Genomics technologies march into new markets

Next-generation sequencing platforms are building market share not only in the research setting but also increasingly in population research and clinical applications.

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The first human genome cost $3 billion and took 13 years to sequence; today such an undertaking costs closer to $1,000 and takes only days, making large-scale genetic analysis feasible and affordable. Short- and long-read sequencers have become established workhorses in biomedical research, and their use is now expanding into clinical applications and beyond. Most notably, the combination of high-throughput genotyping with measurements of other markers of health and disease is opening up the area of precision medicine (PM).

Current research market

Over the past couple of years, Illumina, a global specialist in genetic analysis technologies, has introduced a broad portfolio of sequencers "that has allowed the company to expand its leadership position, build barriers to entry and accelerate the penetration of clinical markets," said Cantor Fitzgerald's Bryan Brokmeier, senior VP of equity research. "The company now has an estimated 80% share of the ~$2.3 billion sequencing market, which we expect to grow into the tens of billions of dollars over the next decade." The company has seen record growth in the past couple of years, fueled by sales of sequencing machines, as well as companion reagent kits for the hardware.

Thermo Fisher Scientific has the next largest slice of the sequencing market share. It offers two platforms; SOLid and Ion Torrent. Instead of nucleotides, the SOLid system uses fluorescently labeled probes that are repeatedly ligated to the lengthening strand, optically imaged and then cleaved off. The Ion Torrent platform uses unlabeled nucleotides on a semi-conductor chip, which senses the release of hydrogen ions when bases attach. Neither technology has seriously threatened Illumina's dominance in the market; in fact, market share for these two platforms shrunk from 2013 to 2014 according to Genome Web.

The other major instrument providers include Pacific Biosciences, Complete Genomics and Oxford Nanopore Technologies. Pacific's single-molecule real-time sequencing technology reports read lengths of more than 10,000 base pairs. The long reads enable full characterization of the complexity of intergenic DNA sequences. In October 2015, Complete Genomics will launch its first commercial product, the Revolocity system, which is based on a two-adaptor, 300-base-pair insert and mate-pair sequencing of 28 bases in DNA nanoballs. It offers end-to-end sample preparation (genomic DNA, blood or saliva), sequencing, analysis, automation and workflow integration. In March 2013, Complete merged with BGI-Shenzhen, after BGI purchased Complete's outstanding shares for $3.15 per share. Complete continues to operate as a separate wholly owned subsidiary.

Oxford Nanopore's MinION, a device the size of a USB stick, uses protein nanopores to sequence single-stranded DNA, using changes in electrical current to identify bases. In 2014, the technology became commercially available, and in July 2015, the company raised $109 million in new funding. Elsewhere, Roche, after scrapping a partnership with IBM in nanopore sequencing, got back in the area, acquiring nanopore developer Genia Technologies in a deal worth up to $350 million including milestones and investing in another startup, Stratos Genomics, which labels each of the four bases with unique reporters that are 50-fold larger, thereby generating robust signals in a nanopore-based detection system.

In the past year, these long-read technologies have also been joined on the market by instruments that convert short reads into synthetic long reads. One example of this is Illumina's Moleculo; more recent examples are developed by 10X Genomics and Dovetail Genomics.

Population sequencing

Although next-generation sequencing (NGS) platforms have become an established tool in the research arena, a highly anticipated area of growth in the research market is the large-scale genotyping of populations. In 2012, UK Prime Minister David Cameron announced a project to sequence the genomes of up to 100,000 people and use their genomic information in treatment and studies of cancer and rare diseases. The project, to be run by Genomics England, a company established by the UK Department of Health in July 2013, has contracted with Illumina to provide the instruments and infrastructure for sequencing and data analysis pipelines (this summer the company opened SeqLab, a service to help labs new to population-based sequencing).

In June 2015, four companies were selected to work on interpreting genomic data from the first 8,000 patients participating in the project: WuXi NextCODE for interpreting variants found in individuals with both cancer and rare diseases, Congenica and Omicia for rare-disease interpretation, and NantHealth for oncology. The study will last 3 years; if it is successful, Illumina anticipates that it will lead to an expansion of the effort to sequence a greater proportion of the UK population.

In the United States, the White House announced the Precision Medicine Initiative at the end of January 2015. This initiative is somewhat similar to the Genomics England project, but it plans to study the whole genomes of 1 million individuals in order to improve health outcomes. Several sequencing companies are seeing opportunities for growth as other governments begin to

PRECISION MEDICINE TOOLBOX

Next-generation sequencing platforms can answer questions related not only to the exome or genome but also to the transcriptome and epigenome of any organism. Sequencing methods differ in terms of how samples are obtained and the data analysis involved.

Whole-genome sequencing (WGS)

WGS detects the 3.2 billion bases of the human genome. The ability to sequence large cohorts is now a reality, and WGS will enable deeper understanding of the regulatory and other features in the human genome, as well as meaningful interpretations of whole genomes. WGS is also important for agriculture and microbial genomes.

De novo sequencing

This method refers to sequencing of a novel genome for which there is no available reference sequence for alignment. The quality of the data depends on the size and continuity of the gaps in the data.

Whole-exome sequencing (WES)

WES captures only the protein-coding part of the genome. Representing less than 2% of the human genome, WES is a cost-effective alternative to WGS. It is used for many applications, including investigating genetic disease, population genetics and cancer studies.

Transcriptome sequencing

This method creates a biological snapshot of expressed genes by capturing RNA and converting it to cDNA before sequencing. RNA sequencing can focus on mRNA, small RNA, noncoding RNA or microRNA, depending on the steps included before cDNA synthesis.

Epigenome sequencing

Epigenome sequencing investigates heritable changes in gene activity caused by environmental factors, such as DNA methylation and acetylation, DNA–protein or RNA–protein interactions, small RNA-mediated regulation and histone modifications.

adapt population-sequencing projects like those of the United Kingdom and the United States.

The interest in carrying out these population-based studies has grown from clinical research projects that have integrated sequencing into trial design. For example, a multi-institutional amyotrophic lateral sclerosis (ALS) sequencing project at the New York Genome Center, funded by the ALS Association and the Tow Foundation, aims to integrate WGS data with other genome-scale data, such as RNA sequencing data, to understand the relationships among mutations, gene expression and mechanisms of disease. In August 2015, Biogen, the ALS Association and Columbia University Medical Center announced a new collaboration aimed at better understanding how genes influence the clinical features of ALS. This project, which currently includes 1,500 people with ALS, is the first to combine NGS and detailed clinical phenotyping with the hopes of ultimately enabling a PM approach for ALS. According to David Goldstein, director of Columbia University's Institute of Genomic Medicine, "It is likely that the most important contribution of PM is not so much matching patients with the right treatments, but rather using the technologies of PM to create entirely new avenues into understanding the basic biology of disease and using that knowledge to create entirely new points of intervention."

Another project is the Alzheimer's Disease Neuroimaging Initiative, which since 2004 has been validating the use of biomarkers and MRI/PET for clinical trials and diagnosis in individuals with Alzheimer's disease (AD). The initiative involves an unprecedented policy for sharing pre-competitive data access to increase the rate of discovery. Plans to add whole-genome sequencing (WGS) for 800 participants with AD will result in the most comprehensive way of looking at AD yet.

These are just a sample of the type of human research studies under way. They not only promise a continued growth in demand for sequencing platforms but also have provided the groundwork for what is perhaps the impetus for crossing the rubicon to clinical practice.

Moving into diagnostics

Companies are going after the clinical sequencing market on two different fronts. First, they are moving their instruments through US Food and Drug Administration (FDA) clearance. In 2013, the FDA cleared Illumina's MiSeqDx system; this helped spur record demand for the MiSeq, including for both cleared and research-use-only versions. Illumina and other sequencing companies have plans to obtain 510(k) clearance for assays for sequencing platforms, primarily in oncology practices.

Second, sequencing-based diagnostics are also being developed. The two early growth markets are oncology (including cell-free DNA tests) and noninvasive prenatal testing. Large pharma company Roche is directly investing in the NGS and diagnostics areas. "With capabilities in both diagnostics and pharmaceuticals, Roche uses a personalized approach to diagnose and treat various cancers. Our diagnostic tools are also used to help manage treatment," said Dan Zabrowski, head of Roche's sequencing and tissue diagnostics units. He added that the company has "diagnostics specialists involved in every project in our drug discovery portfolio, searching for the biomarkers needed for a personalized health care approach." In 2013, Pacific partnered with Roche to develop, commercialize and license diagnostic products for clinical use based on Pacific's technology in a deal worth up to $75 million in up-front and milestone payments. In 2015, in addition to a majority share in Foundation Medicine costing $1 billion plus milestones, Roche bought Signature Diagnostics, with the aim of using its blood plasma and tissue oncology biobanks to develop circulating cell-free DNA tests.

At the end of 2014, Roche acquired Ariosa Diagnostics and its prenatal-testing portfolio. The previous year Illumina had begun noninvasive prenatal screening with its acquisition of prenatal test maker Verinata. It also launched its VeriSeq sequencing technology for pre-implantation embryo screening. Many of the sequencing companies anticipate growth in this market as their platforms are expanded to average-risk women, a market six times larger than the current high-risk genetic defect market.

Growth has been relatively slow in the diagnostic space because businesses face some serious headwinds in today's legal, regulatory and reimbursement environments. Diagnostics has always been a low-margin business, and resource-constrained payers are accustomed to treating them like cheap commodities. What's more, many companies must provide clinical data showing that a new diagnostics test contributes to better clinical outcomes before reimbursement is offered. All of this is in addition to an uncertain regulatory future, even though the FDA recently unveiled its controversial laboratory-developed test guidance. As a result, companies such as Foundation Health have built a substantial clientele in the pharma industry to hedge against the difficulties of obtaining reimbursement and approval for their tests.

Companion diagnostics and PM

Pharma companies are increasingly interested in using sequencing in drug development, primarily for oncology, although other indications are gaining interest. Initially, pharma companies used sequencing primarily for discovery, and mostly outsourced the sequencing to contract research organizations. As time has passed, instrument providers, such as Illumina, and diagnostic companies using sequencing, such as Foundation Health, have increasingly pivoted their businesses to provide services to big pharma, particularly around companion diagnostics, which is moving toward sequencing.

According to the Tufts Center for the Study of Drug Development, 73% of cancer compounds are now studied in the context of biomarker data, and 42% of compounds across all indications employ biomarkers. What's more, investment in personalized medicine is projected to increase by 33% in the next 5 years.

In 2014, Thermo Fisher announced a partnership with Nuclea Biotechnologies to accelerate methods to quantify type 2 diabetes markers. The company has also entered into an agreement with GlaxoSmithKline and Pfizer to develop a universal NGS oncology test for solid tumors that will serve as a companion diagnostic for multiple drug programs. A similar program in oncology was announced in the same year by Illumina, partnering with AstraZeneca, Janssen Biotech and Sanofi.

Companies such as Stephen Fodor's Cellular Research are also using NGS and barcoding to provide a sensitive single-cell genomics platform that provides information on cellular heterogeneity. Cellular Research published the results of their work with this type of platform earlier in 2015; the company already has one confidential large pharma interaction.

Challenges for the future

The real ambition of PM, said Goldstein, "is in transforming the way we develop new medicines." He also believes that "other technological drivers will be in genome editing and stem cell biology, since they together create a clear pathway for *in vitro* models of many human diseases."

Many current challenges exist to further commercial development of sequencing platforms, including ensuring cohorts represent our natural diversity, managing large consortia, questions facing drug regulatory agencies, grappling with new technologies, shifts in intellectual property protection, as well as physician and patient education.

Genomics is helpful for determining predispositions and, in some cases, the utility of certain drugs, but for the vast majority of clinical cases and patients, it will be measurements of real-time health status that will become central for determining individualized treatment. Sam Sia of Columbia's Biomedical Engineering Department and cofounder of biotech incubator Harlem Biospace observed, "Technologies for monitoring individuals' health are becoming increasingly available, especially with consumer electronic devices moving into health measurements. The devices currently measure mostly vital signs, but it is inevitable they will move into blood tests and portable imaging in the future." Consumer diagnostics provider Theranos has a commercially available platform for cheaper lab tests that can detect up to 30 conditions using only drops of blood. The tests are offered through retail pharmacies and are covered by a number of payors.

What is clear is that NGS is already establishing itself in clinical markets such as oncology and reproductive health, in population research and in companion diagnostics. But there are a whole raft of underexploited opportunities yet to be tackled, not only in understanding the role of genetic variation in areas of human disease outside of cancer and childbirth, but also in animal health, crop genotyping and breeding, infectious-disease detection (including food and water testing) and forensics, all of which suggest buoyant commercial prospects for these technologies.

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