Tweak to assay could bolster disease detection

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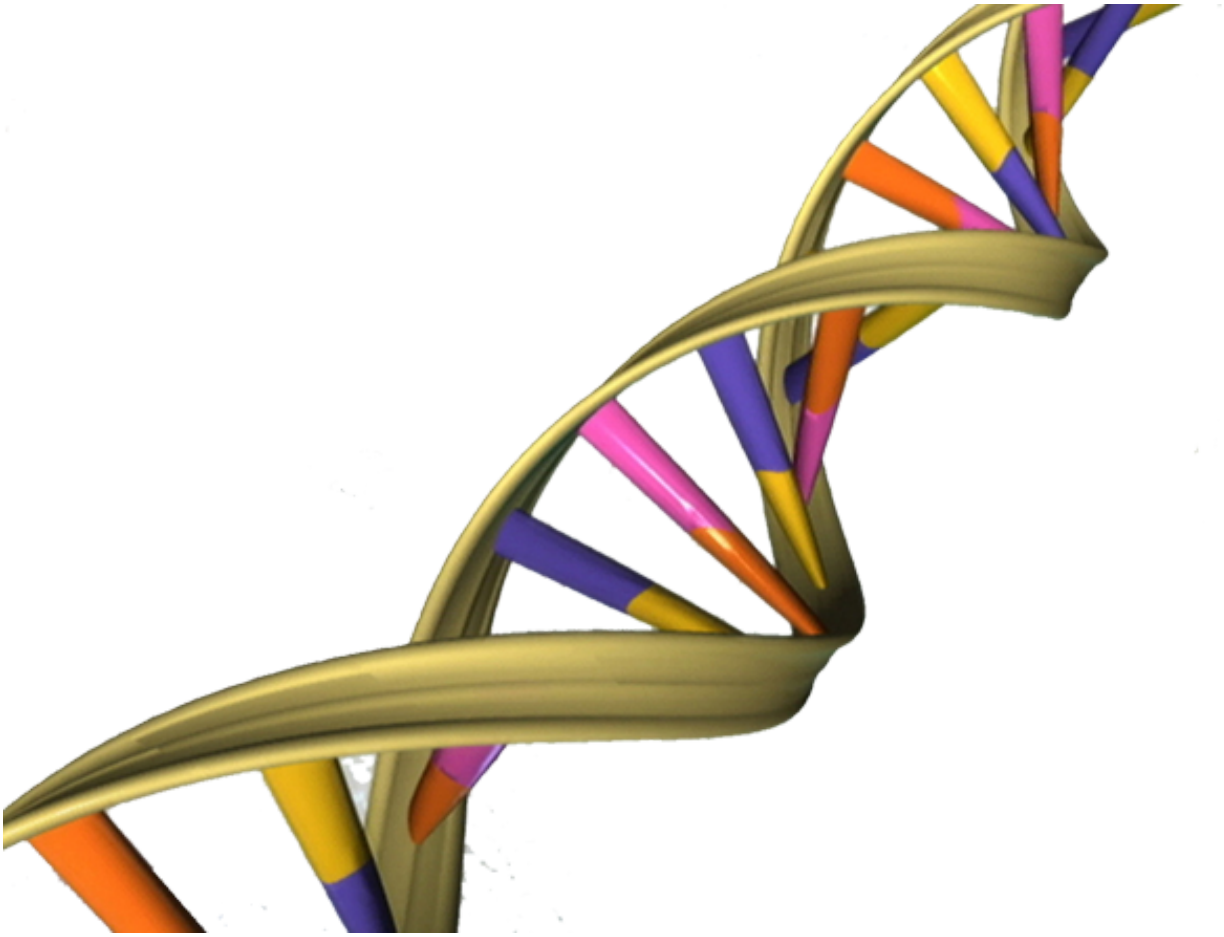

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

A team of School of Medicine researchers has developed a technique that they hope could more precisely detect diseases or disorders such as cancer or a heart attack.

The technique is an improved method to detect some biomarkers—protein signals in blood or tissues that flag unhealthy or diseased cells. If the biomarker of interest is present, a circle of DNA molecules is created that includes specific proteins, called antibodies, that bind only to the biomarker and a set of DNA sequences that facilitate formation of the circle. If the biomarker isn't there, no circle forms.

A paper describing the technique was published online Jan. 16 in the *Proceedings of the National Academy of Sciences*. Ron Davis, Ph.D., professor of genetics and of biochemistry, and senior research scientist Henrik Persson, Ph.D., share senior authorship. Postdoctoral scholar Roxana Jalili, Ph.D., is the lead author.

The technique, a type of assay, is based on an existing method called a proximity ligation assay, or PLA, which converts the biomarker into a DNA sequence. The modified assay, called circular-PLA, uses additional DNA molecules to generate a circle, a step that enhances the accuracy of the approach.

"In order for the detectable circle to form, the DNA sequences have to be perfect matches with each other," Jalili said. "So, if there's no biomarker, or something incorrectly binds to the biomarker, the DNA sequences won't match, and the circle won't form."

Persson likened the technique to introducing "an extra proofreading step" to PLA.

The extra stringency is particularly important because existing tests yield

too many false positives and false negatives, said said Davis, who is also director of the Stanford Genome Technology Center.

"There's too much complacency with the existing detection method used in clinics," Davis said. "I think the medical community needs to push back and just not accept it."

Davis sees potential for the technique to help detect biomarkers of diseases with high rates of false positives and negatives, such as human papillomavirus or Lyme disease. He also notes that the ability to accurately detect molecules has many potential applications beyond medicine, such as the identification of mold in a building.

Davis said he hopes clinics and researchers will raise their expectations of biomarker detection methods. "People tolerate the current method because they think, 'Well this is the technology, what are we going to do?'" he said. "But now we actually can do something about it."

More information: Roxana Jalili et al. Streamlined circular proximity ligation assay provides high stringency and compatibility with low-affinity antibodies, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1718283115

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