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Carrier screening "within the panel"

We read with interest the report by Kirk et al.[1] regarding clinical exome sequencing as the basis for expanded carrier screening in consanguineous couples. We support the premise of expanded preconception carrier screening and recognize the benefits of providing counseling on a "per couple" basis rather than for each individual. However, we have reservations about what they describe as moving "beyond the panel" and using a clinical exome as the basis for carrier screening.

Despite promoting the exome as the basis for an extended carrier screen, the authors restricted their analysis to those genes with a known Mendelian phenotype. This is appropriate as there are many genes for which homozygosity for a pathogenic mutation does not yield an abnormal phenotype.[2] They also excluded, without justification, common recessive alleles with a frequency of >0.01; this step removed common disorders such as cystic fibrosis and α-thalassemia from the screen. The subjects were all consanguineous couples. Their ethnicities were not described, but many spoke Arabic and may have come from same region. Despite this the authors excluded, without justification, alleles that occurred in three or more couples. They did not restrict the screen to disorders that occur in childhood, and did not delineate the sensitivity of their assay in the absence of testing for copy-number variants. In effect, they created a panel of genes without declaring the intent, scope, and sensitivity of the screen.

The number of genes in an expanded carrier screening panel can give a misleading sense of the panel's utility. We assessed the utility of nine commercial expanded carrier screening panels that covered 110–327 genes. We used the proportion of couples in a general population who would be identified as being at 25% risk of having a child with an autosomal or X-linked recessive disorder included in the panel as the measure of utility. The selections of genes, mode of inheritance, and detection rates were as documented in the companies' literature; genes that are not associated with serious childhood-onset disorders were excluded from the analysis. The carrier frequency for each gene was taken from data provided by Fulgent Genetics (fulgentgenetics.com/products/carrierscreening/conditions.html) and held constant for all panels. The proportion of couples so identified using a three-gene carrier screen (cystic fibrosis, spinal muscular atrophy, and fragile X syndrome) was used as the comparator.

When the number of genes in a panel was compared with its comparative utility (the ratio of the panel's utility to that of the three-gene comparator), there was an indeed an association between the number of genes screened and the comparative utility. But there were also some striking exceptions in which screening more than 100 genes failed to match the utility provided by the three-gene comparator. Poorly performing panels were characterized by having fewer X-linked genes and genes with comparatively low carrier frequencies.

It is essential that the content of an expanded carrier screen be determined by an explicit assessment of the purpose and scope of the screen[3] and not by the technology available. This requires that the screen be based on analysis of selected genes, i.e., of a panel. Genome, exome, and clinical exome sequencing may all be a suitable means of analyzing such a panel, but obtaining the sequence is not an end in itself.

DISCLOSURE

The authors are employees of Sonic Healthcare (G.S.) and Douglass Hanly Moir Pathology (K.M.). Douglass Hanly Moir Pathology is part of Sonic Healthcare (Australia) and provides preconception carrier screening.

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