CORRESPONDENCE

Re: Cascade Genetic Testing of Relatives for Hereditary Cancer Risk: Results of an Online Initiative

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We read with interest Caswell-Jin et al.'s report regarding cascade testing in relatives at-risk for hereditary cancer (1). They noted that of 1084 first-degree relatives of individuals with a cancer predisposing pathogenic variant (PV) who underwent multigene cancer panel testing (MCPT), 4.9% tested positive for a PV in a gene other than the one present in their family. These data are important for two reasons. First, site-specific testing versus MCPT has been the standard practice, and MCPT in relatives is not recommended by national guidelines (2). Second, although there are published reports of more than one PV identified in a family, including those identified from MCPT (3), this is the first and largest study describing systematic use of such testing in relatives. Given that the cost of MCPT has dropped considerably (\$250 or less in some US labs), it is not surprising that this testing is being offered more often—not only to index patients but also to their relatives.

There are benefits conferred by MCPT in relatives at risk for a familial PV. For example, family history may not be a reliable predictor of identifying a different PV. Relatives may have a suggestive history on the side of the family without the known PV. And, some identified PVs (about 20% in this report) will be in highly penetrant and actionable syndromic genes.

There are also risks and limitations associated with MCPT. In this report, of the 4.9% of participants with a PV other than the one identified in the index patient, about 80% had a variant in a low-penetrance allele or moderate risk gene. As there is little evidence-based management guidance for individuals with these types of PVs, the clinical utility of these results is unclear (4). In addition, the likelihood of identifying one or more variants of uncertain significance is elevated when multiple genes are assessed (16.8% in the current report), which may cause concern and the need for future follow-up as these are reclassified (5).

Before routine MCPT in first- and second-degree relatives becomes the standard of care or incorporated into national

guidelines, we believe it is important to define the desired outcomes of such testing, analyze cost-utility data, and study how such results affect patient management and behavior. Such analyses could also consider the potential value added from testing these relatives for a multigene cancer panel that also includes genes in which a PV is known to have a high likelihood of clinical utility. For instance, a panel could include all 59 genes recommended by the American College of Medical Genetics and Genomics, which, aside from cancer genes, includes several cardiac risk genes (6). Pharmacogenomics panels could also be included. Indeed, population-based programs in healthy individuals are disclosing these specific types of results to participants (7). Thus, the implementation of cascade testing can have a substantial public health impact that may be bolstered by the use of testing beyond the familial PV. Additional research will be useful to guide clinical care and future policies.

Notes

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Ms Peshkin has performed consulting for Clear Genetics, Inc (San Francisco, CA). Drs. Isaacs and Schwartz have no conflicts of interest to disclose.

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