How to Navigate Carrier Screening

Given technological advancements, carrier screening has evolved from one or two conditions being assessed, ones in which the phenotype, disease frequency, and expectations were more clear, to the ability to test hundreds of conditions with various disease presentations and inheritance patterns. The topic has become complex. This informational sheet serves as a summary of *some* points made in organizational guidelines. Please see original sources for full details.

What's the Goal?

The goal of carrier screening is to assess couples' and individuals' risk for genetic conditions in a cost-effective way. Ideally, screening is offered prior to conception. Carrier screening enables those screened to consider their reproductive risks, reproductive options, and to make informed decisions including preconception planning, prenatal diagnosis, postnatal management, and condition specific counseling and care.

What are organizations saying?

National Society of Genetic Counselors (2023)

- Offer to everyone regardless of ethnicity
- Test conditions that an individual or couple would deem to change reproductive planning. Reproductive planning may include options such as preimplantation genetic testing, prenatal diagnosis, or adoption but also neonatal care and plans.
  - The previous assertions from guidelines of severe/profound conditions is highly subjective and phenotype/genotype correlations are not always clear. The decision to test certain conditions should take into consideration the opinions of members in the disability community and prospective parents.
- Simultaneous testing of both genetic contributors, particularly during a pregnancy, is the goal

European Society of Human Genetics (2016)

- Offer to everyone regardless of ethnicity or population
- Test conditions with severe childhood onset and the variants that have clear clinical significance
  - integrate evidence of analytical validity, healthcare care cost, social and psychosocial impact, interventions available, and public acceptability

American College of Obstetrics and Gynecology (2017/reaffirmed 2020)

- Overall, ethnic, panethic, and expanded carrier screening are acceptable practices as long as each patient is offered the same option/care.
- For expanded carrier screening, conditions should be well defined and have an early and detrimental effect on quality of life as well as a carrier frequency of >1 in 100.

General guidelines/ethnic based:

- Cystic fibrosis (CF) and spinal muscular atrophy (SMA) carrier screening and Complete Blood Count (CBC for all patients
- If a patient has a family history of autism, intellectual disability, premature ovarian insufficiency, or personal history of premature ovarian insufficiency: offer Fragile X carrier screening.
- If a patient has Ashkenazi Jewish ancestry: Carrier screening for Cystic fibrosis, Tay Sachs, Familial Dysautonomia, and Canavan Disease. Additional conditions to consider are: mucolipidosis IV, Niemann-Pick disease type A, Fanconi anemia group C, Bloom syndrome, and Gaucher disease.
- If a patient has Mediterranean, African, West Indian, Middle Eastern, or Southeast Asian ancestry and/or low mean corpuscular volume (MCV) or mean corpuscular hemoglobin (MCH): offer Hemoglobinopathy carrier screening
- If a patient has French Canadian or Cajun ancestry: Tay Sachs carrier screening

American College of Medical Genetics (2021)

- Offer to everyone regardless of ethnicity or population
- Analytical validity and clinical validity should be established; lab reports should be clear on genes assessed, variant classification used for reporting, detection, sensitivity, and methodology
- If a patient has a new reproductive partner, then readdress carrier screening
- Does not replace newborn screening
- If sequential testing approach is taken, then subsequent partner/donor testing should include full gene analysis as opposed to limited panel of variants
- A tiered approach is taken to determine which conditions to screen patients. ACMG recommends tier 3 to all patients and tier 4 when medical history warrants the additional genes such as in cases of consanguinity

Tier 3

- Carrier frequency ≥1/200 of US ethnic populations for autosomal recessive conditions and a 1/40,000 disease prevalence for X-linked conditions
- Disease severity taken into account
- Ongoing curation is needed

Tier 4

- Includes tier 3 conditions
- No lower limit of carrier frequency
- Potential for more complex counseling and less clinical validity due to conditions with poorer genotype-phenotype correlations, variant interpretation, locus heterogeneity, pleiotrophy

click here for supplementary materials

Overall:

Pretest counseling

include risks, benefits, optionality, and consequences of screening with the goal to support patient's informed and autonomous decision making:

- options available should patient(s) learn they are carriers
- possibility of incidental findings
- likelihood of a positive result with more genes assessed
- inheritance patterns
- possible genetic discrimination
- some carriers may manifest symptoms or have health implications that requires follow-up evaluations

Variants of uncertain significance are not recommended to be reported (3, 4) except in specific situations with proper consent of the patient. Some labs may upgrade variants and reissue reports. Counseling on this point is appropriate.

Posttest counseling

include reproductive risk, genotype/phenotype correlations, penetrance

- phenotype may vary and may be more "mild" than classic presentation
- screening reduces the risk of being a carrier but never eliminates the risk

- Preimplantation genetic testing with in vitro fertilization
- Prenatal diagnostic testing via chorionic villi sampling or amniocentesis; electing adoption, parenting, or termination depending on the results
  - Results can be used to plan for neonatal, therapeutic care
- Testing after birth
- Utilizing donor egg, sperm, or embryo
- Choose not to conceive a pregnancy
- Adoption

Resources:

1. "Committee Opinion No. 691: Carrier Screening for Genetic Conditions." Obstetrics and gynecology vol. 129,3 (2017): e41-e55. doi:10.1097/AOG.0000000000001952
2. "Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine." Obstetrics and gynecology vol. 129,3 (2017): e35-e40. doi:10.1097/AOG.0000000000001951
3. Gregg, Anthony R et al. "Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG)." Genet Med vol. 23,10 (2021): 1793-1806. doi:10.1038/s41436-021-01203-z
4. Sagaser, Katelynn G et al. "Expanded carrier screening for reproductive risk assessment: An evidence-based practice guideline from the National Society of Genetic Counselors." Journal of genetic counseling, 10.1002/jgc4.1676. 9 Feb. 2023, doi:10.1002/jgc4.1676
5. Henneman, Lidewij et al. "Responsible implementation of expanded carrier screening." European journal of human genetics : EJHG vol. 24,6 (2016): e1-e12. doi:10.1038/ejhg.2015.271
6. Elsi Hub' Expanded Carrier Screening Resource Section