Israel's Nucleix Targeting US Market With Noninvasive Bladder, Lung Cancer Assays

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NEW YORK – Israeli liquid biopsy startup Nucleix is taking aim at the US cancer detection market with diagnostic assays for early-stage cancers such as lung and esophageal that frequently occur in smokers.

Specifically, the Rehovot-based firm hopes to launch a research-use-only lung cancer diagnostic assay next year, and plans to build a CLIA-certified, CAP-accredited lab in the US later this year to support that product.

In the meantime, Nucleix also recently completed a clinical trial for its Bladder EpiCheck cancer diagnostic assay, which it plans to submit to the US Food and Drug Administration trial with hopes of launching with 510(k) clearance mid-next year.

According to Nucleix CEO Chris Hibberd, who transitioned to the role last week, the firm's EpiCheck technology searches for tissue-specific methylation patterns on circulating tumor DNA (ctDNA) in a patient's liquid sample, including blood and urine.

The assay involves extracting DNA from the sample, digesting it with methylation-sensitive enzymes, analyzing the digested sample on a real-time PCR instrument, and evaluating the data using its EpiCheck software, which produces a numerical score (EpiScore) between 0 and 100 based on the relative methylation levels across the test's markers. If the EpiScore is equal to or higher than a certain numerical threshold, which is established during assay development, then the sample is considered positive for the cancer.

"The cutoff is established … using training sample sets obtained from the target population and is set at the point that provides optimal clinical performance," Hibberd explained. "The performance is then validated on large and independent validation sample cohorts."

Hibberd highlighted that Nucleix can run samples on a variety of commercial multiplex real-time PCR instruments in its lab, including Thermo Fisher Scientific's ABI 7500 and Qiagen's (recently acquired by Thermo) Rotor-Gene Q instruments.

Bladder EpiCheck was CE marked and commercially launched in Europe in 2017, and analyzes 15 methylation biomarkers for bladder cancer recurrence. Urologists seeking to monitor patients after resection surgery send in about 10 ml of a patient's urine sample to Nucleix, which can provide diagnostic results within hours.

"We wanted to demonstrate that the technology works, produce a kit, and go after something that's a reasonable space to target," Hibberd explained. "The clinical feedback has been strong in Europe, and we've done a good job of picking up high-grade bladder cancers."

Hibberd noted that Bladder EpiCheck currently costs roughly $250. In a European validation study published in June 2018, the firm found that the assay had a clinical sensitivity and specificity of 92 and 88 percent, respectively, for bladder cancer detection in a cohort of 353 patients.

The team expects to complete a validation study on Bladder EpiCheck with 11 sites in the US and Canada, including partners at Cleveland Clinic, Vanderbilt University, and the Princess Margaret Cancer in Toronto later this fall. Recruiting over 650 patients, the team has completed patient follow-up and plans to submit the results to the FDA and hopefully receiving 510(k) clearance by early 2021.

Lung cancer

Nucleix is also developing an early-stage lung cancer diagnostic test called Lung EpiCheck to capitalize on what Hibberd believes is the 90 percent of high-risk patients who refuse to undergo standard screening for cancer diagnosis, whether due to exorbitant costs, fear of CT, logistics, inconvenience, or other factors. Hibberd said the test currently analyzes six methylated ctDNA biomarkers in about 8 to 10 ml of patient's blood.

In a prospective European training set, Nucleix used plasma samples from 102 lung cancer and 265 controls to define the panel and algorithm, later validating the assay's performance in two additional cohorts of 320 European and 45 Chinese plasma samples. While the paper is currently under review, the team found that that the test achieved 87 percent clinical sensitivity and 64 percent specificity for non-small-cell lung cancer.

"We looked at our portfolio as a whole and thought we should focus on a high-risk patient population," Hibberd explained. "Wanting to identify cancer before metastasis occurs, we decided to push for lung cancer here the US."

Nucleix is building its lab in San Diego and expects to establish CLIA certification and CAP accreditation for the location by early 2021.

"As part of the company's growth, we've used bladder to demonstrate that the tool works," Hibberd said. "But there's a huge market need for lung cancer detection, as there's only 10 percent of patients being screened now, and that's what we're pushing for in this CLIA lab."

Acknowledging that the team will need to build additional data on the assay, Hibberd believes the firm will eventually offer it as a laboratory-developed test by mid-2021. Hibberd noted that Nucleix plans to publish its first set of validation data for the test early next year.

In order to market Bladder EpiCheck in the US, Nucleix anticipates collaborating with potential commercial partners in certain market segments. Meanwhile, the firm will first reach out to the primary care community to decide the best path for Lung EpiCheck while fleshing out its own salesforce to address the "most attractive segments," Hibberd said.

While insurance reimbursement negotiations are in the early stages, Hibberd noted that Nucleix has performed market research to establish the threshold at which patients would be willing to pay for the test out of pocket.

"If you have technology like ours, where the cost of goods is very low double digits and moving down to single digits, you can deploy the tests in the $100 to $250 range and people will be willing to pay out of pockets for the test," Hibberd explained. "That opens up an opportunity for us to create a two-step process, where we have some self-pay while we work on our reimbursement strategy."

Hibberd envisions Bladder EpiCheck and Lung EpiCheck being used in the US as part of routine screening by primary care physicians.

While other liquid biopsy firms such as Grail and Guardant Health have pivoted only recently toward ctDNA methylation diagnostics for early-stage cancer detection, Hibberd said that Nucleix has been developing and improving its technology since 2008.

Grail's approach uses a targeted methylation sequencing panel that preferentially assesses regions of the genome to both detect the presence of a cancer and identify a tumor's tissue of origin. Meanwhile, Guardant is using a multi-omic approach that includes methylation and fragment-based signals alongside cancer-linked DNA alterations.

Hibberd said that Nucleix's technology stands out because it is much more sensitive as a result of proprietary enzymatic-based approach to methylation does not destroy starting genetic material and maintains a relatively high signal-to-noise ratio), as opposed to other groups that use bisulfite sequencing, which features a harsh chemical treatment that destroys 50 to 90 percent of the DNA and introduces significant noise.

Hibberd noted that Nucleix been issued a "double-digit" number of patents from the US Patent and Trademark Office and international regulatory bodies related to its enzymatic approach, methylated biomarkers, and trade secrets.

In addition to the US and European markets, Nucleix is also garnering interests for its platform in East Asia. With lung cancer a large health issue in China due to a high population of smokers, Nucleix is currently evaluating choices for partners in the country, as well as planning to expand into South Korea and Japan, Hibberd said.

Nucleix has raised about $33 million in funding since 2008 to develop its assays, including a $14 million financing round last summer that involved Israeli investors Orbimed, Aurum, and Zohar Zisapel, as well as Korean investors DSC and OCI.

After launching the bladder and lung cancer assays, Nucleix envisions developing additional methylation diagnostic assays for cancers linked to smoking such as liver and esophageal.