parexel®

New Medicines, Novel Insights: Advancing Precision Oncology

An Executive Summary

In this report

Achieving the vision

Precision oncology, with its vision of treating each patient with the exact right medicine, has been evolving for more than 20 years. Developments in precision oncology treatments for breast, lung, and blood cancers have progressed, with momentum gathering as biomarker discovery rapidly expands. Since 2012, 159 novel active substances (NAS) for oncology have launched, 30 in 2021 alone.[1] The power of precision oncology, and to expanding patient access to clinical trials and biomarker testing, is borne out by the inspiring story of Terry Morey, a ten-year stage-four non-small cell lung cancer survivor.[2]

Today, more than half of all cancer clinical trials are for treating patients with certain genetic characteristics.[3] With increasingly more sophisticated data science and advances in technology including machine learning, deep learning, and artificial intelligence, positive patient outcomes depend on access to biomarkers. In short, advances in precision oncology hinge on the patient. **Precision oncology has been—and will continue to be—a slow unfurling. Patients are our guides and partners in this quest.**

Yet despite advances in trial design and the vast volume of genomic data we have accumulated, precision oncology still cannot help most cancer patients.[4,5] The heterogeneity of cancer, our still-limited understanding of its interaction with the immune system, and inequalities in access to testing and medicines remain persistent barriers.[6]

At Parexel, we believe that the vision of precision oncology will be achieved by solving one challenge at a time. In this report, Parexel experts share insights and best practices that can help drug developers move closer to achieving long-term goals by solving practical short-term problems—all while staying focused on the patient journey, which is our North Star.

Democratizing access to data

In today's clinical research environment, patients have unequal access to genetic tests to profile their cancer. They can't customize how to retrieve and utilize their test results, and they can't quickly identify which, if any, clinical trials they are eligible for. Currently, many patients still can't get their longitudinal health records for a meeting with an oncologist to discuss treatment options. For newly diagnosed cancer patients and their families, even those armed with genetic test results, the landscape of precision oncology trials is complex and chaotic. Few oncologists have time to keep abreast of hundreds of studies testing targeted therapies, and often, patients are left to search on their own.

Patients and society won't reap the benefits of precision oncology unless we democratize this data—that is, make it available to the patients who need it when they need it. We must flip the script to deliver truly patient-centered precision oncology, in a universe in which every patient has the following within days or weeks of diagnosis:

- Precise data about the genetic and metabolic footprint of their cancer
- A portable version of their longitudinal health records
- An accurate list of open clinical trials relevant to their condition
- The ability to get screened for eligibility quickly and remotely, if possible
- Routine travel reimbursement and other assistance to participate in trials
- Trusted relationships with their medical team to enable shared decision-making about treatment options

With a few practical improvements to current care pathways, we could achieve this vision, meet the need for urgency, and empower patients.

Expanding studies to community and regional sites

Another way that access to life-saving treatments is restricted stems from the traditional approach to site selection, with most clinical trials conducted at major academic centers located in urban centers. This limits enrollment to those with the means and ability to travel. And the reality is that the increasing complexity of oncology trials is straining the traditional infrastructure.[7]

To solve this multifaceted problem, Parexel is increasing engagement with regional and community sites while upholding the quality standards typical of major academic centers. We find that community sites are eager to conduct precision cancer trials because they want to bring trials closer to patients. We follow five best practices to position these sites for success and mitigate risks for sponsors.

Collect and curate site data precisely. We maintain a comprehensive profile of oncology sites' interests, geographies, capabilities, patient populations, and principal investigators in our Site Alliance Oncology Network. This enables us to match the right sites with the trials that meet their patients' needs. If a site does not fit the protocol, we don't burden them with unproductive feasibility requests. Study design, phase, and complexity determine whether community sites are appropriate for a precision oncology trial. And as protocols are amended, the answers change. Experience and a well-curated database allow us to revise our site selection quickly.

Partner with sites. We invest time and resources in listening to sites and understanding the burdens and obstacles of clinical trials. For example, we scrutinize the number of new tools and technologies utilized in any given protocol. If a site enters our network, we have already determined that it has the skill sets, expertise, support, and infrastructure to be considered for a trial; we do not increase the administrative burden with unnecessary and duplicative requests.

Strive to reduce the burden of training. Training sites to conduct a clinical trial in compliance with regulatory, clinical, data, and ethical requirements is critical, but it's still an imperfect science. **Many sites find that portions of the mandatory training are repetitive, irrelevant, and time-consuming. CROs and sponsors should provide tailored site training that considers seniority, experience, context, and qualification.** Soliciting input from site staff while developing customized, site-specific training materials will result in a more thoughtful plan.

Advocate for sites. Due to the complexity of oncology trials and the fraught patient experience, Parexel takes a white-glove approach to site support. We do everything we can to ensure that sites are assigned to studies that align with their patients' needs and provide them with more treatment options. We rely on our in-depth data to help sites avoid the disappointment of not being selected. Parexel is available to sites 24 hours a day, seven days a week, in every time zone worldwide. We are the point of escalation for sponsors and provide uninterrupted site support.

Sponsors will always have the final say on where they conduct their trials and whether they will consider community sites. However, when sponsors and CROs manage the risks through due diligence, continuous support, and fast and effective troubleshooting, community sites can accelerate recruitment and enrollment and increase patient access.

Compensate fairly and on time. One of the greatest challenges for sites in clinical research today is getting paid on time.[8] The problem is especially acute in cancer studies, which involve long-term commitments and are resource- and labor-intensive. Sponsors should consider the complexity of a protocol to ensure adequate payment for the work that sites perform. We advocate for sites by characterizing the burden of each protocol separately and have a team dedicated to handling contracts and payments.

Developing regulatory strategies for precision oncology

With the launch of its Project Optimus in 2021, the U.S. Federal Drug Administration (FDA) transformed the study designs and dosing assumptions that had dominated decades of oncology drug development. The agency hopes that the added time and cost of collecting comprehensive dose- and exposure-related data will benefit patients by ensuing that cancer drugs are effective and safe and improve their quality of life. It also should benefit sponsors by defining the benefit-risk profile of new cancer products more precisely.

Recent studies have found that treating patients with lower doses of precision oncology medicines for a shorter duration may lessen toxicities, allowing patients to remain on treatment longer, ultimately leading to better efficacy.[9] Extensive dose optimization requires sponsors to enroll more patients, gather more data, conduct more thorough analyses, and spend more time and resources on early-stage oncology trials. This can be challenging for small biotechs with limited funding and in-house expertise. However, small biotechs play a critical role in

precision oncology, originating 46% of first-in-class cancer drugs approved by the FDA from 2010 to 2020.[10]

At Parexel, we work with sponsors to develop regulatory strategies that achieve comprehensive and compliant dose optimization within their business constraints. We have identified three strategies that work.

Design an integrated first-in-human study. This approach mitigates risks by systematically removing the uncertainties at each stage: dose escalation, dose optimization, and dose expansion. Slowing down for a few months to design a robust, flexible, data-rich, and adaptive Phase 1/2 trial will result in a faster overall development time. A sponsor can always pause between portions of a seamless trial to seek investors or a co-development partner.

Reach agreement with the FDA at each step. The agency has clarified that discussions about dose-finding strategies need not be tied to milestone meetings. Sometimes, a separate meeting is warranted as clinical data becomes available.

We advise sponsors to design a randomized dose-finding study after analyzing all the data from preclinical studies and clinical data from the dose-escalation portion of an integrated trial. Companies need to present a complete data package to justify the dose-optimization plan. We provide extensive guidance to sponsors to help them prepare before meeting with the FDA.

Challenge guidelines with a complete rationale. A regulatory guideline is not the law, and development decisions are the sponsor's responsibility. If sponsors can justify deviating from the guidelines with scientific evidence, they should make their case. Understanding nuances in the attitudes and priorities of regulators is critical to crafting an effective strategy and making compelling arguments.

Planning for a co-developed companion diagnostic test

A biomarker test that can identify patients most likely to benefit from a drug raises the probability of success for a clinical trial and leads to a higher return on investment. [11] Although the FDA has approved several targeted oncology drugs without a companion diagnostic test (CDx), in recent years, a missing assay could negatively impact market update, patient safety, and access.[12]

However, developing a CDx to stratify patients often requires sponsors to transition from a research-grade to a clinical-grade assay. This is a multidisciplinary resource management challenge, especially for emerging companies.

We often work with companies preparing for pre-Investigational New Drug (pre-IND) meetings with the FDA that suspect they will need a CDx to select patients during development but have limited data. From decades of advising CDx developers, we have refined five strategies for maximizing the benefits of IND meetings and streamlining the development process.

Set clear goals for every meeting. For example, if you plan to use a test to stratify patients in the Phase 1 trial, there are three critical objectives:

- Ensure that the FDA agrees that you have done adequate analytical validation of your proposed test, especially around the cutoff.

- Make sure the agency concurs with your assessment of the risks of the testing device.
- Get detailed feedback on your Phase 1 study design, including the number and timing of tests and how the results will be used.

Ask pointed questions. The FDA reviewers do not want to design your study; they prefer to offer targeted comments. It's better to make proposals and request a response than to ask open-ended questions in early-stage CDx regulatory meetings.

Read the room. You can reduce the risk of having your plans changed by the FDA after the fact by presenting a high-level plan first. For example, human factor (HF) studies mitigate risk by ensuring that the assay labeling is understandable to users. We advise presenting the FDA with a high-level summary of the HF study plan, then letting agency reviewers fill in the blanks with their recommendations. At the same time, gauge their responses and body language (if the meeting is in person or in a videoconference) and note their questions.

Have a contingency plan. When you are on a tight deadline, think ahead about whether the FDA will agree with your approach—for example, about how the assay will be used in the study—and be ready to respond.

Adapt quickly. Sponsors must conduct an exploratory study early to determine whether they need a biomarker. By Phase 2, ideally, they must know whether they need a CDx to stratify patients or whether they can test efficacy in an all-comers trial. By Phase 3, they need a validated, clinical-grade selection tool. However, sometimes the FDA can require a CDx unexpectedly. Planning ahead and quickly adapting is more efficient and less burdensome than spending months (or years) recovering from setbacks.

Accelerating biomarker development

Most oncology-focused companies are eager to incorporate biomarkers because they recognize their value in clinical development. It's encouraging to see more oncology drug developers consider collecting and correctly storing patient samples for biomarker research. However, there are no reliable and qualified biomarkers for many cancers. At Parexel, we use next-generation analytic tools and technologies to help clients identify diagnostic, prognostic, and predictive biomarkers that can be validated in subsequent development.

Recent advances in multi-omics and computational analytics have accelerated the discovery and validation of biomarkers in precision oncology. Multi-omics refers to the diverse data streams from genomics, proteomics, and metabolomics, which have transformed how to search for and validate biomarkers in cancer.

Conventional biomarkers measure the level or presence of one modality, such as the protein expression of a single gene (or a set of genes) or a specific type of circulating cell(s). Multi-omics increasingly enables us to construct more complex hybrid biomarkers that may more accurately diagnose, prognose, and predict patient outcomes.

Advances in computational AI analytics, including machine learning (ML) and deep learning (DL), have allowed us to combine conventional omics with newer omics, such as spatial genomics. The ever-expanding body of omics data is so large that we could not make sense of it without these powerful new tools. For example, ML/DL can automate the processing and classification of imaging data from histopathology, which is used to diagnose and prognose cancer patients and predict their response to therapy. The visual interpretation of cellular and tissue biology captured in slide images that have been digitized would not be possible without automating this historically manual process.

It's inspiring to see that AI and other analytical advances accelerate cancer drug development and provide direct patient benefits. You need a diagnostic biomarker for an accurate diagnosis, a prognostic biomarker to stratify the patient population, and a predictive biomarker to find patients with the best chance of a response. These help with the sometimes exhaustive inclusion/exclusion criteria for trials of precisely targeted therapies and guiding treatment with existing therapies.

Broadening patient access

As we conduct much more targeted and focused clinical studies, we can ensure that patients with a high likelihood of responding are included the trial. It's no longer experimental with patients going through several regimens; instead, we better understand the triggers behind the cancer. Hence, we can show a positive result more quickly with smaller numbers of patients, and with less toxicity and fewer side effects.

And as the field of biomarker discovery and application has revolutionized treatment options, regulatory advances relative to accelerated pathways and breakthrough therapies have allowed drugs to come to market far more quickly. **To become widely available to patients, however, payers such as Medicare and commercial and national health insurance providers must agree that the therapies are truly innovative and address unmet needs.** Is there a desirable clinical outcome compared to the standard of care? Is there post-market data relative to the patients' lived experience? Is there demand for the product within the healthcare ecosystem? And, critically, are we seeing the expected results in a larger population?

These questions can be addressed in many cases after regulatory approval by analysis of real-world data (RWD) and real-world evidence (RWE). Quite simply, RWD refers to redacted healthcare records that can provide insights on a broader scale about which patients have characteristics likely

to respond favorably to the treatment. We can analyze data by age, demographics, comorbidities, and increasingly, genomic factors. RWE allows us to look at a population of patients who have a similar diagnosis by tumor type or diagnostic codes. We can look across health institutions, regions, and geographies and understand how those with a given diagnosis are treated. How do they flow through the healthcare system? Who responded and why?

These insights inform our clinical research. We can use this knowledge relative to where we recruit clinicians and patients, considering locations and individuals who might have been underrepresented. Indeed, in the U.S., the Centers for Medicare Services is expecting more equitable access to therapies across the population. The FDA, too, is mandating greater inclusion and representation in clinical studies. **RWE is a powerful enabler to help us meet these expectations, giving us data available in a format that is usable with the computing capabilities now available.** All these factors are coalescing to help us meet the goal of all stakeholders—patients, clinicians, hospitals, payers, regulators, and drug developers—to improve human health and extend life.

For more comprehensive insights on these topics, please explore our interactive digital report on precision oncology. You'll find additional observations and recommendations from Parexel experts who are doing everything humanly possible to advance precision oncology to improve outcomes for patients and their families.

1 Falke, V. (2023, April 19). *Unleashing the NAS wave: Transforming cancer care & world economies*. LinkedIn.

2 Terry Morey: A Stage 4 Lung Cancer Survivor (Lung Cancer Canada, 2020).

3 American Association for Cancer Research, *Nearly Half of Oncology Drugs Approved Since 1998 Are Precision Therapies*.

4 The Future of Precision Oncology (International Journal of Molecular Science, August 9, 2023).

5 For Squamous Cancers, the Streetlamps Shine on Occasional Keys, Most Baskets Are Empty, and the Umbrellas Cannot Keep Us Dry: A Call for New Models in Precision Oncology (Journal of Clinical Oncology, January 8, 2024).

6 Practical challenges for precision medicine (Nature, January 11, 2024).

7 Rising Protocol Design Complexity Is Driving Rapid Growth in Clinical Trial Data Volume (Tufts Center for the Study of Drug Development, 2021).

8 Site Payments Still a Pressing Issue for Clinical Trials, Industry Agrees (CenterWatch, September 26, 2022).

9 Dozens of precision cancer drugs tested at lower doses to reduce side effects and cut costs (*Nature Medicine*, March 5, 2024).

10 Small biotechs versus large pharma: Who drives first-in-class innovation in oncology? (*Drug Discovery Today*, February 2023).

11 Delivering the precision oncology paradigm: reduced R&D costs and greater return on investment through a companion diagnostic informed precision oncology medicines approach (*Journal of Pharmaceutical Policy and Practice*, July 5, 2023).

12 Missing Companion Diagnostic for US Food and Drug Administration-Approved Hematological and Oncological Drugs (*JCO Precision Oncology*, May 4, 2022).

We're always available for a conversation.

With Heart™

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