

TOPICS IN OBSTETRICS & GYNECOLOGY

Practical CE Newsletter for Clinicians

Spinal Muscular Atrophy Carrier Screening for the Obstetric Provider

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Learning Objectives: After participating in this continuing professional development activity, the provider should be better able to:

1. Identify patient populations appropriate for spinal muscular atrophy (SMA) screening.
2. Distinguish the various phenotypes of SMA and interpret SMA carrier screening test results.
3. Plan patient-specific counseling regarding residual risk based on results of SMA carrier screening.

Key Words: Carrier screening, Genetic screening, Spinal muscular atrophy

Spinal muscular atrophy (SMA) is a neuromuscular disease resulting in the degeneration of the anterior horn cells of the spinal column. This can lead to progressive proximal muscle weakness. SMA is caused by a mutation in the survival motor neuron gene (*SMN1*). This gene is responsible for the production of a protein essential to motor neuron function. The estimated incidence of SMA is around 1 in 10,000 live births.^{1,2} SMA is estimated to be the second most common fatal autosomal recessive disorder after

cystic fibrosis, with a carrier frequency ranging from 1/40 to 1/60.^{3,4} The phenotype of SMA is highly variable. SMA is classified into 5 phenotypes based on maximum motor function achieved and age at onset of symptoms.^{5,6}

SMA involves the survival motor neuron 1, or *SMN1* gene, on the q arm of chromosome 5. SMA inheritance is described as autosomal recessive; however, the genetics are complex and can be affected by gene conversion, de novo mutations, and the concept of the “2+0” carrier.

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SMA, Type 0-IV

Because the phenotype varies significantly, 5 types of SMA have been characterized. Type 0 describes the most severe, in utero type of SMA, with life expectancy only until around 6 months of life. Type I, or Werdnig-Hoffmann, is the most common type, with symptomatic onset before 6 months and death from respiratory failure within the first 2 years of life. Type II SMA has typical onset before age 2 and a lifespan that varies from 2 years of age to the third decade of life. Type III, or Kugelberg-Welander, has onset after 18 months of life and a variable symptom profile, with many patients having normal life expectancies. Type IV refers to adult-onset disease. Table 1 demonstrates type

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Baltimore, Maryland**Table 1. Clinical Phenotypes of Spinal Muscular Atrophy**

Type	Age at Onset	Clinical Characteristics	Highest Motor Milestone	Life expectancy
0	Fetal	Contractures Absent movement, reflexes Require mechanical ventilation at birth	None	<6 mo
I	0–6 mo	Hypotonic Weakness Feeding difficulty	Never rolls or sits independently Sits with support	<2 yr
II	6–18 mo	Hypotonic Nonambulatory Proximal weakness	Sits independently May stand Does not walk independently	Around 20 yr
III	>18 mo	Ambulates independently Declines gross motor function in childhood	Stand Walk	Life expectancy usually not affected
IV	Second or third decade	Onset in adult life Develops difficulty with gross motor function	Walks independently in adulthood	Life expectancy usually not affected

0-IV SMA with clinical characteristics. Type of SMA is defined by age of onset and highest motor milestone.^{5,6}

Genetics of *SMN1* and *SMN2*

In 1995, the *SMN1* gene on chromosome 5q13 was linked to SMA.⁷ Nearer to the centromere of chromosome 5 and downstream of *SMN1* is the *SMN2* (survival motor neuron 2) gene. Most cases (around 94%) of SMA are caused by the homozygous deletion of the *SMN1* gene. The other 6% of cases are compound heterozygotes with one deleted copy of the *SMN1* gene and a point mutation in the other copy, or patients affected by de novo mutations.⁸

Individuals in the general population normally have 2 *SMN1* gene copies, but may have up to 4. Copy numbers of *SMN2* gene in the population range from zero to 3.^{3,9}

Approximately 80% to 90% of SMN protein is produced in response to the *SMN1* gene. The remaining comes from *SMN2*. Therefore, those with homozygous *SMN1* deletions may still produce functional SMN protein through *SMN2*. A homozygous deletion of *SMN2* does not lead to SMA when at least one *SMN1* gene is present. Gene conversion between *SMN1* and *SMN2* genes can randomly occur in the gamete, further complicating the genetics of SMA.¹⁰ In addition, the number of *SMN2* genes can affect the phenotype in those with homozygous deletions of *SMN1*.^{8,11,12} However, the *SMN2* copy number with homozygous *SMN1* deletion is not diagnostic for the SMA phenotype.

Because of the complex genetics and limitations in the molecular diagnostic assays available, prediction of phenotype in affected fetuses is limited. If a patient is identified as

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a carrier for SMA, the subtype cannot be determined if there is no family history of the disorder. Therefore, prenatal care providers should have a basic understanding of carrier screening results, residual risk, and genetics of SMA. They should also know when to refer patients to genetic counselors or maternal-fetal medicine given the complex counseling required.

Carrier Screening

Current society guidelines recommend screening preconception or in pregnancy for SMA carrier status. The American College of Medical Genetics and Genomics (ACMG) recommended SMA screening for all patients preconception or early in pregnancy in 2008.⁴ In 2017, the American College of Obstetricians and Gynecologists (ACOG) recommended that providers offer SMA screening to all patients who are pregnant or considering pregnancy. In addition, the ACOG recommends that, in patients with a family history of SMA, molecular testing of the affected individual and carrier testing of that parent be reviewed before screening. If those results are not available, the ACOG recommends testing of the low-risk partner.¹³

SMA disease can be diagnosed based on homozygous deletion of *SMN1* in patients with symptoms. However, carrier testing requires a quantitative polymerase chain reaction assay that gives a measure of *SMN1* copy number. Detection of a single copy of the *SMN1* gene indicates a carrier. However, the location or configuration of the gene can be relevant, as some patients (approximately 3%–4%) have 2 *SMN1* copies on the same chromosome (in cis configuration) and no copies on the other. This technically makes them carriers as one chromosome is missing the *SMN1* allele. Although rare, the typical carrier testing assay does not identify these carriers, who have a 50% chance of passing on the chromosome with a single inactivated *SMN1* gene and could have an affected offspring. These “2+0” carriers may occur more frequently in certain ethnic groups, which affect residual risk. Some laboratories offer testing for a variant gene, which is associated with an increased risk of both copies of *SMN1* being in the “cis” configuration.

Residual Risk

Residual risk is the chance that a patient may still be a carrier despite having a negative screening test. Residual risk remains, even in patients who have 2 or 3 copies of *SMN1* on carrier screening. Table 2 estimates the carrier risks for patients from different ethnic groups in individuals with 2 copies of *SMN1* (residual risk is even lower in patients with 3 copies of *SMN1*, and is often reported on results of carrier screening). Because the “2+0” carriers are more commonly of African American ancestry, the carrier detection is lower in this group and residual risk is higher with *SMN1* carrier testing. If a patient’s screening results return with 2 copies of the *SMN1* gene, they are unlikely to be an SMA carrier. However, patients should be informed of the residual carrier risk based on ethnicity.

Some laboratories may include results on an *SMN1* variant gene. Approximately one-fifth of “2+0” SMA carriers

Table 2. SMA Carrier Frequency, Detection Rate, and Residual Risk (Individuals With 2 *SMN1* Copies) Based on Ethnicity

Ethnicity	Carrier Frequency	Detection Rate	Residual Risk
Caucasian	1/47	95%	1:632
African American	1/72	70.5%	1:121
Ashkenazi Jewish	1/67	90.5%	1:350
Asian	1/59	93.3%	1:628
Hispanic	1/54	90%	1:1061

carry one or both identified variants when *SMN1* copies were in cis configuration.¹⁴ Although absence of these linked variants does not exclude “2+0” carrier status, the presence of the variant does increase residual risk (due to the increased likelihood of “2+0” carrier status) in individuals with 2 *SMN1* copies. Laboratory results that indicate 2 copies of the *SMN1* gene with a variant should report the residual risk. Patients should be counseled regarding their residual risk despite having 2 *SMN1* copies.

If a patient’s screening results indicate one copy of *SMN1* (diagnosing them as a carrier), the patient should be referred for genetic counseling, and encouraged to bring her partner if possible. If a patient has only one copy of *SMN1*, the partner can be tested, presuming that paternity is certain. If the partner carries 2 copies, the residual risk is low of having an affected offspring. Results and risks should be discussed by certified genetic counselors. If the partner has only one copy of *SMN1* or is unavailable for testing, prenatal genetic diagnosis can be offered with chorionic villus sampling or amniocentesis. Postnatal testing is also an option. In addition, several states have incorporated SMA into their newborn genetic screen.

Emerging Therapies for SMA

Both the coding regions and protein products of *SMN1* and *SMN2* have been characterized.⁷ Since then, therapies to target the mechanism of SMA have been developed. In 2016, the FDA approved nusinersen (Spinraza). This medication is an antisense oligonucleotide that promotes production of SMN protein from the pseudogene *SMN2*. Spinraza is administered intrathecal with 4 loading doses in the first month followed by maintenance therapy every 4 months. This medication prolongs survival in in type 1 SMA and increases the motor milestones met by patients with type 2 SMA.^{15–17} In addition to the intrathecal therapy, an orally deliverable medication, risdiplam (Evrysdi) has been approved for therapy for SMA.¹⁸

In addition to SMN-targeted therapy, medications for upregulation of muscle growth, RNA therapy, neuroprotection through mitochondria, and gene modification of SMN are being investigated. However, these therapies are

currently very expensive.^{19,20} Improvement in therapy, life expectancy, and quality of life with emerging therapies will continue to inform prenatal genetic counseling.

Additional Considerations

- Some laboratories offer SMA screening within expanded carrier panel screening.
- Some (but not all) laboratories offer complete SMA testing, including reflex sequencing for *SMN2* copy number analysis in carriers of SMA.
- Any patient with a family history of SMA or known carriers should be referred to a certified genetic counselor.

Summary

SMA is an autosomal recessive disorder caused by mutation or deletion of 2 *SMN1* genes. The disease causes significant neonatal and infant morbidity and mortality. Therefore, the ACOG and the ACMG recommend offering carrier screening to all pregnant patients or patients considering pregnancy. Because the inheritance of SMA can be complex, prenatal care providers should appropriately refer patients to certified genetic counselors if a patient tests positive as a carrier. If carrier screening is negative, providers should understand the residual risk and inform the patient of residual risk.

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1. A 29-year-old, nulliparous patient presents for preconception counseling due to her history of preexisting diabetes. She reports no known family history of inherited conditions. Which one of the following is appropriate to offer as preconception genetic screening?
 - A. noninvasive prenatal screening
 - B. chorionic villus sampling
 - C. SMA carrier screening
 - D. do not recommend genetic screening as part of a preconception visit
2. A 25-year-old G2P1001 woman presents at 29 weeks for a prenatal visit. She has 1 healthy child, age 2 years. She had previously declined any genetic screening but today reports that her brother was recently diagnosed with type IV SMA. Which one is the *most* appropriate next step?
 - A. amniocentesis
 - B. refer for genetic counseling
 - C. growth ultrasound
 - D. induction of labor
 - E. no additional workup is indicated
3. A patient who is 14 weeks' pregnant had recent carrier screening for SMA. Results showed that she has 3 copies of the *SMN1* gene. On the basis of these results, which one of the following statements represents appropriate counseling for this patient?
 - A. The patient is extremely unlikely to have offspring affected by SMA; however, a very small residual risk exists in all cases.
 - B. The patient is a carrier of SMA and should be referred for genetic counseling.
 - C. No counseling is required for SMA carrier screening results.
 - D. The patient should be referred for amniocentesis.
4. A 35-year-old G1 woman at 11 weeks' gestation elects expanded carrier screening. The results indicate that she has 1 copy of the *SMN1* gene. Which one of the following is the appropriate next step?
 - A. no further evaluation
 - B. chorionic villus sampling
 - C. parental karyotypes
 - D. referral to a certified genetic counselor, preferably with the patient's partner present
5. When asked whether she is interested in carrier screening for SMA, a patient asks how a positive screening result would affect her baby. Which one of the following is the appropriate response?
 - A. The distal extremities will be contracted and immobile.
 - B. The infant will have low set ears and abnormal face.
 - C. The condition affects the spinal cord and can lead to progressive proximal weakness; however, affected individuals have variable presentation.
 - D. Refer the patient to a certified genetic counselor for a response.
6. You offer SMA carrier screening to a patient at her first prenatal visit at 10 weeks of pregnancy. She asks whether the testing can wait until after the baby is born. Which one of the following is the appropriate answer?
 - A. No, there are no tests for SMA for newborns.
 - B. Yes, many newborn screens include SMA testing, although you should confirm with the pediatric provider.
 - C. Babies are only screened if born hypotonic.
 - D. Refer the patient to a certified genetic counselor for a response.
7. A patient has a prior child affected by SMA type 0. She unexpectedly became pregnant with the same partner, and is approximately 12 weeks' gestation. Which one of the following is the appropriate next step?
 - A. refer to a certified genetic counselor and maternal-fetal medicine to discuss diagnostic testing
 - B. routine prenatal care
 - C. expanded carrier screening for the patient and her partner
 - D. noninvasive prenatal screening
8. You are counseling a patient regarding SMA carrier screening, and she asks why screening should be performed if there is no treatment for SMA. Which one of the following is the appropriate response?
 - A. There is no treatment for SMA, so screening is for planning purposes only.
 - B. There are new and emerging therapies that improve survival and prognosis for SMA.
 - C. Correct, you do not need screening.
 - D. Refer to a certified genetic counselor for a response.

9. Some patients carry the *SMN1* gene on the same chromosome (“cis” configuration). Approximately how many patients have the *SMN1* gene on the same chromosome?
- A. 1 in 10,000
 - B. 1 in 100
 - C. 1 in 50
 - D. 1 in 5
10. In counseling a patient regarding the *SMN1* gene in “cis” configuration, or on the same chromosome, which one of the following statements is *true*?
- A. There is an advantage to having both *SMN1* on the same chromosome.
 - B. The offspring will automatically be affected by SMA.
 - C. There is a 50% chance of passing on the chromosome with a single inactivated *SMN1* gene, which could result in an affected offspring, depending on the partner’s carrier status.
 - D. There is no correlation between “cis” and “trans” configuration and inheritance of *SMN1*.