Expanded Carrier Screening

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KEYWORDS

- Prenatal carrier screening • Expanded carrier screening • Genetic counseling
- Perceptions of Uncertainties in Genome Sequencing (PUGS) scale

KEY POINTS

- The goal of prenatal carrier screening is to provide information to couples considering or with an ongoing pregnancy.
- Couples who select this elective screening have an opportunity to learn whether there is mendelian risk rather than population risk of an affected fetus.
- Couples that select screening have the option of screening for a limited number of conditions, or an expanded number of conditions.
- The Perception of Uncertainties in Genome Sequencing scale offers a framework around which pretest and posttest counseling can be considered.

SCREENING

The term screening is important to understand. Classically, this refers to applying an imperfect test (eg, Papanicolaou smear for cervical cancer) or process (eg, travel questionnaire used during the Ebola epidemic) to identify asymptomatic patients within a population. The imperfection in a screening test refers to the acceptance of false-positive and false-negative results to improve case finding. Carrier screening in genetics attempts to determine, among asymptomatic patients, those capable of passing genes or genetic risk to future generations. This context refers to the population addressed by screening. Prenatal carrier screening is intended to identify asymptomatic, reproductive-aged individuals, so that risk of carrying an affected child can be specified. The target population is couples who are pregnant or planning to become pregnant.[1] There are 2 other dimensions to which the word screening is attached. These dimensions relate to the number of genes (ie, conditions) and the number of genetic variants. The ability to analyze multiple genes and variants simultaneously (with the same sample) set the stage for screening panels. These panels first reflected

Conflict of Interest: The author reports no conflict of interest.
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Obstet Gynecol Clin N Am 45 (2018) 103–112
https://doi.org/10.1016/j.ogc.2017.10.005 **obgyn.theclinics.com**

genotyping (slow throughput) efforts to return results for more than one gene and variant simultaneously. With current sequencing technology, reported genes and variants are now arbitrary and reflect inconsistent efforts by companies to return results for conditions of interest to society, providers, and their patients. Advances in sequencing technology led to a new term, expanded carrier screening (ECS). In the prenatal setting this expansion allows consideration of panethnic screening, which means the population is not restricted. Expansion also means the number of genes and their variants reported is a function of the laboratories and any restrictions placed on them (eg, time, reimbursement, or regulation). In the clinical setting, ECS has additional implications. Prenatal carrier screening has extended beyond asymptomatic carriers of recessive conditions to include presymptomatic carriers of X-linked and semidominant conditions. The application of screening now has a spectrum and this key concept can be depicted using a Rubik cube (Fig. 1).

The Rubik cube matrix has 3 axes. The X axis depicts the populations screened, the Y axis the variants considered in the screening strategy, and the Z axis represents the genes or conditions being evaluated. Red, blue, and green dots denote the magnitude along each axis from highest (red) to lowest (green). The most intensive screening program would be to interrogate an entire population (panethnic; X axis) using sequencing technology (Y axis) and then reporting out information for a large number of genes (Z axis). The least intensive (all green dots on the cube) would be the application of polymerase chain reaction for delta F508 in a family with a proband known to have cystic fibrosis (homozygous delta F508) based on clinical symptoms and prior application of a diagnostic panel. The least intensive application (all green on the cube) is one in which genotyping methods are used for diagnostic purposes. In this case, the risk of affected family members is mendelian in magnitude. When the risk of an asymptomatic carrier moves from population-based (eg, 1/25 for cystic fibrosis) risk to

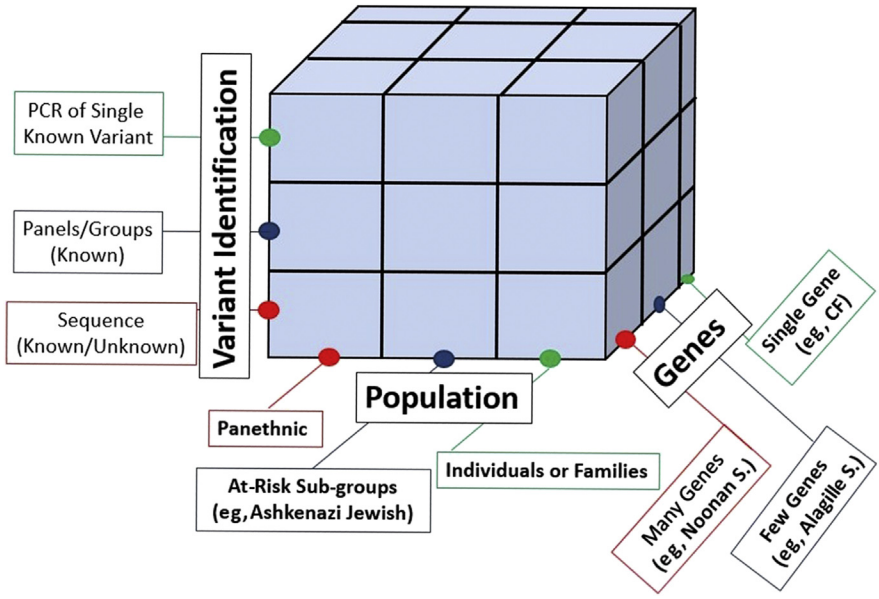

Fig. 1. The Rubik cube model of prenatal diagnosis and carrier screening has 3 axes: population, screened variants, and genes. The red, blue, and green dots indicate stratification across the spectrum. CF, cystic fibrosis; PCR, polymerase chain reaction; S, syndrome.