

Gene-by-gene carrier screening has been available for decades. Initially testing was available for a handful of relatively common autosomal recessive conditions that were associated with a high level of morbidity and a shortened life expectancy. Examples of this include cystic fibrosis and spinal muscular atrophy carrier screening, which is now recommended to be offered to *all* women of reproductive age, or specific panels of genetic conditions depending upon one's ethnicity (i.e. Ashkenazi Jewish descent). In recent years as science advances and the cost of carrier screening declines, laboratories are now able to screen for dozens or even hundreds of conditions at once. Often referred to as expanded carrier screening, the list of conditions that can be screened for has grown and will likely continue to grow.

Several professional organizations have published practice guidelines and policy statements on carrier screening. In 2015, the organizations noted below joined together to publish a [Points to Consider](#) commentary to assist providers in further navigating patient options (click on them to read their specific recommendations):

- [The American College of Medical Genetics and Genomics \(ACMG\)](#)
- [The American College of Obstetrics and Gynecology \(ACOG\)](#)
- The National Society of Genetic Counselors (NSGC)
- The Perinatal Quality Foundation
- The Society for Maternal-Fetal-Medicine (SMFM)

The [European Society of Human Genetics \(ESHG\)](#) also has its own policy.

In general, each organization agrees:

- Decisions to have any form of carrier screening (i.e. single disorder or expanded carrier screen) should be voluntary and in the context of an informed decision.
- Educational materials that provide an overview of screening, the conditions screened for, and the benefits and limitations of testing should be available to all patients.
- Ideally carrier screening should be offered and, if desired by the patient, performed prior to pregnancy to maximize the number of reproductive options available.
- Information about carrier screening should be provided to every pregnant patient.
- If time constraints exist, screening of both the patient and the partner concurrently should be considered.
- Review of the benefits, limitations, and disadvantages of testing are essential elements of informed consent.
- Family history should be obtained prior to carrier screening to ensure appropriate carrier screening may be offered.

- If there is a family history of a genetic condition, referral to an appropriate genetics provider should be considered to ensure accurate risk assessment.
- Expanded carrier screening does not replace genetic counseling, and genetic counseling should be available to individuals prior to testing as desired
- If a carrier or carrier couple is identified, referral to genetic counseling is recommended to review results, additional testing available, reproductive options, and provide psychosocial support.
- If expanded carrier screening is offered, the expanded screen offered should include:
  - Disorders that are of a nature in which most at-risk individuals would consider prenatal diagnosis.
  - An option to opt-out should be provided for any condition included on a panel for which adult onset forms have been reported.
- Laboratories offering expanded carrier screening should abide by the following:
  - Should follow the ACMG laboratory standards for classifying and reporting variants.
  - Pathogenic variants reported must be validated, have clinical association, and be supported by further literature citations that report the variant as pathogenic (a single case citation is not sufficient).
  - Variants of unknown significance, or those with limited data to support their pathogenicity, should not be reported.
  - Should provide estimated residual risk and the information utilized to calculate this risk (i.e. disease prevalence, mutation frequency in population, detection rates).

#### Important considerations:

- Other methods of screening, such as enzyme analysis for Tay-Sachs disease, may have a higher detection rate than molecular testing.
- Carrier screening for some conditions may identify an increased risk of disease for the individual tested. Examples include:
  - Identification of an individual with two pathogenic variants who has an autosomal recessive condition (such as Type 1 Gaucher disease or pseudocholinesterase deficiency, where an affected individual may not have clinical symptoms).
  - Carrier with elevated risk, (such as a slightly elevated risk to develop Parkinson disease in carriers for Gaucher disease, or the increased risk for fragile X-associated tremor/ataxia syndrome for fragile X permutation carriers).
- Carrier screening also has potential implications for the patient's family members. If the patient is found to be a carrier for a genetic condition, their relatives may also be

at increased risk to carry that same mutation.

Below we provide a brief 'to the point' summary from each organization. Click on one to get a more detailed breakdown of their position statement.

### [American College of Obstetrics and Gynecology \(ACOG\)](#)

#### **To the point...**

The ACOG committee opinion stops short of endorsing expanded carrier screening, noting that 'when selecting a carrier screening approach, the cost of each option to the patient and the health care system should be considered'. Rather, ACOG reiterates its recommendations to offer carrier screening for specific conditions, depending on risk as determined by ethnicity:

- Cystic fibrosis carrier screening should be offered to all women who are considering pregnancy or are currently pregnant.
  - Complete analysis of the CFTR gene is *not* appropriate for routine carrier screening and should be reserved for individuals with suspicion based on personal or family history of the condition.
- Spinal muscular atrophy carrier screening should be offered to all women who are considering pregnancy or are currently pregnant.
- A complete blood count (CBC) should be performed in all women who are currently pregnant to assess for the risk of hemoglobinopathies.
  - Hemoglobin electrophoresis should be performed for those with of African, Mediterranean, Middle Eastern, Southeast Asian, or West Indian descent.
  - Solubility tests alone (e.g. "SickleDEX") are inadequate for diagnosis of sickle cell disorders and should not be utilized as a first-line carrier screen.
- Fragile X carrier screening is recommended for women who are considering pregnancy or are currently pregnant with a family history suggestive of fragile X syndrome.
  - This includes women with unexplained ovarian insufficiency or failure, or an elevated follicle-stimulating hormone (FSH) level before age 40.
- Individuals of Ashkenazi Jewish descent, should be offered carrier screening for Canavan disease, cystic fibrosis, familial dysautonomia, and Tay-Sachs disease.
  - Further screening for Bloom syndrome, familial hyperinsulinism, fanconi anemia, gaucher disease, glycogen storage disease type 1, joubert syndrome, maple syrup

urine disease, mucopolidosis type IV, niemann-pick disease, and usher syndrome may also be considered.

- Tay-Sachs carrier screening should be offered to all women who are considering or are currently pregnant if either member of the couple is of Ashkenazi Jewish, French Canadian, or Cajun.

### **American College of Medical Genetics (ACMG)**

#### **To the Point:**

ACMG recognizes that with the advancement of next-generation sequencing, carrier screening can be done for a larger number of conditions with high precision, rapid turnaround times, and lower costs. However, rather than adding all autosomal recessive and/or X-linked carrier conditions, a thoughtful approach to the addition of genetic conditions for any given laboratory should be undertaken.

### **ESHG Policy Statement:**

#### **To the Point:**

ESHG recognizes and outlines the challenges that expanded carrier screening brings to routine clinical care. The aim of the ESHG policy statement is to outline clinical and laboratory guidelines for use with expanded carrier screening, taking into account lessons learned from the history of screening programs for single gene disorders.