Carrier screening

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"To screen or not to screen?" is no longer the question for preconception carrier screening, a long-established practice in reproductive medicine. However, as options have grown in recent years, so have the complexities surrounding which options are best for patients and how clinicians can counsel them on their choices.

Preconception carrier screening is the process of identifying individuals/couples seeking pregnancy who would be at risk for transmitting autosomal recessive or X-linked genetic disorders to their offspring.[1] To understand the basis for screening, it is also important to understand the concept of prevalence, which is the percentage of a population that is affected by a particular disease at a particular time.[2] Without a family history, a higher prevalence of a condition suggests a greater likelihood of finding a carrier.

Carrier screening options

Historically, carrier screening has been offered to individuals who are at high risk for specific disorders based on their race, ethnicity or family history.[2] But as the population has changed, so have screening options.

Ethnic-based screening targets specific ethnic populations at greater risk for specific disorders.[2] An example of this is the screening of individuals of Ashkenazi Jewish decent for Tay-Sachs or Canavan disease. However, the difficulty of determining an individual's ancestry in our current multiracial society poses a challenge to relying solely on ethnic-based screening.

Panethnic (nondirective) screening is available to all individuals regardless of ethnicity.[2] A changing population prompted the need for this type of screening, as previous assumptions regarding prevalence in a specific ethnicity or race might no longer apply.

Expanded carrier screening (ECS) makes it possible to screen for multiple conditions at one time.[2] Historically, ECS had been cost prohibitive for use in routine screening. However, significant advances in technology have dramatically decreased the cost, making it possible to screen a large number of conditions and individuals at the same time using next generation sequencing (NGS). Given its efficiency and economy, ECS has generally replaced panethnic screening.[2]

Depending on the company a clinic chooses, patient screening options can vary from a few to a few hundred different disorders. It can be a challenge for clinicians to choose the option that is best for their practice and their patients.

Screening recommendations

To make an evidence-based decision regarding what level of carrier screening is best for a particular practice, clinicians should understand the recommendations of respective governing organizations.

The American College of Obstetricians and Gynecologists (ACOG) give the following recommendations[2]:

- Ethnic-specific, panethnic or ECS are all acceptable options for prepregnancy and prenatal screening options.
- It is important for the individual clinic or provider to offer the same level of screening to all patients and set a standard practice for the clinic.
- If a patient asks for additional testing that is different from the standard practice, the clinic should be able to accommodate the request.
- All patients should, at a minimum, be offered the following screenings:
  - Cystic fibrosis
  - Spinal muscular atrophy
  - Complete blood count to screen for thalassemias and hemoglobinopathies
  - Fragile X (if there is a family history)
  - Additional testing as identified during counseling

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- In cases of consanguinity, genetic counseling should be offered to discuss the increased risk of recessive conditions.
- Screening is optional.

The American Society for Reproductive Medicine recommendations for prepregnancy counseling align with ACOG guidelines for carrier screening. This reinforces the benefit of obtaining a genetic and family history for both the patient and partner when determining how to proceed with screening.

Developing a screening strategy

When developing a carrier screening process within a clinic, it is important to consider the many options and determine what approach is reasonable and accessible for patients. It is also important to understand that certain options, such as universal ECS, might place an increased burden on a clinic to counsel and educate patients. A 2018 review article offers a comprehensive assessment of important considerations.[1]

In particular, clinics might weigh the use of ethnic-based screening versus ECS. In an increasingly multiethnic culture, offering only ethnic-based screening could be considered an outdated treatment course. It might also raise the ethical dilemma of whether all patients should be given the opportunity to be screened.[1]

For these and other reasons, ECS has largely replaced ethnic-based screening. However, many insurance plans will not cover the cost of ECS, making it an additional out-of-pocket expense for many patients. Additionally, many clinics and providers are not trained to review ECS results with a patient, potentially causing increased anxieties in an already complicated process.[1]

Another consideration is whether to offer initial screening only to the patient or to both the patient and partner. The traditional approach has been to screen the patient first, and if results are positive, to screen the partner.[1] However, this can cause delays in treatment due to the two- to three-week processing time for each specimen sent for screening.

Additionally, clinicians would need to decide whether to screen the partner for the full panel or for only the tests that were positive for the patient.[1] Simultaneous screening might optimize time to treatment and consolidate counseling to one visit, thereby streamlining the pre-cycle phase of treatment. However, this approach would increase the overall cycle cost to the patient.[1]

Variations and limitations of screening

Early carrier screening began with the ability to screen for the CFTR mutation, which leads to either developing cystic fibrosis (CF) or becoming a carrier of the disease.[1] The mutation was cloned and sequenced in 1989, but ACOG did not recommend screening for CF until 2001 because of the complex nature of disease expression and the questionable likelihood that existing screening panels could reliably determine full carrier status.

The variability in the number of mutations screened in carrier screening varies dramatically from company to company, leading to confusion for clinics, providers and patients. For example, Ashkenazi Jewish panels can screen for anywhere from four to more than 100 different conditions, depending on the company a clinic chooses.[1]

ACOG and the American College of Medical Genetics and Genomics (ACMG) proposed the following criteria for disease inclusion in carrier screening[2]:

- Carrier frequency of 1 in 100 or greater
- Has a well-defined phenotype (a set of observable characteristics)
- Has a detrimental effect on the quality of life
- Causes cognitive or physical impairments
- Requires surgical or medical intervention
- Has an onset early in life

Counseling and education

Patients seeking fertility services are a unique patient population. Many are well-educated and motivated to be active participants in their care. As a result, prescreening counseling and education are an important aspect of the precycle phase of treatment.

Carrier screening offers an additional data point for patients. However, access to screening for hundreds of conditions can uncover knowledge that requires proper education and counseling, for which many clinics and providers are not fully prepared. It is vital that clinicians develop a process to ensure that patients receive information that is comprehensive, understandable and serves to decrease any anxiety about carrier screening.

ACOG, ACMG and other groups highlight key aspects of prescreening counseling:

- The disorders being screened require that both parents be carriers (except X-linked disorders).
- Some conditions might have variable or poorly characterized outcomes. For example, some

disorders detected through ECS might be asymptomatic or result in mild symptoms.[1]

- Negative screening results do not remove the risk of being a carrier, and some disorders have higher risks for being a carrier even after a negative result. Carrier screening detects mutations within a gene. However, some disorders are due to mutations that result from duplication or deletion of a gene. These types of mutations are not detectable through NGS technology.

Reproductive specialists often require the support of a genetic counselor to educate patients effectively. Determining whether results warrant progression to preimplantation genetic testing for specific mutations requires the guidance of a trained professional. Genetic specialists can help recommend the best course of treatment for a patient while decreasing anxieties associated with a positive screening result.

After screening, critical discussion occurs in conjunction with a review of the results. This should include more detailed discussion of any positive findings. A standard approach to further evaluation is important. The providers within a practice should determine whether cases that warrant further testing should limit screening to partners or open it to extended family. This evaluation might be done on a case-by-case basis. However, understanding and developing an internal process on how to proceed with further evaluation will help ensure counseling will be consistent for all patients in a given clinic.

Documentation is another important aspect of carrier screening. All discussions, before and after screening, should be captured. Decisions regarding next steps should be carefully documented in a patient's medical record. If a patient decides not to pursue carrier screening, then the declination to screen should also be documented.

Sample screening strategy

Clinicians discuss carrier screening with all patients, and do the appropriate ethnic-based screening on all patients. ECS is discussed and offered to any patient who would like the additional testing. Because this is currently not a covered service for most patients, many pay out of pocket for the screening. The following table helps simplify the process for staff.

Carrier screening

Testing	Female	Male	Frequency and Indications
Ethnic-based screening	Cystic fibrosis	If partner has positive screening, refer to genetics for further evaluation and counseling.	Once, if patient OR partner is Caucasian/ Hispanic
	Hemoglobin electrophoresis		Once, if patient OR partner is Black/ African American
	•Cystic fibrosis •Tay-Sachs •Canavan •Familial dysautonomia		Once, if patient AND partner are Ashkenazi Jewish
	Hemoglobin electrophoresis		Once, if patient HERSELF is Southeast Asian

Extended carrier screening (ECS)

Type of ECS testing	Next steps	Male	Frequency and Indications
Donor sperm	If chosen donor sperm has positive ECS screening, submit consult request to genetics for further evaluation and screening.		Once
Consanguineous relationship	Submit consult request to genetics for further evaluation and screening.		Once
Sexually Intimate Partner (SIP) (confirmed carrier of a recessive disorder)	Submit consult request to genetics for further evaluation and screening.		Once
SIPs (*in vitro* fertilization [IVF] only)	•Offered to couples undergoing IVF •Reproductive endocrinology/ infertility physician orders •Genetic screening test kit given to patient with requisition •Patient goes to lab •**May be an out of pocket expense** •**May be covered by insurance if partner has a documented pre-existing genetic diagnosis**	If positive results with female, referral to Genetics for male testing and counseling **(covered benefit)**	Once

Conclusion

The decision to screen or not is no longer a real question. The discussion within fertility clinics should be about what type of screening to offer and how to ensure consistency within the practice to minimize confusion for patients and staff. As technologies advance, it is critical for clinicians to evolve their practice and offer the comprehensive treatment options patients seek. Education and counseling are key to a successful carrier screening program. Using an evidence-based approach will help staff, providers and patients navigate the complicated world of carrier screening.

About the author

Shalini Gunawardena, RN, MBA, is director at Kaiser Permanente Center for Reproductive Health in Fremont, Calif. She has been practicing in the field of infertility since 1992 and was instrumental in helping establish the country's first IVF clinic in an HMO setting. Since starting her career at the Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine at Weill Cornell Medicine in New York, her work has helped build the foundation from which current Reproductive Endocrinology practices are developed and established. Gunawardena received her undergraduate degree in nursing from the University of British Columbia in Canada and her Master of Business Administration from the University of Maryland. Shalini is a member of ASRM and is a past chair of the Nurses Professional Group. She has presented extensively at ASRM, Midwest Reproductive Symposium and Pacific Coast Reproductive Society.

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