

Genetic testing: Not a one-and-done deal

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Dr. Theo Ross, left, and genetics counselor Jacqueline Mersch say genetic counseling is not static and gene-testing labs should review results as new information is gained. Credit: UT Southwestern

Genetic testing can play a substantial role in medical management by uncovering changes in genes that are associated with an increased risk for hereditary cancers. A new research study from investigators at UT Southwestern Medical Center strongly encourages testing laboratories to periodically review their records and alert physicians when scientific knowledge evolves and genes are reclassified.

That conclusion is based on a study that reviewed [genetic testing](#) results

from 1.45 million individuals and found that nearly 25 percent of "variants of uncertain significance" were subsequently reclassified—sometimes as less likely to be associated with [cancer](#), sometimes as more likely.

The study appears in the *Journal of the American Medical Association (JAMA)*.

When variations from the norm are discovered in a gene, the variants are classified as "benign," "likely benign," "variant of uncertain significance," "likely pathogenic," or "pathogenic."

"If a variant is reclassified to being pathogenic, then it matters to the patient," said Dr. Theo Ross, Professor of Internal Medicine and senior author of the study. "For example, if they have a broken Lynch syndrome gene, then they need different care from their doctor such as having colonoscopies at an earlier age or more frequently—sometimes as often as every year. Or, if they have a broken BRCA gene, they may want to have prophylactic surgery or add MRI scans to their mammogram screening program."

Even a reclassification from "variant of uncertain significance" to "benign" can be important to a patient, providing them with peace of mind.

The typical gene contains about 27,000 [base pairs](#) (A-T, G-C), though some [genes](#) contain as many as 2 million. "Bases are the letters used to spell our DNA, as well as sequences that regulate our genes," said Dr. Ross, who is a member of the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern.

The large number of base pairs in each gene means there are myriad potential variations and there are many gaps in knowledge about the

significance of individual variations. But knowledge about gene variants is constantly growing and evolving.

"We are getting new data all the time. We may identify new families that have an inherited susceptibility to cancer and learn something from their DNA. Labs may determine the atomic structure of the protein product of the gene with the variation and see an abnormal shape or find that cells with the variant gene don't behave as expected. With collective familial, biochemical, and functional data all pointing to abnormal, a variant is reclassified from "variant of uncertain significance" to "pathogenic," said Dr. Ross, who holds the Jeanne Ann Plitt Professorship in Breast Cancer Research and the H. Ben and Isabelle T. Decherd Chair in Internal Medicine in Honor of Henry M. Winans, Sr., M.D.

The research study published in *JAMA* reviewed test results for hereditary cancer genes from a single laboratory, Myriad Genetics, over a 10-year period, as well as associated clinical data from UT Southwestern's Cancer Genetics Program. Of the 1.67 million initial reports, 60,000 amended reports were issued. Overall 24.9 percent of classifications as "variant of uncertain significance" were reclassified, with the majority of those reclassifications being downgraded to benign.

"The implications of this study are three-pronged. Physicians need to be aware of how rapidly knowledge about gene variants is advancing and that reclassifications are common. Labs need to review [gene variant](#) information on a regular basis and alert physicians to changes. Finally, patients and their family members need to be made aware of reclassifications by their physicians so they can make well-informed choices," Dr. Ross said.

More information: Prevalence of Variant Reclassification Following Hereditary Cancer Genetic Testing, *JAMA*. 2018;320(12):1266-1274. [DOI: 10.1001/jama.2018.13152](https://doi.org/10.1001/jama.2018.13152) , [jamanetwork.com/journals/jama/ ...](http://jamanetwork.com/journals/jama/)

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