Oxford Gene Technology Expands NGS Offering Into Constitutional Cytogenetics

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NEW YORK – Oxford Gene Technology recently rolled out its first next-generation sequencing product for constitutional cytogenetics research. The company believes cytogeneticists will adopt its panel to get high-quality single nucleotide variant (SNV) and copy number variant (CNV) data in a single assay.

"I think today, in terms of an informative result, arrays are only giving a small proportion of the results for the samples being tested," said Emma Shipstone, executive vice president of marketing at the Oxford, UK-based company.

Instead, Shipstone said, many labs are relying on a variety of reflex tests – sequencing or fluorescence *in situ* hybridization, for instance – to explore leads picked up on array platforms. These, however, are pushing laboratory costs up.

By enabling users to get the SNV and insertion/deletion data that they would from a sequencing assay, along with the CNV and loss of heterozygosity data that they obtain from arrays, they can therefore simplify workflows and reduce costs.

"If you can get that from one assay, rather than two, or three, or five, that is obviously much more efficient from everybody's perspective," said Shipstone.

That is the concept behind the firm's CytoSure Constitutional NGS Panel, which includes content selected for intellectual disability and developmental delay research. It targets more than 700 genes at the exon level, with a backbone of coverage across the genome, and OGT designed the panel for use with the Illumina NextSeq or NovaSeq instruments. The package includes hybridization capture baits, a library preparation kit, and the firm's CytoInterpret software for analysis.

OGT has served the constitutional cytogenetics market for years, both through its line of CytoSure microarrays and its menu of CytoCell FISH probes. But many of its customers want to transition to sequencing while retaining the quality of the CNV and LOH results they get on the company's chips, in part because, as noted, they want to cut down on assay costs.

"Everyone is under cost pressure, and they want as much performance from their assays for the most reasonable price possible," said OGT CEO John Anson. "By combining the SNV calling and CNV calling into a single assay, there are some cost benefits." Anson declined to discuss pricing.

OGT has also already gained experience in developing NGS panels for cancer. In 2015, the firm rolled out a number of panels for oncology research and it has continued to serve that market. Earlier this month, for example, it launched the SureSeq CLL + CNV Panel to support research into chronic lymphocytic leukemia. The know-how gained from launching such products has allowed OGT to develop a tool that can meet the needs of the constitutional cytogenetics community.

"This has been incubating for a long time," said Anson. "We got started in NGS, got a lot of experience in cancer, and we have taken that experience and broadened it out into the constitutional world."

The company's deep array background also helped. OGT was founded in 1995 to oversee the patent estate of microarray innovator Edwin Southern. The company began to build its array business in 2005, quickly carving out a role for itself in the constitutional and cancer cytogenetics space. That expertise continues to inform its new sequencing products, Anson said.

"The knowledge that we gained over a couple of decades in terms of designing probes for arrays can be used to design probes for next-generation sequencing," said Anson. "It can be used for hybrid capture, for pulling down the areas that we want to sequence," he said. "It's that capability that we've really brought forward into the constitutional area."

It is this knowledge that allowed them to improve CNV calls as well as to preserve LOH data in the new assay. "That is the piece we have really focused on in terms of our R&D effort, our computational biology effort, is to get that CNV calling to be at the same quality, same level, as is seen with our arrays, particularly our version 3 arrays," said Anson.

Shipstone said that it has been this lack of quality of CNV and LOH data that has stalled the adoption of sequencing by the constitutional cytogenetics community. "I think that's why today, next-generation sequencing technologies haven't overtaken arrays for this," she said, "because people are not able to get really robust, single-exon CNV calling from their sequencing data."

Shipstone said the firm's experience from both arrays and its SureSeq NGS panels allowed the firm to optimize its probe design to give uniform coverage regardless of sequence and location. "GC-rich [regions] are usually particularly tricky and through our work both in silico and empirically optimizing these baits, we have been able to improve performance compared to others," she noted.

Another aspect to achieving this performance has been the firm's software algorithms. OGT has designed its own algorithm for calling CNVs from sequencing data, so its innovation was both in the wet lab as well as on the software side. It then rolled these new tools into its existing CytoSure Interpret software architecture, meaning that cytogenetics customers can implement the new panel and look at data as if nothing significant had changed.

"If people are used to looking at array data on CytoSure Interpret, they will immediately get the same look and feel from our NGS platform," said Anson. "The CNV data is presented in exactly the same way, so it gives them immediate comfort that what they are seeing is analogous to what they were seeing before."

Users can also compare back and forth between array and sequencing data and do internal validation using CytoSure Interpret.

One early adopter is Sian Corrin at NHS Wales' All Wales Medical Genomics Laboratory in Cardiff, UK. According to Corrin, whose title is constitutional section lead, the lab uses a variety of technologies in its services, including array comparative genomic hybridization, G-banding, fluorescence *in situ* hybridization, and a range of sequencing-based tests.

The lab has been taking part in a beta trial of OGT's new panel, and Corrin said that its experience with both arrays and sequencing technologies allows it to better assess new tools.

"Evaluating new tests, such as this new panel, is an important part of making sure we are providing the best possible service for patients," said Corrin. "As the NHS, we use millions

of products and suppliers, each of which is regularly evaluated for quality and performance and goes through a robust procurement process to ensure we get the best available product or service to suit the needs of our patients," she said.

So far, Corrin said the lab has been "satisfied" with the performance of OGT's panel.

"The feedback from the technical teams undertaking the wet lab work is that the workflow is much improved compared with previous panels from OGT," said Corrin. "The teams undertaking the analysis have reported that there is good concordance with CNVs and SNVs previously detected using other tests," she said. "We intend to continue to further evaluate this panel."

A 'credible player'

While introducing an innovative product was an objective for OGT, another catalyst for the company has been staying ahead of the curve in what continues to be a volatile market marked by multiple players and ongoing technology upgrades. According to Shipstone, the company intends to launch more sequencing panels around constitutional cytogenetics in the coming years.

"This is around us being a credible player in NGS across the different areas we work in," said Shipstone. "We certainly foresee expanding the portfolio, using the capabilities we developed during the development of this product."

Anson noted that it also allows OGT to raise its profile as the go-to partner for customers, who can now get their FISH probes, arrays, and NGS panels from one provider. "FISH is still used massively around the world for cytogenetics, we've got the array platform, and now we've got NGS," he said. "So if you want to continue with FISH or transition to arrays or NGS or do all three, we are a one-stop shop in terms of being able to supply that."

OGT currently employs around 130 people worldwide and is growing, Shipstone noted. The company was sold to Sysmex, a Japanese *in vitro* diagnostics company, in May 2017.

Anson noted that OGT continues to work with Sysmex on projects that involve OGT's next-generation sequencing capabilities. "Being part of Sysmex, a major focus is around personalized medicine," Anson said. "We are now part of that journey and are incorporated into those efforts around ensuring the technology is as good and robust as possible."

Shipstone also noted that OGT is prepared to meet its customers' needs even now that the UK has exited the European Union. "We have been working extensively from both a supply chain and distribution network perspective and also very closely with our customers to ensure we have been prepared for any uncertainty around Brexit," said Shipstone.

According to Shipstone, these efforts have included ramping up manufacturing and stockpiling raw materials internally and finished goods in distribution hubs outside the UK, so that customers won't be impacted and will have a continued security of supply in the event of any disruptions.