Non-Profit Startup Paradigm Launches Cancer Panel Based on DNA, RNA Sequencing

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By Tony Fong

Non-profit diagnostics outfit Paradigm last month joined a growing list of entrants in the clinical sequencing space with the launch of its next-generation sequencing-based cancer test. But unlike others that have tests sequencing only DNA, Paradigm's assay sequences RNA as well, a trait that could allow for better care and treatment for cancer patients.

Called PCDx, short for Paradigm Cancer Diagnostic, the test was launched in mid-March after being field-tested for six months. Run on Thermo Fisher Scientific's Ion Torrent Personal Genome Machine, the test uses targeted sequencing to identify "all actionable classes of genomic alterations in hundreds of cancer-related genes," including copy number variants, insertions, deletions, base substitutions, rearrangement, and mRNA expression.

Though the test was launched nationally across the US, Ann Arbor, Mich.-based Paradigm is doing what amounts to a soft launch, relying mostly on word of mouth from oncologists and other healthcare providers with whom it already had relationships in order to ensure it can meet demand.

With the number of NGS-based cancer panels available on the market steadily rising, PCDx faces stiff competition from not only industry players — most notably Foundation Medicine — but also academic laboratories, including Washington University's Genome Institute and Dartmouth-Hitchcock Medical Center, that have recently launched such panels.

What makes PCDx different, Paradigm Co-founder and CEO Robert Penny told Clinical Sequencing News recently, is three-fold. First, the test has a rapid turnaround time of between four to five days. For comparison's sake, Foundation Medicine's FoundationOne test has a turnaround time of 14 days.

PCDx also can detect mRNA in formalin-fixed, paraffin-embedded tissue. And it has, on average, 3,000x coverage, one of the highest commercially available.

In particular, Penny called PCDx's ability to detect mRNA in FFPE a "real hallmark for us," as about 80 percent of cancer patients show actionable mRNA findings. "It's nowhere near that for mutations and copy numbers."

Others have also noted the importance of sequencing RNA to confirm DNA sequencing results, including Elaine Mardis, co-director of the Genome Institute at Washington University, who in 2011 said that about only 40 percent of mutations in a patient's genome is actually expressed,
and added that in looking for target mutations for a drug, targeting mutations in genes that aren't even expressed is probably a fruitless exercise.

According to Penny, no one else is commercially sequencing mRNA on FFPE, "so we leapfrog everybody on the technology to be able to get this to patient care," he said.

Ion Torrent, however, is developing an AmpliSeq targeted panel that will include both DNA and RNA, and the National Cancer Institute is developing a DNA/RNA panel for its NCI Molecular Analysis for Therapy Choice (MATCH) trial.

Penny declined to describe in detail Paradigm's methodology of simultaneous DNA/RNA sequencing, citing company policy.

Another differentiating factor of the test is PCDx's 3,000x depth of coverage, Penny said, making it one of the most sensitive and specific tests on the market.

By comparison, FoundationOne test has a minimum 250x depth of coverage, "excluding any molecules duplicated via PCR," a Foundation Medicine spokesman told GWDN in an email. "What is important when talking about coverage is really its relation to test sensitivity and specificity. Our coverage specifications are designed to ensure the high accuracy and reproducibility required for clinical use of the test."

'Not A Research Tool'

Of PCDx, Penny said, "This is not a research tool ... [With] a lot of the research-based platforms that do whole-exome testing ... you make a trade-off, and the trade-off is you can't believe all your negatives.

"Your positives are also hard to believe, but you can confirm that," he said, "but the negatives are impossible to confirm."

Penny credits PCDx's depth of coverage to the fact that it runs on the Ion Torrent PGM platform, which Paradigm uses exclusively, though he declined to say how many instruments the company has.

"That was critical," he said. "It was an important platform that we like and we got quality results. I did not go with the other platforms because the depth of coverage was not enough."

False negatives, especially, are "a huge issue when you get into a broad-based, lots-of-genes [method]," Penny said, adding Paradigm has no plans to do exome or whole-genome sequencing. "You just can't get the depth of coverage. And when you can't get into high numbers like 3000x [coverage], you just lose the ability to believe a negative is really a negative."
PCDx is custom designed and not based on Ion Torrent's AmpliSeq technology, Penny said.

He declined to provide details about the sample preparation or data interpretation steps for the test. Paradigm uses proprietary sample prep technologies — originally developed while he was at the International Genomics Consortium (IGC) — to enhance the percentage of tumor cells required to detect genetic abnormalities.

"And we can typically get all components of the analysis from as little as one" FFPE core biopsy, Penny said.

For data interpretation, Paradigm has developed its own informatics that enables the four-to-five-day turnaround time.

PCDx's mRNA capabilities currently are tailored for 15 broad cancer types, including lung, colon, breast, kidney, pancreatic, and ovarian cancers, among others.

The test is for solid cancers and provides actionable findings of genomic alterations, "as defined by level 1, level 2, level 3 evidence," Penny said. The test, he added, typically reports on about 115 genes "with these levels of evidence."

Paradigm chose its actionable targets based on a "comprehensive review" of the scientific literature for findings "with a level of evidence to be actionable and associated with a therapy or tied to a clinical trial that has a therapy," he said. However, Paradigm's NGS platform does "thousands of interrogations on genomic changes," and in addition to the 115 actionable targets, it provides research targets, he said.

Currently, the company can run about 80 PCDx tests per week "without breaking a sweat," Penny said. While Paradigm plans to ramp up its capacity as demand increases, at this early stage of the test's launch, it wants to limit the number of tests it processes to ensure that it can deliver its rapid turnaround time.

Initially, Paradigm is marketing the test to other non-profits in the Michigan area, such as hospitals and universities, as well as oncologists and oncology groups.

PCDx, which is performed in Paradigm's CLIA-certified laboratory, costs $4,800. It has billed insurers to reimburse for the test, which Penny said he anticipates insurers will start doing in a few months under the code covering analysis of multiple exons by DNA sequencing.

Paradigm has not yet secured approval to market PCDx in the handful of states that require licensure in addition to CLIA certification in order to offer laboratory-developed tests.
While PCDx is just hitting the market, its history is rooted in work that stretches as far back as 1999, when Penny and his colleagues were forming IGC and developed an assay using Agilent's gene expression arrays and performed it on frozen tissue.

While he was at the Molecular Profiling Institute (MPI), which he founded and where he was CEO, that test was launched as Target Now, one of the first commercially available oncology tests to use gene expression in its analysis, he said. The test is now called Molecular Intelligence and offered by Caris Life Sciences, which acquired MPI in 2007.

In addition to IGC and MPI, Penny was the corporate head of genomics at anatomic pathology service provider AmeriPath, has taught at the University of Michigan Health System, and remains a principal investigator with the Cancer Genome Atlas Project.

That collective experience, he said, taught him that in order to truly make headway in cancer care, what was needed was a personalized approach that investigates molecular pathways associated with cancer therapies.

In the summer of 2012, the University of Michigan with IGC spun out Paradigm in order to carry out that goal. They continue to fund Paradigm.

Jay Hess, currently the dean of the School of Medicine at Indiana University, is also a co-founder of Paradigm.

When the company was being formed, using next-generation sequencing as its platform technology was an obvious choice, Penny said. As part of his research through the years, Penny has used microarrays, fluorescent in situ hybridization, immunohistochemistry — basically "any analysis of value that would provide us with meaningful information as to the molecular pathways being used by the tumor and how those would relate to interventional targeted therapy," he said.

All the hype surrounding NGS, he said, is for a reason.

"It was clear to me years back as we got into the Cancer Genome Atlas Project that next-gen sequencing was a very, very important platform," he said. "The goal is [to] harness it to really look at pathways and drive pathways that are associated with therapies and clinical trials into patient care," Penny said.

Paradigm was created as a non-profit, he added, in order to free it from shareholder pressures, and to grant it greater leeway to pursue collaborations with industry, as well as other non-profit partners.
"We're really into it to help figure out where next-gen sequencing is of value and where it's not," Penny said. "The fact is that we can more freely contribute to the benefit of patient care. It's harder to do that when you're a for-profit [because] you've got shareholders."

While Penny expressed interest in eventually exploring proteomic technologies for cancer research, Paradigm's focus for now is on PCDx and adding to the mRNA capabilities of the test.

"We really are about ... helping to promote the space with more robust science, as well as [providing] the oncologist with information about their patient's cancer that's extremely specific to that cancer," he said.