

NEXT-GENERATION DNA SEQUENCING: IMPROVING THE ACCURACY OF ROUTINE CARRIER SCREENING

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Design

Carrier screening is recommended by the American Congress of Obstetricians and Gynecologists (ACOG), the American College of Medical Genetics and Genomics (ACMG), and Ashkenazi Jewish advocacy organizations. However, it is often difficult to ascertain a patient's true ethnicity to determine the appropriate screening to offer. Consequently, several fertility centers now offer screening for the same disorders to all patients, regardless of ethnicity.

Traditional screening assays yield reasonable detection rates in high-risk populations but are suboptimal for patients of low-risk or mixed ethnicities. For centers offering the same tests to all patients, this means that a large number of patients are receiving screening with low detection rates, and being provided with false reassurance. In contrast, next-generation DNA sequencing (NGS) allows for a more comprehensive determination of carrier status because, unlike traditional genotyping assays, it is not limited to a small mutation set, nor is it merely optimized for high-risk ethnicities.

Objective

Our objective was to evaluate the clinical efficacy of NGS for carrier screening across a broad range of ethnicities for society-recommended disorders and determine the frequency of carriers that would otherwise go undetected.

Materials and Method

Using NGS, carrier status was evaluated for up to 14 disorders (as ordered) for patients seen at several fertility centers across the country.

Results

A total of 4,894 patients from six IVF centers were screened, representing a multitude of unique ethnicity combinations. A total of 196 disease-causing mutations were identified. Twelve percent (24/196) of these mutations would not have been detectable by traditional genotyping assays.

Eighty-four of 196 pathogenic mutations (43%) were found in patients who did not identify as the corresponding high-risk ethnicity, including 66 patients who did not provide an ethnic background. Moreover, 13 of these 84 (15%) mutations would not have been detected by traditional genotyping assays.

Conclusion

Carrier screening is often ordered outside of the ethnicity-based guidelines. In these major fertility centers, NGS identified 84 carriers that did not identify as the corresponding 'high-risk' ethnicity. Based on this finding, it is clear that traditional genotyping assays are no longer sufficient for common screening practices in these fertility centers where testing individuals of all ethnicities is routine. NGS addresses the dichotomy of ethnicity-based testing within a multi-ethnic population by providing a more comprehensive determination of carrier status regardless of patient ethnicity.