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Circulating Tumor Cells as Predictive Biomarkers and Living Biospecimens for Cancer Monitoring and Tumor Biology Profiling

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Abstract: ***Background: Circulating tumor cells (CTCs), as intact viable cancer cells shed into the bloodstream, offer unique opportunities for early cancer detection and real-time tumor monitoring. This review evaluates the clinical relevance of CTCs across various tumor types, emphasizing their predictive value and potential as dynamic biospecimens. Methods: A comprehensive literature search was performed across peer-reviewed databases to identify studies examining CTCs as predictive biomarkers and functional biospecimens. Both clinical trials and translational research addressing CTC-based detection, enumeration, and phenotyping were included. Results: Key findings demonstrate that CTC detection can precede traditional biomarkers and imaging modalities, offering earlier insights into disease progression and therapeutic response. In high-risk hepatitis patients, CTCs preceded HCC diagnosis by months; in NSCLC, in vivo CTC capture identified patients with early recurrence; and in breast cancer, CTC-based melatonin receptor (MT1) profiling revealed subtype-dependent receptor patterns that suggest timing and biological context likely influence CTC-based biomarker interpretation. The article also explores the integration of CTC phenotyping with receptor profiling, circadian biology, and host-response markers to refine risk stratification and personalize oncologic care. Conclusions: A translational roadmap is proposed to enhance the clinical adoption of CTC-based strategies through standardized methodologies and multimodal biomarker integration.***

Keywords: circulating tumor cells, liquid biopsy, early cancer detection, receptor profiling, cancer monitoring

Simple Summary

Circulating tumor cells (CTCs) are rare viable cancer cells released from a primary tumor or metastatic deposits into the bloodstream. Unlike blood-based DNA fragments, CTCs represent an intact "living biopsy" that can be repeatedly sampled to quantify tumor burden, capture metastatic heterogeneity, and interrogate tumor biology at the single-cell level. Evidence across liver cancer risk cohorts, lung cancer, breast cancer, and neuroendocrine tumors suggests that CTC detection and dynamic changes can precede conventional markers and imaging, making CTCs among the most sensitive early indicators of disease progression and treatment response. This review synthesizes the provided studies and proposes a framework for integrating CTC enumeration and multi-parameter profiling (including receptor expression, inflammatory markers, and circadian-related signals) into clinical decision-making.

1.Introduction

Despite major advances in imaging, pathology, and molecular profiling, many cancers are still detected late, and therapeutic decisions are often made using single time-point tissue biopsies that cannot be repeated frequently [11, 12]. Tumor evolution under treatment pressure, spatial heterogeneity between lesions, and the emergence of resistant subclones limit the predictive value of baseline tissue data [13]. Liquid biopsy addresses these limitations by enabling minimally invasive, repeat sampling of tumor-derived material in blood and other body fluids [1, 14]. Among liquid biopsy analytes-including circulating tumor nucleic acids (ctNAs) and extracellular vesicles-CTCs uniquely provide intact viable cells that may be expanded, functionally interrogated, and studied at single-cell resolution [15-17].

The epithelial-mesenchymal transition (EMT) represents a fundamentally important process that enables epithelial-derived tumor cells to acquire fibroblast-like properties, exhibit reduced cell-cell adhesion, and gain increased motility-facilitating the escape of tumor cells from primary tumors [18, 19]. CTCs generated through EMT may bear features characteristic of cancer stem cells (CSCs), linking cellular plasticity to metastatic potential [20]. Importantly, CTCs do not represent a homogeneous population; they exhibit a spectrum of EMT states, from fully epithelial to fully mesenchymal, with many cells displaying hybrid phenotypes that may confer enhanced metastatic capacity [21, 22].

Comprehensive overviews of early biomarkers also list CTCs among key circulating cellular markers that can complement genetic and protein-based assays [23, 24]. Accordingly, CTCs can serve two complementary clinical roles: (i) an early, sensitive predictor of progression (appearance, quantity, and dynamics), and (ii) a living biospecimen for defining the biological "character" of a tumor (phenotype, receptor expression, pathway activity, and heterogeneity).

2.Why CTCs Can Act as an Early Predictor of Progression

CTCs originate from primary tumors and/or metastatic sites through active intravasation and passive shedding [25]. Once in circulation, most tumor cells are cleared, but a minority survive-often aided by epithelial-mesenchymal plasticity, platelet cloaking, immune evasion, and metabolic adaptation [26, 27]. Because hematogenous dissemination can occur early in many solid tumors, detection of CTCs can precede macroscopic metastatic disease and may emerge prior to radiographic evidence of metastasis than traditional protein markers or radiographic changes [28]. Importantly, the predictive utility of CTCs does not rely solely on absolute count. Longitudinal trends, emergence of specific phenotypes, and appearance of clusters or receptor-positive subsets can provide sensitive signals of disease acceleration or treatment failure [29, 30].

2.1. Evidence for CTCs Preceding Conventional Markers in High-Risk Cohorts

In a prospective observation of patients with viral hepatitis and advanced liver fibrosis (Metavir F4) despite normal AFP levels and absence of imaging-detectable malignancy, CTCs were isolated using a density-gradient approach (OncoQuick). Patients with detectable CTCs subsequently developed primary liver cancer within 3-6 months and showed a gradual rise in AFP, whereas individuals without detected CTCs did not develop liver cancer during 3 years of follow-up [4]. Even in a control group with mild fibrosis (F1), CTC positivity was associated with later cancer detection (within approximately two years), suggesting that CTCs may enrich surveillance strategies for early tumor emergence [4].

Current hepatocellular carcinoma (HCC) surveillance relies on biannual ultrasonography with or without AFP measurement [31, 32]. However, this approach has limited sensitivity in early disease and may be inadequate, especially in patients with obesity or nodular cirrhosis [33]. The potential of CTCs to complement existing surveillance tools is supported by studies showing that CTC-based markers can detect HCC in patients with early-stage disease who may have false-negative AFP results [34].

3.Methodological Considerations for CTC Detection and Characterization

CTCs are rare (often <1 cell per mL of blood in early disease), and their detection is sensitive to pre-analytical variables (blood draw timing, tube type, storage duration, temperature, and processing workflow) [35]. Analytical strategies generally involve enrichment followed by identification. Enrichment may be based on physical properties (size/deformability filtration, density gradients), immunoaffinity capture (e.g., EpCAM-based), or in vivo devices that expose a functionalized surface to a large blood volume [36, 37]. Identification relies on morphology, immunostaining (e.g., cytokeratins, tumor-specific receptors), and/or nucleic acid analysis [38].

3.1. In Vivo CTC Capture Can Increase Sensitivity

An illustrative example is the in vivo detector CANCER01 (DC01) evaluated in NSCLC. The device was inserted into a cubital vein for 30 minutes to capture EpCAM-positive cells directly from circulating blood. In stages I-IIIB NSCLC, DC01 achieved a 94% sensitivity compared with 5.8% for an in vitro CellSearch assay, while remaining negative in all non-cancer controls (100% specificity) [5]. This approach emphasizes the potential value of sampling larger effective blood volumes for earlier-stage disease.

3.2. Filtration and Cytomorphology Remain Useful for Longitudinal Monitoring

Size-based filtration and cytomorphologic assessment can support serial monitoring due to their simplicity and ability to capture epithelial as well as some EpCAM-low/negative CTCs [39]. In a lung adenocarcinoma cohort treated with platinum-pemetrexed, CTCs isolated by ScreenCell filtration were morphologically evaluated and confirmed by cytokeratin staining; baseline CTC levels were detected in all patients (reported range: 1-67 CTCs/mL) [6]. After two treatment cycles, changes in CTC counts were concordant with imaging-based tumor size changes in a substantial proportion of evaluable patients, supporting CTC dynamics as an early response readout [6].

4.Clinical Evidence Across Tumor Types

The provided studies span multiple tumor entities and collectively support the clinical relevance of CTCs for early prediction and real-time tumor characterization. Table 1 summarizes key examples and highlights how different platforms and biomarkers address complementary clinical questions.

[Table 1: Representative findings from the provided studies supporting CTCs as early predictors and living biospecimens-see end of document]

4.1. NSCLC: From Improved Detection to Early Treatment Response Readouts

In NSCLC, the clinical promise of CTCs is shaped by two pragmatic constraints: (i) low abundance in earlier disease and (ii) epithelial marker variability that can reduce capture when relying solely on EpCAM-based platforms [40]. The in vivo capture approach described in [5] addresses abundance by increasing effective blood volume sampled, potentially enabling detection earlier in the disease course. For patients receiving systemic therapy, serial quantification can provide rapid feedback. In the platinum-pemetrexed cohort, CTC count variation after two cycles aligned with changes in tumor size on imaging in a majority of evaluable patients, suggesting that CTC trends may serve as an earlier marker than imaging alone [6].

4.2. Breast Cancer: CTC Phenotyping in a Circadian and Subtype-Specific Context

Breast cancer offers a compelling setting for CTC-based functional phenotyping, because subtype and hormone

signaling shape both tumor behavior and systemic physiology [41, 42]. MT1 receptor expression on CTCs demonstrated a marked circadian pattern, with peak expression during nighttime sampling (02:00-04:00) and lower expression during daytime sampling (14:00-16:00) [9]. Moreover, MT1 receptor density was higher in less aggressive phenotypes and lowest in triple-negative breast cancer, where expression was absent in some patients [9]. A larger breast cancer cohort analysis integrating melatonin receptor expression on CTCs with systemic markers (MMPs, IL-6, TNF-alpha, and LDH isoenzymes) further supports that CTC phenotyping can be interpreted together with inflammation and metabolism to stratify aggressive subtypes and propose biologically plausible intervention hypotheses (e.g., melatonin supplementation strategies) [10].

The antiproliferative effects of the circadian melatonin signal are mediated through activation of MT1 melatonin receptors expressed in human breast cancer cell lines and xenografts [43, 44]. In estrogen receptor (ERα+) human breast cancer cells, melatonin suppresses both ERα mRNA expression and estrogen-induced transcriptional activity of the ERα via MT1-induced activation of Gαi2 signaling and reduction of cAMP levels [43]. These mechanistic findings provide biological rationale for clinical observations linking MT1 receptor expression on CTCs with tumor aggressiveness and potential responsiveness to chronotherapy.

4.3. Neuroendocrine Tumors: CTCs as Real-Time Readouts of Receptor Heterogeneity

In NETs, overexpression of somatostatin receptors enables both imaging and therapy [45, 46]. However, receptor expression may vary across lesions and over time. CTC-based assessment of SSTR2/5 provides an avenue to evaluate heterogeneity and potential discordance between tissue and circulating compartments [7, 8]. The reported heterogeneous SSTR2 or SSTR5 expression in a subset of patients, together with the discussion of a prospective trial linking SSTR expression on CTCs to outcomes during lanreotide therapy, supports CTCs as pharmacodynamic markers rather than static diagnostic indicators [7].

SSTR2 and SSTR5 expression at high levels on the surface of the majority of NETs enables not only sensitive functional imaging (e.g., 68Ga-DOTATATE PET/CT) but also tumor-targeted therapy with commonly used "cold" and radioisotope-labeled "hot" somatostatin analogues [47, 48]. The ability to track receptor status on CTCs in real time offers advantages over tissue-based assessment, particularly when biopsy is not feasible or when treatment decisions must account for evolving receptor status.

5.CTCs as the Most Informative "Living" Biomaterial to Define Tumor Character

CTCs are not merely numerical surrogates of tumor burden. As intact cells, they can be used to profile the biological state of disease in ways that are not possible using ctDNA alone [15, 16]. CTC-based assays can capture: (i) phenotypic heterogeneity (epithelial, mesenchymal, hybrid, and stem-like states), (ii) expression of therapeutic targets (e.g., SSTR2/5, ALK, or melatonin receptors), (iii) pathway activation signatures (e.g., NF-κB activity), and (iv) metabolic adaptations (e.g., LDH-A/Warburg-like shifts) [49, 50]. These layers of information collectively define the tumor's "character"-its capacity to disseminate, evade immunity, and resist therapy.

5.1. Receptor Profiling on CTCs as a Bridge to Targeted Therapy

Two receptor-focused examples in the provided collection illustrate the power of CTC phenotyping. First, SSTR2/5 assessment on NET-derived CTCs offers a minimally invasive way to monitor receptor status when tissue is unavailable or not representative of all lesions [7]. Second, melatonin receptor profiling on breast cancer CTCs suggests that circadian biology and receptor availability may relate to tumor aggressiveness and could influence therapeutic hypotheses involving melatonin or chronomodulated schedules [9, 10].

5.2. Multi-Analyte Liquid Biopsy and Novel Marker Discovery

The liquid biopsy framework described in [51] emphasizes that CTCs should often be interpreted alongside ctNAs and extracellular vesicles to capture complementary biology. By combining an FDA-approved CellSearch assay with microfluidic platforms and automated DNA karyometry, correlations between biomarker levels and cancer types were reported. Notably, the authors describe a lack or significant decrease of universal nitric oxide synthase (uNOS) in certain cancers and an increase in membrane expression of MT1 and MT2 receptors on CTCs across investigated malignancies [51]. Such findings reinforce a practical concept: CTCs can serve as discovery substrates for pathway-level biomarkers that integrate tumor-intrinsic and host-response biology.

6.Integrating CTCs with Host-Response Biomarkers

Progression is not only a tumor-cell phenomenon; it is also shaped by systemic inflammation, stress signaling, circadian disruption, and metabolic reprogramming [52, 53]. In metastatic NSCLC, stage IV patients with multiple metastases showed detectable CTCs and ctDNA in association with elevated inflammatory markers and profound changes in certain neuromediators (including reduced melatonin and dopamine), whereas stage I controls lacked detectable CTCs/ctDNA in the reported comparison [54]. This supports a model in which CTC release and survival are intertwined with an inflammation- and stress-permissive systemic milieu.

6.1. Inflammation, Stress Pathways, and the CTC Compartment

Experimental work in an NMU-induced breast cancer rat model reported sequential activation of NF-κB not only in tumor tissue but also in circulating tumor cells across initiation, promotion, and progression phases, alongside melatonin suppression and metabolic shifts consistent with

LDH-A dominance [55]. The reported inverse correlation between melatonin levels and NF-κB activation motivates integrated biomarkers that connect tumor dissemination (CTCs) with host physiology [55]. While translational validation is needed, these findings provide a rationale for combined CTC-cytokine-circadian biomarker panels in clinical studies.

7.A Translational Roadmap: From Enumeration to Actionable CTC Biology

Based on the collective evidence, a translational roadmap can be summarized in four steps:

1) Define the clinical question (risk stratification, minimal residual disease, response monitoring, or target selection).
2) Choose the detection platform aligned with abundance and phenotype (e.g., high-volume or in vivo capture for early stages; filtration for longitudinal counts; immunoaffinity plus multi-marker staining for target profiling).
3) Standardize pre-analytical variables, including blood draw timing when circadian-sensitive markers are studied (as suggested by MT1 rhythm on breast cancer CTCs) [9].
4) Move beyond single endpoints: integrate CTC enumeration with phenotypic readouts (receptors, pathway activity) and complementary analytes (ctDNA, exosomes) to improve sensitivity and biological interpretability [51].

8.Limitations and Research Priorities

Several limitations must be addressed for broad clinical adoption:

i. Analytical variability and lack of universal standards across platforms [35, 56];
ii. Biological heterogeneity of CTCs, including EpCAM-low and mesenchymal states that may escape certain capture methods [18, 21];
iii. Need for prospective trials linking specific CTC features (not just counts) to actionable outcomes, such as the ongoing effort to connect SSTR2/5 expression on CTCs with response to lanreotide in NETs [7]; and
iv. Integration of host-response biomarkers with clear mechanistic and clinical rationale, to avoid overfitting multi-marker panels [57].

Future studies should prioritize harmonized reporting (blood volume, processing time, marker panels), define clinically meaningful thresholds or dynamic rules, and validate whether CTC-guided decisions improve survival or quality of life.

9.Conclusions

The provided literature supports a coherent thesis: CTCs are among the most sensitive early indicators of oncologic disease progression and one of the most informative living biospecimens for determining tumor biology in real time. Across high-risk liver disease cohorts, lung cancer, breast cancer, and NETs, CTC detection and longitudinal change provide signals that can precede or complement conventional biomarkers and imaging [4-10]. To maximize clinical utility, the field should transition from enumeration-only approaches toward integrated longitudinal profiling that captures receptor heterogeneity, pathway activation, and systemic host context.

Tables

Table 1: Representative findings from the provided studies supporting CTCs as early predictors and living biospecimens.

Cancer / Setting	CTC Platform / Readout	Key Finding	Potential Clinical Use
Chronic liver disease (HBV/HCV), advanced fibrosis; normal AFP and negative imaging	OncoQuick (density-gradient); CTC presence/absence	CTC-positive individuals developed primary liver cancer within months (F4) or ~2 years (F1); CTC-negative individuals did not develop cancer during 3-year follow-up [4].	Risk stratification; surveillance enrichment; earlier intervention.
NSCLC stages I-IIIB vs. non-cancer controls	In vivo CANCER01 (DC01) EpCAM capture; enumeration	High diagnostic performance (94% sensitivity; 100% specificity); substantially higher detection than in vitro CellSearch [5].	Improved sensitivity in earlier-stage disease.
Advanced lung adenocarcinoma on platinum-pemetrexed	ScreenCell filtration; morphology + cytokeratin	Baseline CTCs detected in all patients (1-67 CTCs/mL); CTC dynamics after two cycles concordant with radiographic changes [6].	Early response monitoring; rapid identification of non-responders.
Neuroendocrine tumors (NETs)	CellSearch + SSTR2/SSTR5 immunostaining	68% had detectable CTCs; 33% showed heterogeneous SSTR2 or SSTR5 expression; potential discordance with tissue [7, 8].	Pharmacodynamic monitoring for SSTR-targeted therapies.
Breast cancer (multiple immunophenotypes)	CTC isolation; MT1 receptor immunocytochemistry; day vs. night comparison	MT1 expression showed circadian rhythm with nocturnal peak; receptor density differed by subtype and aggressiveness [9, 10].	Chronobiology-informed sampling; biologically grounded chronotherapy hypotheses.

Figures

Figure 1. The liquid biopsy landscape: CTCs in context with other circulating biomarkers. Schematic representation of circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and extracellular vesicles (EVs) as complementary liquid biopsy analytes. CTCs provide intact cells for phenotypic characterization, ctDNA enables mutation tracking, and EVs carry tumor-derived proteins and RNA. The integration of these analytes offers comprehensive tumor profiling from a single blood draw. Abbreviations: CTC, circulating tumor cell; ctDNA, circulating tumor DNA; EV, extracellular vesicle; EMT, epithelial-mesenchymal transition.

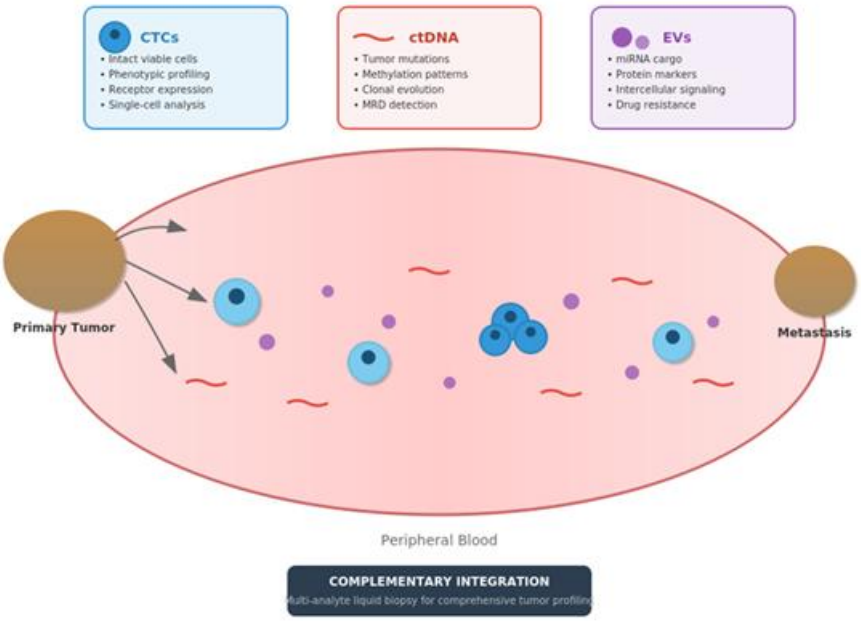


Figure 2. CTC detection platforms: from in vitro enrichment to in vivo capture. (A) Immunoaffinity-based capture using EpCAM antibodies (e.g., CellSearch); (B) Size-based filtration that captures CTCs regardless of surface marker expression (e.g., ScreenCell); (C) In vivo capture device (e.g., CANCER01/DC01) that samples large blood volumes by dwelling in peripheral vein. The in vivo approach demonstrated 94% sensitivity in early-stage NSCLC versus 5.8% for in vitro CellSearch, highlighting the advantage of increased sampling volume. Abbreviations: EpCAM, epithelial cell adhesion molecule; NSCLC, non-small cell lung cancer.

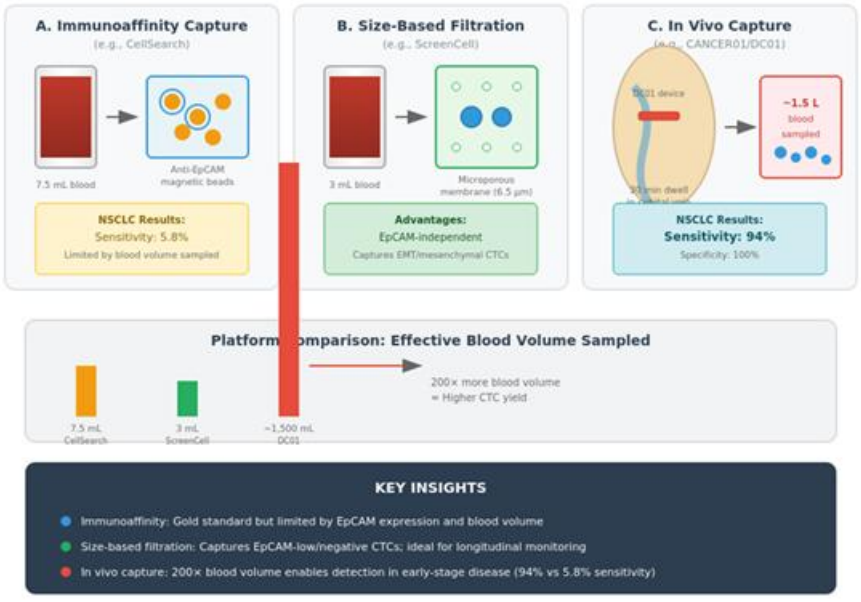


Figure 3. Epithelial-mesenchymal transition (EMT) states in CTCs. CTCs exhibit a spectrum of phenotypes ranging from fully epithelial Є through hybrid (E/M) to fully mesenchymal (M) states. Hybrid CTCs co-express epithelial markers (EpCAM, E-cadherin, cytokeratins) and mesenchymal markers (vimentin, N-cadherin). The hybrid state is associated with enhanced metastatic potential and may confer resistance to standard detection methods targeting only epithelial markers. Key

transcription factors (SNAIL, SLUG, TWIST, ZEB1/2) regulate this plasticity. Abbreviations: CK, cytokeratin; E-cad, E-cadherin; N-cad, N-cadherin.

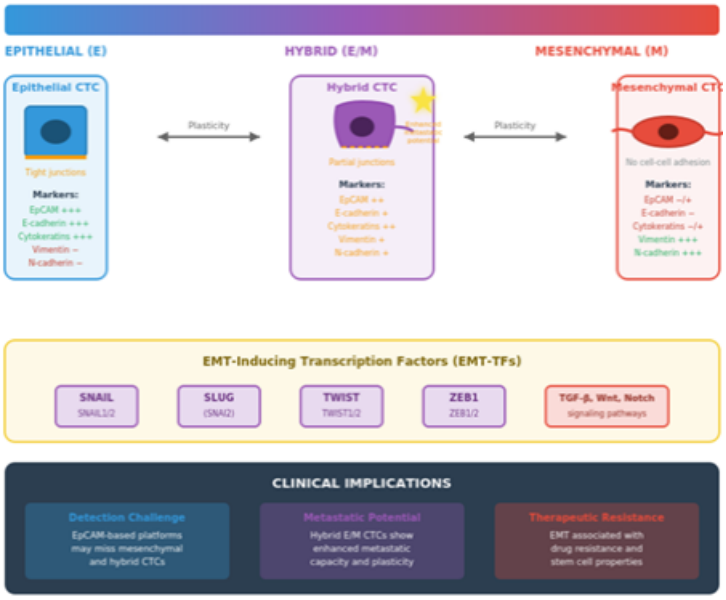


Figure 4. Circadian regulation of MT1 receptor expression on breast cancer CTCs. Schematic depicting the circadian pattern of melatonin receptor type 1 (MT1) expression on circulating tumor cells in breast cancer patients. Peak MT1 expression occurs during nighttime sampling (02:00-04:00), correlating with the nocturnal melatonin surge. MT1 receptor density varies by breast cancer subtype: highest in hormone receptor-positive/HER2-negative tumors, intermediate in HER2-positive tumors, and lowest (or absent) in triple-negative breast cancer (TNBC). This pattern suggests chronobiological considerations for both CTC sampling and potential chronotherapeutic strategies. Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MT1, melatonin receptor type 1; TNBC, triple-negative breast cancer.

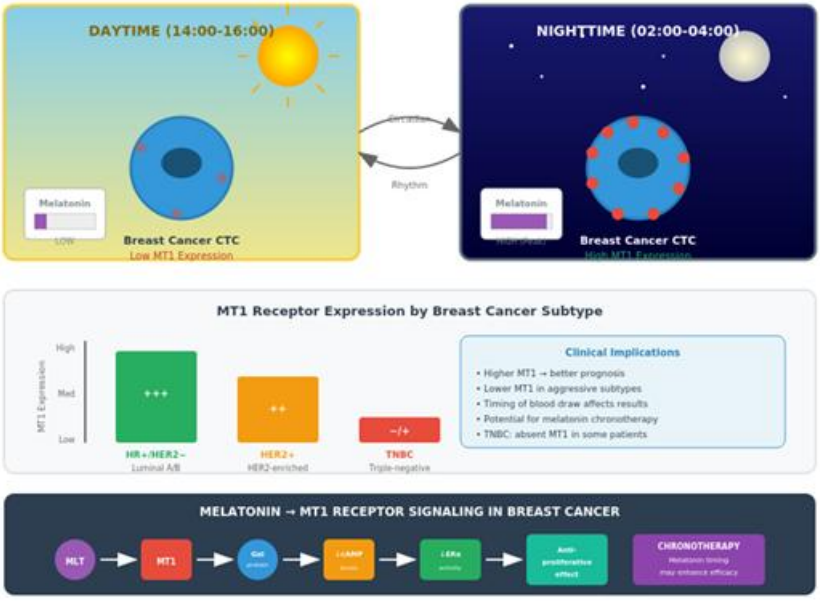
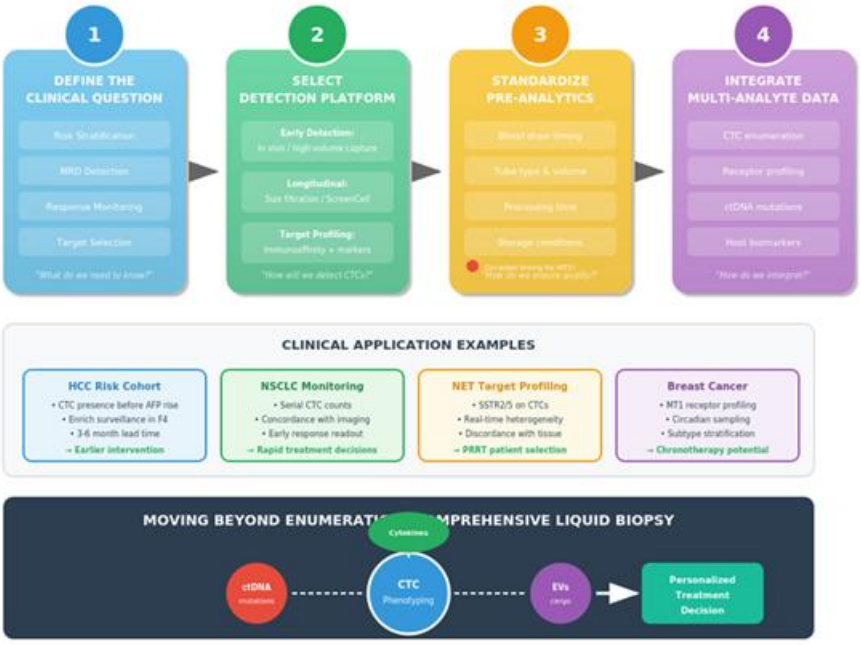


Figure 5. Translational roadmap for CTC-based precision oncology. A four-step framework for implementing CTC analysis in clinical practice: (1) Define the clinical question-risk stratification, minimal residual disease detection, response monitoring, or target selection; (2) Select appropriate platform-in vivo capture for early detection, filtration for longitudinal monitoring, immunoaffinity with multi-marker panels for phenotyping; (3) Standardize pre-analytical variables-including blood draw timing for circadian-sensitive markers; (4) Integrate with complementary biomarkers-combine CTC enumeration and phenotyping with ctDNA, cytokines, and host-response markers for comprehensive disease profiling. Abbreviations: ctDNA, circulating tumor DNA; MRD, minimal residual disease; SSTR, somatostatin receptor.



Author Contributions

Conceptualization, A.T. and R.J.R.; methodology, A.T. and D.K.; validation, R.T.; formal analysis, A.T.; investigation, A.T. and D.K.; resources, A.T.; data curation, D.K.; writing-original draft preparation, A.T.; writing-review and editing, R.J.R. and R.T.; visualization, A.T.; supervision, R.J.R.; project administration, A.T.; funding acquisition, A.T. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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