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Spanish Cancer Company Universal Dx to Commercialize Methylation Method for Lung Cancer Detection

By John Gilmore

NEW YORK – Spanish cancer research firm Universal Diagnostics is gearing up to commercialize a liquid biopsy test that applies methylation biomarkers to detect lung cancer, based on data presented at the International Association for the Study of Lung Cancer 2020 World Conference for Lung Cancer (WCLC) last month.

The Seville-based firm also expects to release clinical data on its next generation sequencing-based colorectal cancer (CRC) assay later this year.

Christian Hense, chief operating officer of Universal Dx, said that the method's workflow begins by collecting about 4ml of plasma from 8ml to 10ml of a patient's blood sample for cell-free DNA (cfDNA) extraction.

After Universal Dx performs a series of processing steps to enrich for targets of interest, Hense said that the team then uses methylation-sensitive restriction enzyme qPCR, or MSRE-qPCR, which applies enzymes that recognize specific "4-nucleotide DNA motifs containing CpG sequences" and digest the unmethylated cytosines.

According to Hense, a methyl group at the fifth position of cytosine renders the group impossible to be digested by the enzymes, and "after successful incubation of DNA with MRSEs and PCR amplification, only methylated DNA results in a detectable PCR result."

Universal Dx then applies its proprietary bioinformatics pipeline to the PCR data to identify patients with potential early-stage lung cancers.

In a study abstract presented at WCLC, Universal Dx and its academic collaborators collected plasma samples from 37 patients with stages I-IV lung cancer, including 11 adenocarcinoma, 10 squamous cell carcinoma, 11 small cell lung cancer (SCLC), and five rare lung cancer subtypes (large cell, carcinoid tumors). The team also collected 71 asymptomatic age, gender, and smoking-history matching controls.

Applying MSRE-qPCR, the researchers built a 10-biomarker panel to identify the methylation status of tumor-derived cfDNA in the lung cancer patients.

The group found that the panel had an area under the curve of 85 percent, with a sensitivity of 73 percent and specificity of 90 percent. The panel also identified 82 percent of the adenocarcinoma, 80 percent of the squamous cell carcinoma, 73 percent of the SCLC, and 40 percent of the rare cancer subtypes as cancer patients.

In an email, Dennis Lo, director of the Li Ka Shing Institute of Health Sciences at the Chinese University of Hong Kong, noted the MSRE-qPCR tool indicates that methylation-based markers in cfDNA in blood "represent promising markers in cancer detection."

His team previously used a similar methylation-based approach to detect liver cancer and is now using a method that analyzes the presence of "jagged-ends" in cfDNA fragments to correlate with fetal and tumor-derived cfDNA.

"I think that it would be interesting to see a comparison between the pros and cons between such a restriction enzyme-based approach versus the more commonly used bisulfite-based approach," Lo said.

However, Lo, who is not affiliated with Universal Dx or with the development of its test, pointed out that the small sample size in the study is relatively low and will require future large-scale validation studies. In addition, he questioned "whether the specificity of 90 percent would be sufficient for clinical use."

Hense believes the initial results from the proof-of-concept study prove that Universal Dx's platform works for lung cancer detection because the study shows how methylation panels could be used to identify the cancer regardless of the subtype. The firm expects to begin larger clinical trials to validate the methylation panel in the second half of 2021.

Following Universal Dx's validation trials for the lung cancer test, the firm plans to eventually convert the methylation panel to run on an NGS platform rather than qPCR as part of its commercialization strategy. Hense said that NGS give back exact sequencing information on a read level, allowing users to identify precise base-level methylation patterns and increase accuracy. He also noted that NGS allows his team to significantly extend the number of analyzed regions, further improving accuracy and providing the ability to examine additional cancer types.

"We expect to add biomarkers to this panel, as well as drop a few as well ... as we go cancer by cancer [to make] sure we have biomarkers that help us distinguish the subtypes of the cancer," he said. "The NGS platform will give us the opportunity to detect lung cancer overall … as it's important [because] it affects the sensitivity and specificity."

Universal Dx will work with international academic partners — including Imperial College of London, the Austrian Institute of Technology, and Barcelona's Polytechnical University of Catalonia — and leverage its network of more than 100 hospitals in Europe and the US to clinically evaluate the lung cancer test. However, Hense acknowledged that Universal Dx has not yet decided which specific clinical application it will develop the potential NGS diagnostic for in the lung cancer space.

While Universal Dx aims to eventually build a commercial version of the lung cancer diagnostic, Hense said that the firm will prioritize commercializing its CRC assay in the US and global markets in the near-term.

Universal Dx expects to publish results on the CRC assay at an academic conference later this year, such as the 2021 American Society of Clinical Oncology Annual Meeting or the European Society for Medical Oncology Congress 2021. Hense said the results will include which commercial sequencing instrument his team will use for the test.

In the meantime, certain biomarkers for CRC, lung, breast, and pancreatic cancer are patent-pending with the US Patent and Trademark Offices.

Universal Dx is still deciding whether to build its own CLIA-certified, CAP-accredited lab or partner with a third party to commercialize the CRC assay as a laboratory-developed test in the US. After it makes it decision, Hense said the firm's envisioned lung cancer diagnostic will follow a similar US regulatory path as the CRC assay.

"Ultimately, this will have to be approved by the US Food and Drug Administration, like Cologuard from Exact Sciences, or [Epi proColon] from Epigenomics," Hense said. "As far as we know, we're expecting a [premarket] authorization pathway, but we will start our conversation to know more later this year."

In addition, Universal Dx aims to apply for a CE mark for the colorectal assay in parallel to its FDA PMA approval process, which it expects to begin later this year.

Hense said that all of Universal Dx's activities are "well funded" into 2022, and that the firm will move forward with its projects to demonstrate the methylation-based assays' commercial value. Universal Dx has raised about $27 million in funding to develop the methylation-based tool since the firm was launched in 2012.