Carrier screening for Genetic Disorders

Recommendations by the Society for Indian Academy of Medical Genetics

Endorsed by Society for Fetal Medicine
&
Federation of Obstetrics and Gynecological Societies of India

This document defines **Carrier screening** as testing of an apparently healthy couple to identify if they are at risk of having a child with a genetic disorder. Carrier screening can play an important role in preventing genetic disorders with high morbidity and mortality.

These carrier screening guidelines were conceptualized, drafted, and formalized by a subcommittee constituted by the Society for Indian Academy of Medical Genetics and were endorsed by the Society for Fetal Medicine (SFM) and the Federation of Obstetrics and Gynecological Societies of India (FOGSI).

The committee deliberated on the prevalence of respective genetic disorders, availability of Indian statistics, and treatability (or otherwise) of the specific disease.

Recommendations for carrier screening

a) *Which disorders should be considered for universal carrier screening in India?*

The committee recommends universal carrier screening for two diseases at present: i. ß-thalassemia and related hemoglobinopathies and ii. Spinal muscular atrophy (SMA). This should be offered to all couples irrespective of risk factors as the carrier frequency of these two diseases is high in India. Both partners can be screened simultaneously (after conception) or sequentially (before conception).

*b) Who should be offered expanded carrier screening (ECS) *?*

*(ECS) – Expanded carrier screening for the purpose of these guidelines is defined as any additional genetic testing other than the universal carrier screening.

- **The society strongly recommends consultation with a qualified clinical geneticist before offering ECS. The committee agrees that the following are possible indications for ECS.**

- Couple with a family history of suspected genetic disorder/s where diagnostic genetic testing is not possible for the proband/s, due to death of proband/s and/or unavailability of probands' biological sample/s. ECS can be offered to such a couple in an attempt to ascertain possible diagnosis in the deceased offspring and estimate the genetic risk to their future offspring. However, this approach is limited by assuming the diagnosis in the proband and does not confirm it in the family.

- Consanguineous families who seek preconception counseling to avoid the risk of an autosomal recessive genetic disorder/s in their offspring. Our ability to detect pathogenic and likely pathogenic variants in such a couple is seriously limited by resources like mutation spectrum availability in our country and options available to couples who carry variants of uncertain significance.

- Special situations such as bad obstetric history including unexplained stillbirth, fetal malformations suggestive of monogenic etiology where the fetal sample is not available for genetic testing etc. in consultation with a clinical geneticist.

- **Pre-test and post-test counseling are a mandatory prerequisite while offering expanded carrier screening.**

c) What technology should be used for carrier screening tests?

- Beta thalassemia screening for the couple to be done by a combination of red blood cell indices and Hemoglobin separation (by HPLC) or other accurate measurements of HbA2/HbS/HbE testing (National Health Mission guidelines).
- Spinal muscular atrophy carrier screening for the couple can be done by Multiplex ligation-dependent Probe Amplification (MLPA), or an equivalent quantitative PCR methodology.
- ECS for the couple by next-generation sequencing technology, except for family history of a genetic disease where an alternative technology is the test of choice.
- A couple karyotype can be considered in special situations of recurrent pregnancy loss, subfertility, bad obstetric history, family history of a translocation carrier, etc.

d) What variants should be considered for reproductive decision-making when using next-generation sequencing-based ECS?

- All pathogenic and likely pathogenic variants when identified in both partners (autosomal recessive disorders)/ female partner (X linked disorder) can be used for reproductive decision-making.
- When a Variant of Uncertain Significance (VUS) is reported in one or both partners, refer to a clinical geneticist for further evaluation.

e) What is the ideal timing of testing?

- Couples or individuals who are planning a pregnancy (preconception)
- In the event the family is not seen in the preconception period, carrier screening (universal and/or expanded as applicable) can be offered in early pregnancy (prenatal).

f) When should a clinical geneticist's opinion be sought?

- The expert opinion of a clinical geneticist should be sought for resolving any conflicting or ambiguous reports, such as variants of uncertain significance (VUS) in one or both partners, reports with risks for more than one genetic disorder, positive family history with negative results on carrier screening, etc.
- It is preferable to consult a clinical geneticist in all situations involving prenatal testing and whenever irreversible reproductive decisions are taken.

g) Should carrier screening be Sequential or Simultaneous?

Expanded carrier screening test is best offered to both partners simultaneously if they are seen after conception. ECS is not offered to an individual. However sequential testing may be offered if couple are seen preconceptionally.

The committee considers *screening is optional and available to all. The couple can opt out of the testing without hampering the quality of care. A negative carrier screening test can reduce the chance of an affected offspring to a certain extent but does not remove the risk of having a child with a genetic disorder. The committee strongly discourages* routine use *of next-generation sequencing for carrier testing in absence of above-mentioned indications in India as we lack sufficient population data on normal and disease-causing variants currently. We intend to update these guidelines once such data becomes available.*

The **IAMG** recruited a panel of experts and curators to develop recommendations for carrier screening for genetic disorders in India. These recommendations are purely an educational resource to enable clinicians to optimize care for families in India. The authors of this document are listed and these recommendations do not reflect a personal opinion but are based on published clinical evidence and practice.

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