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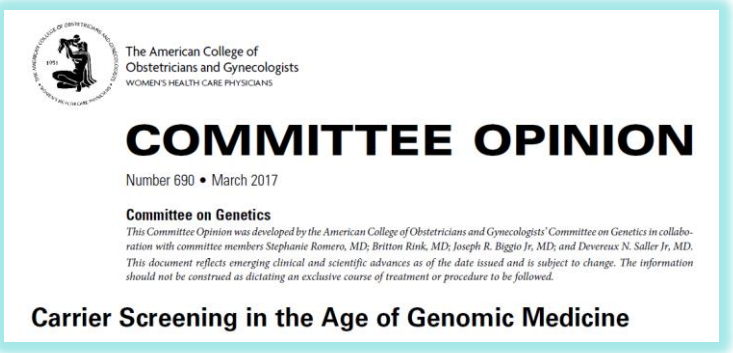
Carrier Screening

CARRIER SCREENING
ACOG COMMITTEE OPINION #690

【Abstract】

The Committee on Genetics of the American College of Obstetricians and Gynecologists released a committee opinion in March of this year focusing on "Carrier Screening in the Age of Genomic Medicine" (Committee Opinion #690).


The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

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Committee on Genetics

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Genetics in collaboration with committee members Stephanie Romero, MD; Britton Rink, MD; Joseph R. Biggio Jr, MD; and Devereux N. Saller Jr, MD. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Carrier Screening in the Age of Genomic Medicine

Carrier screening tests help identify healthy individuals who are carriers of specific recessive genetic disorders and as a result, be at increased risk to have affected children. Knowledge gained from carrier screening tests allows prospective parents to plan reproductive testing and methods, or prenatal and postnatal care management according to their risks, beliefs and values.

ACOG has previously advocated for ethnic-based carrier screening—screening only for those conditions more prevalent in one's ethnic group—for preconception and prenatal genetic carrier evaluation. With ethnic-based carrier screening, the conditions are more focused and selected. However, **ACOG now feels given the increasing complexity of mixed ethnic backgrounds and the advancement in genetic testing methodology, panethnic screening and expanded carrier screening are acceptable strategies as well.** In other words, it is acceptable for patients to consider simultaneously screening for multiple genetic conditions that may or may not be particularly selected based on ethnicity alone. This committee opinion statement also specifically pointed out the risks/benefits/limitations with this approach and gave suggestions on disease selections.

This newsletter will **review the basic concepts and important counseling points related to carrier screening**, as well as i**ntroducing panethnic and expanded carrier screening concepts** as highlighted in this issue of committee opinion.

【Discussion】

What are Carriers?

Carriers are people who are healthy but carry a mutation or an abnormal/malfunctioned

copy of a gene associated with a recessively inherited genetic disorder.

Generally speaking, a person has two copies of every gene—one copy inherited from his/her father and the other from his/her mother. Recessive disorders are genetic conditions that present abnormal clinical features when both copies of the disease-causing gene are abnormal or not functional. Because carriers have one abnormal copy of the disease-causing gene and a normal copy, they generally do not have any abnormal developmental or growth problems and are not affected by the condition. However, they can pass the abnormal copy to their children. If both the mother and the father are carriers, there is a chance that the child inherits both abnormal copies of the gene, i.e. has no normal copy, and be affected by the condition.

What is a Carrier Screening Test?

Carrier screening test is a genetic test, usually through a blood draw or a cheek swab to collect cells containing genetic materials, to determine whether a healthy person is a carrier for a specific condition or not.

What are the Goals of Carrier Screening Tests?

Although carriers do not have health concerns themselves, they are at increased risk/chance to have a child affected with that particular condition. Therefore, **the goals of carrier screening tests are to provide meaningful information to parents or prospective parents so they can better decide on pregnancy plans based on their reproductive risks, beliefs and family plans.**

Who should be Offered Carrier Screening Tests?

The tests are most appropriate to be offered to all patients considering pregnancy or are already pregnant. Pregnancy plans, preconception or prenatal testing options can be arranged according to the test results.

Couples with consanguinity (blood-related relatives) have increased risk for recessive genetic conditions and carrier screening tests can be considered.

Should Individuals with a Family History of Genetic Disorder Undergo Carrier Screening Tests?

The ideal first step is to identify the specific diagnosis and the specific disease-causing genetic mutation in the affected person.

Many different genetic conditions have similar overlapping clinical presentation. Even for the same condition, there could be more than one type of disease-causing genetic mechanisms. The

disease-causing genetic change may be different for different families and screening at-risk healthy relatives for the right genetic change is crucial in identifying carriers and reproductive risks. Thus, it is generally always more effective to first perform genetic testing on the affected family member to find the disease-causing mutation in the family. Once a mutation is identified, testing of other at-risk healthy relatives can be done by targeting at this hereditary genetic change. Such strategy is more precise and specific, less time consuming and costly, and provides a more informative answer.

Without knowledge of the true disease-causing change in the affected relative, while performing general carrier screen for other healthy family members can lower their carrier risk, there is a potential risk of miss detecting a true carrier. If the specific familial disease-causing mutation is not included in the general carrier screening panel, it could result in a false-reassurance test result and a true carrier be missed. A person can still be a carrier since the true familial mutation was not in fact tested, and can therefore give birth to an affected child.

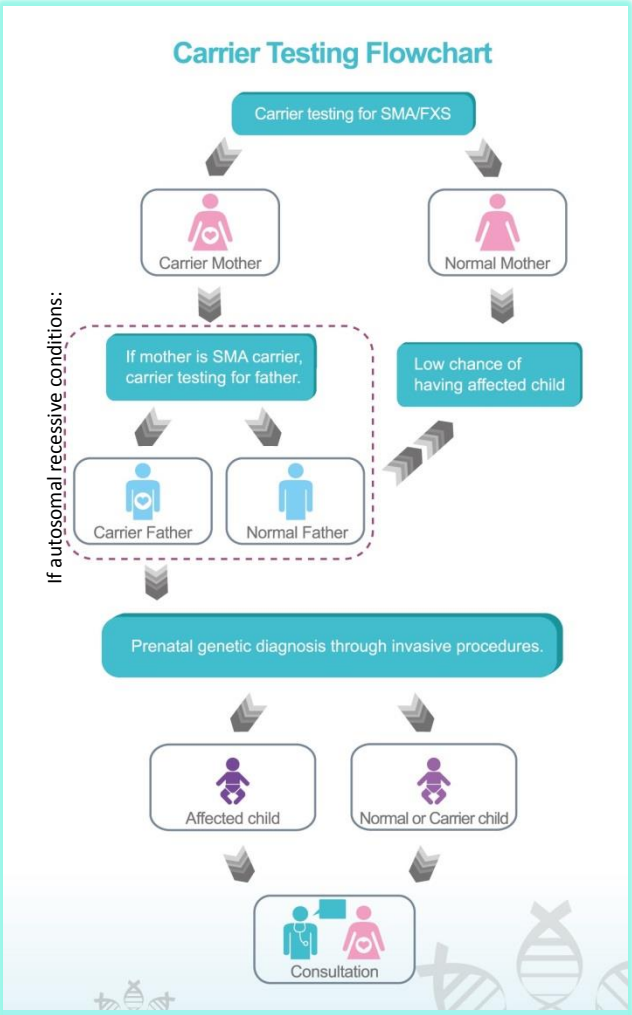
What happens if the Carrier Screening Test Results are Positive/Abnormal?

A positive/abnormal carrier screening test result
= Patient is a carrier; Offspring may be at increased risk to be affected

For autosomal recessive conditions:

If a patient screened positive/abnormal for an autosomal recessive genetic condition, then his/her reproductive partner should be offered carrier screen for the same condition. **If both members of a couple are found to be carriers for the same autosomal recessive condition, each of their pregnancy is at 1/4 (25%) risk to be affected.**

Prenatal testing through chorionic villus sampling (CVS) or amniocentesis, or preconception testing using preimplantation genetic diagnosis (PGD) method can be considered to identify fetus/embryos affected by the condition. Using donor gametes for



Example of prenatal carrier screening strategy. SMA=Spinal muscular atrophy – an autosomal recessive condition; FXS=Fragile X syndrome – an

reproduction is an option as well.

For X-linked conditions:

As the disease-causing gene is located on the X chromosome, typically only females would be carriers (females have two X chromosomes). Males only have one chromosome and will be affected by the condition if his only copy of the disease-causing gene is defective. Therefore, for X-linked conditions, carrier screening is typically only performed for female patients. **If the female patient screened positive for the condition, the pregnancy will be at increased risk to be affected.**

Prenatal testing through CVS or amniocentesis, or preconception testing using PGD can be considered to identify fetus/embryos affected by the condition. Using donor gametes for reproduction is an option as well.

What happens if the Screening Test Results are Negative/Normal?

A negative/normal carrier screening test result

= Patient is unlikely to be a carrier; Offspring at decreased risk (not zero) to be affected

Because **the detection rate of a carrier screening test typically does *not* reach 100%,** the test will identify most of the disease carriers but not all. Thus, a negative/normal carrier screen result lowers the chance an individual is a carrier for that condition, but does not eliminate the risk. Moreover, **new mutations can also arise spontaneously and randomly for each pregnancy.** Therefore, with a screen-negative carrier screen result, the risk to the person's offspring to be affected by the screened condition is significantly lowered *but not zero*.

Post-test counseling for a negative/normal carrier screen result should include a discussion of residual risk--the small chance to still be a carrier and the small chance the offspring can still be affected by the screened condition, even with a negative/normal carrier screening test result.

Types of Carrier Screening Tests

- **Ethnic-based carrier screening:** Genetic conditions selected based on the patients' ethnic background and focuses only on selected conditions that are more prevalent in that particular ethnic population. For examples, Caucasians: Cystic fibrosis, Southeast Asians: Alpha and Beta thalassemia, African American: Sickle cell disease, Ashkenazi Jewish: Tay-Sachs disease.
- **Panethnic carrier screening:** A set panel of genetic conditions is offered to all patients regardless of ethnic background. The panel includes only genetic conditions that have been acknowledged to be more prevalent in at least one ethnic population.

- **Expanded carrier screening:** A set panel of genetic conditions is offered to all patients regardless of ethnic background. The conditions on the panel are not restricted by ethnicity and are flexible. They can be ethnic-specific conditions, or conditions that are generally very rare across all ethnicities. The panel can include as many as over hundreds of genetic conditions.

ACOG traditionally advocated for ethnic-based screening. However, in this recent committee opinion, the group states ethnic-based screening, panethnic screening and expanded carrier screening are all acceptable strategy to be offered for prepregnancy or prenatal carrier screening. The new stance recognizes recent changes in human ethnic admixture, disease prevalence and advancement in molecular genetic testing methodology:

(1) With multiracial society, it is increasingly difficult to limit a person's ethnic background and ancestry to a single population

(2) Particular disorders are less likely to be confined to one specific ethnic group given increased inter-ethnic marriages

(3) The cost of DNA analysis and sequencing has decreased substantially

(4) New technology, namely new-generation sequencing (NGS), makes it possible to perform analysis of multiple genes at the same time at a reasonable cost and time-frame.

At the very basics, **ACOG now suggests all patients to be screened for cystic fibrosis, spinal muscular atrophy, thalassemia and hemoglobinopathies. Fragile X premutation carrier screening is recommended for women with a family history of fragile X-related disorders or intellectual disability suggestive of fragile X syndrome, or women with a personal history of ovarian insufficiency. Additional screening also may be indicated based on family history or specific ethnicity.**

What are Expanded Carrier Screening Tests?

Simultaneously screen for as many as over hundreds of genetic conditions at the same time (Disease selection not particularly dictated by ethnicity)

Expanded carrier screen offers the benefit of screening for multiple genetic conditions with one blood draw within a short time-frame. This is a strategy acceptable by ACOG. This may be appealing for many patients and providers given the large number of conditions that can be evaluated at once and the reassurance it offers.

However, the limitation and risks of such approach should be considered and discussed with the patients as well. For example, the more conditions one tests for, the higher the chance that the

test returns abnormal and he/she is found to be a carrier for a genetic condition. This may increase the need to test reproductive partners, the need for genetic counseling discussion and patient anxiety. Moreover, with some rare genetic conditions, residual risk calculation after a normal carrier screen may not be available given limited information on this condition.

The conditions on the expanded carrier screening panel should be carefully selected considering the risks/benefits/limitations as stated above. **ACOG suggests the conditions screened for should meet the following criteria: carrier frequency is 1/100 (1%) or higher, has a well-defined clinical phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention or have an onset early in life. Prenatal diagnosis for these conditions should be available. Adult-onset conditions should not be included.**

Does Carrier Screening Tests Replace the Newborn Screening Tests?

Regardless of parents' carrier screening test results, newborn screening is still recommended.

Is Carrier Screening Required?

Carrier screening for any condition is optional. All patients may accept or decline testing for any or all carrier screening tests after counseling discussion regarding risks/benefits/limitation.

【Reference】

American College of Obstetricians and Gynecologists Committee on Genetics. Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine. Obstet Gynecol. 2017 Mar;129(3):e35-e40.

Do you have any questions related to genetic counseling?
What topics would you like the GGA Genetic Counseling Newsletter to discuss?
Your suggestions are greatly appreciated so we can further improve our newsletter!
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