Multimodal Blood Test Successfully Screens for Advanced CRC, Adenomas

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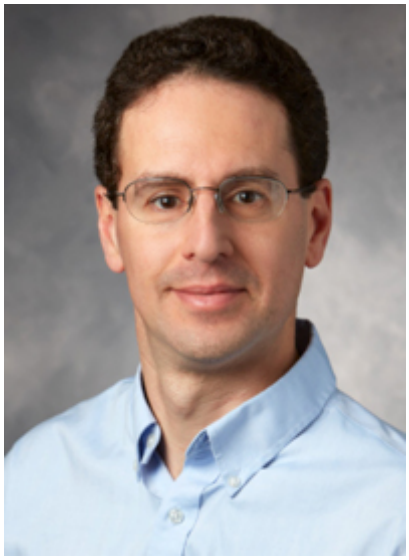

Shai Friedland, MD

The multimodal FirstSight^{CRC} blood test demonstrated higher sensitivity and specificity than standard screening protocols in detecting advanced adenomas and colorectal cancer (CRC), explained Shai Friedland, MD, who added that the noninvasive assay could lead to improved screening compliance.

The test, which evaluates circulating intestinal cells, cell-free DNA (cfDNA), and abnormal methylation of the septin-9 gene, demonstrated 75.5% (95% CI, 61.7%-86.2%) sensitivity and 90% specificity in detecting advanced adenomas and 100% (95% CI, 71.5%-100%) sensitivity in detecting CRC, as seen in results from the ZENITH trial.

These rates compare favorably to the fecal immunohistochemical test (FIT), Cologuard, and Epi proColon assays, added Friedland.

"About one-quarter of individuals over the age of 45 or 50 who should be screened decline all screening tests that exist right now. These individuals are not returning their stool test, and they're not willing to undergo a colonoscopy," said Friedland. "We could immediately offer [this blood test] to these individuals when they go to the doctor."

In an interview with *OncLive*, Friedland, professor of medicine, (gastroenterology and hepatology), Stanford University Medical Center, discussed the importance of screening for CRC, the advantages of the noninvasive FirstSight^{CRC} blood test, and the results from the ZENITH trial.

OncLive: Could you discusses the advantages of a noninvasive screening modality for CRC and advanced adenomas?

Friedland: CRC is a very common cancer in the United States. There are close to 150,000 cases and more than 50,000 deaths a year, but that's not enough of a rationale for screening. You also have to demonstrate some benefit of catching it early. [We know] that there is a marked benefit [in outcomes] if you catch colon cancer early while it's still localized. [If you catch it early], the 5-year survival rate is over 90%, but if you catch it after it has already spread, the 5-year survival rate, even with all of the new treatments we have, is about 14%.

Another unique aspect of colon cancer screening is that if you detect adenomas that are precancerous polyps, you can remove them and prevent them from turning into cancer. Colonoscopy works very well in detecting cancer

early. It also leads to better treatment outcomes and reduces the risk of cancer.

The trouble with colonoscopy is that it's very expensive and very invasive. It requires a long bowel preparation and sedation. While it works well, [the preparation and time it takes is] a big barrier for patients. About one-quarter of people who should be screened aren't getting screening, so there's a lot of room for improvement.

What markers were evaluated with the assay?

Our test looks at 3 different things. It looks for circulating intestinal cells, which are epithelial cells that are shed by cancers and adenomas from the colon that end up in the blood stream. The test also looks at cfDNA, and a panel of mutations in cfDNA, that is shed by polyps and cancers. The third thing the test looks at is abnormal methylation of the septin-9 gene. [Abnormal methylation] affects gene expression. The DNA that's shed by tumors, particularly into the blood stream in colon cancer, has abnormal methylation at septin-9. By combining all 3 of these things, we're able to detect cancers and precancerous polyps quite well.

How do the results compare with standard screening protocols?

In this study, we included a total of 354 patients with 11 cancer types, and the assay detected all 11. There were 53 advanced adenomas; these are large precancerous polyps that are typically larger than 1 cm or have some worrisome features in them. The assay detected 75% of these advanced adenomas. Among the patients who had negative colonoscopies who didn't have any polyps, 89.9% had a negative test. The specificity is close to 90% in individuals who have a normal colon, which stacks up very well compared with alternative noninvasive tests.

The main alternative noninvasive test is a stool test. The FIT, which looks for microscopic amounts of blood in the stool, has been used for many years. It's pretty good at detecting cancer, but it's very poor at detecting advanced adenomas, or large precancerous polyps. There are more large precancerous polyps than there are cancers, so if you look at the combined endpoint of looking for cancers and advanced adenomas, FIT only picks up 28% compared with 80% with the FirstSight^{CRC} assay.

Then, there is a refined stool test called Cologuard, which looks at blood in a microscopic fashion and a panel of mutations in the DNA that's shed by tumors into the stool. That test [showed a 92% sensitivity for CRC and a 42.4% sensitivity for advanced adenomas in the Deep-C study]. There is one FDA-approved blood test [that evaluates] methylated septin-9], which is just 1 of the components of our test. The methylated septin-9 test only picks up 25% of cancers and advanced adenomas. We went back and looked at all 3 components of our test, and we found that we really need all 3 components to detect cancers and advanced adenomas.

We also went back and tried to get a better handle on who would have a false positive. When we looked at these patients' histories, we found that many of these patients had very large polyps that were removed. One of the takeaways from this study, which was a bit of a surprise to us, is that these changes that we detect with the blood test seemed to persist even after removing polyps in some patients. This gives us hope that we can reduce the

false positive rate in the future by not including these patients [in screening protocols]—or, by modifying our assay for these patients since the test can be positive even after [a] large polyp [is removed]. You could argue that these people should [continue to receive] colonoscopy periodically, since it has already been proven that they [could develop cancer].

How could this tool affect standard screening protocols?

The next step for individuals who have a positive test result with the FirstSight^{CRC} assay is colonoscopy. We're not trying to replace colonoscopy. We're trying to help people who don't want to get a colonoscopy. [If the assay] is as good as we think it is, it could help select who should have a colonoscopy. A 90% specificity is pretty good; it means that individuals who have a normal colon [have a] 90% chance that their test would be negative. These patients could potentially be spared a colonoscopy, and only 10% of those individuals with false positives might need a colonoscopy.

One more blood test would be easy to incorporate [into a doctor's appointment]. Compliance would be very high with [a blood test]. If we can show that that this test is as good as our preliminary results in a large multicenter study, we'll have a strong argument for replacing some of the other noninvasive tests, such as FIT or Cologuard.

What are the main implications of these findings?

The ZENITH study shows that a blood test is very good at detecting colon cancers and precancerous polyps. That gives us real optimism that we'll be able to offer people a good noninvasive screening test. This approach could increase compliance. We'll be able to reduce mortality from CRC by getting people screened who otherwise wouldn't be. It's pretty exciting. We're getting pretty good with blood tests that detect cancers in other cancer types, but our blood test is unique in that we can detect precancerous [lesions].

CellMax Life Announces Positive U.S. Study Results for FirstSight Blood Test to Detect Colorectal Adenomas and Cancer [press release]. Sunnyvale, CA: CellMax; May 4, 2020. Accessed May 7, 2020. bit.ly/3b8YUdW