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The Clinical Aspirations of Microarrays

Although most microarray applications are currently research-use-only, this technology appears poised to move to the clinic for genomics-based applications. In fact, some products can already be used in medical diagnostics and many more are in development. For example, microarrays can be customized to detect small, specific genetic changes that indicate a particular disease. In the future, this technology will likely remain a useful tool for both research and clinical applications.

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In today’s translational genomics research, says Seth Crosby, alliance director of the Genome Technology Access Center at Washington University School of Medicine in St. Louis, “The biggest challenge is interpretation.” Available technology makes it easy enough to collect information from someone’s genome. The tricky part comes in interpreting the clinical relevance of that information. “Then, one can say a variation in a particular gene is known to have such and such impact on the patient’s health or treatment options,” Crosby explains.

As an example, Crosby describes a clinically certified next generation sequencing panel of 45 oncology genes offered by Genomics and Pathology Services, Washington University’s clinical genomics laboratory. This panel is actively being used to profile tumors and guide the treatment of cancer patients. “We had to look at hundreds of papers,” Crosby says, “to build a clinical-grade database of authoritative interpretations for each clinically relevant mutation found in these genes.” He adds, “That took hundreds of Ph.D. and M.D. hours, reading through papers to identify the pertinent information.”

Crosby notes that, over time, clinicians might come to understand which changes in the genome impact a patient’s health and which are harmless. “Once the lists of relevant and irrelevant genes are narrowed down, and we have a sense of which polymorphisms are important, these could be used to create a very cheap array that would help detect diseases,” he says. Beyond being economical, microarrays also deliver manageable amounts of data. As Crosby explains, “Much of the genome is invariant.” So with microarrays, he says, “We collect only the data we need.”

Developing Diagnostics

In some cases, clinicians can link specific chromosomal defects with particular diseases, and microarrays bring new capabilities to this karyotyping, or counting and assessing the appearance of chromosomes. Down syndrome is one of the best-known examples, in which the person has an extra copy of chromosome 21. Although additions or deletions of entire chromosomes, and even defects in parts of them, can be seen under a microscope, microarrays reveal fine-detail changes in chromosomes. “Using microarrays as tools in cytogenetics is really accelerating,” says Andy Last, executive vice president of the genetic analysis business unit at Affymetrix in Santa Clara, California. When experts are asked in which areas microarrays are being used the most, many mention copy-number variation—the addition or deletion of specific regions of DNA, particularly those with clinical consequences.

“There are literally hundreds of syndromes [that have] chromosomal rearrangements associated with a particular phenotype,” says James Clough, vice president, clinical and genomic solutions at Oxford Gene Technology (Oxfordshire, United Kingdom). “Depending on the population being tested, traditional karyotyping under a microscope provides a diagnosis about 5–8 percent of the time, and a microarray provides an 18–25 percent diagnostic yield. The resolution is far higher with an array.” Still, he adds, “The challenge is determining if a small aberration is pathogenic or nonpathogenic, or a variance of unknown significance.”
To help researchers make such distinctions, Oxford Gene Technology supplies a range of microarrays, such as the CytoSure ISCA Arrays, which look for genetic defects involved with known syndromes, such as Prader-Willi and Williams-Beuren syndromes.

PerkinElmer (Waltham, Massachusetts) has also developed assays for distinguishing 15 kinds of tumors. Pathwork Diagnostics have identified a set of 2,000 genes that can be used to distinguish a tumor’s gene-expression profile. Using several thousand different transcripts and proprietary computational algorithms, researchers can perform robust statistical analyses which can reveal differences in the distribution of genetic variation between normal and diseased populations.

Creating Custom Tools

To apply microarrays to clinical problems, physicians need approved tools. One FDA-cleared diagnostic tool, the Pathwork Tissue of Origin test from Pathwork Diagnostics in Redwood City, California, uses an Affymetrix microarray to determine the tissue type in which a patient’s cancer started, such as breast or colon. Raji Pillai, senior director, product development and clinical affairs at Pathwork Diagnostics, says, “This test uses formalin-fixed, paraffin-embedded [FFPE] tissue from a patient’s tumor and 2,000 transcript markers to provide a readout of a tumor’s gene-expression profile.” Using several thousand different tumor specimens and proprietary computational algorithms, researchers at Pathwork Diagnostics have identified a set of 2,000 genes that can be used to distinguish 15 kinds of tumors.

When a pathologist receives a cancer sample that is difficult to identify visually, they can send it to Pathwork Diagnostics. “It takes four to five days to report out a result that’s interpreted by a pathologist in our lab,” says David Crawford, the company’s chief commercial officer. A company pathologist reviews the results to ensure the most accurate interpretation of this diagnostic.

In the future, the company hopes to develop microarray tests that determine a tumor’s tissue of origin and also distinguish between tumor subtypes. Such advanced tests might even “provide information on the [patient’s] predicted response to a particular therapy,” Crawford says.

In addition to being used for studying an individual’s genetic profile, microarrays can be used to explore genetic variations across different populations and cultures. For example, Jennifer Stone, market development manager at Illumina in San Diego, California, says, “We developed our Infinium HumanCore BeadChip family of microarrays to provide a solution for population-level or biobank studies.” Such research involves tens to hundreds of thousands of samples. “These genetic studies are on a scale above and beyond what’s historically been done,” says Stone. Because these microarrays accommodate a large number of samples, they provide an opportunity for researchers to perform robust statistical analyses which can reveal differences in the distribution of genetic variation between normal and diseased populations.

The HumanCore microarrays provide a standard set of over 300,000 SNP probes, which covers the entire genome and includes additional probes specifically focused on variants that exist in the population and lead to the loss of function of genes,” explains Stone. These new microarrays can also be customized, so researchers can study variants found in their own experiments or from public databases.

To explore genetic variations across entire populations, researchers need a family of flexible microarrays. Thus the second member of the HumanCore family, the Infinium HumanCoreExome BeadChip, includes the standard set of over 300,000 SNP probes plus 240,000 exome-focused markers. With this combination of markers, a scientist can compare single nucleotide variations between samples and potentially determine how they impact a protein’s production, as indicated by the exome-based markers.

As companies begin to create increasingly customized microarrays, there is a growing challenge in determining if a small aberration is pathogenic or nonpathogenic, or a variance of unknown significance.”
to continue on a microarray platform as you get closer to the clinic or transition to a more suitable and robust technology, such as [quantitative] PCR or sequencing.”

In a recent project, Expression Analysis worked with a client who had what Hurban describes as “a preliminary gene-signature panel that was very useful as a diagnostic in a certain indication area.” Researchers at Expression Analysis worked with patient samples from the sponsor to put that signature on microarrays. “We showed the validity of this panel,” Hurban says. “Ultimately, the sponsor wanted to turn this signature into a diagnostic and became concerned with the microarray results because the precision was a bit of a challenge.” Consequently, the client eventually turned to a PCR-based platform for the final diagnostic. As a result, Hurban says, “You might use a microarray to some point, and then go to another technology.”

**Tomorrow’s Tools**

The ongoing advances in sequencing technology have made more than a few experts predict the demise of microarrays. For example, Elizabeth Chao, director of translational medicine at Ambry Genetics in Aliso Viejo, California, says, “The expression arrays that I’ve been using for 14 years are incredible tools, but RNA sequencing is starting to replace microarrays in research and translation.” She adds, “Sequencing is not replacing microarrays in the clinical setting yet, but it probably will soon.”

The data generated by sequencing can be both beneficial and challenging. Sequencing provides a gigantic amount of data in a short period of time, but it can be difficult to interpret so much data. Chao is confident that interpreting sequencing data will improve rapidly. She says, “Bioinformatics has really come up, and new methods are making it possible to look at sequences across the entire genome.”

To evolve with changes in technology, some companies provide services that teach researchers to use the growing amounts of data. For example, Todd Smith, senior leader, research and application at PerkinElmer, says, “We can help people as they go from microarrays to DNA sequencing.” This can include analytical techniques for handling the higher volume of data. These technologies, though, will likely complement each other, according to Smith and his colleagues. “There are applications where microarrays work best, and others where sequencing works best,” says Williams. “There are areas where sequencing won’t work well, but microarrays can.” As an example, Williams says they are about to start a study that involves 160 samples that must be processed in a matter of weeks. “There’s no way we could go through that with sequencing and get it turned around in time to have meaningful data,” he says. Moreover, Smith says microarrays are superior to sequencing when it comes to searching for structural variations in a genome.

Though some experts may have differing opinions, the general consensus predicts that microarrays will continue to benefit basic research and provide clinical tools related to genomics. In the end, microarrays will advance where they work the best.

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Mike May is a publishing consultant for science and technology.

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In a weakened global economy, many countries have begun to limit their investments in the future. Yet, investments in innovations — including funding for education as well as basic and applied research — represent our best prospect for a sustainable environment and increased economic growth. Economists estimate, after all, that innovation in science and technology are the source of more than half of the economic growth in many countries. By increasing innovation in sustainable products and processes, world economies can continue to enhance human welfare across society.

Innovation springs from the translation, production, and distribution of discovery and invention to society. In the contemporary world, this is not a linear process, but rather, a matrix of interactions. Societies, with support from public and private sectors and institutions, struggle to integrate the necessary disciplines and interests into this matrix. Within the scientific and engineering community, we need to better integrate different disciplines and voices into a consensus supporting innovation. Developed and developing countries that accomplish this will become the economies of the future.

At the same time, it is imperative that we work in ways that are transparent and open to a diversity of contributors and ideas. Assessing risk versus benefit in adopting an innovation is complex and depends upon an open dialogue. Only then will we realize the promise of furthering scientific discovery and innovation to meet pressing global challenges and improve quality of life.

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