

Expanded Carrier Screening

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Carrier Screening

- Genetic testing performed on an asymptomatic individual to determine whether that person has a mutation or abnormal allele within a gene associated with a specific genetic condition
- Identify couples “at-risk” for having a child with an autosomal recessive or X-linked genetic condition
- Goal: Provide individuals with meaningful information to be used in guiding pregnancy planning based on their personal values

Carrier Screening Methods

Ethnicity Based/Targeted

- Caucasian: cystic fibrosis, SMA
- Ashkenazi Jewish: Bloom syndrome, Canavan, Gaucher, Tay-Sachs, etc.
- French Canadian: Tay-Sachs
- Southeast Asian: thalasseмииas
- African: sickle cell

Expanded/Panethnic

- Everyone gets tested for the same set of conditions
- Panels typically >100 conditions
- Screen for many conditions with a single sample

Ethnicity Based Screening Limitations

- Many individuals have ancestors of different ethnicities
- Some people are not aware of details of their ancestry or could be adopted
- Individuals from “low-risk” ethnic groups can still carry mutations
- Most carrier-carrier couples have NO family history

Expanded Carrier Screening

Advantages

- Not ethnicity-dependent
- Increase in information
- Low turnaround time
- Low Cost
- Useful for consanguineous couples without specific family history
- Gives the most reassurance to couples who want testing “for everything”

Disadvantages

- A lot of information
- Not all these conditions are life threatening or “serious”
- Panel detection rates can be as low as <10% for certain conditions- tends to be higher in Caucasian and Ashkenazi Jewish
- Many more partners will need screening, which adds expense
- Does not actually test “for everything”
- Possible adult onset conditions inadvertently identified

ACOG Committee Opinion: Carrier Screening in the Age of Genomic Medicine

Number 690, March 2017

- Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening.
- Provider or practice should establish a standard approach that is consistently offered to and discussed with each patient, ideally before pregnancy.
- If a patient requests a screening strategy other than the one used by the healthcare provider, the requested test should be made available to her after counseling on its limitations, benefits, and alternatives.

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- All patients who are considering pregnancy or are already pregnant, regardless of screening strategy and ethnicity, should be offered carrier screening for cystic fibrosis and spinal muscular atrophy, as well as a complete blood count and screening for thalassemias 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 personal history of ovarian insufficiency.
- Consanguinous couples should be offered genetic counseling to discuss the increased risk of recessive conditions in their children and the limitations and benefits of carrier screening.

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- Disorders included on an expanded carrier screening panel should meet the following criteria:
 - Carrier frequency of 1 in 100 or greater
 - Have a well defined phenotype
 - Have a detrimental effect on quality of life, cause cognitive or physical impairment, or require surgical or medical intervention
 - Have an onset early in life
 - Should be able to be diagnosed prenatally and afford opportunities for antenatal intervention to improve outcome, changes to delivery management, and education of parents about special care needs after birth.
 - Should not be primarily associated with adult onset

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- Providers and practices should carefully evaluate the conditions included on a panel and determine the appropriateness of the panel offered.
- Pretest education and consent should include descriptions of the conditions being screened as well as limitations such as imprecise detection rates.
- Posttest counseling should include discussion of residual risk.

Additional Considerations for Expanded Carrier Screening

- Step-wise approach or concurrent testing of couple?
- Is biological father of pregnancy available?
- Is there a known family history of a specific condition?
- Which panel do you choose?
 - How many conditions? Does lab use sequencing or genotyping?
- How to do pretest counseling? How to discuss posttest residual risk?
- Most panels are not covered by insurance
- Carriers of some conditions may have mild symptoms
- Adult onset conditions have been diagnosed

Case Example

- Jane Doe is a 28 year old G1P0 currently at 10w2d. She is being seen for her first OB appointment today. She reports that her sister just had a baby who was found to have cystic fibrosis after newborn screening. She would like to know if she is a carrier for cystic fibrosis.
 - What are her testing options?
 - What are the benefits of these options?
 - What are the limitations of these options?
 - Should she be offered anything else?
 - Is there any other information that might be helpful for you to help her make a decision?

Case Example

- Jane Doe elects to complete expanded carrier screening because she wants to know “everything”
- Results indicate that she is not a carrier for cystic fibrosis but was found to be a carrier for a mutation in the *ATM* gene associated with ataxia telangiectasia and 2 mutations in the *GSD2* gene associated with glycogen storage disorder type II (Pompe disease).
 - What do these results mean for the patient?
 - What do these results mean for the fetus?
 - What are the next steps?

Case Example

- *CFTR*

- Did the panel use a genotyping or sequencing method?
- Did we confirm the specific mutation in the family? Does this panel test for that mutation?
- Is there a residual risk she could still be a carrier?

- *ATM*

- How do we assess fetal risk for ataxia telangiectasia (recessive condition)?
 - We need to test the partner. Which testing method are you going to use? The same expanded panel or test him only for *ATM* mutations?
- Mutations found in *ATM* have been associated with a moderate increase in risk for breast cancer.
 - Was the patient counseled that testing could identify something that could have a direct impact on her health?
 - Recommendations for increased breast cancer screening

- *GSD2*

- What could it mean that two mutations were identified in this gene?
- What information is still missing?
- What additional testing could provide more information?
- Was the patient counseled she could be identified not only as a carrier but as affected?
- How will a diagnosis of glycogen storage disorder type 2 affect her?

Conclusions

- Expanded carrier screening is an acceptable method for offering carrier screening both prepregnancy and prenatally
- Pretest counseling should include discussion of limitations/risks and possible testing outcomes
- Post test interpretation of results should be careful and complete
- Post test counseling should include discussion of residual risk
- Genetic counseling referral available