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Prospective Study Adds Evidence for CellMax Life Liquid Biopsy Utility in CRC Screening

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NEW YORK – Researchers shared new data this week from a study of the colorectal cancer screening test being developed by CellMax life, providing the first prospective sensitivity and specificity evidence for the assay in an intended use population in the US.

Presenting in a recorded virtual session for the Digestive Disease Week conference over the weekend, investigators from the Veterans Affairs Palo Alto Healthcare System reported that CellMax's FirstSight test detected 100 percent of cancers, as well as 75.5 percent of advanced adenomas (a precancerous lesion typically removed during colonoscopies to prevent malignant progression) with 90 percent specificity for negative controls in a cohort of 354 individuals presenting for colonoscopy.

The assay used to test the cohort represents an expansion from CellMax's initial technology. Alongside the firm's legacy approach of detecting circulating epithelial cells, the current FirstSight test adds PCR-based Septin9 methylation analysis and targeted next-generation sequencing to detect common colorectal cancer mutations in circulating tumor DNA. A scoring algorithm combines these molecular and cell-based features with clinical factors like age and gender to yield a result called the CMx score.

In adding ctDNA analyses, the company is hewing closer to its potential competitors, including companies like Guardant Health, Freenome, and Exact Sciences, many of whom have focused on methylation in particular.

Although CellMax has now made the move to incorporate ctDNA, the firm's test still differs from these others in its continued use of circulating cell capture and, in turn, its potential use for detecting precancerous adenomas in addition to early cancers.

Shai Friedland, chief of gastroenterology at the Veterans Affairs Palo Alto Healthcare System and the presenter of the data this week, explained in his talk that cell capture provides at lease some component of the test's precancer sensitivity.

According to Friedland, as long as a cell-capture method has enough sensitivity, it should be possible to isolate circulating epithelial cells associated with precancerous adenomas, which basic science studies have shown require a connection to the circulation to obtain oxygen and nutrition even at small sizes.

The firm hasn't broken down in detail how specific components of its test contribute more or less to adenoma versus cancer detection, but Atul Sharan, CellMax's president and CEO, said in an interview that the various analytes work to some extent in concert.

"There is sort of an unordered accumulation of genetic and epigenetic factors. And to make the test more generalizable and robust ... [adding these multiple analytes] was part of work we did in between. And it turns out it's a much more stable and robust assay," he said.

However, he added, some of the test components "are more important in the earlier adenoma stages. And some of them are more important than the CRC stage."

Friedland echoed this, saying that based on his team's research with the assay, epithelial cells are essential to the adenoma-detection aspect of the test.

"We know from our data … that [the ctDNA components] are not enough to detect the adenomas. You can detect some … but to get anywhere close to the numbers that we're seeing, you know, for detecting ... 3/4 of advanced adenomas ... you don't seem to be able to get there with just the cell-free DNA and the methylation. You need the combination," he said.

For some specific cancer types like breast and prostate, there is a worry that new screening tests, if not acutely specific to aggressive malignancies, might lead to overdiagnosis and overtreatment — producing a net harm by increasing detection of lesions that never needed to be detected in the first place.

But Friedland said that colorectal cancer is a bit different because of the availability of colonoscopy, which makes the removal of precancers relatively non-invasive compared to a surgical resection. Because of this, the negative impact of both true false positives, and of increased diagnosis of early-stage and potentially benign lesions is neutralized.

"This is why I think actually that colon cancer screening is one of the best targets for a noninvasive test like this … because the consequences of a false positive are not as severe as in other things," he said. "If you have a test for pancreatic cancer and it's a false positive, what do you do now? If you scan the patient, even if the scan's negative, they might still have cancer that's missed on the scan ... and it sets off a big panic."

"But for colon cancer screening, if you have a false positive then it means you get a colonoscopy. And since our alternative was to send everybody to colonoscopy, it's not so bad if 10 percent of the people have a false positive," he said.

In addition, Friedland said, observational studies and modeling suggest that screening colonoscopy works to reduce cancer deaths in two ways: by detecting cancers at an earlier stage, but also by reducing the actual incidence of cancer by removing these precancerous lesions.

"Colon cancer is pretty unique in that way, in that we have a way, with colonoscopy, to relatively non-invasively remove these pre-cancerous polyps to prevent them from becoming cancer. And there's really no morbidity to the patient. That's very different from breast cancer, for example, where if you remove a breast that's terrible [for the patient] but if you remove a colon polyp the person goes back to work the next day … and they don't miss the polyp," he said.

In Friedland and colleagues' prospective VA Palo Alto cohort, there were only a handful of full-blown cancers diagnosed — 11 cases in total, including one Stage I, two Stage II, seven Stage III, and another Stage IV — leaving the current performance data for the test for true cancers fairly limited. Overall, the assay yielded a positive blood-test result (a score at or above a cutoff of 30) for all 11 individuals who had a cancer diagnosed via their subsequent colonoscopy.

Competing firms like Guardant and Freenome have also reported near-100 percent sensitivity for later stage cancers, but with detection dropping for earlier stages.

In a case-control study that Guardant presented last year, for example, its epigenetic method showed 100 percent sensitivity for Stage IV cancers, 95 percent for Stage III, 90 percent for Stage II, and 84 percent at Stage I.

In updated data shared at the same DDW virtual meeting this week, Guardant presented a reanalysis in which it used only colonoscopy-confirmed negative cases as controls, rather than the self-reported negatives used in the initial calculation.

Analyzing results in a validation cohort with this change in place, the company could better tune its detection so that at 91 percent specificity, its test picked up 97 percent of Stage III and 89 percent of Stage I and II cancers.

Whether the CellMax test might maintain the 100 percent sensitivity it achieved in this initial cohort or begin to show a similar distribution as more cancer cases emerge, especially early-stage cases, remains to be seen.

Joining the cancer cases in the CellMax VA Palo Alto cohort, there were 53 diagnosed advanced adenomas. Among these, the company's scoring algorithm picked up about 75 percent.

As is true for existing fecal and blood screenings tests, sensitivity dropped when moving away from cancers and more advanced pre-cancers, offering only about a 50/50 performance in discriminating non-advanced adenomas.

Joining the 90 percent of colonoscopy negatives below the CMx-30 cutoff point were more than half of the cohort's 178 non-advanced adenoma cases. The other half spread above the cutoff, with some scores even exceeding those of confirmed cancer cases. Overall, the sensitivity of the CMx score method was calculated at just 48 percent for these non-advanced lesions.

In his presentation, Friedland compared the calculated performance for the CellMax test in his team's study with reported sensitivity and specificity of existing commercial stool-based and Septin9-only blood testing.

Based on this side-by-side comparison, the CellMax test does appear, at least in this early cohort, to be yielding significantly increased detection rates — 80 percent for advanced adenomas and cancers combined — compared to available options like Exact's Cologuard (about 46 percent), or the Septin9-based Epi proColon (25 percent).

CellMax now plans to expand its prospective validation to several thousand individuals in a study the firm calls Zenith. This will include continuing recruitment at the VA Palo Alto, as well as the addition of new sites across the US. The firm has said previously it hopes to recruit in the realm of 5,000 subjects.

According to Friedland, he and his team have already doubled their recruitment from what was reported in the DDW virtual presentation.

"We are recruiting very quickly because … we're basically taking almost all comers to colonoscopy … with just a few very slight exclusion criteria, like being over age 80 — because you have a lot of genetic changes as you get very, very old — and people with colitis we don't do because they actually shed circulating epithelial cells because of inflammation in their colon," he said.

In the interim cohort that the group reported on this week, 86 percent were asymptomatic and 14 percent had symptoms or positive-fecal test results that led to their recommendation for the procedure.

According to Sharan, now that FirstSight has been tuned to detect more pre-cancers, it might not actually need a full 5,000 subjects for a well-powered prospective validation. The prevalence of CRC in average screening is around .45 percent but this rises to 7 percent for advanced adenomas. This means if you're looking for both you can recruit fewer individuals — closer to 2,000 — to sufficiently power a study, he said.

The company said in early 2019 that it planned to start offering its testing clinically through an LDT model later that year as an interim measure as it continues to work towards collecting data to submit to the US Food and Drug Administration. But Sharan said this week that the test hasn't yet been made available, and while that plan still holds there isn't a precise timeline for a CLIA launch.

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