Clinical NGS Market in China Poised to Take Off as China FDA Looks to Establish Guidelines

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Premium

NEW YORK (GenomeWeb) – The clinical next-generation sequencing market in China is poised to take off, according to experts in the field. Noninvasive prenatal testing currently makes up the majority of NGS-based clinical tests, but preimplantation genetic screening and diagnosis and cancer testing are close behind, and strides are being made in rare disease testing as well.

The market is "moving very fast," Sijia Lu, CEO of Yikon Genomics, told GenomeWeb. "Two years ago, almost no hospitals were using" NGS. Now, most hospitals in major cities have NGS capacity and many offer NIPT, he said.

Last year, in response to the rapidly growing field, the China Food and Drug Administration decided that genetic tests must be approved, essentially halting the field. Companies had to stop offering their clinical NGS assays and submit applications to the CFDA for clearance of the NGS instrument and assay itself.

So far, CFDA has approved three NGS instruments — BGI's BGISEQ-100 and BGISEQ-1000, along with its noninvasive prenatal assay, NIFTY, and Berry Genomics' NextSeq CN500 along with its NIPT assay. In addition, China's National Health and Family Planning Commission has granted approval to BGI to conduct cancer sequencing services. It runs a cancer test branded under the name Oseq in China and Sentis in Europe, which sequences over 500 cancer genes.

And recently, the CFDA launched a pilot program by which certain hospitals could offer clinical NGS-based tests as the regulatory body seeks to establish guidelines that would function similar to CLIA in the US or CE marking in Europe, enabling laboratories to offer clinical tests, despite not being cleared by the CFDA.

China does not have the equivalent of CLIA-certified laboratory developed tests, so when the CFDA decided to regulate the genetic testing market, companies had to stop offering their clinical assays.

Now, with the implementation of the pilot program, test developers can once again offer clinical NGS tests in partnership with specific hospitals that have been licensed by the government, Daixing Zhou, CEO of Berry Genomics, told GenomeWeb. Zhou said that the Chinese government has licensed just over 100 hospitals to implement sequencing-based tests on a trial basis.

The National Health and Family Planning Commission grants licenses to the hospitals in one or more of four specific fields: preimplantation genetic screening and/or diagnosis, NIPT, oncology, and genetic disease, Zhou said.

Test developers then partner with the licensed hospitals to offer tests that are run in the hospitals' own laboratories.

"It is kind of an intermediate stage," Zhou said, between research and CFDA approval. There is no set time frame on how long the program will last, and there is still uncertainty on whether the pilot will eventually become a permanent way that developers bring their NGS tests to market.

Yikon Genomics' Lu told GenomeWeb that he thinks the program will be a way for China to develop its own CLIA-like system to set "specific criteria of what is needed to set up a clinical lab."

Pilot program participants

BGI, Berry Genomics, Yikon Genomics, WuXi NextCode, and Novogene are among the test developers participating in the clinical sequencing pilot program.

BGI's Shenzhen Clinical Laboratory and Tianjin Clinical Laboratory have licenses for the pilot program, BGI spokesperson Bicheng Yang told GenomeWeb. The firm now offers a range of tests in China either through the pilot program or that are already CFDA-approved, including its NIFTY NIPT, a 500-plus cancer gene assay, a hereditary ovarian and breast cancer assay, PGS/PGD, and a newborn screening assay for genetic diseases.

Already, she said, BGI has accessioned more than 700,000 NIFTY tests, since its launch around four years ago.

Yang said the tests run on various platforms, including BGI's two cleared platforms. In addition, she said that BGI is developing a benchtop version of its sequencing platform based on Complete Genomics' technology, BGISEQ-500. Yang said BGI plans to launch its NIFTY test on this platform, which will be able to analyze between 16 and 192 samples per run. The system will include "built-in automatic analysis software," she said, which will enable turnaround time from library construction through data analysis to be done in 24 hours.

Berry Genomics is another main provider of NIPT in China. Because its test is CFDA-cleared on the NextSeq CN500, the company can offer the test to any hospital or clinic, not just those that are participating in the pilot program.

Zhou told GenomeWeb that the firm is also developing other NGS-based tests. Most recently, it launched a PGS test for couples undergoing IVF. For this test, it will work with hospitals within the pilot

program licensed to offer PGS. Berry's PGS test can analyze single cells or a few cells extracted from an embryo. It screens for copy number variations that are 1 mb or larger, which includes aneuploidies — the most common cause of IVF failure. He said that the firm developed its own whole-genome amplification technique to increase uniformity and reduce bias, which it intends to publish in a peer-reviewed journal.

Aside from reproductive health, Berry Genomics is moving into the oncology field and plans to develop a circulating tumor DNA assay, Zhou said. He said Berry Genomics would present results of a clinical trial of the ctDNA assay at the China Society of Clinical Oncology meeting, which began this week in Xiamen. In the trial, Zhou said he compared the ctDNA assay's ability to assess EGFR mutations in lung cancer patients with assays performed from tissue biopsies. Overall, the ctDNA assay demonstrated 96 percent concordance to tissue biopsy, depending on the volume of blood drawn. From just 2 mL of blood, concordance was around 90 percent, he said, but when 4 mL or more of blood was drawn, concordance was close to 100 percent.

Meantime, Yikon Genomics is offering PGS and PGD testing of embryos for couples undergoing *in vitro* fertilization through China's pilot program.

Separate from the pilot, it is also in the midst of a clinical trial at Peking University for couples undergoing IVF and seeking genetic screening because one of them is a carrier of a known Mendelian disease. Last year, the first healthy baby was born to a couple in which the father suffers from hereditary multiple exostoses, an autosomal dominant disorder characterized by multiple bony spurs or lumps on the bones.

Lu said that around 200 patients have enrolled in the clinical trial, which he expects will run through the end of 2016.

Yikon currently runs its tests on Illumina's HiSeq 2500 and MiSeq instruments, which do not have CFDA approval. Lu said that within the pilot program, tests can be run on any NGS platform, but he thinks that in the future there may be "new regulations on specific platforms that can be used in clinical sequencing." For instance, the CFDA may require that the hospitals and developers licensed to participate in the pilot run the assays only on the cleared instruments.

Yikon's PGS test screens for chromosomal aneuploidies, while the PGD offering looks for specific single-gene diseases such as sickle cell anemia and alpha and beta thalassemia. The PGS/PGD tests use a whole-genome amplification technique developed by Sunney Xie's group from Harvard University called MALBAC.

Recently, Yikon also developed a noninvasive prenatal screening test and is moving into the liquid biopsy field as well, although PGS/PGD remains its main focus, Lu said.

Lu said the company is working with both circulating tumor DNA as well as circulating tumor cells, and the firm also is looking to develop an assay that can serve as a way to monitor patients' progression or drug response or to provide guidance on therapy selection.

WuXi NextCode and Novogene are two of the newer clinical NGS providers in China that began primarily as sequencing service providers, but have since begun to transition toward offering clinical

tests.

WuXi NextCode was launched in January of this year when WuXi PharmaTech, which provides lab and manufacturing services for biopharmaceutical and medical device customers, acquired informatics firm NextCode Health. WuXi merged NextCode with its genome center to form WuXi NextCode, which is headquartered in Shanghai.

Earlier this week, WuXi NextCode said it would collaborate with the Children's Hospital of Fudan University to offer whole-genome and exome sequencing to diagnose pediatric rare diseases.

Hannes Smarason, co-founder, president, and COO of WuXi NextCode, told GenomeWeb that these services were part of the CFDA's pilot program for clinical sequencing. Fudan University has been licensed for rare disease testing, Smarason said, and the testing will be done both at WuXi NextCode's genome center as well as at CHFU itself. Ultimately, CHFU "wants the capability to do the testing," Smarason added. "So, the analytical systems and software will be housed there and [CHFU] will perform the interpretation there with experts from WuXi NextCode," he said.

Smarason said that WuXi NextCode is also "continuing to explore" the path toward CFDA approval for its diagnostic exome and genome offerings.

Novogene is China's latest clinical NGS entrant, focused primarily on the oncology market. Last week, the firm told GenomeWeb that it had submitted cancer panel tests to the CFDA for approval.

Decentralized and lower cost

One interesting development in the clinical NGS market in China has been the huge interest by hospitals to run the NGS tests themselves, rather than sending patient samples to the diagnostic developers for testing.

Berry Genomics' Zhou told GenomeWeb that when the company first launched NIPT, it offered it as a service. Increasingly, however, Zhou said that the company is selling the assay and sequencing instrument as a kit.

CFDA approval of Berry's assay and the NextSeq CN500 has helped "enable hospitals to do NIPT on their own," Zhou said. "The hospitals are now taking on the effort of building their own [sequencing] labs," he said, which has caused Berry Genomics to begin to "transform from a pure service provider to more and more product based."

Zhou said the company sells the reagent kits for DNA extraction, library prep kits, sequencing instruments, and its in-house developed software.

Currently, he said, Berry is about half service-based and half product-based. Diagnostic tests provide revenue for hospitals, Zhou said, so although the hospitals don't have the resources to develop the tests themselves, they do have the motivation to buy the instruments to run the tests, and having CFDA-approved NIPTs is enabling the hospitals to get a clinical sequencing lab established.

Yikon's Lu said that the PGS/PGD market would similarly become more product-based. Larger centers

and hospitals offering PGS/PGD will likely "buy their own machines," he said, and test developers such as Yikon would "provide a standardized procedure for them to run the test." Smaller centers, however, that do not have as many IVF cycles would likely continue to send their samples out.

Clinical NGS tests also seem to be priced lower in China than comparable tests in the US. For instance, Yikon's tests range from less than 2,500 RMD ($396) for NIPT, to 3,000 RMD ($471) for PGS and 3,500 RMD ($550) when PGD is included, Lu said.

Berry Genomics has similar prices for its NIPT, although costs vary city to city, Zhou said, and range from 1,700 RMD ($267) to 2,500 RMD ($396).

By contrast, Sequenom, Illumina, and Natera launched their tests at prices well over $1,000, although the companies have not disclosed whether prices have come down. Last year, Ariosa contracted with some payors as an in network-provider at a rate of $795.

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