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Innovative technique greatly increases sensitivity of DNA sequencing

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OICR researchers, together with international collaborators, have invented a technique to avoid a major problem with common laboratory techniques and improve the sensitivity of important cancer tests.

The findings, recently published in the journal *Nature Protocols*, describe a process by which the sensitivity of DNA sequencing can be improved. The technology, called SiMSen-Seq, could aid in detecting the recurrence of cancers, catching possible disease relapses faster than current methods and improving patient outcomes.

To sequence DNA, scientists often use a technique called polymerase chain reaction (PCR) to increase the amount of DNA available from a sample. However, PCR can introduce mistakes that can limit researchers' ability to detect real mutations in the original DNA molecules. To track the original molecules in a sample, molecular tags called DNA barcodes are added. This technique is essential for sensitive detection of mutations but can lead to other errors, as components of the tags can interfere with each other and affect the final results.

"We created a DNA barcode with a hairpin structure that opens up to be read when heated and contracts when cooled. This allows us to 'hide' the barcode and analyze more patient DNA fragments in a single reaction," said Dr. Paul Krzyzanowski, Program Manager of OICR's Genome Technologies Program. Krzyzanowski led the development of analysis pipeline software used in SiMSen-Seq. This software flags errors in sequencing results and corrects them computationally.

Current genome sequencing technologies return results with error rates of about one per cent, meaning that for researchers to be certain that a mutation exists it has to be detected in a sample at a rate of greater than one per cent. SimSen-Seq technology has lowered this error rate 100-fold, meaning that the recurrence of cancers could be detected at lower levels and earlier than before, allowing patients to receive additional treatment sooner.

The team has patented their technique, and while it can conceivably be performed in any molecular biology lab, the group also hopes to make their expertise in using the method available to the research community. "Our paper describes how this process can be carried out, but we think that our experience in using the technique could be leveraged by other research groups and save them the trial and error of instituting a new process," said Krzyzanowski. Those interested in accessing this service can do so through OICR's Collaborative Research Resources directory.

"Ontario is pleased to support this collaborative research project through the Ontario Institute for Cancer Research," said Reza Moridi, Ontario's Minister of Research, Innovation and Science. "This innovative technique that increases the sensitivity of DNA sequencing is a remarkable breakthrough and one that could improve patient outcomes in Ontario and around the world by detecting the reoccurrence of cancers earlier."

More information: Anders Ståhlberg et al, Simple multiplexed PCR-based barcoding of DNA for ultrasensitive mutation detection by next-generation sequencing, *Nature Protocols* (2017). DOI: 10.1038/nprot.2017.006

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