Cerba Research

A best practice guide for laboratory services in oncology trials

Leveraging customization and flexibility

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Insights into the importance of customization:

Gain a deep understanding of essential tailor-made laboratory services required for achieving clinical trial endpoints.

An agile approach for oncology trials:

Learn about oncology trial best practices in laboratory services and why it is important to build in flexibility.

Leveraging laboratory services providers' capabilities:

Discover how you can effectively bring together outsourced laboratory services to advance oncology trials, including customized assays, a global laboratory network and more.

Flexibility and customization to advance oncology trials

Cancer continues to be an important public health threat worldwide.[1] In 2022, there were nearly 20 million reported new cancer cases and 9.7 million cancer-related deaths.[2]

Researchers also predict a steep increase by 2040, with the number of new cancer cases skyrocketing to 28.4 million.

Over the last decade, oncology research advancements have helped reshape our understanding of cancer biology and targeted treatment options, shifting efforts toward more stratified and personalized medicine. At the heart of these advancements are genomic techniques, like broad-based approaches with next-generation sequencing (NGS) and bioanalysis of specific biomarkers for patient and therapy selection.

We have entered the era of precision medicine, where treatments are tailored to individual patients.

Oncology trials are undergoing a transformative shift, developing therapies that directly target cancer cells and aim for more efficient treatments with a better safety profile. This approach aims to improve quality of life, extend progression-free survival rates for cancer patients, and increase overall survival.[3]

In the fast-evolving landscape of clinical research, breakthroughs in tissue microenvironment assays, immunoassays, and genetic/genomic assays have transformed our understanding of diseases at the tissue and molecular levels. As innovation in molecular assays continues, combined with our ever-expanding knowledge, new techniques are emerging for faster diagnosis, more precise prognosis, and greater effective treatment options.

"The shift to precision oncology represents an exciting period in cancer research but also creates challenges for researchers working in the biotech and pharmaceutical communities."

To help tailor treatments to tumors' individual properties, translational oncology research now focuses on understanding the interactions between a tumor's unique characteristics and a particular treatment.

Precision oncology can match drugs that target specific oncogenic pathways for individualized treatment options using small organic compounds and monoclonal antibodies.[4]

These shifts represent an exciting period in cancer research, but they also create challenges for researchers to adapt to a rapidly evolving field and conduct studies that address cancer's complexities.

Having an agile and optimized approach when managing studies, from the first meeting and initiation of the study, is fundamental to overcoming the challenges associated with international oncology clinical research.

This applies to all the outsourced laboratory services from protocol review, project management, assay selection and design, site management, kit and sample shipment/supply management, harmonized test set-up (between processing/third party laboratories) to final data analysis, reporting, and delivery of the study results.

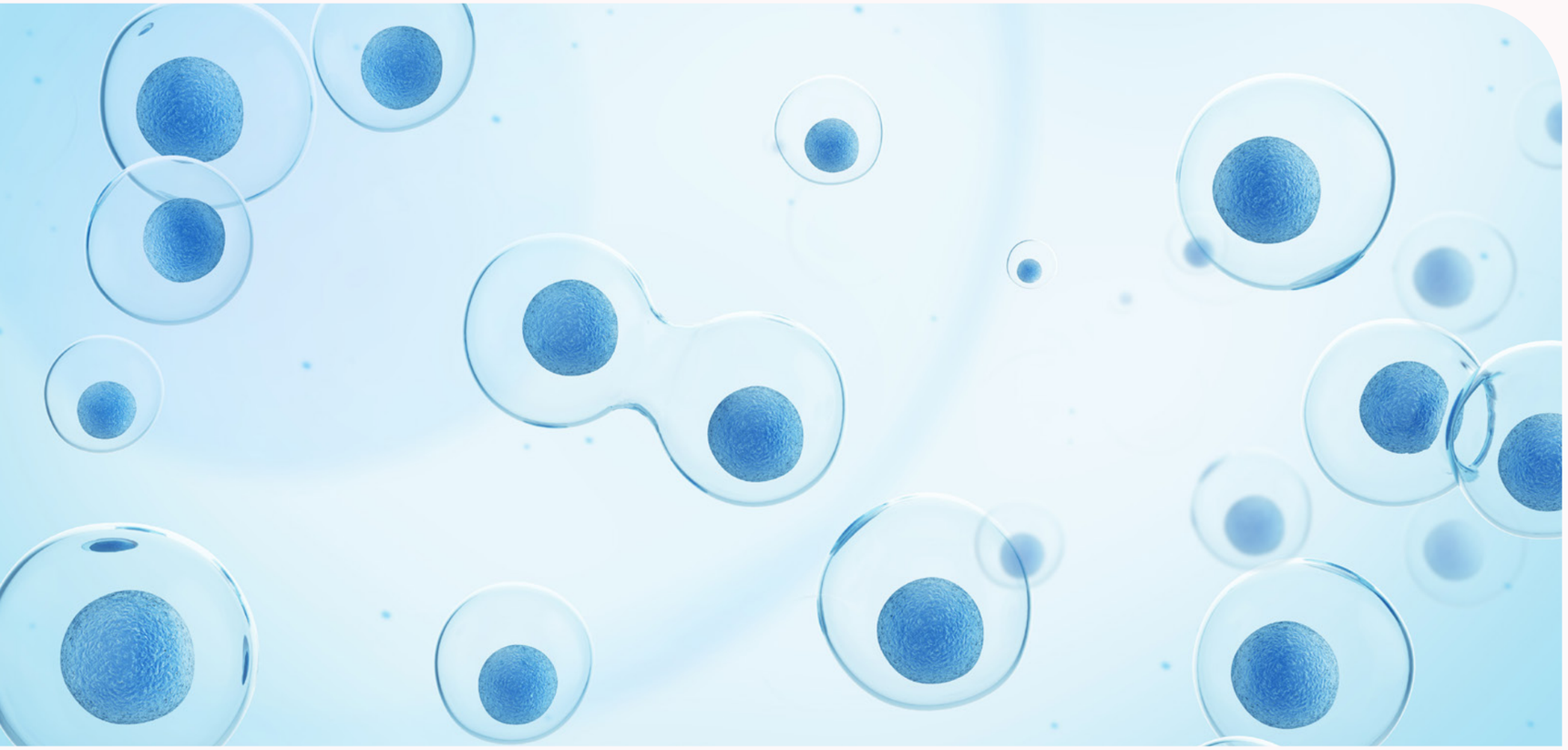
Specialty laboratory service providers recognize and understand the significance of early engagement with customers during the study design phase and how it helps ensure preparedness for agile laboratory testing solutions further down the clinical line. Selecting a specialized laboratory that offers unique immunoassays, advanced flow cytometry, and cutting-edge genomics and histopathology services is crucial for conducting high-quality clinical research in oncology.

This enures the precision and accuracy necessary for advancing medical knowledge and ultimately saving lives.

Chapter 1

Supporting novel trial designs

Precision medicine, or personalized medicine, has become essential in cancer care. It is built on "the usage of phenotypes and genotypes for tailoring the right therapeutic strategy for the right person at the right time."[5]



Central to the era of precision medicine is the recognition that patients with the same disease, or even subtype of disease, are different from one another.[6]

Targeted therapeutic agents were initially studied in traditional clinical development pathways, like those used to study the safety and efficacy of chemotherapy, centered on tumor location and pathology.[3]

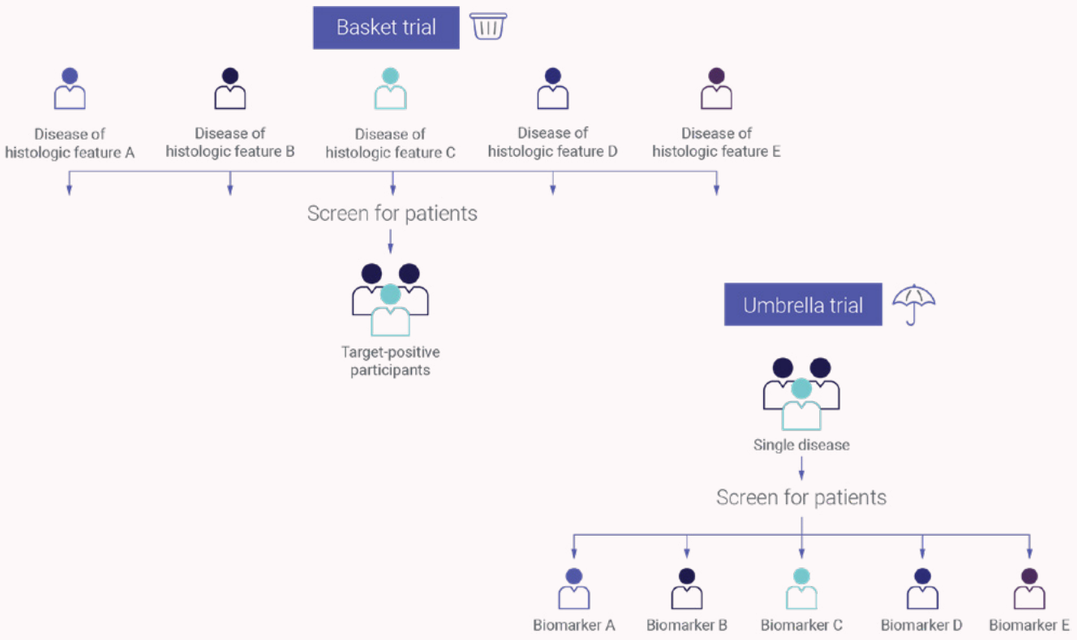
However, when data emerged showing the efficacy of matching treatments to molecular targets independent of tumor type, it ushered in a new era of drug development. The oncology field rapidly responded to create new development pathways.[3]

In the past, a single traditional clinical trial would have been carried out to study a drug in patients with particular clinical characteristics or genotypes.[6]

These "intervention-focused" trials are inefficient, time-consuming, and do not allow for the rapid adoption of effective therapies.[6,7]

Therefore, over recent years, alternative types of clinical trials have become increasingly employed within the field of oncology.[6,7]

This shift in clinical trial strategy plays no small part in the abundance of new treatment options for cancer, many of which are targeted to specific molecular alterations.[6]

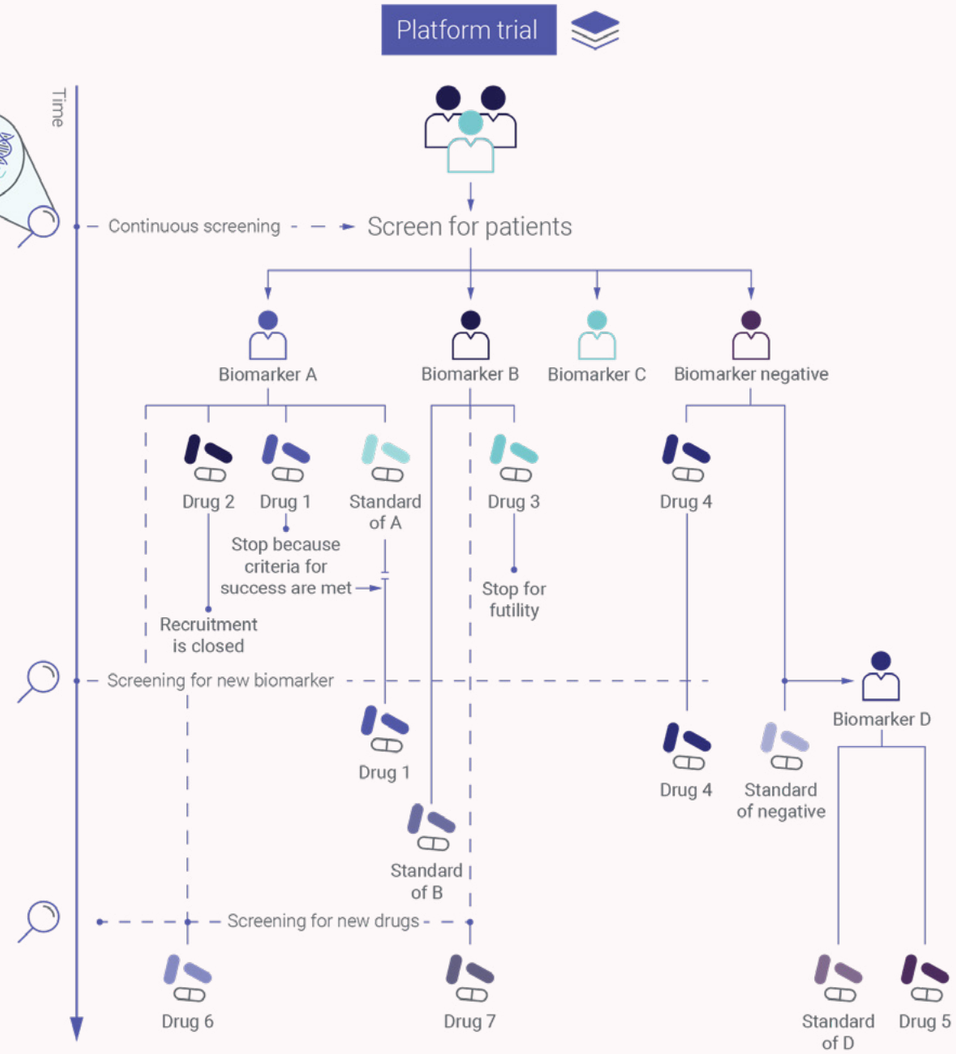


Precision medicine trials

In recent years, significant progress has been made in developing new methodologies in patient-centric trials, namely, using basket, umbrella, and platform trial designs under a master protocol framework.[6] These trial designs test multiple therapies, individually or in combination, and multiple diseases under a single protocol.[8]

An umbrella study investigates different treatments for a single disease according to biomarker status.[6,3] Meanwhile, a basket trial investigates the same therapeutic intervention in patients according to molecular characteristics and biomarkers, irrespective of the tumor type.[6,3] Over the last decade, a different kind of clinical trial, a platform trial, has increasingly been employed.[7]

These trial types employ screening protocols to enroll participants based on molecular characteristics. However, similar to traditional clinical trials, umbrella and basket trials are



based on a fixed protocol with a defined number of interventions and endpoints.[9,6] This has led to the development of platform trials, which incorporate many of the characteristics of umbrella and basket trials but with additional flexibility and adaptability.

Platform trials are "disease-focused" trials that allow the trial design to be adapted based on the data accumulated throughout the study.

For example, an arm can be removed if interventions are ineffective, new interventions are added, or the control arm intervention is changed.[6]

This reflects the dynamics of oncology in which therapeutic discoveries are frequently made[3] and where new standards of care that arise during the trial's duration can be incorporated into the trial design.[9]

Platform trials can theoretically run indefinitely. The largest platform trial to date was the STAMPEDE trial for high-risk localized or metastatic prostate cancer. This lasted for 18 years, enrolling 12,000 participants and studying 11 interventions throughout the trial.[6,10]

These types of trials also directly benefit participants. Due to the inclusion of multiple cancer types and biomarkers, patients are less likely to fail inclusion screening[8] and, once enrolled in the trial, are less likely to be assigned a placebo than if they were to enroll in a traditional registration trial.[11]

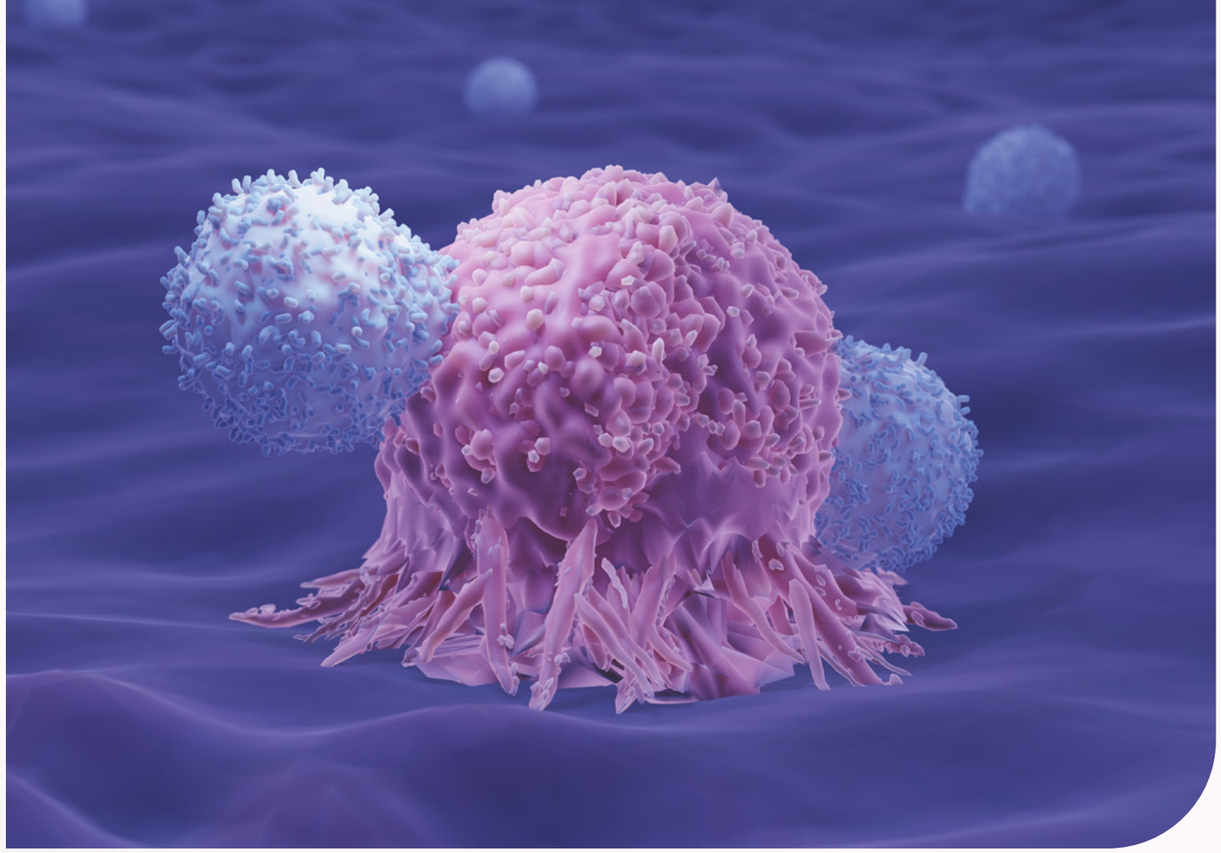
Chapter 2

Customizable assays

Current discoveries about the underlying genetic, epigenetic, metabolomic, and proteomic alterations in cancers are opening doors to personalized therapies and uncovering important biomarkers.[5,13] Scientists now have access to a diverse range of upstream and downstream guideline-compliant protocols.

Typical techniques used to identify and monitor molecular alterations, such as driver mutations and protein over-expression, include broad-panel next-generation sequencing (NGS), immunohistochemistry (IHC), fluorescence *in-situ* hybridization (FISH), and enzyme-linked immunosorbent assay (ELISA) assays.[14]

When setting up the operational execution of an oncology trial, both off-the-shelf and customizable assays must be considered. Here, we discuss the most prevalent assays.



Flow cytometry

Flow cytometry (FCM) is relevant to personalized therapy, as validating biomarkers is central to their use primarily for hematological malignancies and cell and gene therapy trials. Since the development of chimeric antigen receptor-T (CAR T) cell therapies, FCM has gained increasing traction as a critical tool. FCM can be used throughout the lifecycle of CAR T cell therapies, from its manufacturing phase through post-infusion.[21]

With custom-made FCM panels, immune cell activation, immunophenotyping, drug-receptor occupancy, CAR T cells, and minimal residual disease can be monitored to ensure patients receive the most effective and safe treatment.

It is also a particularly powerful tool for biomarker detection and identification of unexpected immune system dynamics and can even be employed for retrospective analysis.

Ligand-binding assays

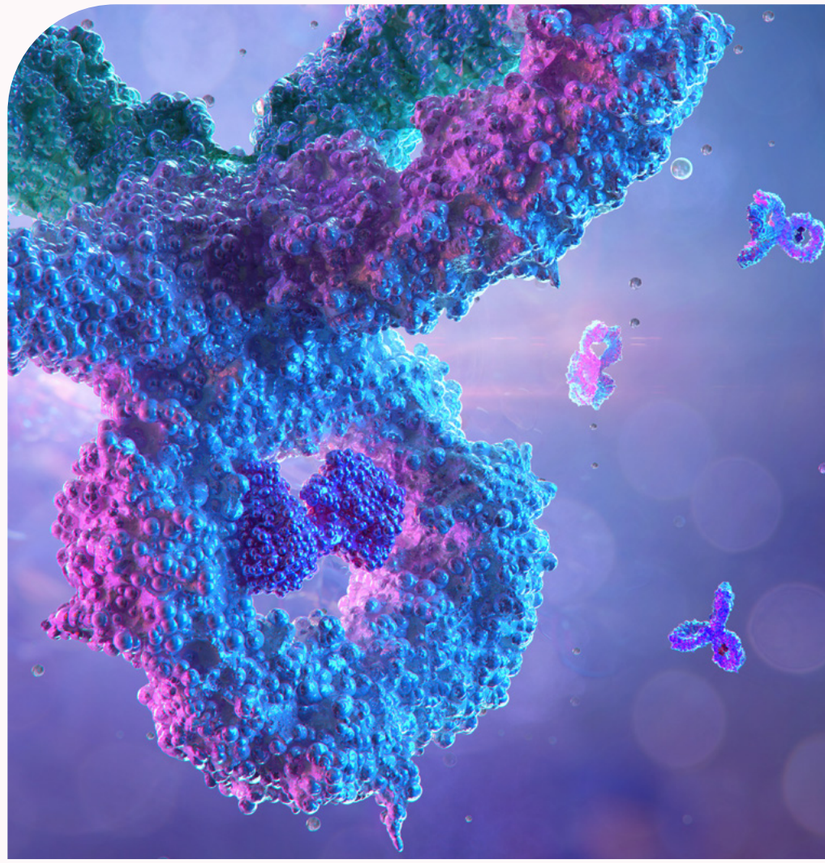
Ligand binding assays (LBAs) are versatile tools designed to work with a broad spectrum of ligands for various applications. One prominent example of an LBA is the Enzyme-Linked Immunosorbent Assay (ELISA), which is utilized for the detection and quantification of soluble substances like peptides, proteins, antibodies, and hormones.

In ELISA, the antigen (target protein) is immobilized on a solid surface, typically a microplate. The detection of the target antigen is achieved by complexing it with an antibody that is linked to a reporter enzyme. The activity of this reporter enzyme is then measured, providing a method to accomplish detection.

This plate-based technique is highly reliant on the specificity of the antibody-antigen interaction, which is considered the most crucial element of the process.

As commercial ELISAs may not be sensitive enough, it is recommended to engage with a laboratory services provider that can customize the development.

A more sensitive approach can then be applied to improve precision and accuracy.

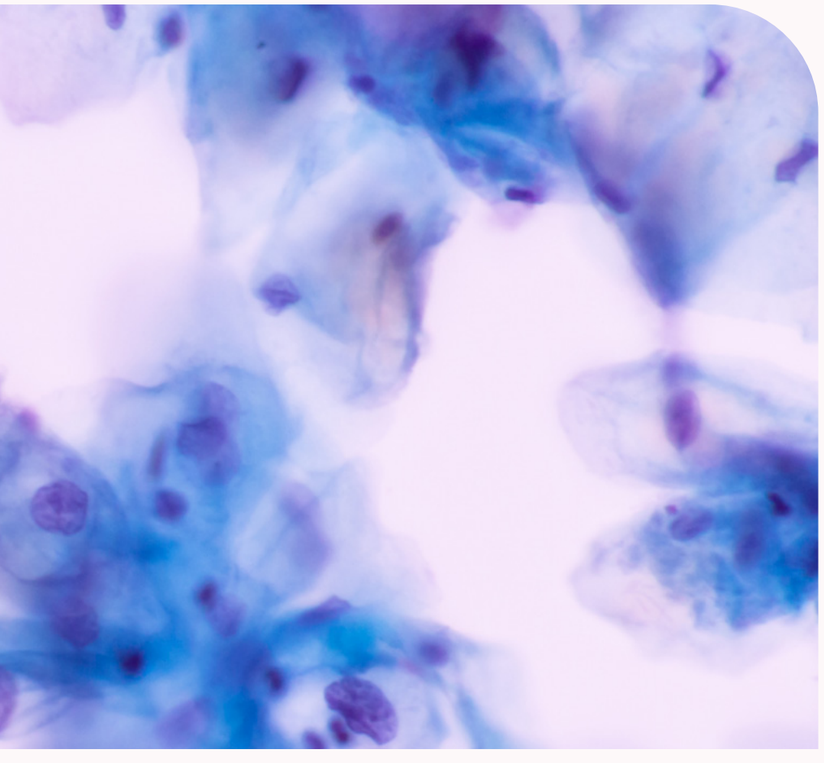


Genomics and Next-Generation Sequencing

With the revolution of high-throughput techniques, molecular sequencing has become a key informant in oncology clinical trials. Recommendations for clinical trials using NGS methods are based on cancer diagnosis and the genomic mutation profile of patients with high sensitivity.[15]

NGS can be performed using targeted gene panels, whole-genome, or whole-exome sequencing. Many clinical trials for advanced solid tumors are now integrating comprehensive NGS assays to identify actionable genomic alterations and mechanisms of resistance.

NGS broad-panels can identify rare and actionable driver mutations, such as rearranged during transfection (RET) fusions and neurotrophic tyrosine receptor kinase (NTRK), and may be carried out using either tissue (e.g., formalin-fixed paraffin-embedded (FFPE)) or blood (e.g., circulating tumor DNA (ctDNA) or liquid biopsy).[16]



ctDNA panels

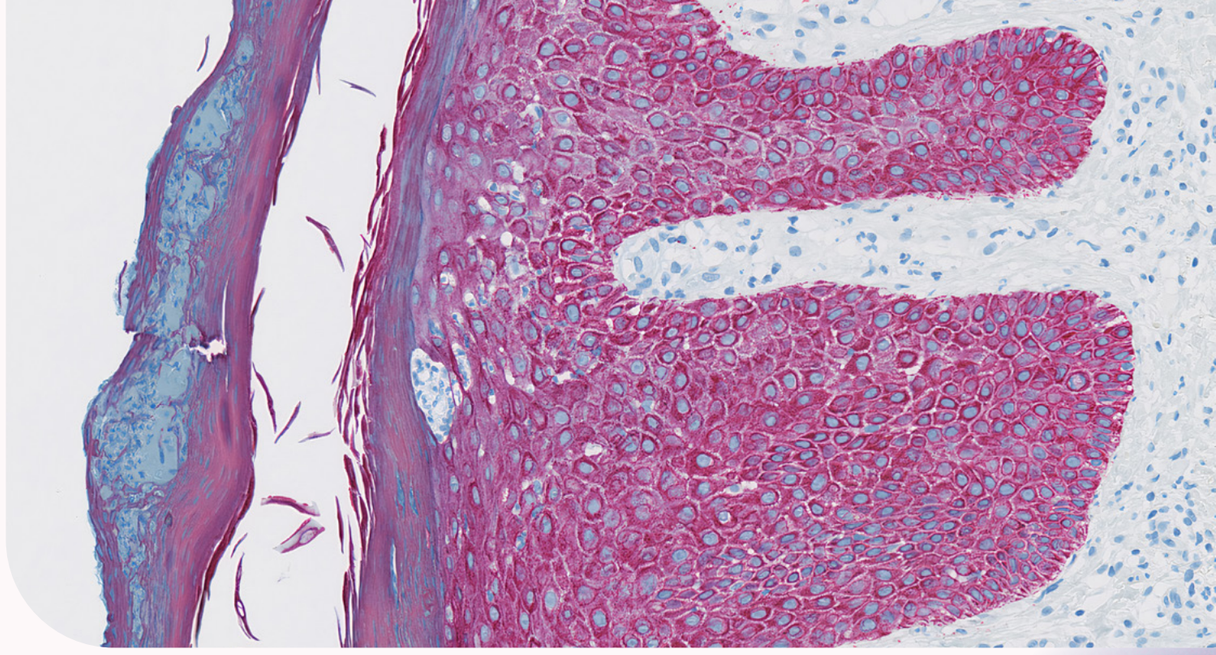
A growing body of evidence upholds the expanding value of liquid biopsies, most commonly known as ctDNA, for the care of patients with solid tumors. This technique reveals information about solid tumor genotyping by examining biomarkers circulating in a cancer patient's peripheral blood.

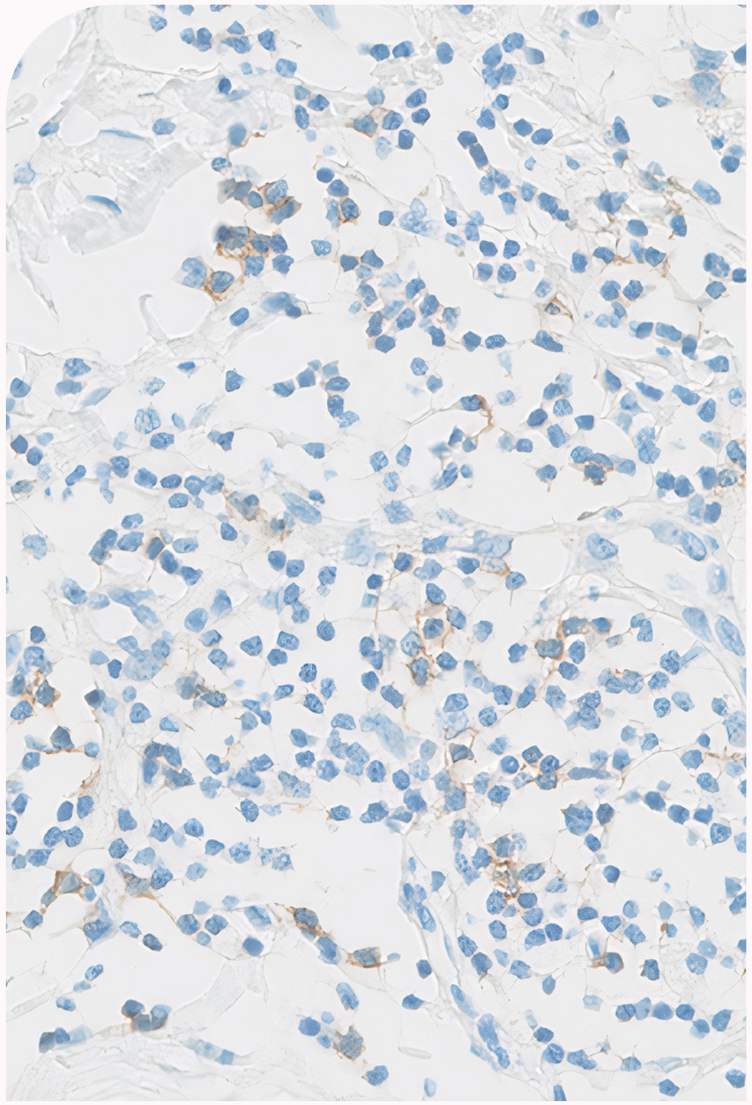
It is proving to be a complementary diagnostic and prognostic tool in conjunction with other methods for solid tumors.

It can also be used for minimal residual disease (MRD) detection and tumor mutational burden (TMB) status, as well as for identifying driver mutations and resistance mechanisms.[17,18]

With extensive expertise in genomic assays, specialty laboratory services providers can offer a range of liquid biopsy assays from its existing ctDNA-based panels, customize a new panel, or add a new gene to an existing panel specific to your trial.

Histopathology and immuno-histochemistry





Immunohistochemistry (IHC) can be deployed as a rapid screening tool for many biomarkers, including ALK, ER, PR, HER2, and PD-L1. Personalized IHC biomarker assays may significantly increase the odds of clinical trial success.

Effective IHC protocol development and validation tailored for anatomic pathology and tissue analysis are essential. This requires the collaborative support of specialty teams working on laboratory analysis, data management, and advanced software solutions for image analysis that incorporate artificial intelligence and deep learning.

NanoString® Technologies

NanoString GeoMx® digital spatial profiler (DSP) provides a spatial and temporal examination of tumors in small, frozen/FFPE preserved tissue samples. High-impact studies have noted the viability of this technology in clinical research. It is believed to result from its increased capacity to assess more biomarkers for immune therapy in different tissue microenvironments.[19]

With NanoString®,[20] over 22,000 genes and 150 proteins can be analyzed from human and other mammalian target samples. A variety of human RNA panels are available for the analysis of whole transcriptomes, cancer transcriptomes, and targeted immune pathway panels.

Chapter 3

Integrating a flexible approach to laboratory services

International clinical trials that enroll large patient populations across many regions in later phase trials produce timely clinical data that can provide evidence for or against using novel oncology treatments much faster.

Geographically diverse patient populations in oncology clinical trials also help to improve the generalizability of clinical results, as opting to include broader genomic, biological, ethnic, and socio-cultural backgrounds helps to broaden the applicability of results to wider patient populations. International collaboration is also vital in facilitating research on rare tumors and particular molecular subtypes.[22,23]

Although the benefits of international collaboration for oncology clinical trials are clear, challenges that hamper their efficiency and effectiveness still need to be addressed. As clinical trials are guided towards precision oncology, they are becoming much larger and more complex, with continuous protocol deviations and complex regulatory compliances.

When selecting a laboratory partner, the key considerations with regard to scale are:

- Which assays do you we need to take into consideration?
- How large is your trial?
- How many samples will need to be processed and when?
- How many countries are you working across?
- Are you looking at 'Non-Traditional Regions' outside of North America & Europe?
- Is your biomarker assessment for primary, secondary or exploratory endpoints?
- Can your laboratory partner reliably manage end-to-end logistics?

Agile approach to overcome operational challenges

To deal with these complex challenges, deep expertise is required on the laboratory operational aspect of clinical trials. It is essential to partner with a laboratory service provider who can offer solutions to such complexities and understands the importance of having the most state-of-the-art expertise and equipment alongside an agile and optimized approach.

This is applicable and advisable for both solid tumor and hematological malignancy trails. Typical diagnostic capabilities to advance oncology trials include:

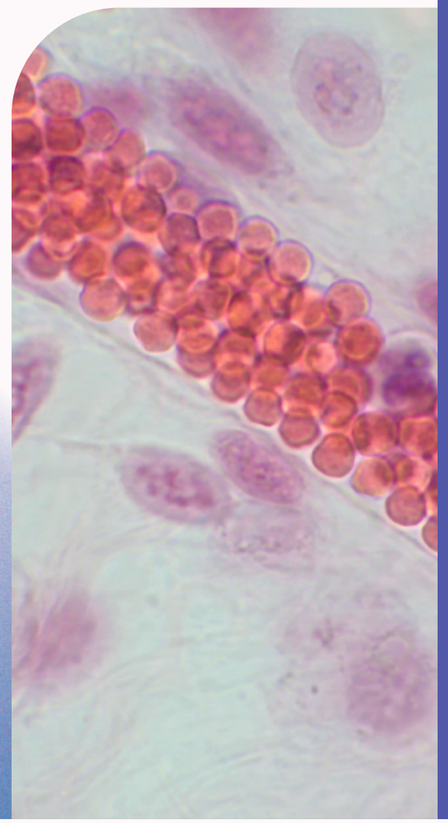
- Early detection of cancer for faster diagnosis, prognosis, and treatment.
- Tumor mutational burden (TMB) status for better prognosis to guide clinical trials.
- Early identification of driver mutations for more optimal precision medicine research and development.
- Real-time evaluation of tumor resistance mechanisms.
- Minimal residual disease (MRD) detection and monitoring by flow cytometry and more.

Peripheral blood mononuclear cells PBMCs

Downstream testing requirements can drive the choice of PBMC protocols.

Many oncology studies use off-the-shelf collecting tube solutions. The isolation of PBMCs serves as a foundational step for numerous downstream applications. These include further isolation of specific cell subsets and extraction of PBMC DNA/RNA for clonal diversity analysis applied by T-cell receptor (TCR)/B-cell receptor (BCR) sequencing, among other techniques.[13] Management of samples around the world, or even across Europe or the US, is mission-critical to any trial, even more so when dealing with labile and critical biospecimens such as PBMCs.

To ensure sample integrity, extensive knowledge of cold-chain management and specialized logistics is required, including regulations and directives outlined by the ADR (European Agreement concerning the International Carriage of Dangerous Goods by Road) and the International Air Transport Association (IATA).

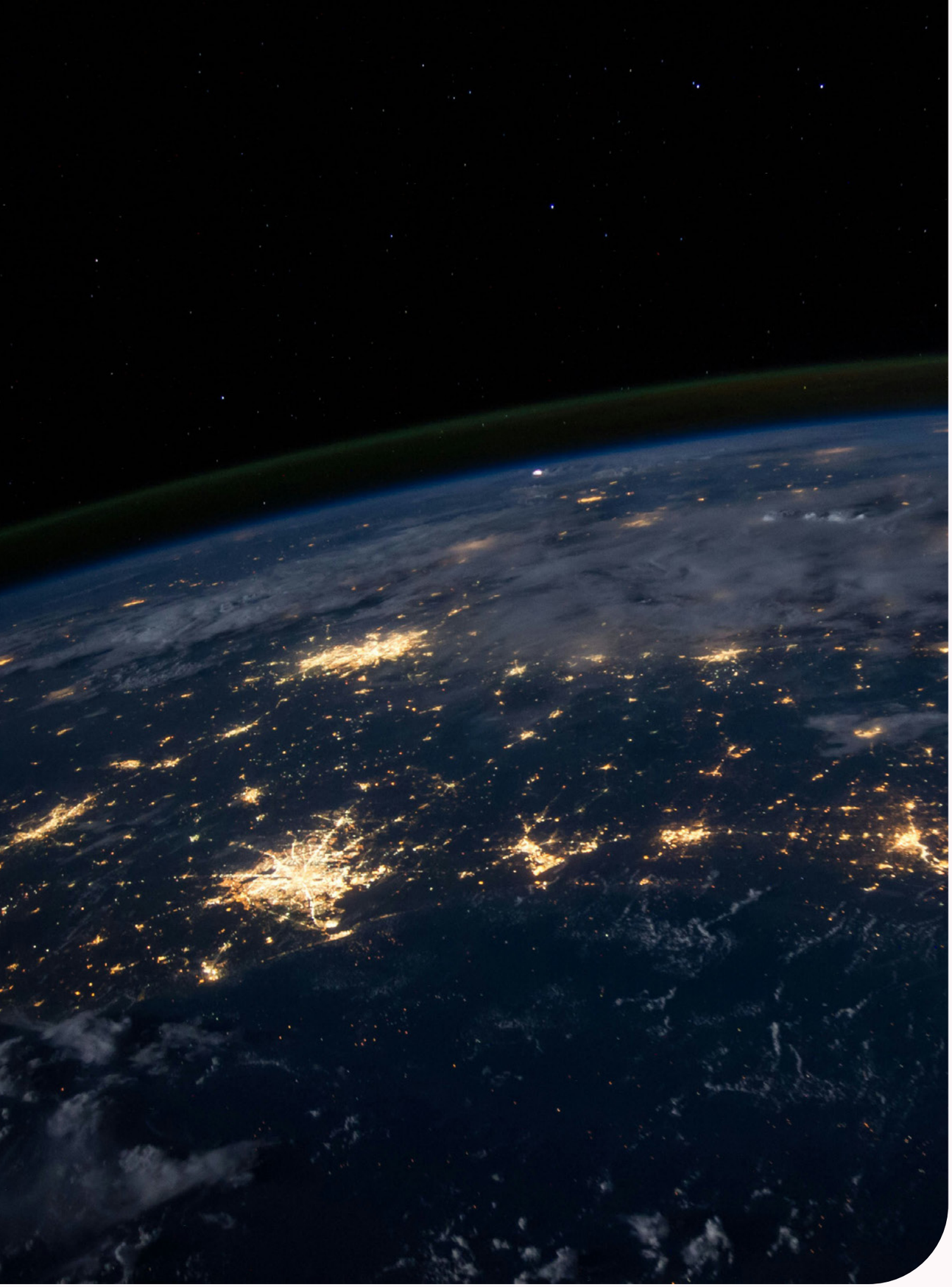


Biobanking and Tissue Acquisition

Effective patient selection is pivotal in clinical trials, and the creation of companion diagnostics for this purpose heavily relies on efficient biospecimen collection.

Biobanks are also becoming increasingly valuable in oncology trials as they bridge the gap between basic and translational research. Biobanks containing thousands of samples of normal and tumor tissues are required for large-scale validation in early cancer detection.[23] With advances in high-throughput assays for genomics, proteomics, and metabolomics comes a further increase in the requirement for bio samples for clinical trials.[24]

Standardized biobanks containing high-quality biosamples and appropriate clinical information in accordance with rules and regulations, are vital for consistent, accurate, and verifiable clinical outcomes. More recently, the establishment of living biobanks, such as organoid biobanks, permits much longer-term storage of viable, functioning tissues. From this, many types of cancer organoids have been produced to model cancer processes, along with cancer screening and drug discovery.[23] Formalin-fixed paraffin-embedded (FFPE) blocks and slides, for example, can be used for fit-for-purpose validation with downstream applications and analyzed in-house by various means, like IHC, ISH, FISH, NGS and NanoString® NCounter.



Operationalizing a global network

Swiftly operationalizing an established global central and specialty network is necessary to run oncology trials. It is of pivotal importance to look into challenges such as:

- How to harmonize assays in the outsourced clinical trial network
- Making sure that the highest quality of data is maintained when interpretating and processing data in a partner laboratory network
- Overcoming operational bottlenecks and scaling up clinical trials
- Accessibility to a network of scientific experts specialized in key aspects of modern-day R&D challenges, including ctDNA detection, broad-panel NGS assays, simplex/multiplex IHC and more.

Chapter 4

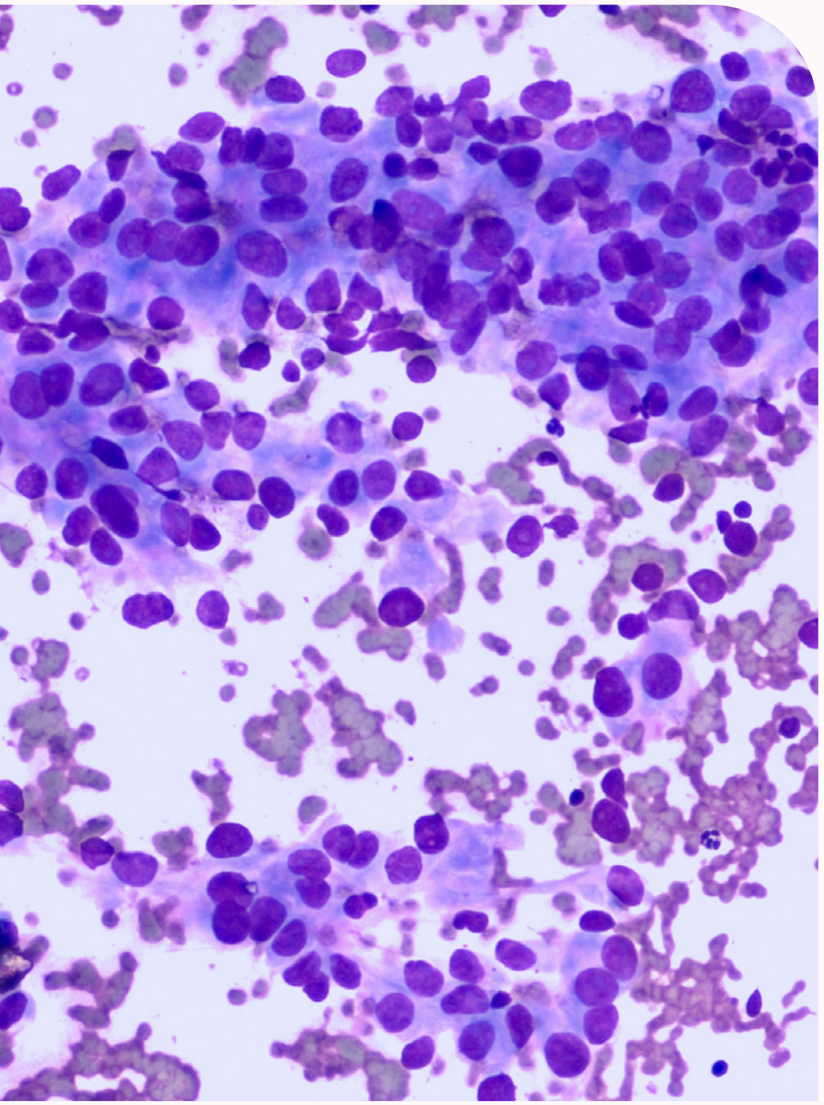
Strategizing for flexibility and customization through early engagement

By refining trial protocols and embracing adaptive design methodologies, researchers can maximize the success of clinical trials. This will ultimately benefit patients by bringing promising therapies to market more quickly.

Tailored assays and meticulous protocol guidance will fast-track drug development programs into clinical practice, ensuring that specialty testing capabilities align with various guidelines such as, but not limited to, the relevant Food and Drug Association (FDA) guidance documents, the International Myeloma Working Group (IMWG) consensus, the National Comprehensive Cancer Network (NCCN) guidelines and more.

Employing the right strategy to meet flexible clinical trial demands requires a synergetic approach to biomarker selection and the evaluation of up and downstream techniques for liquid and solid tumor trials.

Biomarker detection techniques



Biomarkers are measurable characteristics that indicate risk, occurrence, and patient outcome. These characteristics include transcriptional changes, proteomic signatures, germline/somatic genetic variants, driver mutations, and epigenetic signatures.

Biomarkers have many applications in oncology research, including screening and early detection, accurate diagnostics and prognostics, therapeutic response prediction, and monitoring in cancer patients.[25]

Biomarker detection techniques have advanced greatly over recent decades, and screening methods now rely significantly on biomarkers to optimize treatment decision-making. Cerba Research is dedicated to discovering, validating, and implementing novel biomarkers that improve patient selection in clinical trials.

Essential upstream techniques

Depending on the trial-specific requirements, the following upstream techniques need to be considered:

- Global scale, bespoke in-house logistics for comparable clinical studies, improving all stages of clinical trials.
- Peripheral blood mononuclear cell (PBMC) isolation to characterize host immunity to cancerous tumors for faster treatment safety and efficacy evaluation.
- Bone marrow mononuclear cell (BMMC) isolation provides relevant information about the toxicity of potential treatment.
- DNA/RNA extraction from various fluids or biopsy types is used for multiple downstream applications.
- Histopathology (bone marrow biopsy, MRD archival, extramedullary plasmacytoma biopsy, and so on) for faster and precise diagnosis and prognosis tools.

Crucial downstream techniques

A customized approach to downstream techniques will support swift turnaround times*:

- Flow cytometry for immunophenotyping, MRD detection (for multiple myeloma), CAR-T exploratory, T, B, and NK cell assays, and lymphocyte panels for improved antitumor safety and efficacy.
- Cytogenetics and fluorescence *in-situ* hybridization (FISH) to detect chromosomal changes in cells, aiding faster diagnosis and more successful treatment assignment.
- 250+ immunohistochemistry protocols (e.g., PD-L1, ER, PR, HER2) for better prediction of treatment response run in CLIA-accredited laboratories.
- Cell sorting, for example, CD138+ isolation and count, for a more accurate prognosis.
- The NanoString®, nCounter® pan-cancer immune profiling panel can assess about 770 genes in a single assay for faster detection of potential druggable targets. This capability is mostly used for exploratory reasons.[26]
- Genomic profiling assays: Cerba OncoSign 600+ panel (638 genes), Cerba OncoSign FFPE (50 genes), Cerba OncoSign ctDNA (50 genes), and more. Some of Cerba Research's panels can determine tumor mutational burden (TMB), microsatellite instability (MSI) and homologous recombinant deficiency (HRD) status.

*All downstream and upstream techniques align with the appropriate and required guidelines.

Evaluating downstream and upstream techniques and/or assays with a specialty laboratory company at an early stage is important to ensure that high-quality data output is safeguarded.

To ensure high-quality PBMCs, BMMCs, and other specimens, a global network of collection centers with harmonized protocols must be in place.

Upstream and downstream capabilities need to be orchestrated before a clinical trial can be executed.

Project management is crucial in aligning the trial's specialty and central laboratory elements.

Accessibility to a diverse pool of scientists and experts in flow cytometry, immunology, oncology, genetics/genomics, clinical trial operations, logistics, and data management is essential for appropriate protocol advice.

Conclusion

Cancer, is predicted to pose a growing public health threat in the coming years.[1] Nonetheless, advancements in understanding and treating the disease, particularly through the shift to precision medicine, offer hope. This approach focuses on targeted therapies based on molecular alterations and biomarkers facilitated by innovative, adaptable clinical trial designs. It necessitates a sophisticated and collaborative approach to clinical trial design, emphasizing the importance of strategic biomarker selection, flexible trial frameworks, and integrating standard and bespoke assays.

However, the complexity and scale of such trials introduce considerable operational challenges, including regulatory compliance and protocol management. Therefore, partnering with a laboratory service provider that combines cutting-edge expertise, state-of-the-art equipment, and an adaptive operational strategy is crucial to effectively navigating these complexities.

This collaborative and innovative approach promises to improve the efficiency and effectiveness of oncology clinical trials. It brings us closer to realizing the full potential of precision medicine in cancer care.

Find out how you can engage with our scientific experts to develop customized laboratory solutions.

Would you like to learn more?

Contact us

Cerba Research is a leading **speciality laboratory services provider** across all clinical development phases, to pharmaceutical, biotechnology, medical device, government, and public health organizations. It combines the deep scientific expertise of specialist services with the capacity and breadth of a **global central laboratory network.** Cerba Research develops innovative solutions to unique challenges in research and drives operational agility at scale for multiple therapeutic areas, with world recognized expertise in oncology, cell & gene therapy and virology. It is part of the Cerba HealthCare Group with 15,000 employees on five continents, driven to advance health diagnosis.

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