

Proactive Planning to Optimize
the Use of Biomarkers in
Oncology Clinical Trials

Introduction

In an era where unprecedented advances in our understanding of cancer biology have put personalized approaches to therapy in the spotlight, biomarkers are taking center stage in modern oncology drug development. Today, the process of developing oncology drugs is moving from a linear, phasic approach to a more flexible, iterative process that can be leveraged to accelerate proof of concept.

As biomarkers are increasingly used to define the most rational use for a drug, sponsors are facing critical operational considerations in the context of clinical trials. In addition, new technologies will need to be deployed to ingest and analyze the complex biological data generated by biomarker-driven trials to support and gain regulatory approval. In this white paper, we explore the growing importance of biomarkers in oncology development and discuss key considerations for optimizing the use of biomarkers in clinical trials.

Role of biomarkers in oncology drug development

The primary role of biomarkers is to generate useful data and enable more informed decision-making throughout the course of drug development (see Figure 1). Biomarkers can be broadly classified into 3 categories:

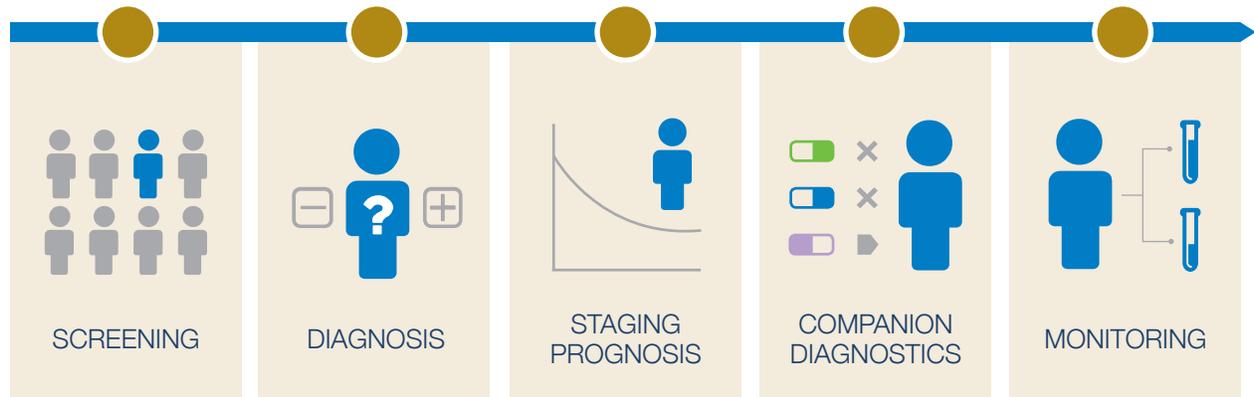
1 Diagnostic biomarkers are biological parameters that aid in the diagnosis of diseases. These can be used to confirm eligibility for clinical trials.

2 Prognostic biomarkers are used to identify the likelihood of a clinical event in patients who have the medical condition of interest.¹ These

are often used as eligibility criteria in clinical trials to identify patients who are more likely to have disease recurrence or progression.

3 Predictive biomarkers are used to identify individuals who are more likely than similar individuals without the biomarker to experience favorable or unfavorable effects from exposure to a therapeutic agent.¹ These can be used either to confirm eligibility for study participation or to stratify patients into biomarker-positive and biomarker-negative groups, where the primary endpoint is effect in the biomarker-positive group.

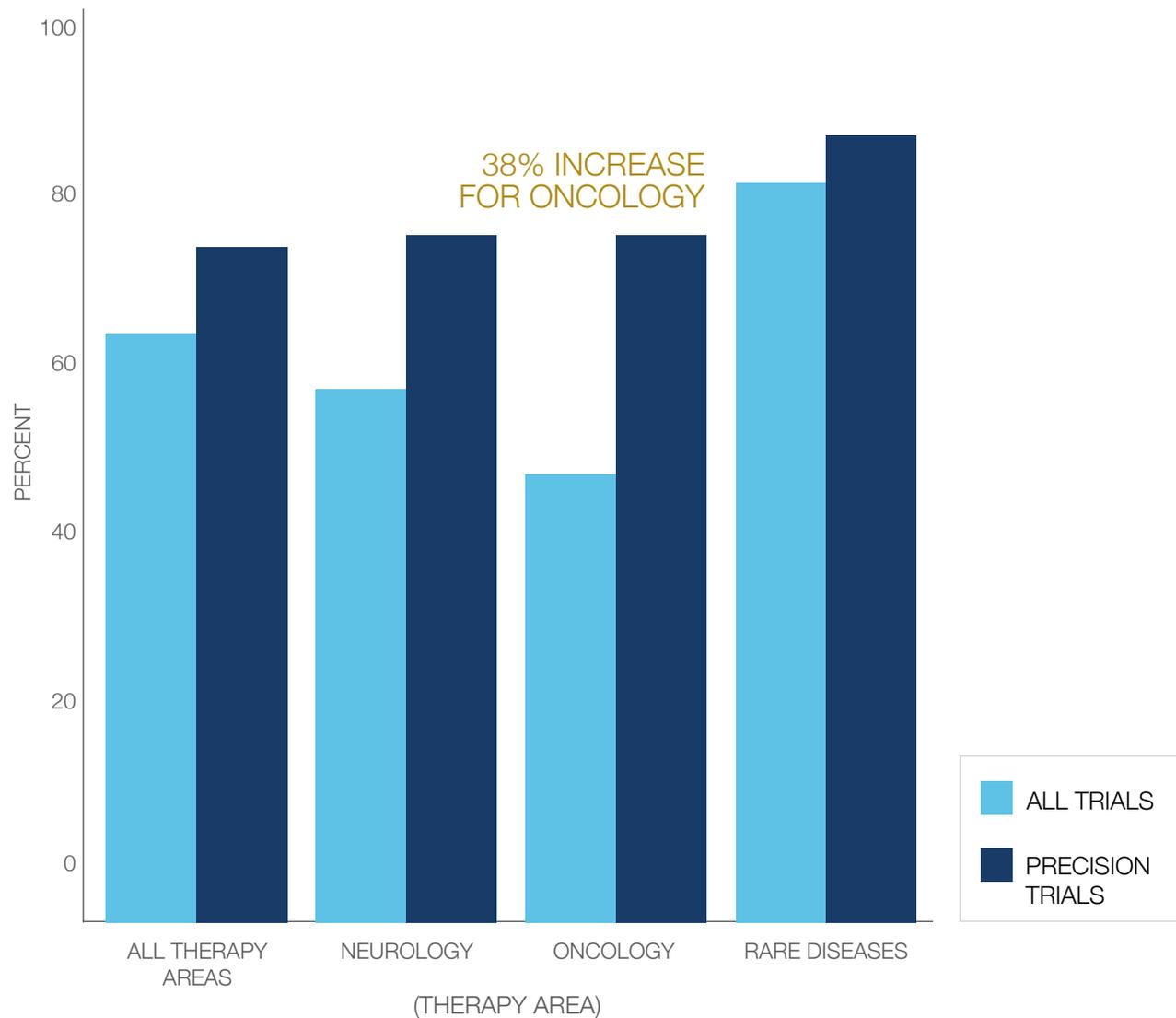
Figure 1. Potential uses of biomarkers.



Over the past 5 years, there has been a significant increase in the number of clinical trials using a biomarker-guided precision medicine design.² According to a recent report, drugs developed using

a precision medicine design were more likely to reach the market. This higher likelihood of commercialization was found across all therapeutic areas, with the most significant difference in oncology (see Figure 2).²

Figure 2. **Biomarker guidance linked to higher probability of commercialization.**²



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. <https://druginnovation.eiu.com/>. Accessed April 12, 2019.

Moreover, an analysis published in May 2018 revealed that precision medicines have faster approvals based on fewer and smaller trials than other medicines. From 2013 to 2017, nearly one-quarter of all novel FDA approvals were for precision medicines, of which almost half were oncology drugs. These precision

medicines took, on average, approximately 2 years less time for approval than nonprecision medicines (5.8 vs 7.5 years). This acceleration in development is likely due in part to the regulatory path taken, as shown in Figure 3.¹

Figure 3. **Regulatory designations: precision vs nonprecision medicine.**¹

Regulatory Designation	Precision Medicine	Nonprecision Medicine
Breakthrough Therapy	48%	19%
Accelerated Approval	30%	13%
Priority Review	85%	48%
Orphan Drug	64%	36%

The overarching goal of precision medicine is to treat based on the patient’s specific biological attributes

Personalized treatment focuses not only on answering the question of how to best match the right patient with the right drug but also on ensuring that each patient is given the right dose at the right frequency to optimize treatment success and improve outcomes.

In oncology, the goal is to individualize a patient’s treatment based on his or her unique tumor profile. Biomarkers are used to link specific tumor expressions or mutations with the targeted therapy that can best influence how that particular tumor grows and spreads. These biomarkers may be proteins, genes, or other molecules that affect how cancer cells grow,

multiply or die, or respond to treatment.

Significant advancements in our understanding of cancer genomics are not only reshaping the drug development process but also reinforcing the critical need for development of biomarker platforms in conjunction with clinical trials to help guide treatment insights and make the practice of precision oncology treatment possible. To optimize the use of biomarkers in oncology drug development, sponsors must engage in proactive planning to fully integrate a clinical and translational development pathway with a clear biomarker-informed development plan.

Application of biomarkers in dose-finding and dose-expansion studies

The emergence of targeted therapies and immunotherapies highlights the utility of biomarkers in early-phase oncology trials. Traditionally, phase 1 oncology trials have relied on a classic 3+3 dose escalation design for defining a recommended phase 2 dose. However, targeted therapies and immunotherapies often have toxicity profiles that are very different from those of cytotoxic agents and may require novel dosing strategies.

With chemotherapy, the goal of dose finding was to find the highest safe dose, or maximum tolerated dose (MTD), to optimize cancer cell killing. In the case of targeted therapies and immunotherapies, these agents may not produce dose-limiting toxicity, even at doses significantly higher than where activity has been identified, and their side effects may not be dose dependent. This makes it challenging to prospectively define decision criteria for stopping dose escalation.

Consequently, it may be more appropriate to identify an optimal biologic dose (OBD) rather than an MTD. Doing so takes into account not only what is happening clinically but also what is happening in the tumor microenvironment that can help lend insight into proper dosing.

An integrated look at biomarker data can help inform the dose-finding and dose-expansion decision process. For example, biomarkers can be used to evaluate:

- Level of receptor saturation
- Degree of drug infiltration into a tumor
- Impact of the drug on subsets of immune cells
- Tumor response

Any or all of these biomarkers can be used to help inform dose finding and, ultimately, selection of a dose that appropriately balances positive impact with tolerable risk.

Using adaptive design to accelerate development

Adaptive designs are commonly used in early clinical development to allow for flexibility based on insights gained as a trial matures. A common approach involves combining phase 1 and phase 2 into one protocol with dose escalation followed by expansion at the identified dose and schedule. The explosion of knowledge around the molecular drivers of cancer, along with the availability of drugs targeted to these drivers, has spurred new paradigms in the oncology development process based on molecular features of a tumor, rather than classic pathology or site of origin.

For some molecular abnormalities, the specific tumor type involved does not matter, but for other abnormalities, the type of tumor is critical. The application of adaptive designs help accelerate the pathway to proof of concept. Umbrella trials typically focus testing multiple drugs or drug combinations on a single type or subtype of cancer to identify what treatment works best within that tumor histology. Basket trials, on the other hand, use a single treatment focused on a particular molecular abnormality across multiple tumor types, eliminating those types that do

not respond and expanding on those that do.

The application of adaptive designs has accelerated the pathway to proof of concept and can even support multiple accelerated approvals with a single trial, depending on the degree of response and the level of unmet need. The increased use of expansive phase 1/2 trials to support approvals has been demonstrated in a McKinsey report that showed an increasing number of approvals relying on earlier phase data rather than just on phase 3 information, especially in the area of oncology.⁴

More recently, we are seeing a trend toward master protocol designs, which may incorporate design features common to both umbrella and basket trials. In September 2018, the FDA released a draft guidance document, *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics*, which provides recommendations regarding the design and conduct of clinical trials intended to simultaneously evaluate more than one investigational drug and/or more than one cancer type within the same overall trial structure.⁵

Engaging a precision medicine research organization to optimize success

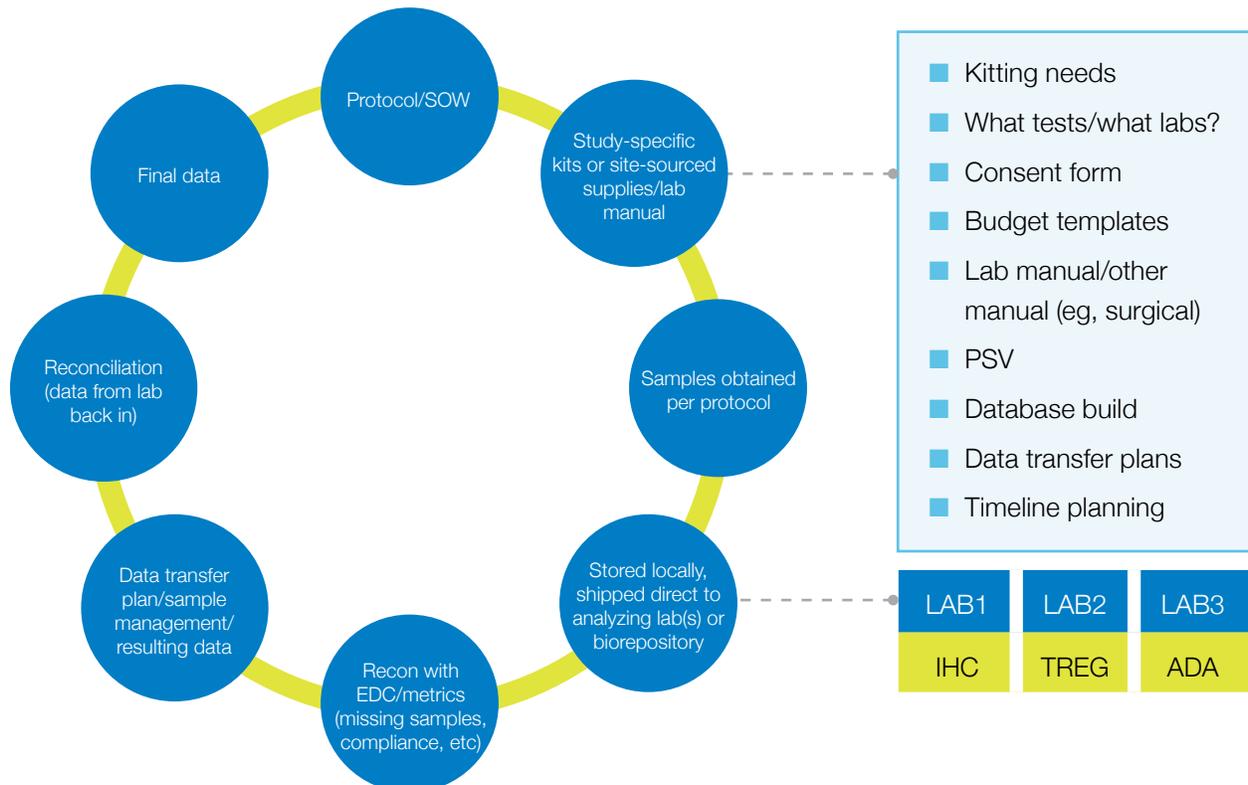
Proper biomarker planning impacts almost every aspect of a clinical trial. Thus, it is critical that biomarker management and clinical trial operations are fully integrated at the very start of the trial to ensure efficient, high-quality execution. To that end, it is critical to engage a highly specialized clinical research organization that specializes in biomarker-driven clinical development, in essence a Precision Medicine Research Organization.

When planning for a clinical trial, details around the biomarker sample collection must be prospectively defined including the type of sample, sample processing and handling, the frequency of collection, and the general use parameters of the resultant data. Lack of an appropriate biomarker plan can have a number of downstream effects on efficiencies of clinical trial operations especially at start-up.

Effective planning for biomarker sampling impacts:

- Informed consent since sample requirements and risks need to be included in the informed consent form (ICF)
- Requirements for sample kits, which must be prepared and sent to sites to support proper sample collection and processing prior to enrollment of the first patient
- Design of the electronic case report form (eCRF)
- Site budgets since the type and frequency of the biomarker specimen collection can impact overall study fees
- Biomarker data management to ensure data sources from multiple labs can be pulled together and combined with clinical data to optimize insights

Figure 4. **Flow of biomarker data.**



For example, a kit definition in a study protocol may be as simple as: “Study drug activity including PK, PD, assay of immune cell population profile by flow cytometry and/or DNA assay, PK, ADA.” However, to

achieve proper kit preparation for First Patient In, this one simple line maps to a long list of requirements for proper sample collection (see Figure 5).

Figure 5. **Sample kit requirements.**

Test	Tube Type
Study Drug 1 PK	4 mL GREEN top Na+Hep
Combo Drug PK & ADA	9 mL RED top / no gel
FC - Blood	10 mL GREEN top Na+Hep
Study Drug 2 PK	1.5 mL AMBER
Combo Drug PK & ADA	2 mL CLEAN cap
Study Drug Levels	2 mL AMBER
Infusion Reaction (serum cytokine & Study Drug PK/ADA)	(1) 10 mL and (1) 5 mL RED top Na+Hep / No gel
Fresh Tissue Flow	5 mL MACS Solution
Tumor IHC FFPE Block	Tissue Cassettes
Tumor IHC Slides	Slider Holder

Sponsors should keep in mind that it is necessary to plot out how much blood is needed over time to ensure that safe volumes are not exceeded at any time throughout a study and that the proper volume is included on the informed consent form. If tissue is

required, sponsors will also need to define whether that tissue can be obtained from an archival source or fresh tissue is required, which comes with an additional set of risks for consent.

Using predictive biomarkers as complementary or companion diagnostics

Predictive biomarkers are the foundation of tests that are designed and validated to identify those patients who are most likely to respond to a drug, as well as those not likely to respond, thereby sparing patients from unnecessary exposure. Accordingly, predictive biomarkers are capable of increasing the net therapeutic benefit of a drug treatment. Their use can exclude from therapy patients who might experience adverse reactions without gaining a positive treatment effect while simultaneously increasing the cost-effectiveness of treatment by minimizing the cost of futile therapy delivered to likely nonresponders. This is certainly of keen interest to payers as well as patients, and the ideal scenario for payers, providers, and patients is to know before prescribing or taking the treatment who is most likely to benefit. Consequently, identifying predictive biomarkers to guide drug treatment is a key goal of precision medicine.

However, drugs and diagnostics are quite different; they have different development pathways (see Figure 6) and are subject to different regulations. If a drug requires a diagnostic to determine patient eligibility for treatment, then sponsors may be faced with executing a co-development pathway that requires an entirely new and different set of device expertise and planning. In addition, although Figure 6 depicts drug and diagnostic development in parallel paths, the stages of development may not necessarily align from start to finish. Predictive biomarkers may be discovered at any time, and part of the challenge—and satisfaction—of the process is figuring out how best to get them to market at the same time. Alternatively, the test may become a “complementary diagnostic”, which is a test that can assist in therapeutic decision making.

Figure 6. **Drug vs diagnostic development pathways.**

Drug Development



Diagnostic Development

When planning a clinical trial, it is important to view potential biomarker(s) as an integral element of the study design and to think forward to how the biomarker test results and patient responses could combine to identify the responding population and ultimately define the indicated patient population. Given that biomarker test development is dynamic and that the goal is to have any required companion diagnostic test commercially available on the day of drug launch, sponsors are advised to plan for the future by considering the following key questions:

- How do we know we are picking the right patients and not excluding those who might actually benefit to some degree?
- What is the optimal balance between likelihood of response in biomarker-stratified patients and resulting breadth of the indicated population?
- What type(s) of prospective sample collection will be needed to allow for end conclusions?
- How easy will it be to collect samples with consistency for future use?
- Does the biomarker assay methodology use samples that are readily and routinely available?
- Will it be necessary to bridge from the clinical trial assay (CTA) to a commercially available version of the test, if needed?
- Can the assay be developed to eventually be readily used in a broad number of laboratories?
- Is there a smooth pathway for payer coverage and reimbursement of the ultimate diagnostic test that will not inappropriately delay or block treatment due to lack of access to the diagnostic test?

In the early phases of biomarker planning, purposeful thinking must be done to ensure that a pathway can be found to take the potential biomarker through to diagnostic approval should the data and strategy support its use. As just one example, the type of

sample and how it is collected requires careful consideration. Sometimes archival tissues are not usable for biomarker testing, and while fresh biopsy tissue might be viable for biomarker discovery and in tightly controlled small research trials, such tissue may not be practical for larger pivotal trials or for routine clinical testing in the end market. Patients would need to consent to biopsies that may be invasive, which can add risk and adversely impact trial recruitment and subsequent adoption in clinical practice. Or the biomarker itself may be labile in fresh tissue and therefore not amenable to routine sample transport in actual clinical use.

The ideal solution would be to find a biomarker testing platform that can be used to characterize what is going on within a tumor at any point in time and uses a readily available sample type. Such platforms currently in development and testing include:

- Circulating tumor cells (CTCs) that are shed into the bloodstream by tumors as they grow. This platform may be applicable in cancers where a higher proportion of CTCs has been shown to correlate with a poorer prognosis or where individual cell analysis can yield the desired biomarker information.
- Circulating tumor DNA (ctDNA) assays, also known as “liquid biopsies,” that can detect unique cancer mutations in microscopic fragments of tumor DNA in patient samples. This platform has the advantage of not requiring isolation or concentration of circulating tumor cells but is only applicable to mutational analysis.

These alternative approaches allow for dynamic molecular monitoring of cancer in real time and can potentially address the challenge of sequential tissue biopsies. However, incorporating these approaches into a clinical trial and planning for sample collection requires forethought and likely a considerable investment in biomarker assay development.

Case Study: Biomarker Development



Challenge: Identify an appropriate adult tumor target with an unmet need that is amenable to testing using a monoclonal antibody previously approved for a rare pediatric cancer indication.



Process: The assay was first confirmed to appropriately test for expression in tumor cells. It was discovered that the published method could not be validated from archival tissues and could only be confirmed through the use of fresh tissue. Adult tumor screening was done by comparing fresh tumor cell lines with fresh normal cell lines. A series of lead tumor targets were clearly defined based on the resultant receptor expression levels as determined by binding with the monoclonal antibody.



Solution: A final tumor target was selected which exhibited both high receptor expression with clear unmet need. Prospective samples were needed, but collecting fresh biopsy tissue from these patients introduced high risk and was not practical; therefore, blood samples were prospectively collected to examine both CTCs and ctDNA to assess the correlation between biomarker expression and drug response.



Goal: Ultimately, the goal is to develop a treatment-selection tool that could be useful in identifying those patients who would benefit most from treatment. If ultimately developed into a companion diagnostic test, this selection tool could help identify patients who would most benefit from the treatment and for whom payers should cover the drug and add to the overall value of the product.

Putting it all together

To truly optimize the use of biomarkers in clinical trials, sponsors must have a plan for data integration and advanced informatics-based approaches/technology platforms to help guide on-trial decisions, as well as to accelerate the development process. Laboratory data from a variety of sources (eg, genomics, transcriptomics, flow cytometry) will need to be

pulled together and combined with clinical data in an integrated fashion which enables ready access to both derived and underlying raw data. It is this integrated view that will provide the most valuable insights into the investigative compound.

With the complexity and diverse nature of the biomarker data being generated as part of translational

programs in clinical studies, especially earlier-phase trials, scientists are spending as much as 80% of their time on tasks related to managing and harmonizing these data—time taken away from activities related to developing key insights needed to drive the programs forward and support decision-making.⁶

Sponsors can leverage technology-based biomarker data management, integration, and informatics solutions to efficiently leverage all of the data being generated and make it seamlessly accessible for visualization, large-scale analytics, and sharing. Key features to look for in a biomarker data integration and informatics platform include:

- Capability for cross-study profiling and interrogation
- Ability to link processed/quantified biomarker data to underlying raw biomarker data, as well as clinical annotations from electronic data capture (EDC)
- Accessibility of biomarker data in near real time to facilitate biomarker-guided decision-making

- Capability to visualize and analyze biomarker data through user-friendly, intuitive web-based tools

As shown in Figure 7, a holistic approach to integrating biomarker data enables the organization to unlock the value of multiomic data within and across trials, leveraging flexible visualization capabilities, applying artificial intelligence-based analyses, and supporting with core informatics work. This robust approach to interrogating often provides powerful frameworks to identify complex biological interactions that lead to stratification strategies or more advanced insights into properties of the drug under study.

However, sponsors should keep in mind that technology alone is not enough. Successful biomarker development requires cross-functional collaboration among data scientists, translational informaticians, biomarker data management programmers, data managers, and translational scientists.

Figure 7. **Turning data into actionable insights.**



Data Generation

- Clinical data
- Genomic data
- Immunophenotyping data

Key Steps to Data Harmonization

- Data cleanup and QC
- Integration of diverse data sources
- Generation of analysis-ready datasets
- Advanced translational informatics

Biomarker-Driven Drug Development

- Target identification and validation
- Mechanism of action
- Study design optimization/optimal dosing
- Patient stratification (complex signatures)

Conclusion

As drug development becomes an increasingly flexible, iterative process, an initial approval may really just be the beginning for an oncology product. Postmarketing surveillance and ongoing translational research may lead to new hypotheses and exploratory biomarkers, which may become new companion diagnostics that help improve patient selection and outcomes to support additional approvals in other indications. Integrating biomarker planning into every phase of development will help define the most rational use of a drug, either alone or in combination, assisting sponsors in accomplishing the ultimate goal of commercializing safe, effective therapeutics that have a positive impact on the lives of patients and their families.



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Dr Devitt Risse is President — Oncology, Precision Oncology & Rare Disease (part of Precision for Medicine), the first precision medicine research organization focused in oncology—combining clinical trial expertise with advanced biomarker solutions.

She provides executive leadership to the company and strategic protocol design and study optimization guidance to sponsors. Dr Devitt Risse has more than 3 decades of broad-based oncology experience in both global and domestic clinical research environments, including large pharmaceutical companies, biotech companies, and CROs. Dr Devitt Risse earned her Doctor of Pharmacy from Rutgers University and was named by *NJBIZ* to the Best 50 Women in Business in 2014. She was a PACT Enterprise Healthcare CEO finalist in 2015, an EY Finalist for Entrepreneur of the Year award for the state of New Jersey in 2015, and a winner of the PACT Enterprise Award for Emerging Healthcare in 2016.

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