PavMed Spinoff Lucid Diagnostics Aims to Market Molecular Barrett's Esophagus Test in 2019

May 29, 2018 | John Gilmore

This article has been updated from a previous version which misstated the potential price of an EsoCheck test.

NEW YORK (GenomeWeb) – Announcing a partnership with Case Western Reserve University earlier this month, PavMed will enter the cancer detection market with its new subsidiary Lucid Diagnostics. The subsidiary will commercialize CWRU's EsoCheck technology, which is a squamous-cell based test that detects Barrett's esophagus (BE), a precursor to esophageal adenocarcinoma (EAC).

PavMed's EsocheckRapid test includes a non-invasive cell sampling device and a diagnostic test for two methylated DNA biomarkers. Recently formed Lucid anticipates releasing a commercial test in the first quarter of 2019.

Standard detection for BE involves a clinician performing endoscopy, which uses a thin, flexible tube to search for inflammation, ulcers, and tumors. While endoscopy is effective for diagnosing conditions like esophageal cancers, it is invasive and could cost up to$3000 per procedure, according to Amitabh Chak, co-inventor of the technology and a professor of medicine at CWRU. This also deters BE detection until visible symptoms occur, which may be too late in up to 95 percent of cases of EAC.

Chak explained that the sample collection process for the EsoCheck technology involves a patient swallowing a capsule containing an inflatable balloon. After the capsule arrives in the stomach, the balloon inflates and is slowly pulled through the lower esophagus. Once the endoscopist feels the esophagus constrict around the balloon, he then deflates the collection device using an attached syringe and retracts the balloon inside the capsule.

According to Chak, the technician would then "slice the balloon off the capsule, freeze it, [and] extract DNA using a buffer," then send the sample to a reference lab for PCR and next-generation sequencing. Chak noted that on average, the initial sample collection step takes around five minutes.

Regarding the DNA biomarker portion of the assay, Sanford Markowitz, an EsoCheck co-inventor and professor of cancer genetics at CWRU, had shown with others over a decade ago that one of the biomarkers, methylated vimentin gene (mVIM), is an indicator of colorectal cancer. Markowitz and his team found that the biomarker also occurs in precancerous esophagus lesions and began developing a test for BE based on the biomarker.

The researchers subsequently added another DNA biomarker, work that was published in January in *Science Translational Medicine*. Specifically, the team performed genome-wide screening in squamous cell samples to find regions targeted for recurrent aberrant cytosine methylation in BE, identifying high-frequency methylation within the *CCNA1* locus. The team tested *CCNA1* DNA methylation as a BE biomarker in cytology brushings of the distal

esophagus of 173 individuals with or without BE, and found that the biomarker performed identically to mVIM.

When Chak and his team combined both biomarkers in a next-generation bisulfite sequencing assay, they were able to detect both BE and EAC with 95 percent sensitivity and 91 percent specificity in a multicenter clinical study of 408 patients. Chak noted that the test's detection was comparable to endoscopy-directed brushings.

The overall process — sample collection, PCR amplification, next-generation sequencing, and automated software analysis — currently requires about a three- to four-day turnaround time.

Limitations of the study included the fact that sample collection with the balloon device only occured at a single institution, so the researchers will need to repeat the procedure in other centers and in community-based populations. The team's study also included mostly male Caucasians due to the high prevalence of BE in the targeted population. Chak noted that his team will need to repeat the study in female and other ethnic groups to generate widespread results.

In addition, the team encountered failures in patient groups to swallow the ballon device or obtain enough cell samples, shortcomings that will be a main focus of improvement in future studies.

Chak said that his team has filed for several patents regarding the technology, including a provisional patent for the balloon device in addition to using the *CCNA1* biomarker for BE.

Since the team published the paper in January, it has initiated a large, multicenter, National Institutes of Health-supported study with five other research organizations — the Cleveland Clinic, Johns Hopkins, Mayo Clinic, Washington University in St. Louis, and the University of North Carolina — in order to establish clinical evidence for EsoChek's widespread use as a screening test for BE.

PavMed also spun off Lucid, which licensed the technology from CWRU to develop Esocheck to diagnose BE in patients with inflammation caused by acid reflux in the esophagus. Lucid will primarily market the diagnostic test toward Caucasian males in their fifties and older, where heartburn and BE most often occur. PavMed CEO and Chairman Lishan Aklog said that he believes the patient population that the test could potentially help diagnose will be well over 50 million individuals.

Several other research groups and firms have been developing similar technology to diagnose BE and predict EAC. Researchers at Columbia University have recently performed next-generation sequencing on pre-cancerous formalin-fixed, paraffin-embedded tissues in patients with Barrett's intestinal metaplasia, which is related to BE. The group found mutations in TP53, APC, CDKN2A, KRAS, FGFR, and PDGFRA genes.

In addition, Medtronic Solutions has commercialized the Cytosponge test, which involves a patient swallowing a gelatin-covered capsule attached to a string. Traveling down into the stomach, the capsule expands into a small mesh balloon sponge. The clinician then pulls balloon out of the stomach with an attached string, collecting squamous cells while it passes through entire esophagus.

Aklog argued that methods like Cytosponge lack the ability to perform targeted sampling in the lower esophagus, where BE normally occurs. In addition, he pointed out that Cytosponge deals with contamination from other cells in the esophagus. Instead of being paired with definitive biomarkers, the test requires a cytologist to examine the sponge to find cells that indicate BE from an array of different cells.

"This is important, since if you're not getting a pure sampling of the cells from the lower esophagus, you're dependent on expensive cytology," Aklog noted.

In contrast, Aklog highlighted that the Esocheck test delivers accurate, automated results and does not require an operator for cell detection. Lucid removes the pathologist from the equation by sending the specimen to a reference lab, where researchers perform PCR amplification and sequencing on the sample. Using a customized algorithm to track the number of methylated sites per cell, the researchers can detect whether the patient has BE and decide the patient's risk potential for EAC.

Aklog said that Lucid is aiming to receive both US FDA 510(k) approval for its EsoCheck device and CLIA/CAP approval for its reference laboratory by the end of the year. The firm is targeting the first quarter of 2019 for an initial commercial launch of EsoCheck as an LDT product.

While declining to disclose the test's price, Aklog said that EsoCheck will be much cheaper than a standard endoscopy.

Aklog also sees an opportunity for the device to monitor BE's eventual progression to cancer. If patients have been identified with BE but do not have a high-enough threshold for intervention, researchers could perform the relatively inexpensive procedure every six months instead of an endoscopy to track the condition's progression.

In addition, Aklog also envisions applying the EsoCheck technology to diseases like esophageal squamous cell carcinoma —caused by excessive smoking or alcohol use — in vulnerable populations. By using biomarkers commonly used for cancer detection, Aklog believes the technology could expand in scope and be performed on patients with a variety of cancers.

"If the balloon device could be used with some procedural alterations, [we] could screen for cells in different populations," he said. However, "we will need to line up the [test] with a biomarker that detects the precursor to the condition."

Initially, Lucid will focus on patients scheduled for endoscopies. If EsoCheck produces positive results, then the patient can pursue endoscopy for further validation. If the test is negative, the clinician can later follow up with an additional procedure in six months to see if the patient's risk has elevated.

Aklog said that the firm hopes to offer doctors the ability to screen anyone with frequent (more than once a week) heartburn for BE, which could qualify up to 20 million patients. In addition, clinicians could eventually screen patients who are at risk for the condition but do not exhibit symptoms.

"Up to 40 percent of patients have acid reflux but do not have symptoms, and therefore the risk is worrisome for populations with the potential risk," Aklog explained.

"If we can prove the value of such a simple, non-invasive method ... imagine seeing the test in a pharmacy," Aklog said. " You come in for your your fourth refill of Prilosec or Nexium, and the pharmacist might say 'You want to get this test done, which we can do on the spot.' "

Lucid is currently engaged in internal conversations about a potential Series A funding round. In the long term, PavMed will look at market conditions and its own capital position to decide whether it will raise money or self-fund Lucid. In addition, Lucid has entered a managing service agreement with PavMed.

"Over time, as we get to commercialization, Lucid will build out its own independent management team," Aklog said.

According to Aklog, Lucid aims to initially launch the product using independent distributors or through a partnership with a larger company in the US, rather than spending capital to build an internal capital sales force. The test has also received interest from international partners, with particular interest from European groups, Aklog noted.