

Executive Summary

Sequencing the human genome triggered the development of new research modalities, such as DNA microarray technologies, which contributed to a partial shift from hypothesis-driven to discovery-driven life sciences research. Early efforts in “omics”-driven research appeared to quickly and painlessly uncover new multi-analyte biomarkers that promised pharmaceutical companies and physicians enhanced information content and utility. In response to this promise, a variety of multiplex assay technologies were commercialized as delivery vehicles for the routine analysis of large numbers of samples for these biomarkers. When, say, five or more analytes need to be assayed, it is generally wise to use a multiplex technology. For fewer analytes, parallel single assays suffice. Both situations are covered in this report.

In the intervening years, relatively few multi-analyte assays have found their way to diagnostic laboratories or to large Phase III clinical trials. However, they have proven highly useful in applications where they can provide useful information without users having to go through expensive, time-consuming, large-scale assay validation studies. Multi-analyte assays are particularly useful in preclinical development for both safety and efficacy-related studies. Although predictive toxicology using multiplex biomarkers has not yet become a prevalent modality, it has shown great promise and should gain in influence during coming years.

All major pharmaceutical companies have significant biomarker discovery and implementation programs, and a few are quite serious about personalizing medicine through use of companion diagnostic assays. Since pharmas are generally not experienced in the commercialization of such assays, they have tended to establish collaborations of various types with biomarker discovery, technology platform, and integrated in vitro diagnostic companies.

Many of the assays that have surfaced to date are of the single-analyte variety. Multiplex or multi-analyte transcriptomic assays for breast cancer prognostication have been on the market for several years now. Following their introduction, at least two companies have begun offering transcriptomic assays for determining the tissue origin of malignant tumors. Few additional examples of commercially available multiplex or multi-analyte assays exist, yet a number of companies appear to be pursuing new ones. For example, Satoris believes they have discovered a multiplex protein assay for early diagnosis of Alzheimer's disease, and Ridge Diagnostics has evidence for the utility of a protein panel diagnostic for a major depressive disorder.

Essentially all major pharmaceutical companies have translational medicine functions in one form or another and all center to a large degree on employment of biomarkers as guides to early drug candidate attrition, predictive toxicology, patient selection for clinical studies, and companion diagnostics. Two companies stand out in their efforts along these lines: Novartis and Lilly (although at least a few others are likely to have effective programs with less public visibility). Novartis has increased the number of candidates entering early trials by following a strategy focusing on drug candidates for indications that are well understood mechanistically, but may not themselves constitute large markets. Success with these compounds then encourages diversification into related disease areas. Lilly stresses the development of a biomarker strategy for all programs, and at some point the determination is made whether a diagnostic test needs to be associated with the drug. A number of programs already have such diagnostics in use or in development.

The market for multiplex “omics”-based analysis remains active and vital. The three leaders in the DNA microarray market sector—Illumina, Affymetrix, and Agilent—have been impacted to various degrees by economic conditions, but all have sufficient new products and applications to assure continued vitality in the DNA-based assay sector. Affymetrix is late to the market with low-level multiplexing capability, but is rushing to catch up after its acquisition of True Materials' relevant technologies. Illumina has had such technology available for some time now, but has come to rely for much of its growth on next-generation sequencing technology, which appears poised to capture significant market share in the transcriptomics sector once informatics issues become stabilized. Next-generation sequencing has opened a new market for DNA microarrays via applications to capture particular genome segments in situations where less than a whole genome is to be sequenced.

DNA microarray technologies divide into two-dimensional and encoded bead categories. Agilent and Affymetrix feature the former, while Illumina has taken over market leadership while offering the latter type. NanoString, a spin-out from the Institute for Systems Biology has generated great excitement and market activity with its no-amplification technology for quantitative “digital” detection of hundreds of genes. The technology features imaging after capture on a surface to detect labels and identify codes.

Several companies, Randox, Theranostics Health, and Aushon Biosystems for example, offer multiplex protein analysis systems, but the clear leader in the field remains one of the earliest entrants, Luminex. Luminex has adopted a kind of “Intel Inside” strategy, which allows other systems providers and biomarker companies to license their core encoded bead technology for commercialization.

Mass spectrometry is highly useful in the discovery of protein biomarker panels, but has found limited use in routine detection of such panels in multiple biological samples. Sensitivity, speed, and lack of parallelism remain key issues in this regard. In the area of metabolomics, mass spectrometry is the major approach to routine analysis, but the same issues limiting multiplex protein assays apply here as well. In fact, despite some key advantages relative to other “omics”, the multiplex metabolite field has failed to develop markedly.

Ultimately, it is complexity that limits the number of validated multiplex biomarkers. In the early days of clinical diagnostic medicine, a large number of biomarkers entered routine medical practice. These largely had relatively direct and obvious connection to particular organ pathologies and disease states. They might be considered the low-hanging fruit of diagnostic medicine. Later, the introduction of new biomarkers came to require an extensive and time-consuming effort in an era of greater regulatory participation. Some examples are: CEA (carcinoembryonic antigen), PSA (prostate-specific antigen), and CRP (c-reactive protein). Each has value, yet is far from ideal of “yes it does, no it doesn’t.” For multiplex or multi-analyte biomarkers from which results are processed through some algorithm to give a diagnostically meaningful score, complexity is multiplied many-fold. Variabilities of each assay contribute to the overall variability of the score, and different analytes in the biomarker may respond differently to variations among test subjects. Consequently, it becomes difficult to capture the anticipated enhanced information content from viewing multiple parameters simultaneously.

Yet some early examples have survived and are currently used in medical practice. More assays are in advanced stages of validation, and at least several can be expected to enter active medical practice in the near future. Regulatory ambiguities and timing issues have so far limited their direct use of multiplex biomarkers in Phase III clinical studies, however industry observers believe that here too relief is on the way and examples can be expected to emerge in the next several years. As for new medical modalities in general, it is not surprising when general adoption is much slower than anticipated.

A survey of people working in the biomarker and translational medicine fields in big pharma, biopharma, CROs, and academic/non-profit institutions indicated growing interest in utilization of multiplex biomarkers in translation medicine, with the caveat that the complexity of validation tends to limit their use versus single-analyte biomarkers, especially in later development stages.