# Liquid Biopsy Obstacles and Opportunities in Clinical Research

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In clinical medicine, tissue biopsy is a standard procedure involving the removal of sample cells or tissues for examination. A few years ago, the term “liquid biopsy” (LB) was coined[1,2] to describe the use of circulating tumor cells (CTCs) as candidate tumor biomarkers in breast cancer. The existence of CTCs is not new, as their presence in the bloodstream was already documented in the middle of the 20th century.[3]

Originally reserved for the measurement of tumor cells or nucleic acids circulating in the blood, the term LB has now broadened to include the measurement of a variety of biomarkers in bodily fluids, such as urine, saliva, and cerebrospinal fluid (CSF). Recent advances in technology enable LBs to examine a spectrum of matrices, from CTCs and circulating tumor DNA (ctDNA) to soluble proteins, cell-free (cfDNA), cell-free RNA (cfRNA), and exosomes.

LB research has undergone an exponential evolution with rapid implementation in clinical practice. Some authors and clinical associations have proposed the introduction of LB in diagnosis[4] and treatment protocols, and different commercial systems have received government approval for clinical use.

In this review we explore the opportunities and challenges associated with LB and will focus on the following:

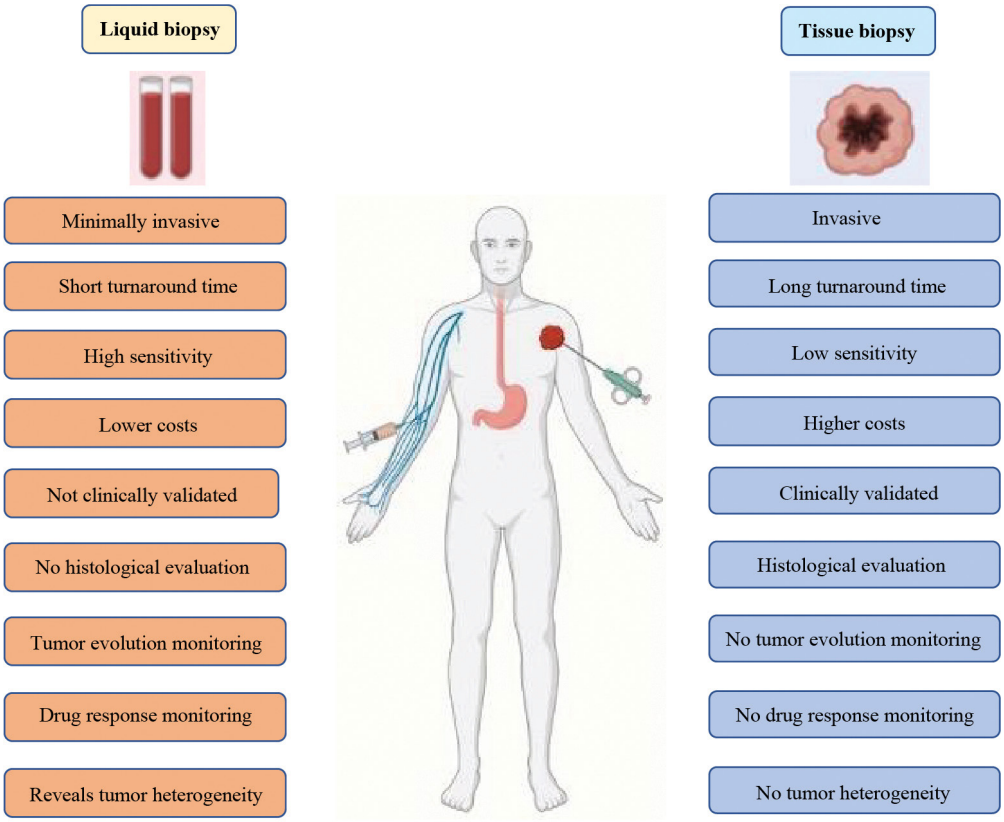
- The role of LB in relapsed or refractory solid tumors
- The role of LB in early-stage disease and minimal residual disease, and its potential application in drug-development
- Selection of biological markers for CTC detection
- Application of CTC-based LB in a Phase 3 Trial
- An overview of Precision for Medicine
- Conclusions and future perspectives

## The role of LB in relapsed or refractory solid tumors

Cancer is a spatially and temporally dynamic disease displaying substantial differences between primary and metastatic tissues and intratumor heterogeneity, which may lead to underestimation of the genomics landscape portrayed by a single tumor biopsy.[5] Though deemed the gold standard, imaging-guided biopsy of metastatic solid tumors is invasive, not amenable to repetition, and might be technically unfeasible or associated with unacceptable procedural risks.

LB, mainly encompassing ctDNA and CTCs, is swiftly advancing as a noninvasive complement—even often an alternative tool—to tumor biopsy and represents a paradigm shift for detecting tumor-specific genetic and epigenetic abnormalities and monitoring treatment response and resistance (see **Figure 1**).

**Figure 1:**




Comparison of traditional tissue biopsy and LB, with the advantages that LBs have gained over traditional invasive tissue methods over the past decade.

[1] Lianidou ES, et al. What's new on circulating tumor cells? A meeting report. *Breast Cancer Res*. 2010;12:307.
[2] Pantel K, et al. Circulating tumour cells in cancer patients: challenges and perspectives. *Trends Mol Med*. 2010;16: 398-406.
[3] Engell HC. Cancer cells in the circulating blood, a clinical study on the occurrence of cancer cells in the peripheral blood and in the venous blood draining the tumor area at operation. *Ugeskr Laeger*. 1955;117:822-823.
[4] Gregg AR, et al. Non invasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical genetics and genomics. *Genet Med*. 2016;18:1056-1065.
[5] Gerlinger M, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *NEJM*. 2012; 366:883-892.

The relapsed or refractory solid tumor setting is where LB provides the best clinical utility by guiding therapeutic decisions, informing trial eligibility for new drugs, and differentiating subjects who may benefit from dose escalation or early discontinuation strategies. Traditionally, Phase 1 trials of novel agents have recruited patients with all solid tumor types, whereas contemporary studies increasingly restrict accrual to specific molecular profiles in tumor-agnostic or tumor-informed settings.

ctDNA is tumor-derived DNA that is composed of small fragments of nucleic acid that are not associated with cells or cell fragments, and it is protected from blood nucleases by histones. ctDNA carries tumor-related alterations, which can be detected with next-generation sequencing (NGS) and polymerase chain reaction (PCR)–based methodologies.[6,7] Extensive and carefully controlled trials have shown elevated concordance rates (up to 90%) between plasma and tissue samples obtained concomitantly. Though wildly varying among subjects, ctDNA levels in individual patients correlate well with dynamic changes in tumor burden and may detect clonal heterogeneity in metastatic progression, which would not be captured by a single tumor specimen.[8] For instance, genomic profiling of more than 3,000 patients with metastatic castration-resistant prostate cancer found consistently increased ctDNA levels in those progressing on multiple treatment lines, likely representing a greater disease burden. In addition, the concordance rates between plasma ctDNA and patient-matched tumor specimens were greater with contemporary than with older tissue biopsies, highlighting the ability of ctDNA to track genomic alterations as they evolve with therapy.[9]

Treatment resistance commonly follows tumor response to targeted therapies. For oncogene-addicted tumors, ctDNA may quickly detect emerging genetic alterations linked to primary or acquired resistance to targeted agents and be used to tailor newer-generation therapies in highly and rapidly progressing metastatic patients. For instance, though lung cancer patients typically respond to first- or second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), the majority inevitably relapse within 1 year. Genomic profiling of relapsed tumors has revealed that most cases acquire a TKI-resistance mutation (T790M), which prevents TKI blockade by increasing adenosine triphosphate (ATP) affinity and steric hindrance. Irreversible third-generation TKIs can target both sensitizing EGFR mutations and T790M, and the assessment of EGFR mutations in ctDNA is now routinely included in the lung cancer workflow.[10]

For non-oncogene–addicted cancers, tumor mutational burden (TMB) quantified by ctDNA is actively being investigated as a predictive marker for response to immune checkpoint inhibitors (ICIs). Recently, an analysis of 2 independent cohorts of relapsed or refractory lung cancer patients receiving ICIs showed that blood TMB correlated well with matched tissue TMB and with tumor response and progression-free survival.[9,11] Still, rapid ctDNA clearance or decline has been associated with prolonged progression-free and overall survival, confirming that ctDNA may be an early predictor of outcome after treatment with ICIs.[10,12] Responses to ICIs may also be challenging to interpret because tumors often shrink slowly or can appear transiently enlarged due to inflammation (pseudoprogression).

[6] Alese OB, et al. Circulating Tumor DNA: An Emerging Tool in Gastrointestinal Cancers. 2022 ASCO Educational Book. https://doi.org/10.1200/EDBK_349143.
[7] Larribère L and Martens UW. Advantages and Challenges of Using ctDNA NGS to Assess the Presence of MRD in Solid Tumors. *Cancers*. 2021;13:5698.
[8] Corcoran RB, et al. Application of cell-free DNA analysis to cancer treatment. *NEJM*. 2018;379:1754-1765.
[9] Tukachinsky H, et al. Genomic analysis of circulating tumor DNA in 3,334 patients with advanced prostate cancer identifies targetable BRCA alterations and AR resistance mechanisms. *Clin Cancer Res*. 2021;27:3094-3105.
[10] Herbst RS, et al. The biology and management of non-small cell lung cancer. *Nature*. 2018;553:446-454.
[11] Wang Z, et al. Assessment of blood tumor mutational burden as a potential biomarker for immunotherapy in patients with non–small cell lung cancer with use of a next-generation sequencing cancer gene panel. *JAMA Oncol*. 2019;5.5: 696-702.
[12] Zhang Q, et al. Prognostic and predictive impact of circulating tumor DNA in patients with advanced cancers treated with immune checkpoint blockade. *Cancer Discov.* 2020;10:1842-1853.

Therefore, another scenario where ctDNA may be helpful is for distinguishing true progression from pseudoprogression, which has a 10% incidence in solid tumors after ICI therapy.[13]

In contrast to standard serum tumor markers that have half-lives of days to weeks, ctDNA has a short half-life (2.5 hours or less), which can be advantageous for quantifying real-time tumor burden in response to therapy.[14] Intriguingly, mounting evidence shows that molecular response can be detected earlier than radiological response using quantitative ctDNA analysis, thus accelerating the identification of responder and non-responder cases.[15] In ovarian cancer patients, baseline levels and post-treatment ctDNA decreases significantly correlated with progression-free survival, making them more informative than serum cancer antigen (CA) 125 levels.[16] Conversely, an early increase in ctDNA has been reported to correlate with disease progression in metastatic breast cancer patients, with an average lead time of 5 months before radiological progression and increased accuracy compared to serum markers such as CA15-3.[17] In colorectal cancer patients, KRAS mutations have been discovered by ctDNA analysis as a mechanism of emerging resistance to anti-EGFR therapy. Of note, ctDNA assessment anticipated the emergence of KRAS-resistant subclones with a 10-month lead time versus imaging progression.[18] Numerous other studies have reported that while ctDNA analysis cannot yet fully replace tumor imaging, it may provide an earlier tumor response assessment than traditional imaging evaluation.[19]

Notwithstanding the dramatic efficacy noted in some subjects receiving chimeric antigen receptor (CAR)-T cells, many patients will not achieve a complete response or relapse. Thus, the ability of ctDNA to identify individuals at high risk for relapse or toxicity earlier in their therapy course would be of value. In one study, ctDNA analysis was successful in detecting a tumor clonotype in 96% of relapsed or refractory lymphoma patients receiving CAR-T cells. High baseline ctDNA levels were associated with tumor progression and cytokine release syndrome or neurotoxicity. Overall, 70% of durably responding versus 13% of progressing patients exhibited undetectable ctDNA levels 1 week after infusion, with high ctDNA levels detected before radiological relapse in 94% of cases. All durably responding patients had undetectable ctDNA within 3 months of infusion.[20]

CTCs only recently gained considerable traction beyond their approved use as prognostic markers in several tumor types a decade ago. While ctDNA concentration is commonly associated with tumor burden, mechanisms governing tumor cell invasion, migration, and extra- or intravasation do not evoke an obligatory link to tumor size. Small primary tumors can metastasize, while large tumors do not always do so. The differing, albeit incompletely understood, underlying mechanisms resulting in ctDNA shedding and CTC dissemination emphasize the complementarity of these distinct LB approaches. Notably, CTCs also can measure proteins such as programmed death-ligand 1 (PD-L1) expression.[21]

For precision oncology implementation, it is crucial to detect molecular markers that enable prognosis estimation, predict treatment response

[13] Siravegna G, et al. How to use liquid biopsies to treat patients with cancer. ESMO Open 2021;6.2:100060.
[14] Corcoran RB, et al. Application of cell-free DNA analysis to cancer treatment. *NEJM.* 2018;379:1754-1765.
[15] Alese OB, et al. Circulating Tumor DNA: An Emerging Tool in Gastrointestinal Cancers. American Society of Clinical Oncology Educational Book 2022; 42:1-20.
[16] Parkinson CA, et al. Exploratory analysis of TP53 mutations in circulating tumor DNA as biomarkers of treatment response for patients with relapsed high-grade serous ovarian carcinoma: a retrospective study. *PLoS Medicine*. 2016;13.12:e1002198.
[17] Dawson SJ, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. *NEJM*. 2013;368:1199-1209.
[18] Misale S, et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. *Nature*. 2012;486:532-536.
[19] Goldberg SB, et al. Early assessment of lung cancer immunotherapy response via circulating tumor DNA. *Clin Cancer Res*. 2018;24(8):1872-1880.
[20] Frank MJ, et al. Monitoring of circulating tumor DNA improves early relapse detection after axicabtagene ciloleucel infusion in large B-cell lymphoma: results of a prospective multi-institutional trial. *J Clin Oncol*. 2021;39:3034-3043.
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or resistance, and guide therapy choice by characterizing somatic alterations involved in tumor progression.

Precision for Medicine's ApoStream technology has the ability to measure multiple proteins to phenotype/characterize CTCs into EPI (CTCs positive for epithelial markers) or EMT (CTCs positive for mesenchymal markers). Even more important is the ability to measure one or multiple biomarkers of interest so assays can be run at multiple timepoints for pharmacodynamics purposes. From a clinical research perspective, there is interest in validating these assays to select patients for enrollment, and eventually, in bringing the assay to a companion diagnostic (CDx) level. One of these examples is human epidermal growth factor receptor 2 (HER2) programs (especially after the new low-HER2 findings). On the genomics side, Precision for Medicine has the ability to run a variety of assays (PCR, NGS, etc) on CTCs in bulk or with single-cell resolution.

In the relapsed or refractory setting, the role of ctDNA as an efficacy or toxicity biomarker could be particularly beneficial for go/no-go decisions in early-stage drug development. In addition, as a predictive marker, ctDNA would allow the rapid identification of subjects who are most likely to derive benefit from an experimental drug and facilitate the development of a CDx.

## The role of LB in early-stage disease and minimal residual disease, and its potential application in drug development

LB assays play an important role in the early stages of drug development for targeting the right treatment to the right patients at the right time. There is now substantial data supporting the analytic and clinical validity of LB for implementation in routine practice for advanced disease genotyping to predict the benefit of target drugs.[22,23,24] In addition, a growing body of evidence suggests that LB allows the non-invasive analysis of any tumor-derived component detected in a bodily fluid at a single point in time, providing relevant prognostic and predictive information in different phases of disease progression, from diagnosis to evaluation of the response to treatment.[24,25]

Currently, there is particular interest in the use of ctDNA to detect the presence of tumors in patients with no clinically evident disease after curative-intent treatment (molecular or minimal residual disease [MRD] concept). The primary application of ctDNA assay in early-stage cancer treatment is its ability to identify MRD after primary tumor resection, allowing researchers or clinicians to determine which patients harbor residual disease immediately after surgery or adjuvant treatment and which patients have been cured of their disease. As such, LB has the potential to improve clinical decision-making in precision oncology by enabling precise selection of not only patients who could benefit from adjuvant treatment after surgical resection from adjuvant treatment, but also patients who are not likely to benefit and could avoid undergoing potentially toxic chemotherapy.[7,26]

Precision for Medicine recognizes the potential of ctDNA MRD-based interventional clinical trials, accommodating this personalization approach for adjuvant/consolidation therapy. Based on MRD assessment, the design may escalate or de-escalate standard treatment, omit standard treatment, direct systemic therapy after standard adjuvant treatment, or measure response to

[22] Gambardella V, Tarazona N, Cejalvo JM, et al: Personalized medicine: Recent progress in cancer therapy. *Cancers*. 2020;12:1009.
[23] U.S. Food and Drug Administration. Precision Medicine. http://precision.fda.gov. Accessed August 22, 2022.
[24] Dang DK, Park BH. Circulating tumor DNA: current challenges for clinical utility. *J Clin Invest*. 2022;132(12):e154941.
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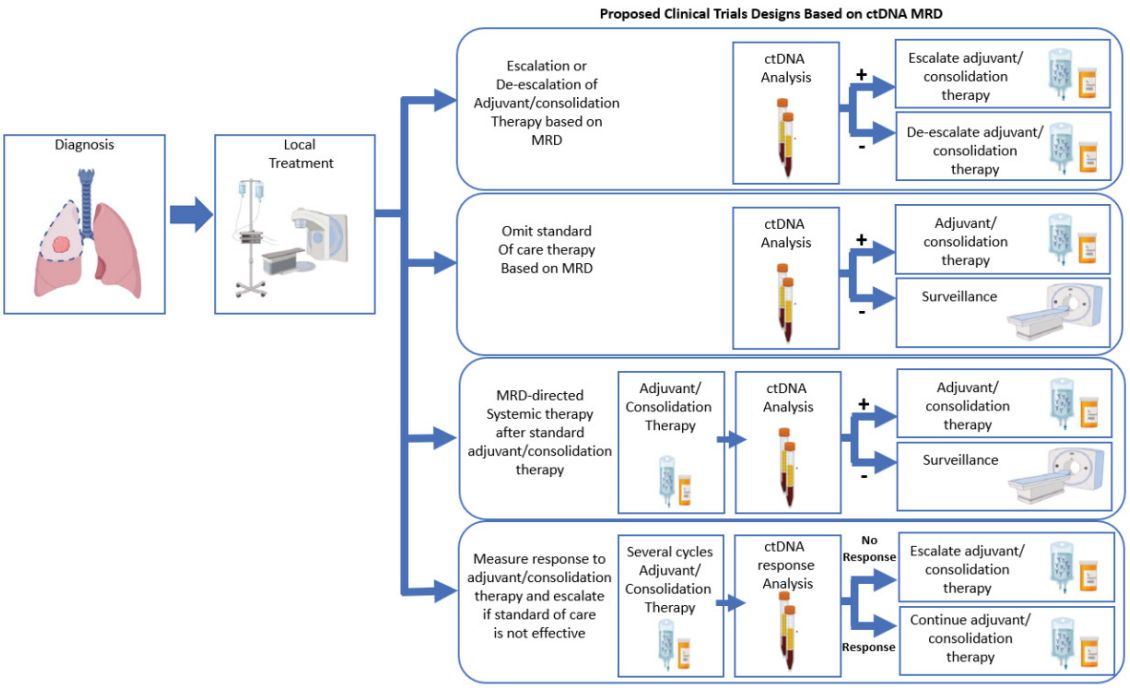
[26] Ryan B. Corcoran and Bruce A. Chabner. Application of Cell-free DNA Analysis to Cancer Treatment. *N Engl J Med*. 2018;379:1754-65.

adjuvant/consolidation therapy and escalate if the standard of care is ineffective. Accordingly, potential clinical trial endpoints for ctDNA MRD studies include survival (overall survival or event-free survival) compared with a control arm or historical cohort, and ctDNA clearance or change in ctDNA concentration (see **Figure 2**). Furthermore, ctDNA clearance may serve as an endpoint to assess the effectiveness of treatment, providing an opportunity for genome-based therapy before rapid disease progression.[27,28]

**Figure 2: Examples of clinical trial designs based on ctDNA MRD.**




## Adapted

- Bruna Pellini, et al, *JCO*, January 2022.
- Moding, et al, *Cancer Discov*, June 2022.

Across cancer types, the clinical specificity of ctDNA detection for predicting relapse in the absence of further treatment is high, often ≥90% if no further treatment is administered after the positive test result. MRD-positive patients might benefit the most from additional treatment.

Data from early-stage lung and bladder cancer suggest that the benefit of adjuvant/consolidation immunotherapy is potentially restricted to ctDNA-positive patients.[29,30]

The recent introduction of ICI studies as part of

[27] Coakley M, Garcia-Murillas I, Turner NC. Molecular Residual Disease and Adjuvant Trial Design in Solid Tumors. *Clin Cancer Res*. 2019;25:6026-34.
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[31] Moding EJ, Liu Y, Nabet BY, Chabon JJ, et al. Circulating Tumor DNA dynamics predict benefit from consolidation immunotherapy in locally advanced non-small-cell lung cancer. *Nat Cancer*. 2020;1:176-183.

consolidation treatment for patients with stage III non-small cell lung cancer (NSCLC) allowed assessment of the ability of ctDNA to predict patients' response to adjuvant ICI. Data analysis showed a large group of patients who did not benefit from ICI addition. Moreover, more than 30% of those patients experienced at least one grade 3 or 4 adverse event. Therefore, the first results showed that ctDNA-negative patients did not benefit from ICI consolidation (after chemoradiation) compared to those with no further treatment, suggesting that ctDNA testing would help spare this therapy to patients who are unlikely to respond.[31,32]

Multiple early-stage breast cancer studies detecting and monitoring ctDNA showed that high ctDNA levels prior to neoadjuvant treatment were associated with tumor size, aggressivity, and lower pathological complete response (pCR) rates, while clearance of ctDNA after treatment was associated with longer survival even in patients who did not achieve pCR.[33,34]

In a locally advanced gastroesophageal adenocarcinoma study, pretreatment ctDNA-positive patients showed non-variable shorter disease-free survival after curative-intent resection than those who had negative ctDNA results. Therefore, resolution or persistence of ctDNA helped predict nonrecurrence and recurrence of disease respectively.[35,36]

A prospective ctDNA-guided study in adjuvant stage II colorectal cancer demonstrated that a ctDNA-based approach was non-inferior to standard management with respect to 2-year recurrence-free survival and less chemotherapy use in the ctDNA-guided group (15% vs 28%) in comparison with the standard-management group.[37] This study marks a paradigm improving precision oncology treatment for stage II colorectal cancer patients. Also, it highlighted the concept and application of MRD assessment, the potential clinical implementation of which will be established with the results of similar ongoing studies.

LB, and more specifically ctDNA assays, are in high demand in new clinical trials, especially in situations where tissue biopsies are suboptimal or time is crucial. Thus, as more evidence accumulates, it is critical to continue prospective clinical trial work to confirm ctDNA MRD as a strong predictive biomarker and whether ctDNA MRD detection after solid tumor surgery or chemoradiation can be used to personalize treatment decision-making. The Precision for Medicine team enhances this tool and its impact on drug development—the opportunity to improve patient survival outcomes in the era of precision medicine.

## Selection of biological markers for CTC detection

Currently, there is no standard or consensus on criteria for the "right" or "best" marker for CTC detection. Optimally, the selected CTC marker would be expressed only on CTCs, and it would be expressed throughout the progression of the disease. The most commonly used markers are epithelial lineage markers for positive selection, nuclear markers for negative selection of red blood cells and platelets, counterstain markers for negative selection, and disease-specific markers. To be effective, disease-specific markers should be more highly expressed in cancer cells than in normal cells. However, it has been shown that de-differentiation and subsequent loss of tumor-specific markers may occur in aggressive cancers that have CTCs.

[32] Nabet BY, Esfahani MS, Moding EJ, et al. Noninvasive Early Identification of Therapeutic Benefit from Immune Checkpoint Inhibition. *Cell*. 2020;183:363-376.e13.
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[36] Azad TD, Chaudhuri AA, Fang P, et al. Circulating tumor DNA analysis for detection of minimal residual disease after chemoradiotherapy for localized esophageal cancer. *Gastroenterology*. 2020;158:494-505.e6.

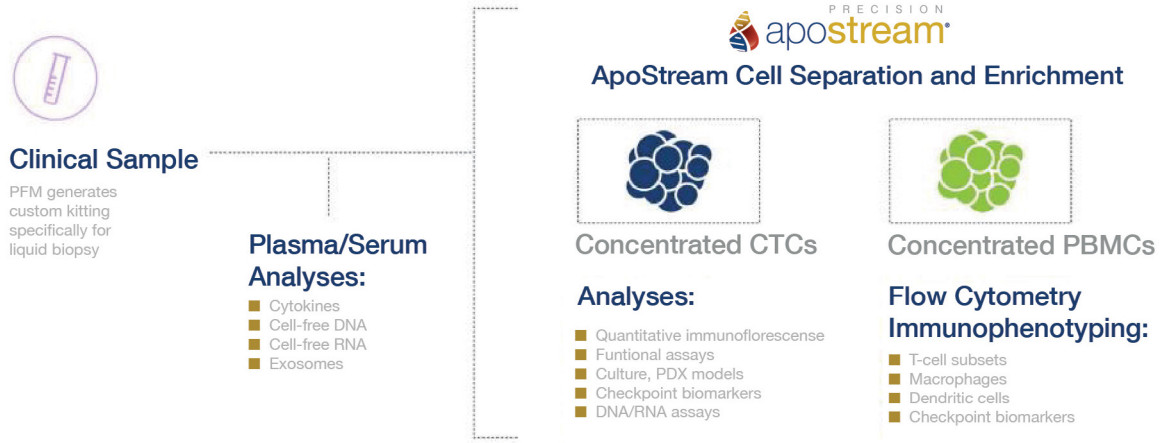
## Application of CTC-based LB in a Phase 3 trial

A few years ago, Precision for Medicine was involved in the BEACON Trial, a large Phase 3 study comparing a long-acting topoisomerase-1 inhibitor (etirinotecan pegol [EP]) against treatment via physician's choice (TPC) in advanced breast cancer patients who had previously been treated with anthracycline, taxane, and capecitabine. CTCs were successfully isolated from 97% of the 1,431 blood samples collected throughout the study using ApoStream, Precision for Medicine's proprietary CTC platform. This technology uses a dielectrophoresis-based, antibody-independent separation approach to isolate and enrich CTCs for downstream analysis using multiplex immunofluorescence (mIF), NGS, fluorescence in situ hybridization (FISH) or ISH, *in vitro* assays, and even animal models (see **Figure 3**).

ApoStream® can also be used to isolate other rare cell types, including stem cells, progenitors, and differentiated immune cells such as CAR-T cells and other difficult-to-identify immune cell populations.

Using multiplex immunofluorescence, the CTCs were analyzed for a number of markers—topoisomerase 1 (Top1), topoisomerase 2 (Top2), Ki67, RAD51, ABCG2, γH2AX, and terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL). Results showed the EP-treated patients with low Top1 expression in CTCs on cycle 2 day 1 (C2D1) had improved overall survival (OS) compared with those with higher positivity (see **Figure 4**), suggesting that CTC Top1 expression following EP treatment may identify patients who are most likely to have an OS benefit.[38]

**Figure 3: CTC isolation and enrichment enable multiple assays from a single tube.**




[37] Tie J, Cohen JD, Phil M, et al (DYNAMIC Investigators). Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer. *N Engl J Med*. 2022;386:2261-2272.

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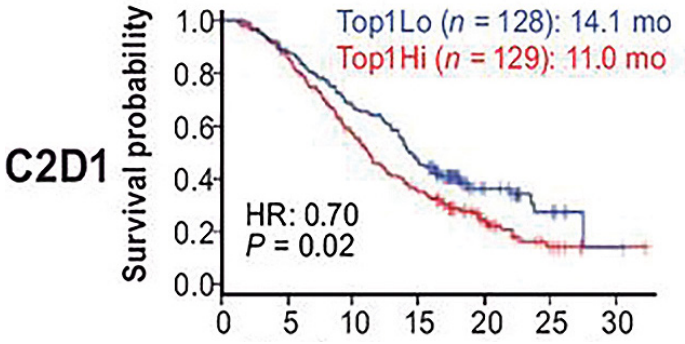
**Figure 4: Low Top1 expression on C2D1 correlates with improved OS in advanced breast cancer patients treated with EP.**

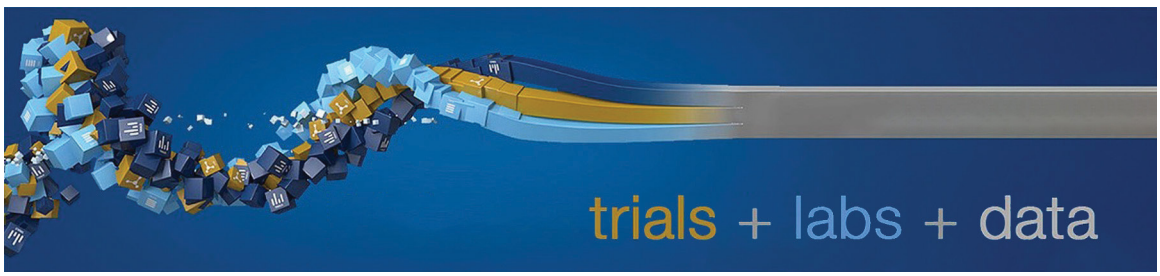



## An overview of Precision for Medicine

As an end-to-end solution for biomarker-driven studies, Precision for Medicine leverages the combined power of trials, labs, and data to drive development. We integrate clinical trial execution with deep scientific knowledge, specialty laboratory expertise, and advanced data sciences to maximize insights into patient biology and accelerate the pace of discovery and approval. Precision for Medicine helps advance the most challenging clinical development programs by leveraging a unique blend of proprietary technologies, flexible processes, and creative problem-solving abilities developed over the course of more than 2 decades supporting successful oncology, rare disease, and advanced therapy trials.

## Conclusions and future perspectives

Until recently, the clinical applications of LB were limited to assays targeting single genes. Now, researchers are actively investigating the use of LB for detecting cancer, screening for disease recurrence, monitoring treatment, and assessing residual disease at the molecular level. As technologies continue to advance, the clinical applications of LB will continue to expand across therapeutic areas, enabling data-driven decision-making and propelling precision medicine forward.



### Darren Davis, PhD

Senior Vice President

Visionary leader with more than 25 years of distinguished biotechnology and clinical translational research experience. Founded ApoCell in 2004 and later was instrumental in developing and commercializing the ApoStream® rare-cell liquid biopsy technology. Globally recognized cancer researcher and the author of more than 100 peer-reviewed publications. Dedicated and committed to improving the lives of patients with debilitating diseases.

### Etleva Pashaj, MD

Vice President, Medical

Strategic, innovation-drive, drug discovery veteran—and board-certified oncologist—with extensive international (EMA and FDA) regulatory experience. Record of excellence in clinical development, medical monitoring and medical strategy, and managing and mentoring cross-functional and global teams for phase 1-4 oncohematology studies.

### Ivan Barrera, MD

Medical Director

Medical degree with 14+ years of clinical research experience in different health care systems and facilities. Methodic and strategist key player amoung interdisciplinary groups in drug development, wide experience in solid tumours; especially Gastrointertinal Oncology including Neuroendocrine Tumors, FIH, and Phase I-III studies.

### Antonio Lambiase, MD

Medical Director

Medical Doctor with fellowship in Oncology and more than 30-years of experience in Academia and Pharma for clinical development from phase 1 to 3 of several compounds. Prior broad experience in oncological and hematological malignancies. Extensive expertise in developing targeted therapies, immunotherapies, and cell-based therapies. In-depth understanding of the drug development process: clinical research, medical monitoring, safety, and regulatory submissions.

### Jesus Garcia, PhD

Scientific Liaison

Tissue and liquid biopsy expert with extensive experience in a wide range of histopathology assays and digital pathology solutions. Part of the implementation of new technologies at MD Anderson Cancer Center in collaboration with immuno-oncology leaders. Currently focused on partnering with biopharma to develop tissue and liquid biopsy biomarker strategies for clinical trials, and to implement digital pathology and AI in the drug development process.

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