CSO VIEWPOINT: **STEVE ANDERSON**

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Significant advances have been made in the identification and utilization of biomarkers to guide clinical development of new therapies. Most pharmaceutical trials today are biomarker-driven. Drug developers recognize that incorporating a predictive biomarker into trial design results in about a threefold greater likelihood of success advancing from early stage trials to approval of the therapy.

Biomarkers may be exploratory in nature, or they can be used to stratify patient populations, or be used as an inclusion or selection criteria in specific trials. Biomarkers might be genomic or proteomic in nature, ranging from tissue-based biomarkers in oncology to soluble biomarkers in neuro-degenerative disease, like Alzheimer's disease.

Biopharma companies are moving away from simpler SNP analysis to identify more complex genetic alterations such as gene amplification and deletions that have implications on disease progression and drug resistance. Similarly, in proteomics, interest is shifting from single proteins / receptor immunohistochemistry (IHC) to next generation IHC using multiple tags to look at post-translational modifications. Metabolic technologies are gaining traction, particularly in immuno-oncology where the microbiome may have a major influence on disease progression and metabolites may act as surrogate biomarkers.

In oncology today, many drugs have received accelerated or breakthrough therapy designation; and the registration of trials that have been traditionally a Phase 2 trial, so we're seeing approvals based on smaller populations, and then often a commitment to do a follow-on trial. By selecting the population using a specific biomarker, you're actually potentially decreasing the population size that would be needed to power your trial. Moreover, not all patients respond to immuno-oncology drugs, but there's a series of biomarkers like deficiencies in mismatch repair, micro satellite instability or tumor mutation burden, that will potentially help differentiate and be more directive in a personalized approach in a tumor-agnostic fashion.

The trend in biomarker assays is increasingly less invasive, from traditional tissue biopsy approaches to today's liquid biopsy and circulating tumor cell applications – requiring smaller patient samples and sample sizes, enabling serial sampling for early detection, disease monitoring and drug resistance, and in some cases, are less costly to run. At the same time, we're seeing a paradigm shift from one assay / one drug to multi-analyte assays / multiple drugs, such as multiple gene mutations as measured by NGS. These new technologies and assay validation studies have been more complex for both test developers and the FDA but they hold great promise.

Taken together, advances in technology and biomarker identification help to provide a better categorization of disease and a more targeted approach to therapy, to achieve better patient outcomes.

COMPANION DIAGNOSTICS

The clinical and financial implications of utilizing biomarkers are profound – demanding a deep knowledge of disease biology, relevant targets, a drug candidate's mechanism of action and the ability to determine the appropriateness of a companion diagnostic (CDx) co-development approach. In 2018 we observed the 20th anniversary of the first companion diagnostic, which coincided with the launch of Herceptin. Now there are more than 40 CDx available across some 25 therapies.

Companion diagnostics offer significant benefits and value, helping streamline clinical studies and enabling clinicians to identify patients most likely to respond to treatment (and thereby increase patient response rates), helping to avoid unwanted side effects and minimizing wastage in non-responsive patients. These are important tools for pharma companies to differentiate their medicines and facilitate access to them via favorable pricing and reimbursement.

At LabCorp / Covance, we view the path from exploratory biomarker to CDx as a continuum, rather than discrete, sequential steps. Regulatory considerations for what might ultimately become a CDx inform early stage trial design. Drug developers can't afford to get to the tail end of a long, expensive clinical development process only to learn that a key regulatory step is missing, delaying the launch and getting the Rx / Dx combination to the patients who need it.

Access to the CDx – simultaneous with drug launch – is essential. It needs to be on a platform that laboratories routinely use. Value and cost are important factors, as well as scientific and clinical evidence, for the uptake of the technology. Currently, in vitro diagnostic regulations, product requirements and quality management systems vary across Europe, North America and Asia-Pacific, but many regulators are working to align guidance and approval processes.

Precision medicine is both the present and the future of our approach to drug development. There will be an increasing appreciation for other types of biomarker assays that may not be predictive but still add value as complementary diagnostics, which help clinicians understand the potential benefits and/or risks to the patient of a given therapy. We are at the cusp of an entirely new cascade of biomarkers that will be useful in managing a patient's disease.