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Circulating Tumor Cells as Actionable Biomarkers: Integrating Liquid Biopsy into Targeted Oncology

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ABSTRACT

Liquid biopsy enables repeated, minimally invasive assessments of tumor evolution and therapeutic responses. In addition to cfDNA, circulating tumor cells (CTCs) provide intact cellular material for capturing comprehensive genomic, transcriptomic, and proteomic features. Currently, the most established utility of CTCs is prognostic; in metastatic breast cancer, patients with ≥5 CTCs per 7.5 mL of blood exhibit significantly shorter OS (approximately 10 months vs. 18 months). While the use of CTCs to direct targeted therapies remains largely investigational, emerging evidence suggests that CTC characterization, including epithelial-mesenchymal transition and rare states detectable by single-cell RNA sequencing, reflects critical tumor heterogeneity and plasticity. Future progress will depend on reducing preanalytical variability, addressing platform-dependent capture bias, and establishing harmonized clinical thresholds. Integrating these refined CTC readouts with other liquid biopsy modalities is essential to enable clinically deployable multimodal strategies and optimize personalized treatment outcomes

Keywords: Circulating Tumor Cells; Biomarkers; Liquid Biopsy; Neoplasm Metastasis

INTRODUCTION

Liquid biopsy represents a paradigm shift in oncology, moving from static surgical biopsies to dynamic, blood-based monitoring. Unlike tissue biopsy, which is invasive and provides only a spatially limited snapshot of the tumor, liquid biopsy approaches, such as circulating tumor DNA (ctDNA), cell-free DNA (cfDNA), and circulating tumor cells (CTCs), offer minimally invasive alternatives [1,2]. Importantly, the persistence of cfDNA after surgery is strongly associated with a higher risk of cancer relapse, making it a powerful prognostic tool. In addition, dynamic changes in CTC levels during treatment can help evaluate therapy response early and identify ineffective treatments [3].

CTCs were first described by Ashworth in 1869, who observed tumor-like cells in the bloodstream of patients with cancer. Since then, advances in detection technologies have enabled their clinical application as minimally invasive biomarkers, particularly following the development of systems such as CellSearch [4,5]. CTCs are malignant cells shed from primary or metastatic tumors into the bloodstream and serve as precursors to distant metastases. Their clinical relevance is underscored by the fact that their enumeration and characterization can predict clinical outcomes in various solid tumors [6,7]. The clinical validity of CTC enumeration as a robust prognostic marker has been firmly established across diverse oncological contexts, supported by large-scale analyses involving over 5,500 patients. In metastatic breast cancer, a pooled analysis of 1,947 patients showed that a baseline of ≥5 CTCs per 7.5 mL is a powerful independent predictor of progression-free survival and overall survival (OS), regardless of subtype or therapy line. This significance extends to early-stage disease, where studies of over 2,000 non-metastatic patients identified even a single CTC (≥1 CTC per 7.5 mL) as a "level-of-evidence 1" biomarker for predicting local relapse, distant recurrence, and disease-free survival [8,9]. In addition, a comprehensive meta-analysis of 1,573 patients with non-small cell lung cancer (NSCLC) confirmed that elevated baseline CTC levels correlate with advanced tumor stages, lymphatic metastasis, and significantly shorter survival [10]. Together, these findings transition CTCs from experimental tools to promising dynamic biomarkers, potentially valuable in clinical management to optimize risk stratification, monitor

disease severity, and guide personalized therapeutic interventions in targeted cancer therapy.

Tumor heterogeneity is a major driver of treatment failure. Russano et al. [11] argued that because cancer is dynamic, predictive biomarkers are often not uniformly present in all cells. CTCs, which originate from multiple metastatic sites, reflect tumor heterogeneity better than single-site tissue biopsies [12].

Despite this strong biological rationale, clinical translation is limited by methodological heterogeneity. Different enrichment approaches (e.g., EpCAM-dependent capture versus marker-independent size/deformability or microfluidic methods) can preferentially isolate different CTC phenotypes, whereas preanalytical variables (tube type, processing time, fixation, and handling) can materially affect yield and downstream profiling. These sources of variability complicate cross-study comparisons and limit generalizable cutoffs for clinical decision-making. Cross-platform reference materials, standardized reporting of preanalytical variables, external quality assurance, and harmonized analytical pipelines are essential, especially as CTC assays are combined with cfDNA and other liquid biopsy signals in integrated models.

Biology and Heterogeneity of CTCs

Epithelial-Mesenchymal Transition (EMT)Barriers to Care and the Need for Early Intervention

CTCs often undergo EMT, a process in which they lose epithelial markers (such as EpCAM) and gain mesenchymal features, thereby enhancing their ability to invade and migrate. This transition is crucial for the survival of CTCs and the initiation of new tumor growth at distant sites [13]. The traditional view of EMT as a binary process has been revised by accumulating evidence demonstrating the existence of hybrid epithelial-mesenchymal (E/M) states. Cells in this intermediate phenotype retain both epithelial and mesenchymal features, enabling enhanced plasticity and adaptability. Importantly, hybrid E/M cells have been shown to exhibit increased invasiveness, therapeutic resistance, and a greater capacity to drive metastasis than cells in purely epithelial or mesenchymal states. These cells are also frequently associated with collective migration patterns and are commonly observed within CTC clusters, which further amplify their metastatic potential [14,15]. Collectively, these findings suggest the critical role of hybrid E/M phenotypes in cancer progression and underscore their significance in CTC biology.

Also, CTC clusters have emerged as a critical driver of metastasis, demonstrating a markedly higher metastatic potential compared to single CTCs, with studies reporting a 23-50-fold increase in metastatic efficiency. These clusters are thought to arise through mechanisms of collective invasion, whereby groups of tumor cells detach and migrate together while maintaining cell-cell junctions. CTC clusters are strongly associated with hybrid E/M phenotypes and exhibit stem cell-like properties, both of which contribute to enhanced survival, immune evasion, and colonization capacity at distant sites [16]. Recent advances, including deep learning-based classification approaches, have further improved the identification and characterization of CTC clusters, underscoring their growing significance as both biological and clinical focus in cancer research [17].

Kozuka utilized single-cell RNA sequencing (scRNA-seq) to demonstrate that EMT status in CTCs significantly indicates clinical outcomes in metastatic colorectal cancer [18]. This transition enhances the invasive potential of cells and is a key factor in surviving circulation.

Single-Cell RNA Sequencing for CTC Characterization

The shift from simple enumeration to deep CTC characterization has been further advanced by high-throughput scRNA-seq, which provides an unprecedented view of the transcriptomic landscape of metastatic precursors. Recent studies, including comprehensive reviews of scRNA-seq work lows, have highlighted how the analysis of thousands of individual CTCs can uncover the immense cellular heterogeneity and phenotypic plasticity that drive cancer progression. By identifying rare subpopulations and tracing molecular signatures such as EMT, this technology reveals the speci ic resistance mechanisms that allow certain CTCs to survive in circulation and colonize distant organs [19]. Integrating these single-cell insights into the clinical work low not only improves patient strati ication but also bridges a critical knowledge gap, allowing the discovery of novel therapeutic targets that are often masked in bulk tumor analyses.

Advances in scRNA-seq have enabled researchers to identify rare CTC subpopulations. This technology enables "deep transcriptomic pro iling", revealing distinct phenotypic states that contribute to metastasis, as highlighted by Orrapin et al. [20]. Tieng et al. [19] further provide a practical 12-step work low for scRNA-seq, aiming to standardize how we capture these rare cells. Furthermore, Longo et al. [21] discussed how the integration of single-cell data with spatial transcriptomics can elucidate the intercellular dynamics that drive tumor progression.

CTCs as Actionable Biomarkers

The term "actionable" refers to information that can feasibly change a clinical decision and is supported by appropriate evidence. For CTCs, the level of evidence differs by use case: prognostic enumeration has the strongest clinical footing, whereas therapy selection, resistance tracking, and minimal residual disease (MRD) applications are promising but still evolving and often platform and context dependent.

A clear distinction can be made between established clinical uses (where standardized CTC enumeration is

consistently associated with patient outcomes) and emerging applications that still require standardized methods and prospective validation to confirm their clinical value

Therapy Selection and Targeted Oncology

CTCs may express targetable proteins and harbor clinically relevant genomic alterations relevant to precision oncology; nonetheless, in most settings, this remains an emerging application rather than a routine practice. For instance, the clinical actionability of CTCs is powerfully demonstrated by the CirCe T-DM1 trial, which addressed the phenomenon of HER2 discordance between primary tumors and circulating cells. A clinical trial revealed that even when a traditional tissue biopsy classifies a tumor as HER2-negative, a subset of patients possesses HER2-amplified CTCs that reflect the true phenotype of the tumor. By treating these specific patients with trastuzumab emtansine (T-DM1), the trial demonstrated that targeting the molecular profile of CTCs can lead to significant clinical benefits, including disease stabilization and partial responses in patients who had otherwise exhausted standard treatment options [22]. This evidence indicates the shift from static biomarkers to dynamic CTC characterization, proving that liquid biopsy can identify hidden therapeutic targets and guide personalized treatment strategies that tissue-based methods might overlook.

Kojima showed that single-cell NGS of CTCs in neuroblastoma can detect clinically important alterations, such as MYCN amplification, supporting risk stratification and hypothesis generation for developing treatment strategies [23]. Likewise, discordant HER2 expression on CTCs compared with the primary tumor may identify candidates for anti-HER2 therapy [24].

However, implementation is limited by platform-dependent capture bias, assay variability, uncertain cutoffs, and the need for prospective studies showing that acting on CTC-derived targets improves outcomes beyond current tissue and cfDNA-guided approaches.

Real-Time Monitoring of Therapy Response

CTCs offer immediate clinical utility by showing "early change" in cell counts during treatment, often before these changes are visible on imaging. A decrease in CTC numbers after early cycles of chemotherapy or targeted therapy often signals a good clinical response, whereas an increased count indicates disease progression [25]. While these dynamics are often prognostic, the role of CTC changes as a direct trigger for treatment switching is still being defined and likely depends on the tumor type and therapy. Beyond mere counting, surface biomarkers on CTCs can provide real-time updates on whether a drug is effectively hitting its target, thereby allowing us to decipher the "evolving landscape" of cancer, as noted by Gilson et al. [26]. For example, in NSCLC, Rieckmann et al. [27] used diagnostic leukapheresis to identify distinct CTC phenotypes associated with different outcomes, illustrating how richer profiling could complement standard monitoring once analytical and clinical validation are strengthened.

Predicting Resistance and Minimal Residual Disease (MRD)

The persistence of CTCs after radical surgery or curative therapy indicates the presence of MRD. In early-stage colorectal cancer, preoperative and postoperative CTC counts have shown significant prognostic value for recurrence-free survival. Molecular analysis of these persistent cells can uncover resistance mechanisms, such as novel mutations or phenotypic shifts, before they become visible on imaging [28]. Nevertheless, MRD implementation faces practical constraints, including low CTC abundance in early disease, sampling and processing variability, and uncertainty regarding optimal thresholds and timing. Molecular profiling of residual CTCs could reveal resistance mechanisms, such as new mutations or phenotypic shifts, before relapse becomes visible on imaging. However, this strategy will likely be most robust when interpreted alongside cfDNA-based MRD assays and other liquid biopsy components within integrated, prospectively tested clinical pathways.

Advanced Technologies in CTC Characterization

The rarity of CTCs (often one cell per billion blood cells) necessitates highly sensitive technologies for their enrichment and detection.

Cell Search Platform

Cell Search is the most established and widely used platform for CTC enumeration and is FDA-cleared for metastatic breast, prostate, and colorectal cancers. It uses EpCAM-based immunomagnetic enrichment and identifies CTCs as cytokeratin-positive, CD45 negative, nucleated cells, which supports standardized and reproducible counting across different centers. The main limitation of this method is marker dependency; CTCs with low EpCAM expression or EMT-like features may be under-detected [7,29]. Overall, CellSearch remains a benchmark for clinical translation and for comparing newer CTC technologies.

scRNA-seq and Machine Learning

scRNA-seq has provided unprecedented insights into CTC heterogeneity; however, its application is accompanied by several technical and analytical challenges. scRNA-seq data are inherently high-dimensional and often contain substantial levels of noise and dropout events, which can complicate downstream analyses. Moreover, CTCs represent a rare cell population in peripheral blood, making their efficient isolation and capture particularly challenging. These limitations necessitate the use of advanced computational approaches, including artificial intelligence and machine learning algorithms, to accurately identify, classify, and interpret CTC populations [19]. Consequently, while single-cell

technologies hold great promise, overcoming these challenges is essential for their robust clinical translation.

Pastuszak developed machine learning based classifiers using Smart-Seq2 sequencing data to differentiate CTCs from peripheral blood mononuclear cells with 95% accuracy [30]. Similarly, Iyer et al. [31] integrated transcriptomic data with machine learning to characterize the "EMT spectrum" of single CTCs, providing a more nuanced understanding of their metastatic potentials.

CTC-Derived Organoids

One of the most exciting developments in this ield is the creation of CTC-derived organoids. Li et al. [32] review how these 3D models mimic the tumor microenvironment and retain the heterogeneity of the original tumor. These organoids serve as "ex vivo" models for drug testing, allowing clinicians to observe how a patient's speci ic cancer cells respond to various treatments before administering them.

The integration of advanced isolation methods with diverse downstream molecular and functional analyses provides a comprehensive framework for clinical actionability, as summarized in Table 1.

Category	Technology / Method	Key Features & Characterization	Clinical Utility & Actionability
Detection & Isolation	Physical properties or surface markers (e.g., EpCAM)	High-purity isolation of these rare cells from blood	Real-time monitoring when tissue biopsies are inaccessible or inadequate
Prognostic Assessment	CTC Enumeration (Standardized Platforms)	Counting the number of CTCs per volume of blood (e.g., ≥5 CTCs per 7.5 mL in metastatic breast cancer)	Strong prognostic value; predicting shorter overall survival and monitoring disease progression
Molecular Profiling	Next-Generation Sequencing (NGS)	Identification of dynamic molecular biomarkers and genetic mutations	Tracking therapeutic response and identifying resistance mechanisms
Phenotypic Analysis	Single-cell RNA sequencing (scRNA-seq)	Analysis of individual cell gene expression, phenotypic plasticity, and EMT	Detection of resistant clones and rare states before treatment failure
Functional Models	CTC-derived Organoids	Generation of 3D biological scaffolds that simulate in vivo environments	Ex vivo drug screening, CRISPR gene-editing target validation, and CDX model establishment
Precision Medicine	Surface Protein Biomarkers (HER2, PD-L1, EGFR)	Tracking the "true phenotype" and protein expression of live cells	Stratifying patients, guiding immunotherapy decisions, and monitoring MRD

Table 1: CTC Detection, Characterization, and Clinical Actionability

Challenges and Future Perspectives

Despite clear promise, several barriers limit clinical translation. Standardization is a priority: different platforms capture, different CTC subsets (epithelial, mesenchymal, and hybrid states), and preanalytical variables can change the yield and measured phenotypes. This heterogeneity makes it difficult to compare studies, define universal cutoffs, and build reliable clinical algorithms. Equally important is integration; CTC information should be combined with cfDNA, exosomes, and host response signals to improve sensitivity and interpretability, particularly for early disease and MRD. Progress will likely require multicenter prospective trials, shared reference materials and benchmark datasets, and clinically aligned endpoints that test whether CTC-guided strategies truly change management and improve outcomes. The future of oncology lies in "integrative liquid biopsy", where real-time CTC analysis guides dynamic treatment adjustment of targeted therapies, potentially turning metastatic disease into a manageable chronic condition.

CONCLUSION

CTC-focused liquid biopsy is moving from a promising concept toward a clinically actionable decision-support tool, but its real impact will depend on whether the field can convert biological richness into reproducible and clinically interpretable results. The next phase is likely to be "integrative" by default: CTC phenotypes and single-cell programs will be read alongside cfDNA, exosomes, and host immune signals to generate composite risk and response models that can be acted upon in real time. Key unanswered questions remain: Which CTC features truly cause metastasis or resistance, rather than merely correlating with them? How stable are CTC states under treatment pressure, and what sampling frequency is sufficient to capture clinically meaningful changes? Can we

define thresholds that generalize across tumor types, stages, and platforms without losing rare but decisive subclones?

Recent advances have demonstrated the importance of hybrid E/M states in CTCs, which exhibit increased plasticity and metastatic potential. These hybrid phenotypes are closely associated with the formation of CTC clusters, which demonstrate a significantly higher metastatic efficiency than single CTCs. In parallel, single-cell technologies have enabled a deeper characterization of CTC heterogeneity; nevertheless, they introduce challenges, such as high-dimensional noisy data and difficulties in capturing rare cell populations. Furthermore, integrating multi-omics single-cell datasets remains a major computational challenge due to batch effects, data sparsity, and platform variability.

However, progress is currently limited by several factors. Methodological fragmentation occurs when different enrichment technologies select different CTC subsets. Additionally, preanalytical variables, batch effects, and computational pipelines can influence the results as much as the underlying biology. Overcoming this will require cross-platform reference standards, shared benchmark datasets, and clinically aligned endpoints (e.g., MRD clearance and time to treatment failure) rather than purely technical metrics. Advances in scRNA-seq analytics and machine learning may help, but only if the models are transparent, externally validated, and feasible in routine workflows. CTC-derived organoids offer a path toward functional precision oncology; nevertheless, scalability, turnaround time, and representativeness of the original disease remain practical hurdles.

If these barriers are addressed, CTC research could realistically shift care by enabling earlier therapy switches, improving MRD-guided surveillance, and reducing overtreatment through confident risk stratification. There is unlikely to be a single "endpoint"; instead, the field may converge on standardized multimodal assays that continuously update a patient's tumor profile, turning metastatic cancer management into an adaptive process. Whether CTCs become the central pillar or one component of a broader liquid biopsy ecosystem will depend on how quickly standardization, cost reduction, and prospective clinical trials translate biological insight into outcomes that patients can feel.

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