BENEATH THE SURFACE: UNCOVERING HIDDEN HEALTH RISKS WITH COMPREHENSIVE CARRIER SCREENING

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Background:
An increasing number of recessively inherited conditions are gaining recognition for the risk of symptom manifestations in carriers, leading to blurred lines between recessive and dominant inheritance. As the scope of carrier screening (CS) panels has expanded in recent years, more individuals are receiving results with potential implications for their own health [1].

Objective:
To assess the scope of potential health risks that may be identified for patients undergoing preconception CS in a fertility center setting.

Materials and Methods:
Retrospective review of all patients who underwent CS using the same gene panel between March and September 2024 was performed. For individuals reported as biologically female, testing was performed for a total of 558 genes (515 autosomal recessive and 43 X-linked). For individuals reported as biologically male, only the 515 autosomal recessive conditions were included. In accordance with professional guidelines, only variants classified by the laboratory as pathogenic (P) or likely pathogenic (LP) were reported, while variants of uncertain significance and benign or likely benign variants were not reported. Genes and variants with potential health implications for carriers were determined by the laboratory and noted on the results report. Frequencies of these genes and variants were tallied.

Results:
CS results were obtained for 1577 patients (902 female and 675 male). At least one P/LP variant was identified in 416/558 genes among our patient cohort (79.8% of autosomal recessive conditions on the panel; 11.6% of X-linked conditions). 51/416 genes with positive results (12.3%) were noted by the laboratory to have potential health implications for carriers; of these, 5/51 (9.8%) were X-linked and 46/51 (90.2%) were autosomal recessive.

In total, 1315/1577 patients (83.4%) tested positive for at least one condition on the panel, and 423/1577 (26.8%) tested positive for at least one condition that was flagged for potential health implications in carriers. Of the 51 genes with potential manifestations, 19 were found to have only variants that were not associated with these risks. Of the remaining 32 genes, 430 variants with potential health risks were identified and collectively affected a total of 12.2% (193/1577) of patients.

Conclusions:
While the primary goal of CS is the identification of high reproductive risk for autosomal recessive and X-linked conditions, the increased incidence of results bearing personal health risks and

autosomal dominant inheritance challenge the traditionally understood scope of this screening tool. As current CS guidelines do not adequately address reporting or management of these findings, establishment of a standardized framework for both laboratories and clinicians is critical. The wider implications of these findings within the field of reproductive genetics warrant further exploration, particularly in the context of preimplantation genetic testing for monogenic disease, gamete donation, and prenatal diagnosis.

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References:

1. Gbur S, Mauney L, Gray KJ, Wilkins-Haug L, Guseh S. Counseling for personal health implications identified during reproductive genetic carrier screening. Prenat Diagn. 2021 Oct;41(11):1460-1466.