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# New Framework for Categorizing Inherited Cancer Genes Will Have Wide-Ranging Impact

By Julie Grisham, **Thursday, November 1, 2018**



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## Summary

MSK clinical geneticist Michael Walsh discusses how updated guidelines for interpreting genetic tests will affect people who have been screened for cancer genes.

Every gene is made up of thousands of As, Cs, Gs, and Ts, which spell out the instructions for making all the proteins in our cells. Errors in those instructions — known as mutations or variants — can occur anywhere in these long strings of code.

For genes linked to diseases, including cancer, researchers are focused on determining which mutations matter. Some don't affect risk, but others actually change the functions of proteins and could have a negative effect in the body.

“Understanding the significance of the variants we find in cancer genes is important,” says Memorial Sloan Kettering clinical geneticist **Michael Walsh**. “We need to know if they are harmless or harmful, so when we learn that someone has inherited one of them, we can tell them what it means. Should they have more frequent cancer screenings? Should their family members get tested as well?” In addition, for those who already have cancer, inherited gene variants may influence what treatments they are given.

## The Tremendous Task of Finding Meaning in Gene Variants

The field of cancer genomics took off in the early 1990s. At that time, scientists, including geneticists Mary-Claire King and MSK's **Kenneth Offit**, began to report details on some of the first genes connected to cancer. These genes, *BRCA1* and *BRCA2*, are associated with an increased chance of developing certain cancers, **especially breast cancer and ovarian cancer**. But what predisposes people to cancer are specific alterations in the genes. These changes can cause the proteins to malfunction in such a way that cancer may develop.



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As genomic sequencing has become easier and less expensive, it has become much more commonplace. Huge amounts of data are now being generated. New cancer genes and variants are frequently being discovered. When the dozens of variants in hundreds of genes linked to cancer are taken into account, the task of determining which variants are significant may seem Sisyphean.

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To help address that challenge, a few years ago the American College of Medical Genetics and Genomics (ACMG) released recommendations on how to classify the variants found in inherited cancer genes. Variants found in any gene may be classified in one of five categories: benign, likely benign, uncertain, likely pathogenic, or pathogenic. What remains a problem are the many variants that fall under the “uncertain” grouping, also called “variant of unknown significance.”

Now the ACMG is releasing an updated framework for classifying inherited variants in cancer genes. It focuses on integrating both tumor data and biomarker data. Dr. Walsh, a member of MSK’s [Robert and Kate Niehaus Center for Inherited Cancer Genomics](#), is the lead author of the new guidelines, which were [published](#) November 1, 2018, in the journal *Human Mutation*.

“In the past, the ACMG has provided guidance for testing labs, saying that people who get their genomes sequenced should be informed about which of their genes harbor variants. But in some ways that was like putting the cart before the horse,” Dr. Walsh says. “We didn’t know enough to determine what many of these variants meant.”

He explains that researchers are starting to make some headway in pulling together all the tumor and biomarker data that’s being collected. There may now be evidence about whether certain previously unknown variants cause harm.

## A Rapidly Changing Field with Real Consequences

As the new guidelines are adopted by labs around the country, variants will continue to be reclassified. As a result, earlier genomic screening will need to be revisited on a regular basis.

“As labs begin to apply these new rules, there will be some people who had testing in the past who will need to be contacted with updated results,” Dr. Walsh says.

Even as the guidelines are still being phased in, the issues that they are expected to bring up are already apparent. A [recent study](#) from investigators at the University of Texas Southwestern Medical Center in Dallas found that nearly one-quarter of the variants that had originally been classified as being of “unknown significance” were later reclassified as being either likely or unlikely to be associated with cancer. The investigators reviewed the results from 1.45 million people who were screened for cancer genes with a test developed by Myriad Genetic Laboratories.

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**Michael F. Walsh**

Geneticist and Pediatric Oncologist

Dr. Walsh says that people who have had testing in the past should consider contacting the labs and clinics where the testing was performed. The incremental change in rule classification will impact few people overall, so it is important that appropriate channels are established between patients and providers, he adds. MSK encourages people who have been tested here to contact their doctor or genetic counselor at regular intervals to see if there are any updates pertaining to the tests they had.

“Communicating is key and delivery of information needs to be in such a way that the information is useful and not frightening,” Dr. Walsh notes. “These changes in gene classification can have meaningful implications for people’s lives.” Some people who learn that gene variants they carry are linked to cancer will likely want to explore questions surrounding screening guidelines, risk-reducing surgeries, and even family planning. Others who learn that their variants are harmless after months or years of worry may be able to breathe a sigh of relief.

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