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Insights

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China's Next-Generation Sequencing Market – State of Implementation

The rapid pace of advanced technology adoption in China and the presumed need for local ties to achieve commercial success is evident by the number of strategic alliances that have taken place recently in the area of Next-Generation Sequencing (NGS). While the majority of NGS end-users in China are primarily research institutions, NGS is a disruptive technology and has the potential to play a prominent role in the clinical diagnostic space.

Helping to transition NGS technology to the IVD market in China is a large population (>1.3 billion people) and growing economy with a focus on increased health care access. Current areas of NGS technology application include Non-Invasive Prenatal Testing (NIPT) along with oncology and Human Leukocyte Antigen (HLA) testing. All markets are in various early stages of development without an entrenched firm or leader in China, but commercial activity by Multi-National Companies (MNC) is increasing with the goal to position themselves early and to take advantage of China's investments in health care and related technology.

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Penetration remains a challenge due in part to technical issues with NGS, but with increasing local competition, it is becoming evident that a local network of credible partners will be essential in establishing significant market leadership in China.

China's Next-Generation Sequencing Market

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The rapid pace of advanced technology adoption in China and the presumed need for local ties to achieve commercial success is evident by the number of strategic alliances that have taken place recently in the area of Next-Generation Sequencing (NGS). Technical hurdles and other challenges associated with the implementation of NGS, not the least of which are physician education and bioinformatics, will have to be overcome to accelerate technology adoption.

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Clinical Applications

To date, the China Food and Drug Administration (CFDA) (formally known as the SFDA) has yet to approve any NGS system for IVD use, but cell-free fetal DNA (cfDNA) based Non-Invasive Prenatal Testing (NIPT) is one of the initial clinical uses for NGS that is gaining adoption. Other applications of interest are in the Oncology Testing and HLA Screening markets.

Non-Invasive Prenatal Testing

By the end of 2013, the top two China firms offering NGS-based NIPT are expected to have conducted a combined total of more than 250,000 prenatal screenings since their respective launches, whereas the U.S.-based Sequenom performed its 100,000 prenatal screening in April 2013 with a 2011 launch. Companies that offer NIPT services continue to perform clinical trials demonstrating the effectiveness of using cfDNA for genetic screening purposes as they move toward widespread government approval. Currently, the U.K.-based Public Health Genetics Foundation has teamed up with Professor Dennis Lo (the discoverer of cfDNA in pregnant women) from the Chinese University of Hong Kong in the world's first formal NIPT clinical trial. According to the National Coalition for Health Professional Education in Genetics and the National Society of Genetic Counselors, NIPT can detect at least 99% of all pregnancies with Trisomy 21 (Down's Syndrome). Other serological screening methods only detect 85-95% of fetuses with Trisomy 21 and have a false positive rate of 3%-6%. Amniocentesis and CVS directly assess the chromosome constitution of the fetus, but are associated with increased risk of miscarriage or other adverse pregnancy outcome.

The China government has a national prenatal Screening Policy focused primarily on Trisomy 21. According to a 2009 article in Modern Preventative Medicine (Ke-sheng *et al.*), the incidence of Trisomy 21 increased significantly in China over the 1997-2004 time frame (from 2004-2007 there has been a non-statistically significant decrease) with evidence indicating pregnancies at an older maternal age and environmental pollution may be the underlining causes. Additionally, China's one child policy, poised for change, places a greater emphasis on Trisomy 21 screening than other countries. While currently only serological-based prenatal screening is partially reimbursed (newborn screening is fully reimbursed) and FISH-based screening is recommended for women that are more than 10 weeks pregnant (according to new management rules for prenatal screening and diagnosis announced by the Beijing Municipal Bureau Health in November 2012), NIPT has become more widespread and is offered by laboratories such as BGI, Berry Genomics, and a limited number of commercial laboratories (see below). There is a large fee associated with such tests (RMB 2,500-3,500; approximately $395-$554 per test) and patients must pay in full, providing physicians with personal incentive for ordering them. Growth of NIPT and of firms like BGI and its partners was so rapid that local media has started to question the practice of profiting from IVD testing that employs unregulated and unapproved tests. However, the City of Shenzhen, Guangdong Province, recently announced a three-year (2013-2015) initiative to support Non-Invasive Prenatal Testing (NIPT) in the area. Effective May 21, 2013, any local pregnant woman can receive a RMB 600 ($95) government subsidy for each NIPT test performed at four area hospitals, including Shenzhen People's Hospital, Shenzhen Second People's Hospital, Shenzhen Maternal and Child Care Center, and Peking University Shenzhen Hospital. To further assist local women with NIPT, the local government established a supplemental maternal care insurance fund for the local residents. Any woman who enrolls in this program needs to pay only RMB 705 ($112) for each NIPT test.

Oncology

Oncology represents another opportunity for NGS to have a clinical impact. Cancer therapeutics are necessary to extend life and usually expensive, driving the need for diagnostics that can deliver actionable treatment decisions. Improvements in turnaround time will be critical to cement adoption of NGS for oncology testing. While the China NGS Oncology market has yet to take shape, initial applications will likely be in the form of screening panels of known oncogenes since they are cost and resource efficient compared to whole genome sequencing. Longer term, NGS will likely have clinical implications in tumor profiling for gastric cancer given it is the most common cancer type in Asia. While the mortality rate of gastric cancer has dropped in North America and Europe, it has remained high in East Asia. Gastric tumors are highly heterogeneous with each patient exhibiting a distinct genetic profile requiring personalized

therapy. Prior sequencing studies performed in China employing NGS technology have indentified genetic candidates for gastric cancer drivers, but these studies had small sample sizes with limited statistical power that was compounded by sample heterogeneity. However, two consortium projects, the Cancer Genome Atlas and the International Cancer Genome Consortium, have been systematically characterizing different cancer types and both are in the process of profiling gastric cancer with the aim of discovering novel therapeutic targets.

Human Leukocyte Antigen

China now has the second-largest demand for organ transplants, according to China's Ministry of Health. About 300,000 patients suffer organ failure each year, but only 10,000 transplants are performed annually due to a lack of donors. In the U.S., about 28,000 organ transplants occur annually. HLA sequencing provides opportunities for the use of NGS in improving the transplant success rate as the technology progresses and makes it easier to sequence one of the most complex regions of the human genome. A total of 165 hospitals across China have been cleared to conduct organ transplants.

Competitor Discussion

With increased prosperity, the China government has placed an emphasis on health care spending. This spending is on display in the construction of a 10 square mile medical research center in the city of Taizhou, given the moniker "China Medical City." More health care spending in conjunction with other government policies, notably the 1979 one child policy to control population growth and a national prenatal screening program, has created an attractive environment for the implementation of advanced diagnostic technologies, including NGS. This has resulted in several strategic alliances and partnerships involving domestic companies and MNCs that offer NGS. Currently, in descending order, Illumina, Life Technologies, and Roche/454 Life Sciences dominate the RUO market for NGS testing in China.

Select MNCs

Illumina has the largest installed base in China with BGI alone accounting for approximately 8% of Illumina's global HiSeq installed base with a purchase of 137 instruments in 2010. In April 2013, Illumina entered into an agreement with Kindstar, the largest esoteric test provider in China. Under the agreement, Kindstar will validate and implement Illumina's NGS-related TruSight content set, Infinium DX CytoSNP-12 assay, and NuPCR reagents. This deal increases Illumina's local footprint as Kindstar services more than 3,300 hospitals across China from its centralized laboratories in Beijing, Shanghai, and Wuhan. In addition, the following month, Kindstar entered into another NGS-related agreement with Metabiomics to license and distribute a microbiome-based screening test for colon polyps and colorectal cancer; testing is performed on Illumina MiSeq instruments.

Life Technologies (in the process of being acquired by Thermo Fisher) has worked to establish a local footprint in China, but with far fewer Ion Torrent placements than Illumina HiSeq instruments. In March 2013, Life Technologies announced the CFDA had approved its Sanger-based Applied Biosytems 3500xL Genetic Analyzer (a 24-capillary system) and the launch of 10 assays from a joint venture with the China company DaAn Gene. Life Technologies showcased its 3500Dx sequencer (an eight-capillary Sanger system), the Ion Torrent, and the DaAn Gene joint-ventured assays at the 10th National Congress of Laboratory Medicine in Xi'An, Shaanxi Province in early May 2013. Assays included genetic test kits for virus resistance gene testing (HBV, HCV, TB, and HIV/AIDS), companion diagnostics for targeted cancer therapy (EGFR and KRAS), tumor susceptibility gene testing (BRCA1/2 and TP53), and prenatal screening (only the Sanger-based Trisomy 21 prenatal screening test is CFDA-registered). The joint venture has completed clinical trials for most of the developed assays in five Level IIIA (Tier One) hospitals, for use on the 3500Dx or 3500Dx XL.

In Q2:12, Life Technologies announced that it had acquired a distributor in Northern China and established a Global Center of Excellence in Singapore. The acquisition of the consumables distributor, Beijing Maojian United Star Technology Company, creates a more effective supply channel in the region. The facility in Singapore addresses strong customer demand within and outside of the Asia Pacific region. Asia Pacific is one of Life Technologies' key regional growth drivers with sales growing +9% for 2011 in the region (excluding Japan), according to the company. The center will design and manufacture NGS and other molecular diagnostic instruments; this facility is Life Technologies' only instrument manufacturing facility outside of the U.S.

China Companies

Local Laboratory Service Companies

Beijing Genomics Institute (BGI) is the strongest competitor in the China market and the largest sequencing provider in the world. BGI generates revenue from fee for service sequencing from both research and clinical institutions with revenue surpassing 1 billion RMB three years running ($158 million). More specifically, BGI Health, the branch of BGI that offers the NIPT services with its NIFTY test, had revenue of RMB 140 million ($22 million) in 2012 compared to RMB 20 million ($3 million) in 2011, according to Entrepreneur Magazine. BGI partners with ~200 hospitals in China and several health care facilities around the world to conduct NIPT services. As of June 2013, it has completed nearly 140,000 NIPT tests screening for Trisomy 13, Trisomy 18, and Trisomy 21.

BGI has been looking to expand both in and out of China and has been aggressively pursuing strategic alliances and acquisitions to meet these goals. In March 2013, BGI completed its acquisition of the whole genome sequencing company Complete Genomics for upwards of $118 million (an 18% premium). Although Complete Genomics will operate as an independent company, the deal does afford the opportunity for BGI to expand into the U.S. market. Prior to this, BGI had entered into partnership deals with prenatal service providers in Czech Republic, Hungry, Turkey, Dubai, Singapore, and Australia.

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Berry Genomics is the second most prominent China company in the NGS space and is partnered with over 300 hospitals around the country. Berry Genomics launched the NIPT BambniTest in 2011 for RMB 3,400 per test ($538) and has a current turnaround time of 10 days. As of February 2013, it had conducted 50,000 NIPT tests using Illumina's HiSeq 2000 technology with total volume expected to exceed 100,000 by year end. The founder and CEO of Berry Genomics formerly worked for Solexa (later acquired by Illumina), who sold the first Illumina product (first-generation sequencer) to BGI.

Local Diagnostic Equipment Manufacturers

HYK Gene Technology Company (revenue of RMB 17.6 million; $3 million in 2011) was established in 2008 and is claimed to be the only China company with proprietary NGS technology. Its PSTAR-II, PSTAR-IIe, and SeqExpert-IIIA were released in 2010, 2011, and 2012, respectively. These technologies have short read lengths but offer flexibility in sequencing reaction with multiple DNA polymer labeling options and combinations (Table A). In addition to manufacturing, HYK Gene Technology Company also operates its own genetic testing facility.

Agene Bioinformative Technologies is smaller and less known than HYK Gene Technology Company. It was founded with an initial investment of RMB 7 million ($1 million) in 2008 with the goal of developing NGS products for both research and clinical purposes. In 2011, two AG-100 NGS products were placed at BGI.

••• *Conclusion* •••

Technical hurdles and other challenges associated with the implementation of NGS, not the least of which are physician education and bioinformatics, will have to be overcome to accelerate technology adoption. The workflow is difficult to manage and often resource constrained. Laboratory quality control measures need to be adopted to track sample identity and to recognize which are to be overcome to accelerate technology adoption; this applies equally to China as to the sample-preparation failures and failed sequence runs. Sample preparation and processing will have to become more standardized, allowing for greater ease-of-use. A large amount of data is generated with NGS, and ethical concerns regarding who has access and storage remain. The reimbursement status also remains ill-defined to date.

Adoption of NGS technology in China is occurring steadily, driven by the implementation of NIPT. MNCs are aligning with relevant service laboratories as well as identifying credible, local academic and manufacturing partners to position themselves for future market growth, the expectation being that NGS use will soon expand beyond NIPT and gain traction in oncology and HLA testing.

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