The Biomarker to Companion Diagnostic Continuum

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The Role of Biomarkers

Biomarker is a term that is broadly used to describe a variety of features of cells, tissue types or organisms relevant to a biologic process – whether that be an understanding of basic biology, disease processes, cellular function and/or defining targets for therapeutic intervention. Just as there is a diversity of potential applications for biomarkers, the analyte of interest may also reflect the diversity of biomarker type and may be genetic, proteomic or metabolomic in nature.

Biomarkers in Drug Development

When we focus on the role of biomarkers in support of the drug development process we consider several potential uses, including pharmacodynamic and pharmacokinetic assessments, determination of the mechanism of action of a new therapeutic, understanding of prognostic factors relevant to the course of disease, or predicting response to the new therapeutic. These applications are outlined in **Figure 1** which categorizes the role of biomarkers into the assessment of the drug target, evaluation of the mechanism of action of the new therapeutic or the impact on the modification or progression of disease.

Drug development and the associated clinical research activities in today's world are very much driven by the need for a comprehensive biomarker strategy. Studies have shown that the likelihood of success for a new molecular entity increases from approximately 9% to greater than 25% when a biomarker strategy is incorporated into the development program.[1] In recent years that has resulted in >40% of the approved new therapeutics having a personalized, biomarker driven approach.[2]

Biomarkers as Companion Diagnostics

Arguably, the best use of a biomarker is when it is incorporated as a companion diagnostic for a new therapy, with the assessment of the biomarker a necessary requirement for the safe and effective use of that new therapy. The value and importance of companion diagnostics has been demonstrated »

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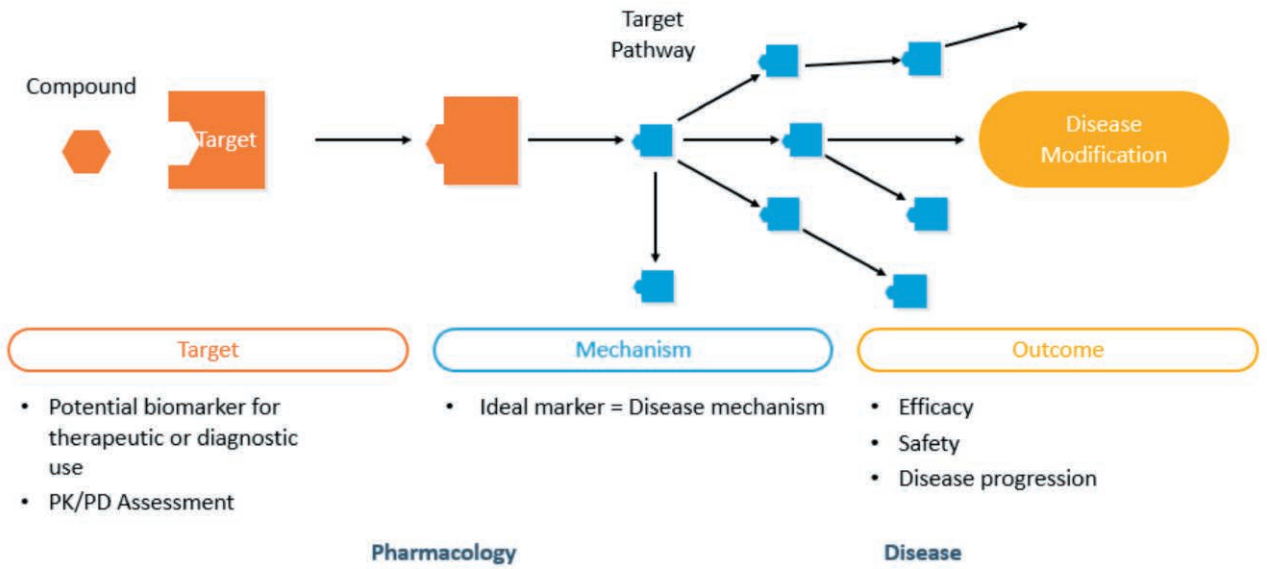


Figure 1: Utility of Biomarkers Throughout the Drug Development Process

first and foremost in Oncology, where 98% of the current companion diagnostics have their use.[3] As the biology of disease(s) becomes better defined in other non-oncology areas, through the identification and validation of appropriate biomarkers, we will see the interest in companion diagnostics expand into other therapeutic areas like neuroscience, immunology and rare diseases.

Strategic Considerations for the Use of Biomarkers

A well-conceived biomarker strategy includes elements such as the choice of the appropriate technology platform for the assay, the indication for the use of the biomarker, a fit for purpose validation strategy for the biomarker assay, a detailed regulatory strategy that allows for the rapid transition from an exploratory assay format to one suitable for use in a clinical trial, and finally a commercialization strategy for the introduction and marketing of the diagnostic assay. In this article we will highlight the key features that facilitate that approach, considering the continuum from the early development of a biomarker assay all the way through the potential use as a companion diagnostic. A partnering approach involving all parties- biopharma, diagnostic developers, and service providers-is an effective way to evaluate the therapeutic pipeline and biomarker candidates to best evaluate which therapy may be addressed through a potential companion diagnostic.

Evolution of Technologies and Platforms for Biomarker Evaluation

In the last decade we have seen a rapid evolution in the technologies that are used in biomarker assay development. These changes have driven new approaches around assay platforms and development strategy, providing a better match with the complexity of the biology of the specific disease state. Currently, there is a rapid shift from single analyte evaluations on platforms such as the polymerase chain reaction (PCR), immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH), to multiplexed assays such as next generation sequencing (NGS) and comprehensive proteomic technologies. In today's environment, both for clinical trials and within the clinic, adoption of multiplexed technologies such as NGS has been somewhat limited for reasons not related to the analytical performance of the tests but more by factors such as access to testing and reimbursement. In addition to technical advancements, we are also experiencing a transition to less invasive sample collection technologies, along with the convergence of imaging and therapeutic delivery methods.

The interplay of these assay technology and sample collection advancements also requires adjustments in our planning for how biomarker assays are developed to support both drug development and diagnostic applications. The importance of the assessment of germline and somatic variants in human cancers has grown in parallel with the ability to use information obtained by NGS methods for both tissue and plasma. For example, mutation analysis from the plasma of cancer patients, via a "liquid biopsy", provides not only a less invasive method to obtain information about the patient's tumor and thereby

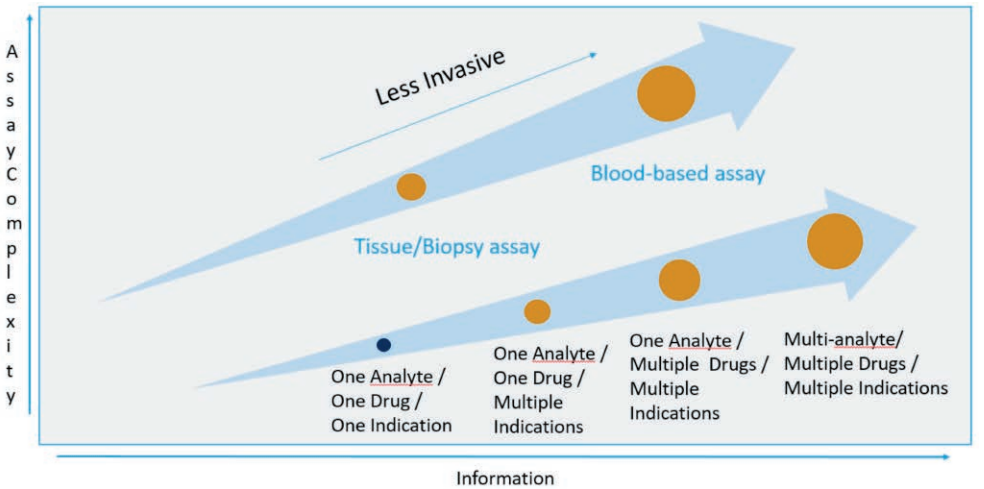


Figure 2: Technology and Informatics Evolution of Biomarker Assays and Applications

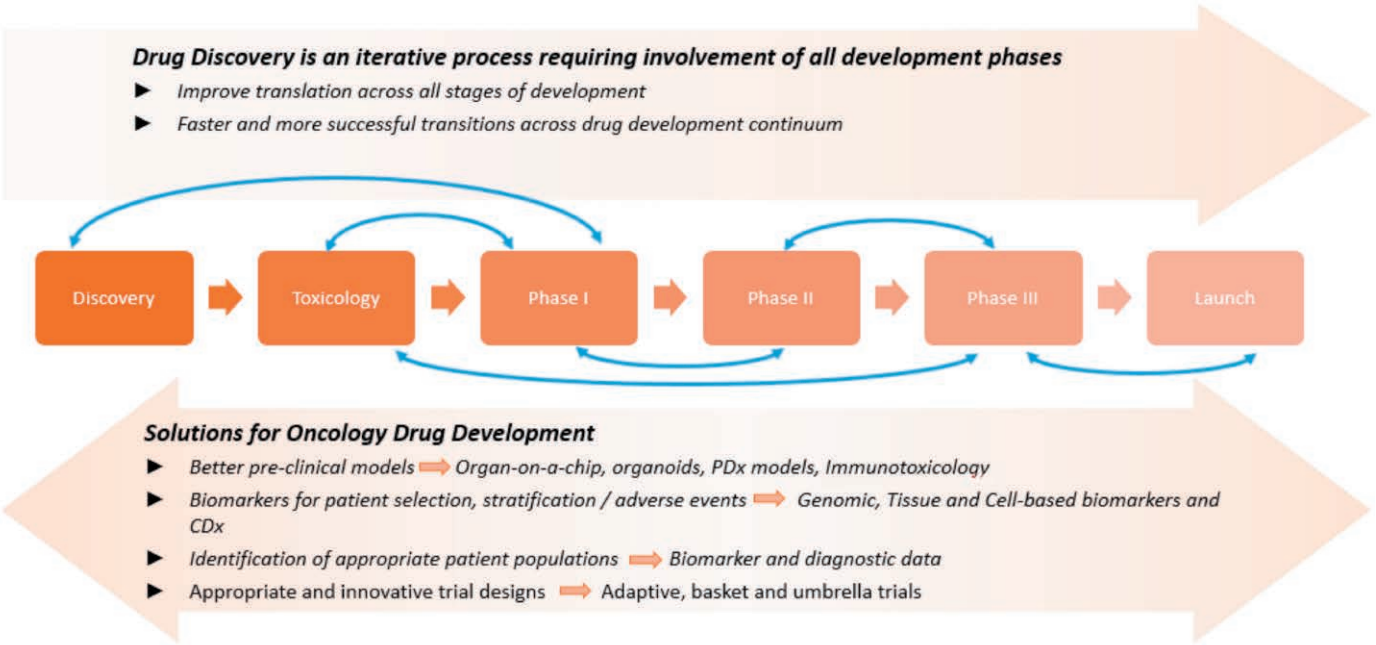


Figure 3: Iterative Approach to Drug Development

guide therapy, but also facilitates the means to measure response and confirm minimal residual disease.[4] Proteomic and cell-based assessments of biomarkers in the blood has long been a staple for the evaluation of disease recurrence, but now has also been validated for use in the measure of response to treatment and potential adverse events in areas like oncology and cell-based therapies.[5]

Multiplexed technologies provide increased information and in doing so are also impactful for how we analyze and interpret the data sets in the context of the biology of disease, the selection and monitoring of therapeutic approaches for individual patients. The interplay of these components in the evolving technology and data arena are summarized in **Figure 2**.

Biomarker Strategy for Drug Development and Diagnostics

The focus on biomarker-driven drug development has also necessitated changes in how clinical trials are planned and executed. We have seen a shift from a linear model (preclinical-first in human-phase 2/3-registration-post marketing) to an iterative model (see **Figure 3**). The iterative model involves a more fluid process that is based on findings at each stage of the development process, and how the data can be used to refine hypotheses and reinitiate the program at the right phase in the development spectrum.

This iterative approach with mechanisms to revise the development process has been piloted in areas like oncology and immuno-oncology, where

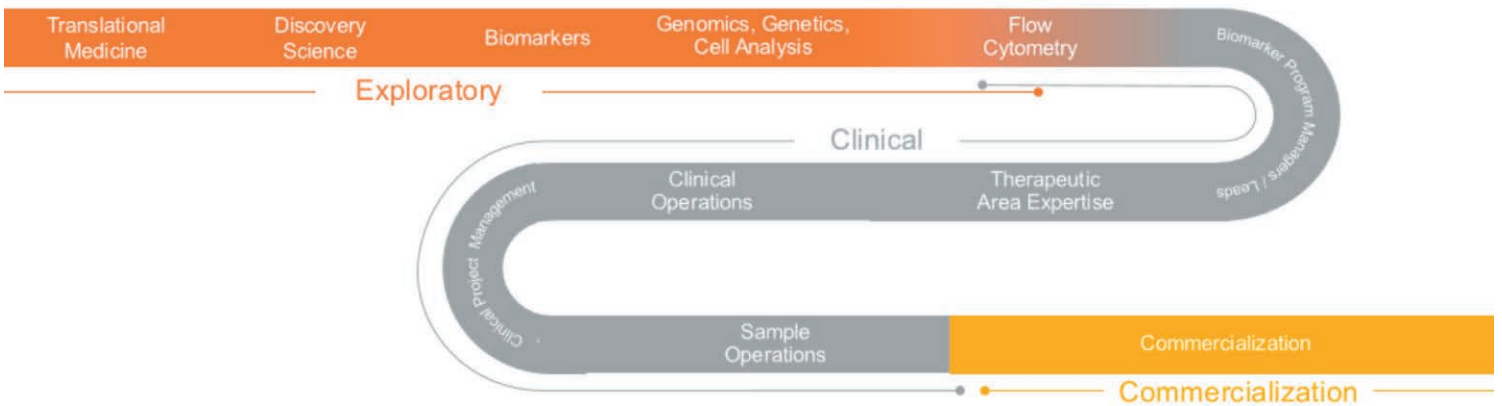


Figure 5: Transition Phases through the Biomarker to CDx Continuum

Figure 4: Key Factors that Determine the Utilization of Biomarker and Companion Diagnostic Assays

either rare genetic alterations with less well-defined biology or new combinations of therapeutic agents are being considered.[6,7] This "reverse-translation" approach will continue to evolve, with biomarkers and a thoughtful, comprehensive biomarker strategy as a key component.

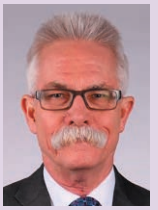
Factors that Impact Adoption of Biomarker and Companion Diagnostic Assays

Because biomarkers are increasingly important to the development program for new molecules and therapeutic approaches, there is now an appreciation for the early engagement of diagnostic partners to help understand the key elements for test development and use post-approval of a new therapeutic. That appreciation has been an important advancement in the seamless coordination of the drug and diagnostic development pathways. There are several key features that relate to the assay (analytical platform, assay performance, specimen type etc), the regulatory approach (lab developed test, PMA approved CDx); and commercial strategy (geographic considerations, reimbursement, ease of use for clinicians etc.). These key elements and pathways are highlighted in **Figure 4**. In marketing considerations as well as clinical uptake, fundamental areas such as turn-around-time, ease of use, and reimbursement are of equal importance to the analytical performance of the assay and benefit provided by the new therapeutic.

As new therapies with a similar mechanism of action, or with expanded indications come to market these factors are critical to the uptake of the competitive products. For example, will the new therapy be accompanied by a companion diagnostic or will the biomarker only provide complementary information to other clinical factors of response. While the use of a companion diagnostic may be thought to restrict patient access to the new therapy, the increased benefit seen in the selected population may differentiate the therapy and increase the market potential relevant to other competitive products. We have observed this play out in the highly competitive immune checkpoint inhibitor market, where the selection of appropriate patients based upon a biomarker result provides an advantage over an all-comer strategy.[8] This is particularly important in balancing efficacy and safety evaluations.

Conclusions

There is a growing body of evidence supporting the need for a well-defined, comprehensive biomarker strategy implemented early in the drug development process in order to enhance the likelihood of the approval of a new therapeutic. For both the drug and diagnostic development teams, early engagement and knowledge of the appropriate assay platform and other factors that impact ease of use for clinicians needs to be a part of the biomarker strategy, helping to ensure commercial success of both the drug and diagnostic. This step is best achieved in parallel with a well-defined partnering agreement between parties. Understanding the need for a comprehensive strategy for a flexible and iterative development process (**Figure 5**), rapidly becoming the normto provide a more efficient and successful outcomein the continuum approach for companion diagnostic-drug development. JoPM



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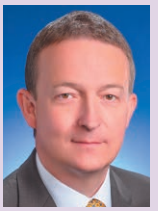

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Dr Roberts received his PhD in Pharmaceutical Sciences from the University of Nottingham (UK) and has worked in the clinical diagnostics arena for over 30 years holding senior positions in both the *in vitro* diagnostic and reference laboratory industries. He joined Covance at the end of 2012 to develop and lead the Company's Companion Diagnostics initiative designed to assist Pharmaceutical and Diagnostic Companies in drug/companion diagnostic co-development and continued in that role following the acquisition of Covance by labcorp.

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