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Carrier screening for single gene disorders

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A B S T R A C T

Screening for genetic disorders began in 1963 with the initiation of newborn screening for phenylketonuria. Advances in molecular technology have made both newborn screening for newborns affected with serious disorders, and carrier screening of individuals at risk for offspring with genetic disorders, more complex and more widely available. Carrier screening today can be performed secondary to family history-based screening, ethnic-based screening, and expanded carrier screening (ECS). ECS is panel-based screening, which analyzes carrier status for hundreds of genetic disorders irrespective of patient race or ethnicity. In this article, we review the historical and current aspects of carrier screening for single gene disorders, including future research directions.

1. Introduction and historical perspective of carrier screening

Advances in molecular technologies, especially next generation sequencing (NGS), are changing the landscape of clinical genetic testing. These newer technologies have resulted in a rapid increase in the availability and complexity of screening and testing, including carrier screening. “Traditional” carrier screening is based on family history of a specific genetic disorder, or screening for disorders with increased carrier frequency based on ethnic/racial background. Contemporary screening now also includes expanded carrier screening (ECS), which screens for hundreds of disorders in a single test.

Historically, screening for single gene disorders began in 1963 with the introduction of newborn screening (NBS) for phenylketonuria (PKU). Newborn screening is the largest population-based genetic screening program in the USA. The primary objective of newborn screening is to identify potentially lethal or disabling conditions in the newborn. This program differs from carrier screening because it is designed to identify a clinical disorder rather than asymptomatic carrier status. Currently, NBS involves screening for 34 core conditions, and secondary conditions as determined by individual states [1]. Due to the more sensitive methodologies utilized for NBS, carrier status may also be identified. NBS also differs from traditional carrier screening in that it is state mandated, whereas carrier screening is voluntary. Many of the disorders on the NBS panel are also included on ECS panels, which are discussed in Section 3.3. Thus, confirmed positive results from an NBS may have carrier screening implications for family members.

On the historical timeline, implementation of NBS was followed by carrier screening for Tay–Sachs disease, and was implemented in the 1970s. Tay–Sachs disease has an increased incidence in individuals of Ashkenazi Jewish (AJ) descent, with carrier frequency of one in 25 to one in 30 in this population. The late 1980s and 1990s ushered in a time of rapid gene and mutation discovery. Thus, as additional genes and associated mutations for disorders with increased carrier frequency in the AJ population were identified, additional carrier screening tests also became available. In 2004, the American College of Obstetricians and Gynecologists (ACOG) published a statement recommending discussion of nine disorders and preconception screening for four disorders for individuals of AJ descent [2]. Additional information on screening for individuals of AJ descent is included in Section 3.2.

Also during the late 1990s and early 2000s, recommendations regarding carrier screening for cystic fibrosis (CF) were published; CF has a carrier frequency of approximately one in 25 in the Northern European Caucasian and Ashkenazi Jewish populations. The National Institutes of Health published the first statement in 1997 recommending that screening be offered to individuals/couples with a family history of CF, and couples undergoing prenatal testing [3]. In 2001 the American College of Medical Genetics and

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Genomics (ACMG) [4] (reaffirmed in 2013) and American College of Obstetricians and Gynecologists (ACOG) published guidelines recommending CF screening for individuals of Northern European and Ashkenazi Jewish descent. ACOG guidelines were updated in 2011 and, in 2017, recommended that screening be offered to reproductive age women, regardless of ethnic background [5]. This current article has updated screening recommendations for spinal muscular atrophy, CF, hemoglobinopathies, fragile X, and individuals of Eastern and Central European Jewish descent [5].

In 2009, carrier screening transformed from a single test based on ethnicity to simultaneous screening for approximately 100 disorders, regardless of ethnicity, via various commercial laboratories [6]. This panel-based screening for multiple disorders is referred to as expanded carrier screening (ECS). Over the past several years, the number of laboratories offering ECS and the number of disorders included on the panels has continued to increase. Several laboratories have come "full circle," with an emphasis on comprehensive ECS, but also offering basic or "ACMG/ACOG Panels" and even customizable panels, allowing the patient and her provider to make specific screening decisions.

The evolution of carrier screening is closely tied to gene discovery and advances in molecular techniques. Prior to definitive identification of causative genes and associated mutations, carrier screening relied on biochemical techniques, utilizing measurements of enzyme activity and/or substrate levels. As genes and mutations were identified, molecular-based screening became the standard. The discovery of the polymerase chain reaction (PCR) has played a crucial role in gene and mutation discovery, as well as in the development of current molecular methodologies. PCR is a technique whereby a small quantity of a specific DNA fragment is amplified by orders of magnitude [7]. The amplified DNA can then be analyzed for variations in size and sequence. The development of multiple techniques for mutation analysis of PCR products soon followed, including Sanger sequencing analysis of PCR products. Sanger sequencing provides specific mutational information, but is time and labor intensive [8]. The last decade has witnessed a rapid advancement in sequencing technology, referred to as next generation sequencing (NGS). NGS utilizes massively parallel sequencing with rapid speed and throughput and the capacity to generate information about multiple genes, the whole exome or even the whole genome within days, and often at a cost less than that of Sanger sequencing [9]. NGS, now utilized routinely in clinical diagnostics, has had recent significant impact on molecular testing, including carrier screening (Fig. 1).

2. Basic genetic principles for carrier screening

In the rapidly evolving setting of genetic testing, it is essential for medical providers to understand the basic principles of carrier screening, types and timing of testing, management of positive test results, and limitations of screening in the context of current societal guidelines.

2.1. Genetics of carrier states and implications for family members

Familiarity with basic patterns of inheritance is important for understanding carrier screening. Carrier testing is distinct from many other laboratory tests, as these genetic test results often have implications for family members of the patient and/or her partner. Most of the disorders included on carrier screening panels are inherited in an autosomal recessive (AR) manner. AR disorders occur when both copies of a gene at a particular autosomal (non-sex chromosome) locus have a mutation. The affected individual inherits two copies of the abnormal gene, one from each parent. Carriers, who have one abnormal copy and one normal copy of the gene, are phenotypically normal. However, if a patient and her partner are both carriers for the same autosomal recessive disorder, the couple is at 25% risk for having an affected child.

Recessive mutations are most often transmitted in a stable manner through generations, rather than due to de-novo mutation. Identification of an AR disease carrier also has implications for family members. The sibling of an individual affected with an AR disorder has a two-thirds risk of being a carrier. For a patient who is identified as a carrier with negative family history, first degree relatives are also at 50% risk for carrying the mutation. It is important that familial mutations are identified, as this information enables efficient site-specific analysis for the known familial mutation. Family members who are negative for the familial mutation(s) are at low risk for having an affected child, and cannot transmit the known familial mutation.

Carrier screening may also be performed for autosomal dominant (AD) disorders. Autosomal dominant diseases are due to a mutation in just one copy of a gene at an autosomal locus. Typically, mutations responsible for an autosomal recessive disorder – such as Huntington disease or hereditary breast and ovarian cancer syndrome – are initially identified in an affected family member. Some of today's ECS panels also include a small number of autosomal dominant (AD) disorders. Therefore, it is possible that an AD disorder may be incidentally identified through ECS. Importantly, disease penetrance and variability may affect symptoms and severity of disease. First-degree relatives for the carrier of an AD disease are at 50% risk for carrying the mutation. Once the familial mutation is identified, site-specific mutation analysis can be offered to family members at risk. Family members who test negative for the mutation are not at risk for transmitting the mutation to future generations.

X-linked disorders, which are due to a mutation in a gene on the X chromosome, may also be part of a carrier screen. Some expanded carrier screens also include X-linked disorders, for example, fragile X and Duchenne muscular dystrophy (DMD). In males, X-linked

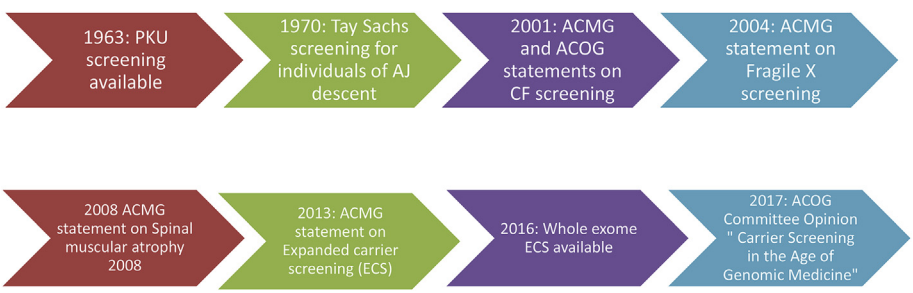

Fig. 1. Carrier screening timeline.
AJ, Ashkenazi Jewish; ACMG, American College of Medical Genetics and Genomics; ACOG, American College of Obstetricians and Gynecologists; CF, cystic fibrosis.

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