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LETTER TO THE EDITOR

Placing negative multi-gene panel results into clinical context

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We appreciate Dr. Sorscher's comments [1] in response to our report on multi-gene panel testing [2]. We fully agree with his main conclusion, that personal and family histories are important metrics for assessing cancer risk and making recommendations for cancer surveillance. One of us (M.E.W.) has published extensively on this topic [3] and it is a regular feature of our practice and of national recommendations for cancer genetics care [4].

Regarding some of the specific points raised in the letter:

We acknowledge that a negative result from panel testing does not exclude a pathogenic variant in a gene that is as of yet not included in panels. However, we note that further genome-wide searches are not expected to find highly penetrant genetic variants for common cancers, although they are expected to identify variants associated with low to moderate penetrance. Such variants will surely need to be evaluated in the context of personal and family history.

Individuals can be reassured that their "negative" panel genetic testing result is a "true negative" only if it is found in the context of a known pathogenic variant in the family. This could occur if a panel is ordered in an individual for whom a pathogenic variant is present in a relative, but other family history suggests a reason to look for a variant in a different gene.

There is one other scenario in which a negative panel test can change management. Some cancer risk models (e.g., the Tyrer-Cuzick model, [5]) incorporate genetic results as one parameter to determine risk. A negative panel test could lower risk for some individuals from just above to just below the 20% threshold that could affect screening recommendations.

All of these observations support our original points that panel testing offers important clinical information, which must be placed into the proper context of personal and family history in order to provide maximal benefits.

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