Using Selection Biomarkers and Unravelling the Resulting Data to Drive Clinical Trial Success

PEER REVIEWED

Introduction
The use of biomarkers in drug discovery and development has exploded at an unprecedented rate since the turn of the century. With recent scientific and technological breakthroughs – including genomics, advanced cellular and tissue profiling, and complex imaging – biomarkers can now be leveraged to address many questions about biological activity, safety, and clinical efficacy throughout the drug discovery and development process at a fraction of the cost and with turnaround times unimaginably less than a decade ago. These advances in precision medicine are driving a paradigm shift in drug discovery and development as innovators are now focusing on programmes with narrow indications, shorter development times, and lower costs.[1]

Biomarkers play a key role in characterising the biological pathways and processes that drive response and potentially define patient populations. In fact, as targeted therapies and immunotherapies proliferate, biomarkers are increasingly relied upon for patient selection and for determination of eligibility for clinical trials. Treatment selection biomarkers are of particular interest in contexts such as cancer, where treatment effects are heterogeneous and where efficacy may be variable, the risk of toxicity is potentially significant, and/or the cost of the treatment is high.[2]

However, having a biomarker strategy is only part of the equation. As assay technologies have been refined and their costs have significantly decreased, many development teams find themselves overwhelmed with biological data and completely under-resourced to capitalise on the tens of millions of data points they have created. To address this gap, *biomarker data processing* is increasingly recognised as the new frontier in the practical application of a biomarker strategy in drug development. In this article, we discuss biomarker use in clinical trials, as well as the importance of a proactive biomarker data processing strategy to ensure valuable insights are not lost in the morass of data.

Biomarkers in Clinical Trials

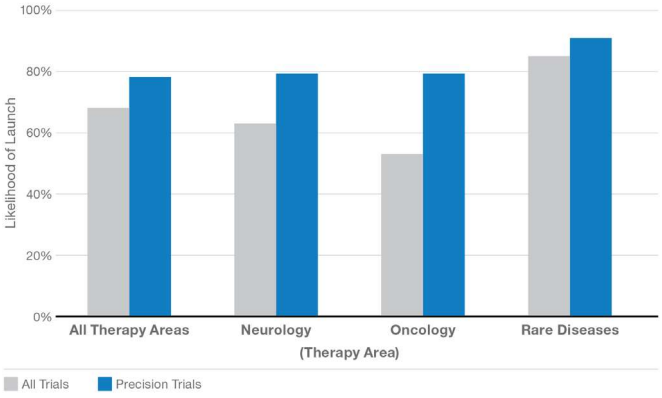
The primary objective of biomarkers is to generate informative data and enable better decision-making throughout the course of drug development. In general, biomarkers can be grouped into four categories:

1. Markers of toxicity in pre-clinical safety studies
2. Diagnostic markers of clinical safety and efficacy
3. Biochemical or pharmacodynamic markers associated with the compound's mechanism of action
4. Markers of disease progression or reversal

Evaluating biomarkers in clinical trials and integrating speciality lab data – such as flow cytometry, gene expression profiling, and immunosequencing – with pharmacokinetics, safety lab, imaging, and clinical data can provide a broader foundation for assessing the pharmacodynamic effect, safety, and efficacy of an investigative compound. Importantly, surrogate biomarker endpoints may also allow for assessment of treatment effects at earlier times than the clinical endpoint of interest, enabling studies with an adaptive design.

Over the past five years, there has been a marked increase in the number of clinical trials citing a biomarker-guided precision medicine design.[3] Notably, according to a recent report, drugs developed using a precision medicine design were more likely to reach the market. This higher likelihood of commercial launch was found across all therapeutic areas, with the most significant difference in oncology (see Figure 1).[1]

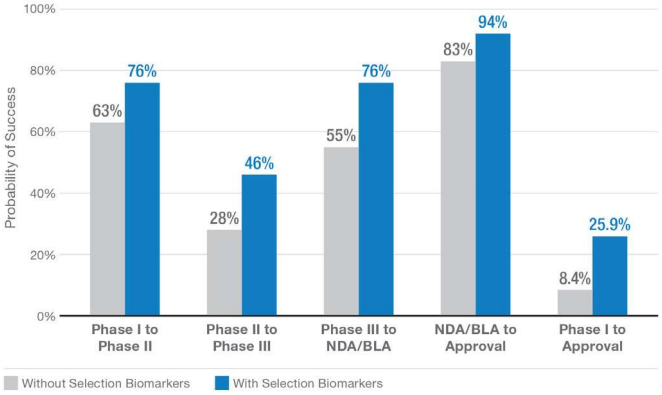
Figure 1. Biomarker Guidance Linked to Higher Likelihood of Launch, Particularly in Oncology



Adapted from TrialTrove | Pharmaintelligence, 2018. Data: 2012–2017. Adapted from The Economist Intelligence Unit. The Innovation Imperative: The Future of Drug Development Part I: Research Methods and Findings.

In particular, the use of biomarkers as inclusion or exclusion criteria for clinical trial enrolment (also known as "selection biomarkers") may be a powerful predictor of success. In a BIO industry analysis that examined clinical development success rates from 2006 to 2015, programmes that utilised selection biomarkers had higher success rates at each phase of development. This analysis revealed that the use of selection biomarkers led to a threefold increase in the likelihood of progressing all the way through to approval (see Figure 2).[4]

Figure 2. Use of Selection Biomarkers Increases Probability of Success



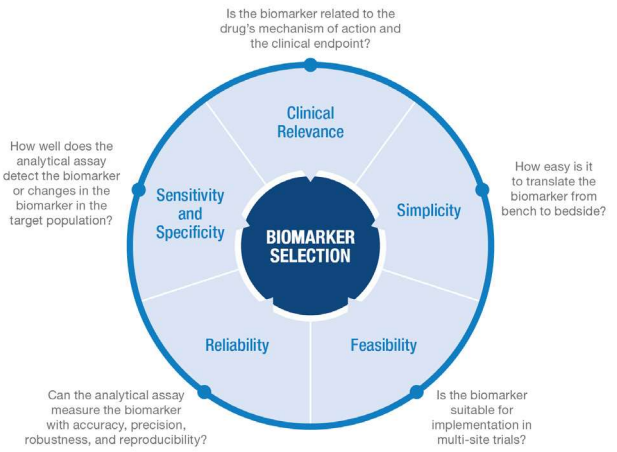
Adapted from David W Thomas, Justin Burns, John Audette, Adam Carroll, Corey Dow-Hygelund, Michael Hay. Clinical Development Success Rates 2006–2015. (2016) A BIO Industry Analysis white paper.

Selecting Appropriate Biomarkers

When selecting biomarkers for a clinical trial, clinical relevance is a key driver. Specific biologic or genomic profiles can be used to differentiate patients. This can lead to a subset of patients more likely to respond based on safety or efficacy.

Clinical relevance is one factor to weigh in selecting the right biomarker; there are also practical considerations to evaluate (see Figure 3).

Figure 3. Selecting an Appropriate Biomarker



Translating a Biomarker to a Clinical Study

The translation of predictive biomarkers to the clinic requires a cross-functional team that includes scientists, clinicians, biomarker experts, regulatory personnel, and assay developers.[5] When developing a biomarker strategy and method or assay, sponsors will need to balance the need to simplify sample preparation procedures and minimise the number of samples required with the need to maximise the amount of useful, high-quality data collected. Key practical issues that should be considered when planning to use a biomarker to determine eligibility for a clinical study include:[6]

- **Sample Collection Considerations.** Where possible, the collection method should utilise non-invasive or minimally invasive techniques. The amount of specimen needed for analysis, and potential reanalysis, should be minimised. In addition, the collection and preservation methods should be technically and logistically feasible within the context of a clinical study.

- **Assay Considerations.** If an assay needs to be developed, it is important for the team to build adequate time into the clinical trial timeline. The lead time required can vary greatly depending on the platform chosen, as well as the complexity of the assay.

- **Sample Analysis Considerations.** Turnaround time can have a significant impact on recruitment and other clinical trial activities. While using a local laboratory may decrease turnaround time, it may also come with the risk of greater variability resulting from different methods, instruments, validation standards, and quality control processes which can have a significant impact on the success of the study. Especially for eligibility decisions, having assays validated in a centralised testing lab are usually preferred.

- **Regulatory Considerations.** Sponsors should keep in mind that in the United States, predictive biomarkers used to balance arms of a study or to select patients for enrolment into a clinical study may fall under the purview of both the Centers for Medicare & Medicaid Services in the form of the Clinical Laboratory Improvement Amendments (CLIA) and the US Food and Drug Administration. In addition, some states may have additional laws governing in-state clinical laboratories or the analysis of their residents' samples, regardless of where the analysis is conducted.

If multiple biomarkers are to be used to stratify patients in a clinical trial, the complexity of the study may increase, requiring greater planning and the need for specialised translational science teams to help design and execute these novel programmes. Success of these programmes will depend on upfront planning of assay selection, sample handling and processing methods, global logistics, and timing such as real-time patient selection assays.

Managing Vast Amounts of Biomarker Data

There is a broad spectrum of biomarker assays available, from targeted genomic panels to high-content or high-throughput experiments, with applications ranging from characterising mechanism of action and guiding dosing to optimising study design and enriching study populations. Technologies are evolving in tandem and large volumes of data are now being generated at unprecedented rates. To further complicate the diversity and complexity of biomarker assays, the resulting data are often generated in different formats, making data harmonisation, interpretation, and accessibility difficult.

In order to optimise the value of generated biomarker data, drug developers and clinical researchers must be able to rapidly and efficiently interrogate data within and across platforms, trials, geographies, and even companies. This interrogation capability informs hypothesis rule-out, as well as generation of new hypotheses which can be used to shape a drug development programme. In addition, to better harness the collective intelligence of the company, drug developers and clinical researchers need to be able to distribute information seamlessly within and across relevant organisations.

Historically, due to resource limitations and lack of appropriate technology, there has been no efficient way to leverage the volumes of data being generated throughout a drug development programme. According to a survey by Forbes, nearly 80% of scientists' time is spent collecting, cleaning, and organising data sets.[6] Clearly, if all of these data could be made accessible for visualisation, large-scale analytics, and sharing, drug developers and clinical researchers would benefit from a significant multiplier effect in value generated and insights gained.

A prerequisite to productive data interrogation and analysis is a harmonised data set that is quality-controlled and correctly mapped together, transforming millions of data points into actionable insights. Today, sponsors can leverage cutting-edge technology solutions to harmonise disparate sources of biomarker data and warehouse them in near real time for effective on-study decision-making, as well as downstream use. Technology solutions also exist for organising these data as part of end-of-study activities and regulatory submission. These technologies enable tighter integration between clinical operations and biomarker data, facilitating go/no-go decision-making between trial phases and potentially leading to shorter timelines, reduced costs, and faster approvals.

A number of industry trends, including partnerships, licensing agreements, and combination therapies, underscore the critical

importance of being able to share data within and across both platforms and organisations. Those organisations that are able to provide access to complex, organised biomarker data sets will be well-positioned to detect and convey signs of positive biological response in early-phase trials.

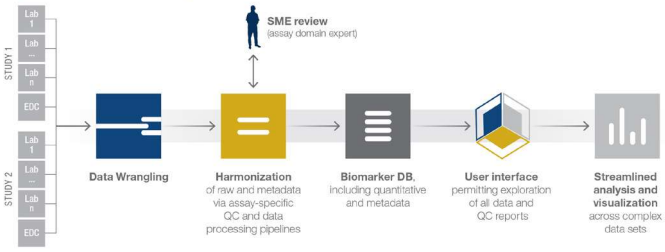
Selecting a Biomarker Data Management Platform

Drug developers who are contemplating the use of biomarkers for their trials should consider a biomarker data management platform, and ask:

- Does the platform have a centralised database for storage and access to all speciality lab data, regardless of which or how many labs are providing data?
- Does the platform include assay-specific workflows and quality control parameters, as well as a capability to incorporate custom workflows?
- Does the platform have data reconciliation capabilities to expedite time-consuming reconciliation activities between LIMS and EDC?
- Does the platform include plug-in modules for translational research/biomarker data management?
- Can the platform generate submission-ready data sets that comply with Clinical Data Interchange Standards Consortium (CDISC) standards and can be adapted to regulatory shifts?
- Is the platform compatible with other software tools (e.g., GraphPad Prism)?

To handle the complexity and throughput of biomarker assays and make data actionable, the biomarker data management platform should also be able to simultaneously integrate and deliver multiple workflows with dynamic reporting. The technology solution should also enable sponsors, translational researchers, and clinical trial teams to visualise and analyse biomarker data through user-friendly, intuitive web-based tools so they can harvest insights from all available data sources to inform their decision-making (see Figure 4).

Figure 4. A Flexible Data Ingestion and Harmonization Framework



Conclusion

In order to maximise the benefit of using selection biomarkers and other biomarkers in drug development, sponsors will increasingly need to contemplate logistics related to biomarker programmes, ensure the viability of these programmes globally, and then leverage technology platforms that enable them to optimise the data they collect. As drug developers and clinical researchers strive to deliver on the promise of precision medicine, technology-based solutions for biomarker data management will become a prerequisite for clinical trial operations. To unlock the full potential of biomarker data and bridge the gap between translational research and clinical medicine, these technologies will need to be supported by a multidisciplinary team of translational informaticians, programmers, data managers, and innovative data scientists. This combination of cutting-edge technology and biomarker expertise can facilitate efficiency, flexibility, and even compliance, reducing clinical trial costs and bringing novel therapies to the patients most likely to benefit from them.

The use of biomarkers to predict and select likely-to-respond patient populations is a transformational aspect of today's drug development process and is reducing both the time and cost of development. By successfully reducing time and cost, innovators are capable of bringing novel therapeutics to patients at an unprecedented pace. All of these advancements are bringing the promise of precision medicine to fruition.

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Chad Clark

Chad Clark is president and a life science executive at Precision for Medicine, focused on the implementation of biomarker driven clinical programs. His industry expertise includes combining advanced technologies, strategic program design, and operational excellence to help life sciences companies effectively accelerate research initiatives through biomarkers and advanced informatics. Clark's previous experience spans the execution of phase I–IV global clinical trials, specialty lab services, translational sciences, risk management, and patient support initiatives.

Scott Marshall, PhD

Scott Marshall PhD, Managing Director Translational Informatics and Diagnostic Sciences at Precision for Medicine, has extensive industry expertise across the pharmaceutical and biotech space – Dx regulatory submissions, translational informatics, biomarker R&D – with a focus in precision medicine-guided efforts as well as strategy development and medical device/ diagnostic development. Globally responsible for translational informatics R&D efforts at Precision for Medicine, Marshall has led the development of novel methodologies for patient stratification and biomarker guided clinical trial design.

Cliff Culver

Cliff Culver, Senior Vice President, Precision Medicine Group at Precision for Medicine, is a corporate strategy executive specializing in the development of software platforms for the life science industry at Precision for Medicine. Culver's particular focus is on increasing the efficiency of preclinical and clinical contract research & development operations. He has prior experience as founder, advisor, and general manager in rapidly scaling technology-enabled businesses.