Paper TT04

Integration of Biomarkers Data in Clinical Trials

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ABSTRACT

Center for Drug Evaluation and Research (CDER) has shown increased involvement in the biomarker development in recent years resulting in the establishment of CDER's biomarker qualification program. This program provides an evidentiary framework to support qualification of biomarkers as a surrogate endpoint for an established context of use without requiring re-qualification of the biomarker. This action has resulted in interest from various biotechnological and pharmaceutical companies in biomarker development.

CDER has expressed its goal of using biomarkers to add supporting information to clinical trials outcomes. It will provide a framework for the review of biomarkers for use in regulatory decision-making. As attrition in the drug development has become a frequent occurrence, so have the use of biomarkers as surrogate endpoints in clinical research and target identification. Such use of biomarkers not only reduce the cost of clinical trials but also help direct clinical research towards worthwhile drug candidates.

INTRODUCTION

Two significant factors that frustrate and deter decision-makers in the planning and implementation of future clinical studies, are the increasing costs of conducting clinical trials and the unpredictable enrollment of the subjects in the study. There have been numerous futile or failed clinical trials in recent years, leading to substantial loss of research and development investments. Many organizations have tried to minimize the loss through early termination of clinical studies or applying some creative and proactive strategies such as adaptive trial designs. On the other hand, there have also been several innovative ideas and emergent technologies to reduce the cost of drug discovery and to develop targeted leaner clinical trials. Biomarkers play a critical role in substituting costly clinical endpoints with alternative outcome measurements that can provide equally conclusive results and are supported by regulatory authorities such as the Food and Drug Administration (FDA). This approach can also substantially shorten the time to obtain the safety and efficacy outcomes of the study. Such advances have also opened new horizons for many unmet patient needs.

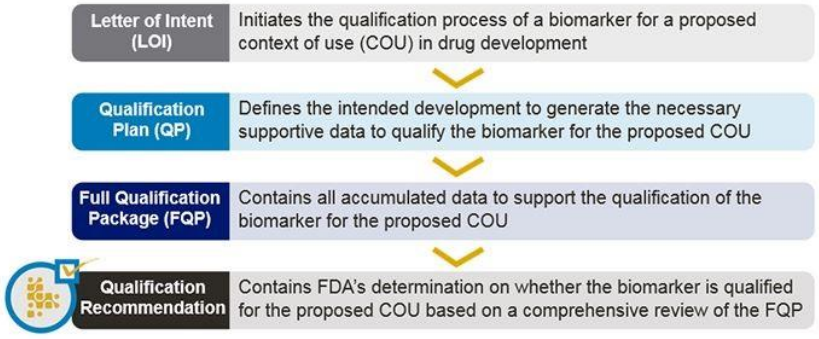
Interest in the inclusion of the biomarkers data in clinical trials has increased with the Twenty-First Century Cure Act enacted by Congress and signed into law on December 13, 2016. This act is certainly an encouraging development for both the scientific community and patients alike in many therapeutic areas where innovation in science is needed. Though it addresses many issues, the subtitle B – Advancing Precision Medicine is particularly relevant to biomarkers development. This law includes a provision for innovations in the projects funded by the National Institute of Health (NIH) and FDA with substantial funds available to promote and support the research in the field of biomarker development to cure diseases. Consequently, the FDA has established a biomarker qualification program within CDER to work with the industry to expand the number of biomarkers for a selected context of use. This program sets out a three-stage submission process (Fig. 1) for the qualification of a biomarker as a surrogate endpoint for a specified disease or biological phenomenon. There are dedicated resources that explain this process and lay out specific requirements, including a qualification plan detailing the context of use and measurement methods. If the plan is approved, a full qualification package is submitted. Once a biomarker is qualified for a given context of use, the biomarker does not need a further qualification in future studies.

Furthermore, there have been progressive technological advancements in high-throughput sequencing that has allowed rapid detection of genetic alteration and the quantification of gene expression at a lower cost. The advances in computational genomics coupled with innovations in long-read sequencing technology, also called third-generation sequencing, have allowed de novo genome assembly and identification of individual sequence variations. Furthermore, the third-generation sequencing requires smaller samples and is more portable. Such developments continue to provide much needed technological innovations in the shift towards precision medicine. There have also been advances in the methods for the isolation and detection of small quantities of peripheral gene products. As these newer tests become CLIA (Clinical Laboratory Improvement Amendments) certified and accepted by FDA as measurement methods, the field of biomarker development and its application in clinical research is bound to grow.

To facilitate collaboration among various public and private organizations, the FDA has taken many initiatives. In one such initiative, the FDA teamed up with NIH in the establishment of a standard terminology glossary named,

“Biomarkers, EndpointS, and other Tools (BEST) resource.” This tool defines the terms related to the biomarkers as well as describes the hierarchies, connections, and dependencies. The FDA and NIH intend to use this tool to communicate in matters related to biomarkers to ensure consistent usage and understanding of the terms across the industry and in multiple areas for studies. This tool further classifies the biomarkers based on various attributes and applications.

Figure 1: Biomarker approval process



Source: fda.gov

WHAT IS A BIOMARKER?

The understanding of biomarkers varies widely, and it may mean different things for different people. The CDER’s BEST tool defines a biomarker as “a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.” This tool further breaks down the biomarkers into four types, which are Molecular, Histological, Radiological, and Physiological characteristics. While there are numerous biomarkers used in the clinical trials as safety parameters and efficacy endpoints, there has been an interest in molecular biomarkers in recent years. A particular focus has been on using biomarkers to understand and explain complex multifactorial diseases, such as rheumatoid arthritis or malignant tumors.

Table 1: Categories of biomarkers

Category	Description
Susceptibility/risk biomarker	Indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.
Diagnostic biomarker	Used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.
Monitoring biomarker	Measured serially for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent
Prognostic biomarker	Used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.
Predictive biomarker	Used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.
Pharmacodynamic/response biomarker	Used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.
Safety biomarker	Measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse effect.

Source: FDA/NIH BEST (Biomarkers, EndpointS, and other Tool) resource

International Conference on Harmonization (ICH) has published several guidelines to facilitate the integration of genomics markers in drug development and regulatory decision making. The ICH E15 guideline defines Genomics Biomarker and related terms and expands on sample coding categories. According to this guidance, a Genomic Biomarker is “A measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions.” It further elaborates on specific examples of what constitutes the genomic biomarkers and provides guidance on the coding of genomics data. In E16, ICH has also outlined its recommendation for the regulatory submission aimed at the qualification of the genomic biomarkers. Such submission is aligned with the common technical document (CTD) format for the marketing authorization application, such as an NDA or a MAA.

BIOMARKER IN DRUG DEVELOPMENT

Biomarkers can play a crucial role at various stages in the drug discovery process ranging from basic research, clinical development to post-market safety surveillance. During the basic research, the goal is not only to use known biomarkers to understand the effects of disease on various molecular pathways and to find out the mechanism of actions of the drugs, but the biomarker research efforts can also yield new markers that can be further studied and validated. During the pre-clinical studies, the biomarkers can help with the target selection and assessment of the toxicity of the drug. As the discovery progresses forward, the identification of the new biomarker can be used for exploratory analysis to gather evidence supporting the association with a clinical or phenotypic trait. It can be further analyzed for establishing equivalency with clinical endpoints used in the trials. During clinical trials and post-market studies, predictive biomarkers can be used for enrichment and stratification during the design of clinical trials. Additionally, biomarkers are used to assess the risk-benefit profile of the study medication and enhance the value of the safety data. The qualified biomarkers can be used as a prognostic indicator or surrogate endpoints.

BASIC RESEARCH

Association of genetics and genomics biomarkers with the disease or pathological processes can help with the target selection and design of the drug prototypes. In this post-genomic era, there have been rapid advances in technology to assess gene-level changes, such as sequence variation or gene expression. Many pharmaceutical companies utilize the latest technologies to perform genomics experiments. Such approaches result in a large amount of genomics data, which can be analyzed to assess results such as gene-phenotypic trait correlation, differential gene expression between treatment groups, or overrepresentation of biochemical pathways in the sample.

Over the past few years, the use of sequence-based quantification of transcripts based on high throughput next-generation sequencing platforms such as RNA-Seq has been a significant development in genomics. Such technologies allow rapid detection of gene activities by using short-read sequences to estimate the abundance of transcripts in the samples. The new third-generation platforms utilize long-read sequences and provide better estimates of gene expression as well as identification of the sequence variants.

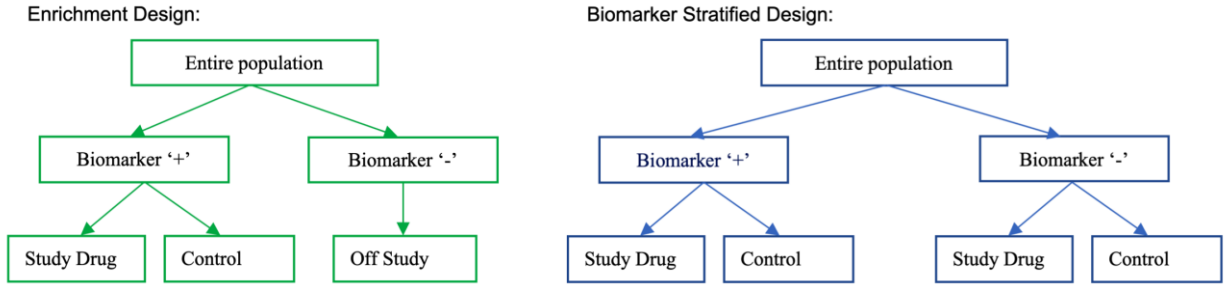
R language has been the primary programming language to import, store, transform, prepare, analyze, and visualize the genomics data. As the number of R packages has grown over past decades, there has been a concerted effort by an open-source bioinformatics platform, *Bioconductor* (biocondutor.org), to create a validated set of R packages for the scientific community to download and use them for genomics data analysis. This R archive has streamlined the process of implementation of the latest scientific knowledge and analysis methodologies. Additionally, many validated packages and workflows are available that are based on consensus methodologies from the academic community. An extensive amount of open-source programming tools for genetic data analysis are present in *Bioconductor*. Given the rate of growth in scientific knowledge and technological innovation, *Bioconductor* has established a streamlined and methodical process to incorporate new information and release validated upgrades. Such packages include many commonly used workflows such as differential gene expression and gene set enrichment analysis. Additionally, all validated R packages are well documented.

CLINICAL DEVELOPMENT

During clinical trials, the focus is on peripheral biomarkers such as circulating gene products that can be measured with accuracy. With increasing interest in biomarkers, many studies include an exploratory analysis component that evaluates the association of the biomarkers with the clinical endpoints. Biomarker analysis is particularly common in studies involving biologics and in precision-based studies. The selection of biomarkers often involves the pre-existing understanding of the role of the circulating gene products, and applicable molecular pathways attributed to the causation of the disease and mechanism of action of the drug. Such a study often includes a separate analysis plan for the evaluation of biomarkers. In addition to summary statistics, the focus of such analysis is the correlation of the biomarker with the clinical endpoint of the disease activity and the pharmacokinetics parameters of the study medication.

Many clinical studies can utilize biomarkers such as prognostic or predictive biomarkers during the design of the clinical trials. Such biomarkers have been used for both enrichment and stratification of the clinical trials. Enrichment studies assess the subjects for the presence of biomarkers before randomization, and those subjects with negative status are excluded from the study. Biomarkers can be used for stratification of the subjects as well. In such cases, effect of the study medication is analyzed in relation to biomarker status and conclusion is made based on the treatment effect within the stratum.

Figure 2: Biomarker-driven phase III clinical trial designs



CDISC has also taken an interest in handling and presentation of genomics data and published a separate SDTM implementation guide to tabulate the study data. This document addresses specific issues relevant to genomics and genetics data, such as data representing the handling of biospecimen. It further proposes specific SDTM domains as well as structure and relationship between such domains.

With increasing interest in biomarkers, many studies include exploratory biomarkers to evaluate association with the clinical endpoints. Biomarker components are particularly common in studies involving biologics and also in precision studies. The selection of biomarkers often involves the understanding of the role of the circulating gene products relevant to the disease, and the molecular pathways attributed to the causation of the disease.

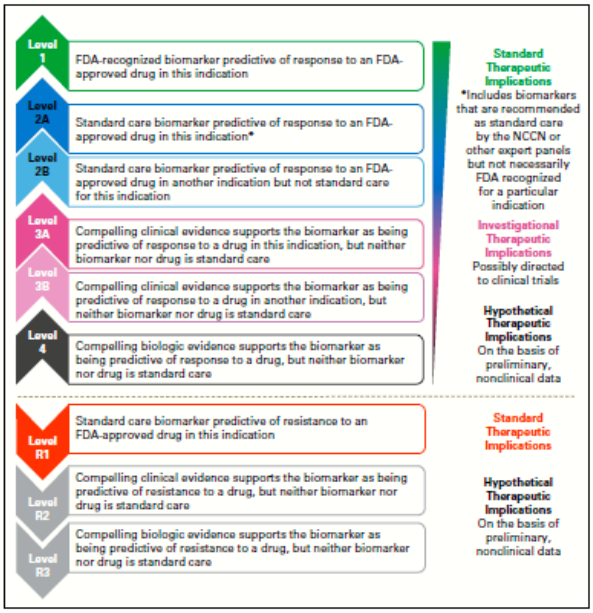
The effectiveness of many treatments varies based on the patient characteristics, and often only a minority of patients benefit from the therapy. Additionally, some patients suffer more frequent and severe adverse events from the treatment. Any predictor of such efficacy outcomes or toxicity would greatly benefit the patients and are desirable prerequisites of all clinical studies if attainable. As number of biologics with molecular targets have increased in the market, accurate identification of such patients remains a challenging task for health care providers to minimize the safety risks while fully realizing the advantageous effects of the treatment. Hence, it has become a necessity for many drug developers to not only market the drug but also to provide the biomarkers for selecting the patients who will respond to drugs.

IMPLICATIONS FOR PATIENT CARE

An accurate diagnosis is essential for the treatment of the patients, particularly for diseases requiring biologics with specific molecular targets — biomarkers testing plays a critical role in clinical practice for both diagnostic and therapeutic purposes. There are occasionally multiple biomarkers associated with the disease complicating the decision-making by the clinicians. There have been initiatives to address this problem from organizations. For example, NCCN (National Comprehensive Cancer Network) has created a Biomarkers Compendium, which consolidates the biomarker testing information based on the latest clinical practice guidelines. Additionally, there are efforts to create clinical decision support tools utilizing a growing biomarker knowledge base. One such tool includes OncoKB, a comprehensive precision oncology knowledge base offering evidence-based information on genetic findings associated with the tumors to help make optimal treatment decisions. The OncoKB categorizes the associated biomarkers based on a classification system utilizing the level of evidence (Figure 3). This system also includes the site and nature of genetic alteration as well as the indication or other relevant information.

As more data are collected from various post-marketing surveillance, registries, and other phase IV studies, such information can feed into further development of biomarkers. Integration of various sources of biological data such as basic research, clinical development, and post-market studies provide unique challenges as well as opportunities for the data scientists to look at the full continuum of information pertinent to disease and a holistic approach to drug development. It also helps add value to patient-centric evidence-based medicine.

Figure 3: Levels of evidence classification system for biomarkers to predict response to a treatment



Levels of evidence: Individual mutational events are annotated by the level of evidence that supports the use of a certain drug in an indication that harbors that mutation.
Level 1: Standard therapeutic implications include Food and Drug Administration (FDA)–recognized biomarkers that are predictive of response to an FDA-approved drug in a specific indication
Level 2A: standard care biomarkers that are predictive of response to an FDA-approved drug in a specific indication
Level 2B: Investigational therapeutic implications include FDA-approved biomarkers predictive of response to an FDA approved drug detected in an off-label indication
Level 3A: FDA- or non–FDA-recognized biomarkers that are predictive of response to novel targeted agents that have shown promising results in clinical trials and
Level 4: non–FDA recognized biomarkers that are predictive of response to novel targeted agents on the basis of compelling biologic data

NCCN: National Comprehensive Cancer Network.

Source: OncoKB.org

CONCLUSION

There has been increasing interest in biomarkers as indicated by more than two hundred seventy-one thousand articles on this topic over the past five years alone (PubMed search, Jan 21, 2020). The nature of drug development is changing, and precision-based medicine with accompanying diagnostic indicators to select the intended patients have become more of the norms rather than the exception in a new era of treatment of complex diseases using biologics for specific molecular targets. The well-planned use of biomarkers can benefit clinical drug development in many ways. It can help find the mechanism of action of the drug, select the target, predict the efficacy, and monitor toxicity. Biomarker integrated clinical development can also achieve a higher return on the investment from drug discovery by saving time and eliminating some of the costly investigations. Scientific evidence and technological innovation in biomarker development and its application in clinical trials continue to evolve. There is still a lack of standardization across the industry and the potential for errors and biases. However, with increasing collaboration among industry and involvement of regulatory authorities, the integration of biomarkers in clinical trials is bound to grow and play an increasingly significant role in efficient and productive clinical trials.

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