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Parabase Offering Dx Exome, Plans to Launch Targeted Newborn Test This Quarter

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By Monica Heger

Parabase Genomics is now offering a diagnostic exome test for rare genetic diseases and is planning to launch this quarter a targeted sequencing-based test that assesses 227 genes related to around 217 genetic disorders in newborns.

Parabase began offering its exome test, dubbed LifeTime RareDx, at the beginning of the year and uses Illumina's HiSeq 2500 sequencing platform.

The test, when billed directly to institutions, will cost $5,000. Parabase will also bill insurance companies. Turnaround time for the test is four weeks. The company also offers a clinical research exome with a two-week turnaround time.

The test includes whole-exome sequencing of the proband as well as follow-up testing in both parents with Sanger sequencing to confirm the putative findings.

Gabor Bethlendy, the company's chief commercial officer, said the firm has run around a dozen clinical cases so far for various children's hospitals, and hundreds of research samples. In the US, it has been working with the Children's Hospital of Orange County, Brigham and Women's Hospital, and Vanderbilt University. It is also receiving samples from Mexico.

Parabase returns results related to the patient's clinical presentation. It does not automatically provide incidental findings from the 57 genes recommended by theAmerican College of Medical Genetics and Genomics. However, families can request to receive those findings, as well as additional incidental findings, but they must receive pre- and post-test genetic counseling.
The firm is not the only clinical sequencing provider to not adopt the guidelines, which have sparked debate in the field. Laboratories have taken a range of responses. Some, like GeneDx and Ambry, provide information on the recommended genes as a default, but also allow the family to opt-out of receiving those results. Others, like Arup Laboratories, have adopted the guidelines in full.

PartnersHealthcare, meantime, reports not only the ACMG recommended variants as a default, but also additional variants associated with monogenic diseases, carrier status, and pharmacogenomics markers. However, it does give patients the choice to opt out of receiving any incidental findings.

"I think families struggle just to understand the basics of exome sequencing," Bethlendy said. While the families can "literally get [all the results]," he said, "we've never had that happen."

The firm does keep all the data for multiple generations, so as new discoveries are made, the data can be revisited and reinterpreted, Bethlendy said.

Thus far, Parabase's customers have mainly been symptomatic newborns. Andy Bhattacharjee, Parabase's CEO, said the diagnostic rate has been around 50 percent, but he anticipated that as the company sequenced more cases, the diagnostic rate would fall to around 30 percent to 40 percent, which is more in line with what other clinical laboratories offering diagnostic exome tests are reporting.

One early user of Parabase's test has been Brigham and Women's Hospital. Richard Parad, a neonatologist at BWH and a member of Parabase's scientific advisory board, told *Clinical Sequencing News* that the hospital has ordered two clinical exome tests for babies in the NICU. The baby in the first case presented with multiple congenital anomalies and prior to ordering the test, Parad, along with clinical geneticists, generated a list of potential disorders and candidate genes corresponding with those disorders. As it happened, the number one gene on the list turned out to be the one, Parad said. However, the baby had two mutations in that gene, one of which had never been reported before. "So, if we had gone with a hotpsot test, we would have found one mutation, but not the other," he said.

Unfortunately, the diagnosis was not a good prognosis, Parad said. The disorder itself is extremely rare and only a few cases have been reported in the literature. "We were able to tell the parents the diagnosis and that what we know from the literature, the child's lifespan is likely to be very short," he said. While the diagnosis did not ultimately point to a treatment, it "allowed for planning instead of being in the dark."

Parad said results from his second case are still being analyzed. In that case, the baby presented with hyperinsulinemia, and the physicians generated a list of eight candidate genes. A preliminary analysis of those eight genes from the exome data did not identify any mutations. Parabase is now analyzing the rest of the data, Parad said.

Being able to rule out those eight genes in one test and still have additional data to comb through is an advantage over previous methods of diagnosing genetic conditions in newborns, Parad said. Prior to next-gen sequencing, a typical course of action after coming up with the eight candidate genes would be to test those genes one by one. Each single-gene test could cost anywhere from $1,000 to $3,000, Parad said. "That's expensive and takes a long time," and in this case, would not have yielded a result, leaving the clinicians back at square one with no additional data. "In this case, we went through those first eight genes and did not find any obvious mutations," Parad said. "But there's more analysis that can be done — more genes to go through, [including] looking for deletions and copy number variations."

Parad said in both of the clinical cases he's tested with Parabase, an exome test made more sense than Parabase's more targeted LifeTime NewbornDx test. In the first case, the candidate gene is

not included in the targeted test, since it is such a rare disorder. In the second case, he said the clinical presentation was so unusual that they wanted to make sure the test was comprehensive.

Nonetheless, Parad said that Parabase's LifeTime NewbornDx test, which will initially analyze 227 genes when launched, is good for clear phenotypes where more is known about the disease and how to treat it, for instance in cases of hearing loss and inborn errors of metabolism.

Going forward, Parad said he is currently in discussion with the hospital administration about how to offer such a test. Ordering tests from providers outside of an in-patient hospital can be tricky, he said, and usually requires pre-approval, which can take time. "It's a complicated and time consuming process," he said.

These first two experiences have initiated discussions about how to set up a more streamlined protocol for ordering these types of genetic tests. One option that is being discussed, he said, is to develop a contract with a vendor for a certain number of tests. Hospital clinicians will have an annual number of tests they can order without going through the evaluation process. "We're not there yet, but heading down that road," he said.

Targeted test

Parabase intends to launch its LifeTime NewbornDx test this quarter, which will be targeted both to babies in the NICU and those in outpatient clinics. The clinical test will cost $4,500 and currently has a turnaround time of four weeks. It will also be offered as a clinical research test for $3,500 with a two-week turnaround time.

Currently, the firm is running samples on the HiSeq 2500. However, Bethlendy said the company would likely transition the test to the MiSeq, and it is also working on ways to reduce the turnaround time to one week by the end of the year.

The test includes 126 genes related to newborn screening disorders, 84 hearing loss genes, seven genes related to failure to thrive disorders, eight hypotonia genes, and two hepatosplenomegaly genes.

Bethlendy said that although deafness is not a life-threatening condition, like the other genetic disorders included in the test, early diagnosis of a genetic predisposition can result in better outcomes. Additionally, newborns admitted to the neonatal intensive care unit are sometimes given antibiotics that can exacerbate hearing loss if the baby has certain variants.

Eventually, Parabase will expand the test to include around 500 genes, which Bethlendy said would capture around 80 percent of newborns in the NICU with a suspected genetic disorder. The firm plans to use the LifeTime NewbornDx test as an initial test for babies in the NICU with

suspected genetic disorder. If the test comes back negative, those patients will reflex to the exome test, Bethlendy said.

Bethlendy said the company has two papers that it plans to submit to peer-reviewed journals and the test has demonstrated 99 percent sensitivity at 200x average sequence coverage.

One aspect that sets Parabase's test apart from others is that sequencing can be done from as small a sample as a dried blood spot collected on filter paper. The test can also use as little as 1cc of blood and can be run on DNA extracted from saliva, according to Bhattarjee.

Small sample size is especially important for babies in the NICU because a "newborn in crisis doesn't have much blood to give," Bethlendy said. Such babies may weigh only 1,200 kilograms and an exome or whole-genome test currently requires around 3 to 10 milliliters of blood.

He said a rapid test that can provide actionable results is critical for newborns in the NICU because "if you don't help them in the first one to two weeks, they are in a pretty bad state."