Diatech Pharmacogenetics Explores Long DNA as Biomarker of Colorectal Cancer in Stool

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NEW YORK (GenomeWeb) – Italian diagnostics firm Diatech Pharmacogenetics is busy these days. The company, which sells more than a dozen diagnostic test kits for the precision oncology market, bills itself as the owner of more than 70 percent of the Italian molecular diagnostic market. Now, it wants a share of the global stool-sample colorectal cancer testing market, too.

Until the last five years, using stool samples to test for colorectal cancer didn't really exist — the conventional wisdom was that there was so little human DNA in stool that it would be impossible to check for the genetic mutations that are indicative of cancer. For most people, the only option was to undergo screening with colonoscopy in five or 10-year intervals. And although other options exist, such as fecal occult blood testing (FOBT) or fecal immunochemical testing, direct imaging of the colon seemed to be the most reliable way to check for early signs of cancer.

It wasn't until Madison, Wisconsin-based Exact Sciences showed that it was indeed possible to use stool for cancer screening that at-home colorectal cancer testing was made possible. Exact is spending a fair bit of time and money these days trying to convince middle-aged people that a colonoscopy isn't their only option for colorectal cancer screening. The firm's television ad campaign — in which a cheerful anthropomorphic Cologuard test kit box gently lectures people on colorectal health — seems to have been fairly successful: Exact's preliminary fourth quarter and full-year 2018 earnings report indicated that testing volumes are up 66 percent for the quarter and 64 percent for the year.

Exact's success so far has come from providing patients with a relatively painless alternative to the dreaded colonoscopy. The firm's breakthrough was in finding a way to screen for cancer in stool samples, enabling patients to collect their own samples and send them to Exact's lab for processing. ("Get, go, gone," as the marketing tagline goes.) It obviates the need for the fasting, intestinal cleansing processes, trips to the hospital, and anesthesia that can be a part of colonoscopies.

The test itself — which was developed in collaboration with the Mayo Clinic — is an automated assay for tumor-specific DNA changes, including aberrant methylated BMP3 and NDRG4, a mutant form of KRAS, beta-actin, and hemoglobin.

At the JP Morgan Healthcare conference in San Francisco in January, Exact Chairman and CEO Kevin Conroy said that even despite its rapid adoption and its 115 percent compound annual growth rate from 2014 to 2018, Cologuard has penetrated only 4 percent of its total addressable market, which is valued at greater than $14 billion.

And the company is also seeking approval from the US Food and Drug Administration to expand the label for Cologuard testing to include not only people who are between 50 and 85 and at average risk of getting colorectal cancer, but also those aged 45 to 49 who are at average risk. That would increase the market opportunity for the test by 19 million people, a potential $4 billion, according to Conroy.

Given the profit yet to be made in the at-home colorectal cancer testing market — and since Exact has already demonstrated that it's possible to test for cancer in stool — it's perhaps not surprising that there are now other companies that see potential in this diagnostic methodology.

As part of its EasyPGX line of CE-IVD real-time PCR tests, privately held Diatech has launched the EasyPGX ready FL-DNA kit for the diagnosis of colorectal cancer from stool samples. But although the sample type is the same as Cologuard, the test itself is quite different.

Rather than searching for mutated KRAS or methylated BMP3 and NDRG4, Diatech's kit searches stool samples for fragments of long DNA — pieces of DNA that are 200 basepairs or longer and which characterize non-apoptotic DNA that has been shed into the fecal stream from diseased mucosa. Long DNA in the stool can be used as a biomarker for early diagnosis of colorectal cancer, according to the company and the Istituto Scientifico Romagnolo Meldola per lo Studio e la Cura dei Tumori (IRST), which first developed and owns the patents on the technology.

"Several studies have shown that the analysis of DNA fragments with dimensions more than 200 bp allows [for the identification of] cancerous lesions," Diatech CEO Oliva Alberti said in an email. In tumor cells, in which apoptosis is inhibited, the DNA undergoes a lower degree of degradation, so tumors will typically shed fragments that are longer than 150 to 200 bp. In healthy individuals, meanwhile, exfoliated cells undergo apoptosis with consequent DNA degradation in small fragments, she added.

Alberti also noted that when conducted in conjunction with FOBT, the EasyPGX ready FL-DNA test can help to identify an individual's probability of developing colorectal cancer, increasing the chances of catching the disease in the early stages.

"The aim of the solution is to provide early advice in order to speed up the monitoring process for colorectal cancer," she said.

In a *Cancer Epidemiology, Biomarkers & Prevention* study published in November 2014, researchers from Diatech, the IRST, and elsewhere tested the FL-DNA method in combination with FOBT in more than 1,000 patients, with the aim of improving diagnostic accuracy for the detection of early malignant lesions in a population undergoing colorectal cancer screening. They found that FL-DNA analysis improved the accuracy of FOBT testing.

After the completion of the clinical study, the company signed a commercialization agreement with the IRST to develop the test, Alberti said. The subsequent R&D activity and CE-IVD validation for the kit took about 12 months, and the kit was launched in mid-2018.

One minor disadvantage is that the FL-DNA test must be done in conjunction with FOBT in order to provide maximum benefit. But because they use the same sample type, a patient only needs to submit one sample for both tests, Alberti said. And because the sampling is non-invasive, it can be done as often as needed.

"The FL-DNA is in combination with FOBT in order to have a complete picture of the patient status," she noted. "If the test [indicates] high risk, together with FOBT, the patient will have to be included into the standard CRC protocol. The advantage of the test is accelerating the time to diagnosis for CRC and to avoid unnecessary colonoscopies."

Further, she added, because it uses qPCR for analysis, the samples can be run at any hospital or lab with the necessary equipment, without the need to submit them to a central lab. Stool samples can be tricky to analyze correctly — a factor that led to Exact's decision to have Cologuard kits analyzed at its own central lab, despite the use of real-time PCR for analysis. But Diatech's test has been validated with dedicated extraction reagents that can be used by standard molecular biology laboratories, and detection reagents that include an internal control specifically developed to conform to the difficult sample type and avoid false-positive results, Alberti said.

Each kit comes packaged with the reagents delivered in eight-well strips, pre-loaded with the complete master mix needed to complete the reaction. The mix allows for the co-amplification of the target DNA and an exogenous control gene. After the sample is added to the extraction reagents, the extracted sample is then added to the eight-well strip, which is loaded onto a thermal cycler. According to Diatech, the test requires less than 10 minutes of hands-on time and about three hours of total run time, from extraction to result.

The FL-DNA kit is one of several that Diatech sells in the EasyPGX line, all of which conform to this same kit model. This is the only kit that works with stool samples, however, with the other tests running from plasma, whole blood, cytological samples, fresh, frozen, or formalin-fixed paraffin-embedded tissues.

Diatech produces the reagents and sells the complete FL-DNA test to hospitals and laboratories that have purchased the kits. The hospitals and labs are the ones that perform the service as required by clinicians for their patients, Alberti added, noting that as of now, the firm has customers that perform the test at "three major sites." However, she declined to specify how many kits have been sold since the test was launched.

Whether there will be an Italian cousin to Exact's TV mascot remains to be seen. The IRST owns patents in Europe, the US, and Canada on the molecular early diagnosis of colorectal cancer by quantitative evaluation of DNA extracted from stool and a method for the identification of colorectal tumors.

Though the firm is currently concentrating on selling the kit in markets that accept CE-IVD validation, Alberti said that Diatech is "working to promote the [EasyPGX ready FL-DNA test] worldwide," adding that the company plans to approach the US market "within the next three years with a full FDA validation."

The firm is also exploring the possibility of detecting FL-DNA in other sample types, such as blood, for colorectal cancer and for other cancers.

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