nRichDx Targets Liquid Biopsy Space With Magnetic Sample Prep Platform

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NEW YORK – Launching its semi-automated magnetic-based sample prep platform last week, nRichDx now aims to establish a foothold in the liquid biopsy space by offering a platform that collects a variety of genetic material, such as cell-free DNA (cfDNA), circulating tumor DNA (ctDNA) circulating tumor cells, and more.

The Irvine, California-based firm said that its new "Revolution" system offers recovery rates of 70 to 90 percent for multiple liquid sample volumes and types, which it believes has initial applications for downstream cfDNA analysis.

According to nRichDx CEO William Curtis, the firm began in 2016 when rare cell isolation firm WaveSense rebranded to target some of liquid biopsy testing's biggest challenges, such as low sensitivities for early-stage cancer detection. Partnering with several different academic institutions, including Massachusetts General Hospital and Dartmouth Hitchcock Medical Center (DHMC), nRichDx has spent the last few years improving WaveSense's original "nRichDx" system.

Curtis noted that nRichDx intends to offer Revolution as a Class 1/low risk *in vitro* diagnostic tool.

"When I came in, the intent was to create a sample prep solution to resolve problems inhibiting liquid biopsy testing" Curtis explained. "As a sample prep technology firm, our goal is to provide the highest yield of any downstream instruments or kits."

In 2018, nRichDx established a scientific advisory board including Columbia University researcher Helen Fernandes, MGH researcher Ryan Corcoran, and DHMC's Laboratory for Clinical Genomics Director Gregory Tsongalis.

Curtis explained that the Revolution System consists of three major components: the Revolution Processor, Revolution nRicher Cartridge, and Revolution cfDNA Isolation Kits. The system's reagents include magnetic beads that Curtis said are surface-treated to target and capture cfDNA.

"Unlike most other sample prep systems that have multiple transfer steps, our cartridge is unique because there are no transfer steps in our process," Curtis said.

After adding a liquid sample and custom reagents to the nRicher Cartridge, the researcher puts the cartridge into the processor, where it undergoes an incubation and binding process. During the binding process, magnetic beads target and capture the cfDNA in the sample.

After waiting 20 minutes, a researcher removes the cartridge, adds reagents, and puts it back on the processor to perform a 30-minute binding process. A technician then puts nRichDx's Mag Capsule on the cartridge and places the cartridge back on the processor for

15 minutes, allowing the magnet to isolate the magnetic beads that have the cfDNA attached to them in a 2-ml micro-vial component of the nRicher cartridge.

Once the processor captures the target material, the researcher washes the magnetic beads off the cfDNA and elutes the remaining substance, leaving a concentrated sample of cfDNA for downstream analysis.

According to Curtis, nRichDx's sample prep technology currently collects cfDNA from urine and plasma samples. The firm initially chose cfDNA as a target over other types of genetic material because of its high demand in downstream applications within the liquid biopsy space.

Curtis said that the team is now developing Revolution further to collect total cell-free genetic material (DNA and RNA), exosomes, and circulating tumor cells. Noting the tool can run 3 ml to 20 ml of a sample, Curtis argued that processing a higher volume of sample will lead to greater access to a larger concentration of targets.

"Target material is extremely rare, and it becomes even more rare as you get into lower level of frequencies and earlier stages," Curtis said. "We thought that the demand for a larger sample was going to be necessary in order to be able to deliver that kind of sensitivity to downstream assays."

Highlighting that efficiency and recovery rate have been some of the "biggest distractions" in the sample prep industry, Curtis believes that higher sample sizes — in contrast — translates to significantly higher sensitivity that allows cancer detection at earlier stages from lower allele frequencies.

"Even at 100 percent efficiency, if you're only processing 1 to 5 ml of sample, there's not enough target material to have the sensitivity in a downstream tool detect [cancer] at an early stage," Curtis said. "The [field's] current focus has been on efficiency because current sample prep systems cannot process larger size samples."

While nRichDx has not published any peer-reviewed studies on Revolution, Curtis said that the platform has shown a recovery rate of between 70 to 90 percent in internal studies and can process up to 20 ml of a sample per run. If researchers use a 5ml liquid sample, they can produce results in about 90 minutes.

At the same time, Curtis acknowledged that the Revolution platform needs slightly additional time for large samples, requiring about 2 to 2.5 hours for a 20 ml sample.

Curtis also noted that the biggest issue his team has encountered while improving the Revolution platform has involved reagent and cartridge development. The group has spent the past few years ensuring that the sample prep tool maintained high reproducibility at different sample volumes.

"We want to ensure we're working toward the highest efficiency rates and consistently achieving those rates," Curtis said. "For sample prep, the consistency is essential so that we can rely on the system to produce a target yield to ensure downstream use is efficient, effective, and reliable as possible."

Curtis noted that nRichDx began working with Tsongalis' lab at DHMC in April 2018 to evaluate the platform. Tsongalis said his team has since piloted several validation and performance studies using Revolution and is now examining the tool's "typical performance characteristics during cfDNA extraction."

According to Tsongalis, his group decided to work with nRichDx's technology because of current limitations with cell-free DNA analysis. Like Curtis, he highlighted that limited

quantities of cell-free nucleic acids collected during extraction can restrict researchers from having enough sample for downstream robust and reproducible analysis.

Corcoran added that his team found nRichDx's technology appealing because the system allows for a higher likelihood of finding rare tumor-derived genetic material. As groups in the liquid biopsy sector target multiple biomarkers linked to different diseases, he sees nRichDx's tool as a method to help process higher plasma input for the downstream applications.

"With some of the emerging technology out there that aims to detect residual disease after surgery, or even early detection of cancer, the cell count is so low that the tools can't always detect the target in the blood sample you've analyzed," Corcoran said. "If you can start with higher extraction volumes of starting material and enrich the input material for some of these applications that require sensitivity, the chances of finding the material definitely go up."

Curtis noted that nRichDx owns a patent that primarily focuses on the nRicher Cartridge, combining extraction, enrichment, and concentration of sources of genetic material at a high efficiency, as well as "other tangential patents."

While nRichDx raised an undisclosed amount of funding from private investors in 2016, Curtis noted that the firm now anticipates soon launching an institutional funding round to further develop isolation kits for other types of genetic material.

According to Curtis, researchers can purchase the Revolution system and cfDNA isolation kits — which can run up to 24 samples at once — for use in their own labs. He said that the Revolution system —including the processor and accessories— currently costs $9,995, with each isolation kit costing about $600.

In addition, nRichDx is preparing to partner with unnamed academic institutions on studies using its platform to prep cfDNA for downstream use with next-generation sequencing, PCR, and other applications. In certain cases, the groups will measure any potential increase in sensitivity of downstream assays when using Revolution at the front end of the process.

Curtis said that nRichDx expects to launch isolation kits for CTCs and cell-free genetic material by early 2020. He also noted that nRichDx is partnering with liquid handling companies to potentially offer a solution to automatically perform washing and elution steps. In the long term, nRichDx is developing its own fully automated system, which it anticipates launching by the end of 2020.