New, simplified genetic test effectively screens for hereditary cancers

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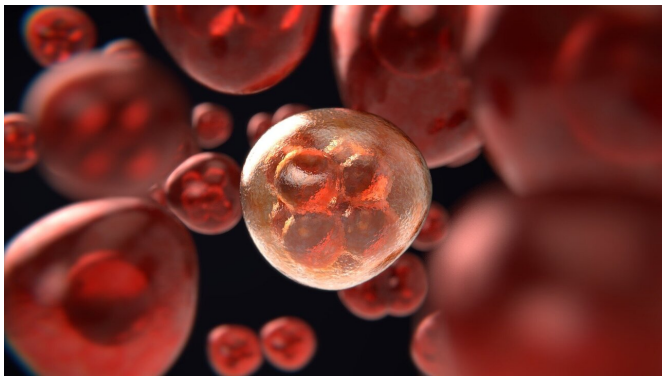

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Researchers have developed a new integrated genetic/epigenetic DNA-sequencing protocol known as MultiMMR that can identify the presence and cause of mismatch repair (MMR) deficiency in a single test from a small sample of DNA in colon, endometrial, and other cancers. This alternative to complex, multi-step testing workflows can also determine causes of MMR deficiency often missed by current clinical tests. Their results are presented in the *Journal of Molecular Diagnostics*.

MMR genes monitor and repair errors that can occur in normal cell replication and recombination. In some inherited and acquired cancers, one or more of the MMR genes are deactivated. "The impact of MultiMMR is broad. Tumors with MMR deficiency respond well to new cancer immunotherapies," explains lead investigator Trevor J. Pugh, Ph.D., Department of Medical Biophysics, University of Toronto; Princess Margaret Cancer Centre, University Health Network; and Ontario Institute for Cancer Research, Toronto, ON, Canada. "Determining whether an individual has an inherited form of MMR deficiency can also allow clinicians to enroll patients in active surveillance, engage in risk-reduction strategies, and provide genetic testing to relatives—potentially improving patient outcomes."

Standard clinical testing for MMR deficiency can be inconsistent, requiring multiple tests and types of expertise, resulting in suboptimal care for patients. Next-generation sequencing tests have gained popularity and are being used in clinical laboratories. However, they do not identify all genetic variations for MMR deficiency, and additional testing is often required.

The MultiMMR simultaneously tests for promoter methylation, mutations, copy number status, copy neutral loss of heterozygosity, and microsatellite instability from a small amount of DNA. In this study the researchers sequenced DNA from 142 specimens (82 normal and 60 tumor samples) from 82 patients with MMR-associated colorectal, endometrial, and brain cancers. As a positive control, the results for 45 patients were compared with previous clinical testing using conventional assays. They also used MultiMMR to profile a commercially available DNA control that includes 11 variants that are challenging to detect with next-generation sequencing.

To detect the presence of MMR deficiency, MultiMMR promoter methylation and microsatellite instability analyses found 95 percent and 97 percent concordance with clinical testing, respectively. In detecting variants responsible for the MMR deficiency, MultiMMR matched the clinical testing results in 23 out of 24 cases. The test identified all 11 mutations in the synthetic mix in multiple sequencing runs and identified the mismatch repair deficiency in 29 patients with incomplete or inconclusive testing. The panel was able to identify causes of MMR often missed by the current clinical cascade.

"We have shown that the presence and cause of MMR can be determined in a single test, from a single aliquot of DNA, thereby making best use of

available tissue, streamlining workflows, and improving integrated reporting for Lynch and related hereditary cancers," comments lead author Leslie Oldfield, MSc, Department of Medical Biophysics, University of Toronto; and Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada.

The researchers note that current cascade testing protocols may not be able to meet increased demand for universal tumor testing in patients with colorectal and endometrial cancers. Many next-generation sequencing tests do not screen for microsatellite instability and promoter methylation alongside somatic mutations, for example.

"Eligibility for immunotherapy is often contingent on MMR status, so timely and robust testing is important," adds Ms. Oldfield. "MultiMMR streamlines the process and distinguishes the type of MMR deficiency with improved turnaround time, can scale well with increasing demands, and can provide clinicians with important information to inform patient management and treatment decisions."

More information: Leslie E. Oldfield et al, An Integrative DNA Sequencing and Methylation Panel to Assess Mismatch Repair Deficiency, *The Journal of Molecular Diagnostics* (2020). DOI: 10.1016/j.jmoldx.2020.11.006