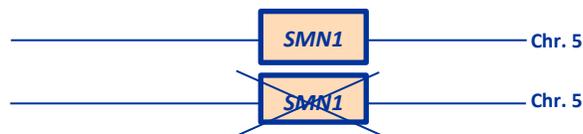
## SMA Carrier Screening:

- **Test Description:** Quantitative PCR-based assay that provides a measure of *SMN1* copy number.
- **Target population:** All women who are considering pregnancy or are currently pregnant.
- **Expected Test Results:**

### Normal (Negative- 2 *SMN1* Copies)



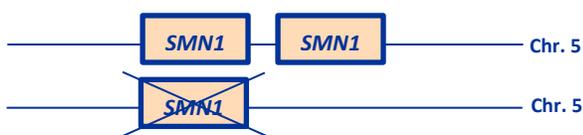
### Carrier (Positive-1 *SMN1* Copy)



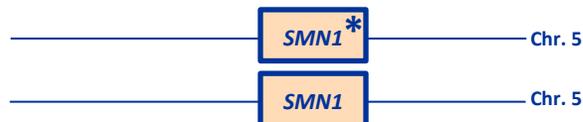
### - Test Limitations:

- Unable to detect the missing *SMN1* copy in 3–4% of the carrier population, and higher in African Americans, that have two *SMN1* copies on one chromosome with no copies on the other. Carrier screening test would reveal normal results due to *SMN1* duplication (false negative):
- *SMN1* point mutations, found in 2% of the carrier population, are not detectable by current carrier screening dosage analysis-based methods. Carrier screening test would reveal normal results due to normal *SMN1* copy number (false negative):

### False Negative (2 *SMN1* Copies)



### False Negative (2 *SMN1* Copies)



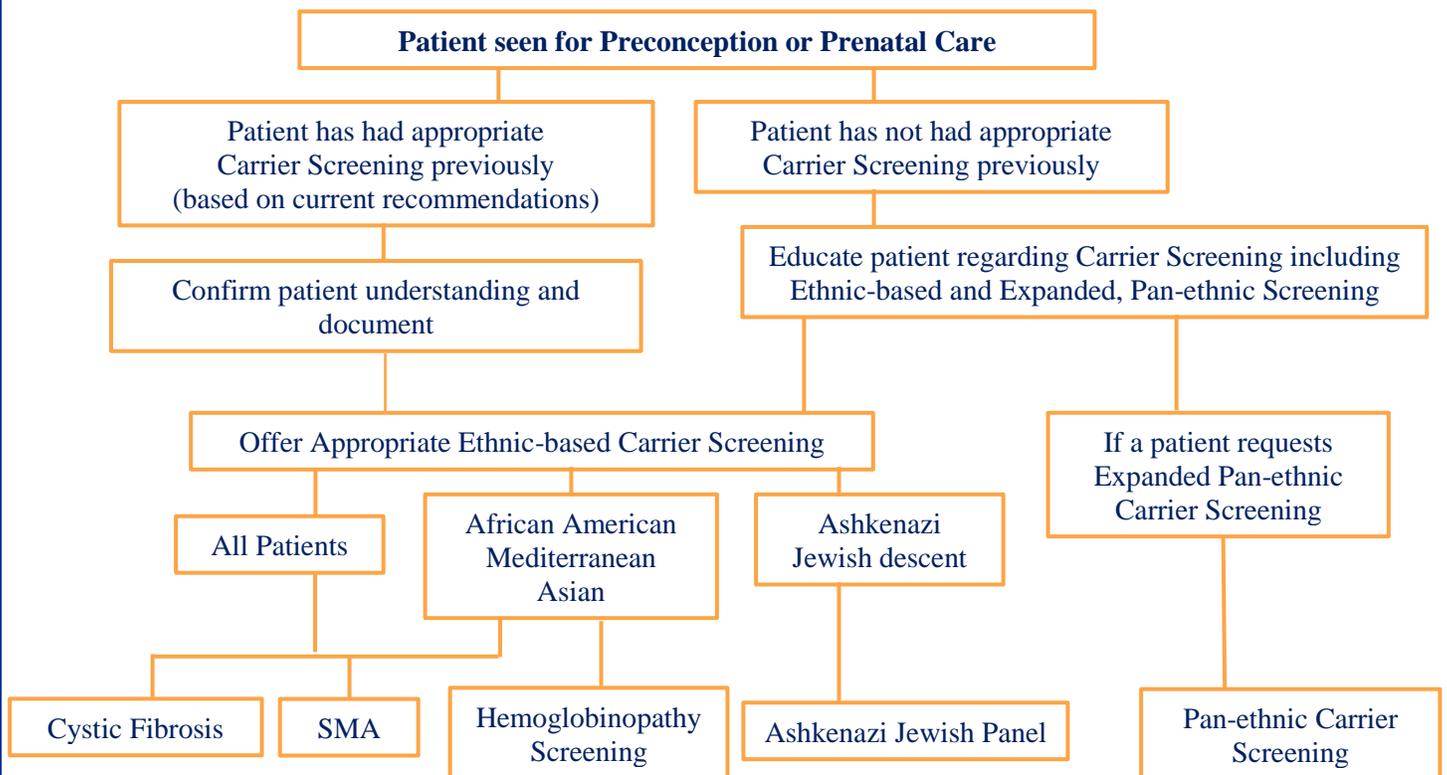
## - Genetic Counseling:

**Pre-Test:** Review of family history; discussing possible range of severity, carrier rate, and detection rate.

**Post-Test:** Discuss residual risk after negative screening based on the number of *SMN1* copies present or provide further genetic counseling after positive screening and consideration of genetic testing in partner.

## Carrier Screening at the UPMC Center for Clinical Genetics and Genomics

The following algorithm demonstrates the approach to carrier screening offered to women during preconception or prenatal periods. The algorithm is based on recent ACOG/ACMG guidelines:



### Notes:

1. For patients who screen positive for Cystic Fibrosis through the Magee Genomics lab, partners are tested free.
2. All abnormal carrier screens and Variants of Unknown Significance (VUS) should undergo post-test counseling.

## CONTACT US

Center for Clinical Genetics and Genomics  
Prenatal/Adult Genetics Clinic  
Magee-Womens Hospital of UPMC  
300 Halket St.- Suite 1651  
Pittsburgh, PA 15213  
Tel: 412-641-4168, 1-800-454-8155  
Fax: 412-641-1032  
<http://pittgenomics.org/>