What do my gene variants mean? Study finds conflicting interpretations in cancer risk screening

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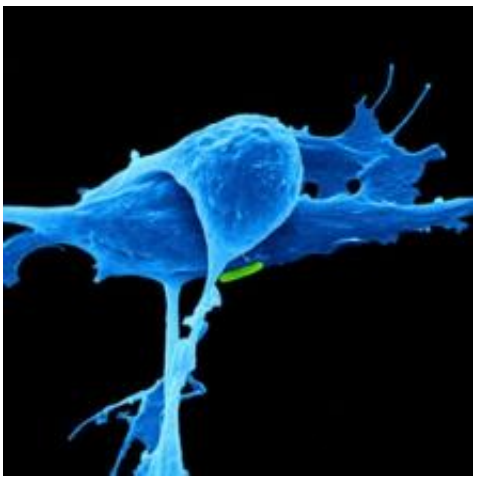

With surprising frequency, clinical laboratories that test people's blood samples for genes and genetic mutations that increase cancer risk provide conflicting interpretations of the risks associated with particular gene variants. The finding comes from an analysis of gene-testing data in a new online registry, which determined that 26 percent of the gene variants identified in patient samples came with interpretations that differed among participating laboratories. In some cases, for example, genetic mutations were deemed "likely" or "definitely cancer-promoting" by some labs, and "of unknown significance" by others. The

study, led in part by researchers at the Perelman School of Medicine at the University of Pennsylvania, is published this week in the *Journal of Clinical Oncology*.

The study follows advances in DNA sequencing technology that have made possible the development of "multiplex" test panels that simultaneous screen for dozens of risk genes. Such screening is now increasingly common for people who have a newly diagnosed cancer or a close relative with cancer. The gene variants detected in such tests are generally classified as benign, having unknown significance, or conferring some extra risk of cancer.

"Care providers use risk interpretations to guide their recommendations to patients. A failure to recognize the true significance of a gene variant could mean unnecessary or inadequate follow-up testing or treatment," said senior author Susan M. Domchek, MD, the Basser Professor in Oncology at the Perelman School of Medicine at the University of Pennsylvania, and Executive Director of the Basser Center for BRCA at Penn's Abramson Cancer Center. "Our findings confirm the need for initiatives to share these data and harmonize interpretations, so patients are able to process information accurately, and providers can advise patients on appropriate paths forward."

For the study, Domchek and colleagues, including lead author Judith Balmaña, MD, a principal investigator at Hospital Vall d'Hebron and Universitat Autònoma de Barcelona and a visiting scholar at Penn Medicine at the time of the study, used data from the PROMPT (Prospective Registry Of Multi-Plex Testing) registry. PROMPT was co-founded in 2014 by Penn Medicine, Dana-Farber Cancer Institute, Mayo Clinic, and Memorial Sloan Kettering Cancer Center, aims to address some of the more challenging issues surrounding cancer susceptibility testing.

The data for the study came from tests on 518 individuals enrolled in PROMPT. About 95 percent were women, and 68 percent had a cancer diagnosis. Collectively, the tests on these individuals detected hundreds of distinct gene variants – changes in the usual DNA sequence of a gene, which may alter the function of the gene's protein product in a way that increases cancer risk over the patient's lifetime. The study included the 603 variants for which interpretations by more than one laboratory were available for comparison. (Reports on variants of BRCA1 and BRCA2 – the two best known cancer risk genes – were excluded.)

Of these 603 gene variants, most (74 percent) were interpreted in a consistent way in different laboratories' reports. But a significant minority (26 percent) of the detected gene variants had interpretations that were not consistent among the participating laboratories.

Most of the inconsistencies involved gene variants deemed "benign" by some labs and "of unknown significance" by others. The "unknown significance" label generally means that a variant DNA sequence within a cancer-related gene has an uncertain impact on the function of the protein that the gene encodes, and thus has an unknown impact on cancer risk. On its own, that shouldn't alter the management of the patient, but there is a risk that in some cases it will make patients anxious enough to want unnecessary preventive surgery, for example to remove breasts that are perfectly healthy and unlikely ever to develop cancer. "It is important to understand that variants of unknown significance should not be managed in the same way that known harmful mutations are," Domchek said.

Potentially worse were the 36 percent of discrepancies – affecting about one in nine of the tested individuals – in which a variant was considered likely or definitely cancer-promoting by at least one lab, and of "unknown significance" by others. "A discrepancy like that can make a real difference in how a doctor manages a patient," Domchek said.

These clinically more relevant discrepancies were found most commonly for variants of CHEK2, PALB2, and BRIP1 – tumor-suppressor genes with important roles in cells' response to DNA damage.

Discrepancies in risk interpretations arise when gene variants are incorporated into testing panels before a consensus has developed on their risk impact. The risk conferred by a given gene variant can be estimated from genetic studies of large groups of people, biological studies of the variant protein's function, and even algorithm-based predictions of variant protein function. But, these estimates often leave considerable room for disagreement. Some gene variants are also quite rare in the population, which makes it inherently difficult to estimate their associated risks.

The authors urge more sharing of data in online registries – sharing that should make plainer to patients and doctors where discrepancies exist, and in turn should nudge scientists and testing laboratories to resolve those discrepancies wherever they can. The authors also suggest that laboratories provide registries with more details on how they arrive at their risk interpretations, so that the reasons for any discrepancies become clearer.

"Internet-based registries have an important role to play in efforts to standardize classifications of gene variants—the goal of which is to minimize potential medical harms due to false alarms or false reassurances following cancer genetic testing," Domchek said.

Provided by Perelman School of Medicine at the University of Pennsylvania