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Genetic test results for Lynch syndrome improved with new computer program

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Many patients who have genetic testing for Lynch syndrome, a hereditary predisposition to colon cancer, receive the inconclusive result "variants of uncertain clinical significance." This can be a problem, as people with Lynch syndrome have a much higher probability to develop colon cancer, and often develop colon cancer at an earlier age than is common among the general population; consequently, they need to begin screening at a much younger age.

Now, between two-thirds and three-fourths of these genetic variants can be classified into categories that indicate the most appropriate screening and treatment guidelines, according to two complementary papers published in this month's *Human Mutation* Early View e-publication. The two papers, both co-authored by Sean Tavtigian, Ph.D., a Huntsman Cancer Institute (HCI) investigator and associate professor in the Department of Oncological Sciences at the University of Utah, provide a model that could help physicians as they assess their patient's risk to develop cancer.

According to the American Cancer Society, about 143,460 new cases of colon cancer will be diagnosed in the United States this year. The National Cancer Institute estimates that two to four percent of all colon cancer is attributable to Lynch syndrome.

Mutations in mismatch repair genes, which proofread DNA to correct genetic typos that occur during the replication process, are known to be the cause of the syndrome. "Some people in families with Lynch

syndrome have already known mutations, and a small number of missense substitutions have also been classified as pathogenic," said Tavtigian. "But a fair number have other missense substitutions for which the clinical significance could not be determined, creating uncertainty concerning proper screening and treatment for patients and physicians alike."

The first of the two studies reported on standardizing several already available computer programs that grade the severity of missense substitutions (at the genomic level, these mutations affect only a single structural unit of DNA rather than an entire gene; at the protein level, they affect only a single amino acid rather than the entire protein). The second describes how clinical data concerning the tumors, family history, and other factors were combined with that initial information about severity. Taken together, the procedures described in the two papers allow previously unclassified genetic variations to be assessed for the level of risk they pose in colon cancer development.

"Using these tools, we can evaluate any particular missense substitution and come up with a percentage indicating the probability that it is pathogenic," said Tavtigian. "I'm very careful to avoid saying pathogenic or neutral as an either-or statement. With missense substitutions, I don't believe in a binary classification." A scale developed by his team in 2008 indicates the appropriate level of clinical action for a given percentage of risk, he adds.

Tavtigian is senior author on the first study. Amanda B. Spurdle, Ph.D., associate professor of molecular cancer epidemiology at the Queensland Institute of Medical Research, Brisbane, Australia, is senior author of the second paper, and Tavtigian is a co-principal investigator.

As a result of this research, HCI now has a Web site that physicians, researchers, and even the public can use to look up the probability that a

missense substitution in any of the four colon cancer mismatch repair genes is pathogenic. In the future, HCI plans to develop a "suite of Web sites dedicated to unclassified variants in many clinically important cancer susceptibility genes," according to Tavtigian.

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