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Praxis Genomics Bets on Bionano Optical Maps, Sequencing to Solve Complex Rare Disease Cases

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NEW YORK – Rare genetic disease diagnostics firm Praxis Genomics hopes to solve cases of patients who have remained undiagnosed despite multiple molecular tests, betting on a combination of Bionano Genomics optical genome maps and sequencing data.

The Atlanta-based startup was founded a year ago by molecular pathologist Peter Nagy and became operational in early July.

Nagy, who serves as the firm's chief medical officer and laboratory director, has extensive experience developing clinical genomic tests from his previous positions at Columbia University Medical Center's Laboratory of Personalized Genomic Medicine and at MNG Laboratories, which was acquired by Laboratory Corporation of America last year.

At Columbia, for example, he helped launch an exome sequencing test for inherited genetic disorders in 2013, followed by a combined exome and transcriptome test for cancer the following year. At MNG, he was involved in launching several genomic tests, including transcriptome and methylome assays, to improve the diagnosis of rare inherited neurological disorders.

With the availability of novel genetic technologies, in particular Bionano's optical mapping platform, he saw an opportunity to strike out on his own and founded a company that he hopes can serve the 50 percent or so of rare genetic disease patients who haven't obtained a molecular diagnosis despite extensive testing by classical cytogenetics, microarrays, gene panels, and exome or genome sequencing.

Large diagnostic laboratories, for the most part, don't offer patients access to this type of cutting-edge technology, Nagy said, because they are reluctant to adopt it. Reasons include a lack of reimbursement or the expertise required for the isolation of long DNA molecules. Praxis Genomics is under no such constraints because it has the expertise and will initially not rely on insurance coverage but bill institutions and patients directly for its services.

The company, which is privately funded and has a team of four full-time employees and two contractors, including former colleagues of Nagy from Columbia University, is already accepting patient samples for clinical testing after receiving CLIA certification in July. It is waiting to have its lab inspected by the College of American Pathologists, a visit that was delayed by the coronavirus pandemic but is expected to happen before Jan. 15 of next year.

The lab is currently equipped with a Bionano Saphyr instrument and became a Bionano certified service provider last month, the first CLIA laboratory to receive this designation. It also has access to an Illumina NovaSeq sequencer owned by a company next door and might in the future start using its neighbor's Pacific Biosciences sequencer, as well, or acquire its own PacBio machine.

What sets Praxis Genomics apart from other diagnostic firms that have adopted the Bionano platform, like PerkinElmer and GeneDx, Nagy said, is that it analyzes optical mapping data in combination with sequencing data from transcriptome, exome, or genome sequencing. Patients often bring their own genomic data from previous tests, or Praxis can generate it for them. Combining these data types allows the company to resolve the breakpoints of structural variants at the sequence level, Nagy explained, which can be important for the clinical interpretation. Praxis uses the Genoox analysis pipeline to interpret and annotate findings from the different technologies, he added.

Overall, the Bionano platform is especially useful for determining structural variants that don't cause copy numbers changes, he said, such as translocations or inversions, and particularly in size ranges that sequencing cannot pick up. In addition, optical mapping can determine the position of duplicated segments in the genome, which copy number data alone cannot, as well as the size of large repeat expansions. What it cannot see are large translocations of whole chromosome arms that span the centromere, he added, but which classical cytogenetics can easily identify.

As an example of a complex case his team has been able to solve using optical mapping and whole-genome sequencing, Nagy cited a patient with congenital adrenal hyperplasia with unusual symptoms, in whom they detected homozygous splice site mutations in CYP21A2, a partial duplication in that gene, and a copy number-neutral chromosomal translocation. For two other patients, with myotonic dystrophy, they identified repeat expansions in the DMPK and CNBP genes, respectively, using whole-genome sequencing, and sized the repeats by optical mapping.

Alexander Hoischen, associate professor of genomic technologies and immuno-genomics at Radboud University Medical Center in the Netherlands, said he can confirm that Bionano's optical mapping can be helpful in diagnosing unsolved rare disease patients.

So far, his team has solved or found an interesting lead for five out of 20 cases – each case consisting of a single patient, a family, or multiple independent samples – that had undergone extensive previous testing, including with CNV microarrays, exome sequencing, or genome sequencing. Bionano's unbiased genome-wide structural variant detection "shall offer improvements to routine cytogenetic tests and also allow a significant yield for unsolved rare disease patients," he said.

The tests aren't cheap, though. Praxis Genomics currently charges $2,000 for analyzing a sample with Bionano and $1,000 for a transcriptome analysis, though discounts are available for family trios and volume orders. The official turnaround time is four weeks, but most samples are currently completed within two weeks, Nagy said. The company offers not only a clinical report but also counseling services to discuss the results with patients and their doctors.

Praxis accepts samples from all over the world and has seen significant interest from countries in Asia and South America, Nagy said. For clinical diagnostics, it is currently focused on inherited diseases, including carrier testing, but it might add cancer testing in the future.

Nagy said the company is working with Bionano to generate data that will support future reimbursement of optical mapping tests. He is also confident that Bionano is committed to making its system more user friendly and amenable to regular clinical labs. Bionano's recent acquisition of diagnostics service provider Lineagen and the hiring of its first chief medical officer, he said, demonstrated that the firm "clearly made the decision that they are moving into clinical diagnostics."

Bionano itself has touted the recent adoption of its Saphyr system by clinical laboratories and hopes that forthcoming clinical validation studies will prove its value as a possible replacement for other cytogenetics

technologies.

Nagy said his goal for the next few months is to grow the company "at a reasonable pace." Ideally, he wants to acquire enough samples – about 100 a month or so – to warrant the purchase of a second Bionano Saphyr machine.

In addition to clinical testing, Praxis offers research services on the Bionano platform for scientists and clinicians who want to analyze patient cohorts. "I think Bionano has a lot of potential for diseases that have been just really stubborn, resisting finding a solution," Nagy said. "Diseases that are almost Mendelian but still, we have not found the cause. A lot of these disorders will end up being due to repeat expansions or regulatory changes due to structural variants that have just not been identified yet."

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