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Expanded carrier screening: A review of early implementation and literature

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ABSTRACT

Carrier screening is the practice of testing individuals to identify those at increased risks of having children affected by genetic diseases. Professional guidelines on carrier screening have been available for more than 15 years, and have historically targeted specific diseases that occur at increased frequencies in defined ethnic populations. Enabled by rapidly evolving technology, expanded carrier screening aims to identify carriers for a broader array of diseases and may be applied universally (equally across all ethnic groups). This new approach deviates from the well-established criteria for screening models. In this review, we summarize the rationale for expanded carrier screening using available literature regarding clinical and technical data, as well as provider perspectives. We also discuss important avenues for further research in this burgeoning field.

Introduction

Rapid changes in genomic analytic technologies now enable new implementations of carrier screening, the practice of screening individuals or couples in order to identify those with the highest odds of conceiving children affected by genetic disease. Like the traditional carrier screening practice discussed by Wick and Rose in this journal issue, the newer approach also targets autosomal or X-linked recessive diseases that primarily affect newborns and children by causing cognitive and physical disability and/or shortened life span. Both approaches share the same objective—to inform couples of their risks so that they may consider reproductive options.

Where the approaches differ are in the number and types (including inheritance, severity, and treatability) of diseases screened and the individuals to whom they are offered. Carrier screening has historically assessed a relatively small number of diseases selected based on similar characteristics—high frequency in a certain subpopulation and association with severe morbidity or mortality. Now, "expanded carrier screening" (ECS) is the practice of screening all individuals for dozens to hundreds of diseases, some with lower frequencies or severity grades, typically without tailoring to a person's reported ethnicity.

Widespread ECS is achievable only because new technologies have dramatically increased the amount of genomic area that can be analyzed at a reasonable cost. These same advances have enabled other genomic tests, such as whole-exome- and whole-genome sequencing, that may be used in a diagnostic setting. In contrast to those, ECS is targeted at diseases already described in the medical literature and recognized by medical geneticists. As such, ECS represents the recognition of the newfound practicality of screening a large number of known diseases, rather than a protocol for discovery of novel diseases or genotype–phenotype correlations.

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In this article, we describe the rationale for expanded carrier screening as well as its current landscape, including professional organization statements, provider perspectives, published laboratory and clinical data, and counseling considerations. Given its relative infancy, significant contributions to the medical literature on ECS will continue to accrue rapidly. Consequently, we conclude the article by highlighting the most prominent knowledge gaps, and suggest directions for future work.

Rationale for ECS

As described above, ECS encompasses two components that are departures from long-standing screening protocols: a larger list of diseases coupled to pan-ethnic application. In the context of decreasing costs for genomic analysis, we will expand on each of these components.

The reasons for ethnicity-driven screening protocols in the United States (US) are described in the previous article by Wick and Rose. However, pan-ethnic or universal screening for two diseases, cystic fibrosis and spinal muscular atrophy, has been recommended by the American College of Obstetricians and Gynecologists[1] (ACOG) and/or the American College of Medical Genetics and Genomics[2,3] (ACMG). In the case of spinal muscular atrophy, ACMG considered the relatively high prevalence in all ethnic groups (though there has since been data that establishes some inter-ethnic variability, ACMG nonetheless reaffirmed its position in 2013). In contrast, cystic fibrosis demonstrates wide ethnic disparity in its prevalence. Screening guidelines for cystic fibrosis originally targeted Caucasians and Ashkenazi Jewish (AJ)[4] populations. However, in 2005 ACOG updated its recommendation to justify pan-ethnic screening as "it is becoming increasingly difficult to assign a single ethnicity to individuals."[1] Ross[5] extended this reasoning to hemoglobinopathies and other diseases screened in targeted populations, calling for equitable access to reproductive information.

Recent demographic changes in the US have created challenges to reliable ethnic identification, consequently leading to increased likelihood of disease occurrence in non-targeted groups. For example, up to 12% of infants diagnosed with a beta-hemoglobinopathy via newborn blood-spot analysis in California during the early 1990s were outside of the groups included in ACOG's carrier screening guideline.[6] Such demographic changes are sure to continue, indicating that pan-ethnic carrier screening will improve detection of at-risk couples. The 2010 Census shows substantial increases in individuals reporting mixed racial ancestry, especially among those of reproductive age and younger.[7] Similarly, the Jewish intermarriage rate is currently 48%,[8] assuring that diseases currently screened in the AJ population will persist in other groups, as has occurred with Tay–Sachs disease.[9] The shift to pan-ethnic offering of any disorder screened can be summarized most simply as an equitable, effective model for an evolving population.

In addition to removing ethnicity considerations, the ECS model also proposes expanding the list of diseases identified in routine carrier screening. Current guidelines stipulate screening only for cystic fibrosis, spinal muscular atrophy, and/or hemoglobinopathies in the largest U.S. subpopulations.[1,3,10] Tay-Sachs disease screening is offered to individuals of Cajun or French Canadian ancestry.[11] Individuals of AJ ancestry may be offered screening for an additional three or eight diseases, depending on the professional guideline that is followed.[11,12] While screening guidelines already enumerate more diseases in AJ individuals than in any other population, addition of even more diseases has occurred. Scott et al.,[13] assessed acceptability, uptake and results of screening for 16 disorders in the New York-based AJ population, finding it to be feasible and acceptable. An at-home testing model for 19 diseases in the AJ population is being evaluated on an ongoing basis,[14] and a comparison of six laboratories found "AJ panels" of up to 25 diseases.[15] While screening criteria have typically focused on the most severe diseases with carrier frequencies exceeding 1%, these panels depart from strict adherence by including diseases that have variable or milder expressivity (e.g., Gaucher disease), or lower carrier frequencies (e.g., *NEB*-related nemaline myopathy). ECS is well underway in the AJ population.

Considering an expanded disease list in all populations is reasonable when noting that Mendelian diseases account for 20% of infant mortality and 18% of infant hospitalizations in the US.[16]

Many public health and individual benefits of ECS were proposed by Kingsmore, including greater availability and utilization of treatments and preventions, diagnostic cost and time reduction, quality of life improvement, and decrease of unnecessary treatments, among others.[16] There are few "common" inherited diseases (of a frequency comparable to sickle cell disease, alpha-thalassemia, and cystic fibrosis), but the collective incidence of "rare" diseases surpasses the incidence of those common ones.[17] Since population screening has consistently resulted in reduced incidence of the diseases of interest,[18,19] it is reasonable to assume that large-scale ECS implementation would likewise impact a larger portion of related mortality and morbidity.

The increasing number of expanded carrier screens performed in recent years has enabled more objective estimations of carrier frequencies and associated risk, including those of rare diseases. For instance, data from a large multiethnic population showed that the risk of a collective group of 89 diseases exceeded that of open neural tube defects or trisomy 21 pregnancy for a 20-year-old woman.[20] Since the prevalence of trisomy 21 and open neural tube defects has been used to justify universal screening for these disorders,[21,22] and since recessive disease prevalence is likewise typically cited as an important criterion for screening,[12] similar data for rare disease raise consideration for population-based implementation.

Beyond reproductive decision-making, an expanded disease panel may also widen the scope of objectives that can be achieved through carrier screening. There has been reliance on newborn screening to detect recessive diseases postnatally where early interventions result in improved outcomes. Prenatal awareness of substantial risk may confer even greater benefits, since certain diseases (e.g., medium chain acyl-CoA dehydrogenase deficiency) may cause long-term sequelae even before newborn screening results are available, or may be diagnosed at ages by which another affected