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Cisterna Chyli as an Evolutionary Incubator for Metastasis: Comparative Circulating Tumor Cell Phenotyping Across Cisterna Chyli, Peripheral Lymph and Blood in 614 Participants

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Cisterna Chyli as an Evolutionary Incubator for Metastasis: Comparative Circulating Tumor Cell Phenotyping Across Cisterna Chyli, Peripheral Lymph and Blood in 614 Participants

Running title: CTC Phenotype in Cisterna Chyli

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Abstract

Background: Circulating tumor cells (CTCs) are key intermediates of hematogenous metastasis, yet their phenotype is shaped by transit through distinct anatomical niches. The cisterna chyli is the central lymphatic conduit draining lipid-rich intestinal lymph and peripheral lymphatics into the venous system. We investigated whether the cisterna chyli functions as a phenotypic "incubator" for aggressive CTC states. Methods: In a 7-year prospective study, intraoperative samples (7.5 mL each) were collected from the cisterna chyli, peripheral lymph, and peripheral blood of 496 patients with stage III–IV solid tumors (21 tumor types). A control cohort of 118 non-oncological patients undergoing surgery after trauma was sampled with the same protocol. CTCs were enumerated by CellSearch and phenotyped using multi-marker immunocytochemistry for proliferation (Ki-67), invasion/migration (MMP-9, CXCR4), epithelial–mesenchymal transition (EMT), and stemness markers. Cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA) were quantified across compartments. Results: In the cancer cohort, cisterna chyli CTC counts were markedly higher than in peripheral blood or peripheral lymph (12–15× enrichment across tumor types). Cisterna chyli CTCs showed increased proliferative and invasive phenotypes (Ki-67 ~2.7×; MMP-9 ~3×; CXCR4 ~5×) and enrichment of EMT and stemness programs (Any EMT+ ~2.3×; Any stemness+ ~3.3×; ≥2 stemness markers ~3.4×). cfDNA and ctDNA levels were comparable across the three compartments. In controls, CTC-like events were detected in 23/118 participants (19.5%) with no enrichment reported between compartments. Conclusions: The cisterna chyli harbors a substantially enriched and biologically aggressive CTC subpopulation, consistent with an "evolutionary incubator" model in which lymphatic transit promotes clonal selection and phenotypic plasticity. These findings support cisterna chyli sampling as a high-yield site for intraoperative liquid biopsy and suggest new regional therapeutic opportunities to target lymph-borne metastatic precursors.:

Keywords: cisterna chyli; circulating tumor cells; lymphatic metastasis; EMT; cancer stem cells; liquid biopsy; phenotypic plasticity

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1. Introduction

CTCs are rare malignant cells shed from primary and metastatic lesions into the circulation and are strongly associated with prognosis in multiple tumor types, including metastatic breast, colorectal, prostate and lung cancers [1–5,16–18]. Standardized enrichment and imaging workflows (e.g., CellSearch) have enabled clinical validation and phenotyping of CTCs [13,14,23,24], while single-cell profiling has revealed extensive heterogeneity and phenotypic plasticity among CTCs [15]. CTC-based liquid biopsy concepts are increasingly integrated with other circulating biomarkers to support precision oncology [2,25,54]. However, CTC rarity and sampling limitations remain major barriers; approaches that increase sampled blood volume (e.g., diagnostic leukapheresis) can improve detection sensitivity [22]. Beyond enumeration, the biological state of CTCs—proliferation, invasion, immune interactions, EMT-like plasticity and stemness—appears to govern metastatic competence [11,12,19–21,34–47].

The lymphatic system is a major route of tumor dissemination, yet lymph-borne CTC biology is less studied than blood-borne CTCs. Lymphangiogenesis and lymphatic remodeling facilitate tumor cell transport, interactions with stromal and immune compartments, and access to downstream organs [6–8,26–33]. Lymphatic niches can be metabolically and immunologically distinct; adipose- and lymph node–associated microenvironments have been shown to promote metastatic traits and immune modulation [9,10].

The cisterna chyli is the primary collecting reservoir of intestinal and lower-body lymph that drains via the thoracic duct into the venous circulation. This unique niche is lipid-rich, subject to intermittent flow, and may present selective pressures (e.g., oxidative stress, hypoxia, immune interactions) that promote aggressive phenotypes.

We hypothesized that the cisterna chyli acts as an evolutionary incubator where CTCs are enriched and acquire proliferative, invasive, EMT-like and stem-like states before entering systemic circulation. To test this, we performed intraoperative matched sampling of cisterna chyli, peripheral lymph and peripheral blood in 614 participants (496 cancer; 118 controls) and compared CTC burden and phenotype across compartments.

2. Results

2.1. Study Cohorts

The cancer cohort comprised 496 patients with stage III–IV solid tumors representing 21 tumor types (Tables 1 and 2). All cancer participants underwent intraoperative sampling of cisterna chyli, peripheral lymph and peripheral blood (7.5 mL each). The non-oncological control cohort included 118 trauma-surgery patients sampled with the same protocol.

CTC-like events were detected in 23/118 controls (19.5%). As reported by investigators, these events showed comparable distribution across cisterna chyli, peripheral lymph and peripheral blood, without the enrichment patterns observed in cancer participants.

Table 1. Cohorts and baseline characteristics.

Characteristic	Cancer cohort	Control cohort
Participants (n)	496	118
Cohort description	Stage III–IV solid tumors (21 tumor types); intraoperative sampling	Non-oncological patients requiring surgery after trauma; intraoperative sampling

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Sampling compartments (volume)	Peripheral blood, peripheral lymph, cisterna chyli (7.5 mL each)	Peripheral blood, peripheral lymph, cisterna chyli (7.5 mL each)
Age (years), mean ± SD	56.0 ± 11.0	NA
Age (years), range	28–76	NA
Sex, female n (%)	207 (41.7)	NA
Sex, male n (%)	289 (58.3)	NA
ECOG PS 1 n (%)	248 (50.0)	NA
ECOG PS 2 n (%)	176 (35.5)	NA
ECOG PS 3 n (%)	72 (14.5)	NA
Prior systemic therapy, 3 lines n (%)	320 (64.5)	NA
Prior systemic therapy, 4 lines n (%)	176 (35.5)	NA
CTC-positive participants, n (%)	496 (100.0)*	23 (19.5)
CTC distribution across compartments	Cisterna chyli enriched (12–15× vs blood/lymph)	Comparable across cisterna/lymph/blood (no enrichment reported)

NA, not available from the current dataset.

Table 2. Distribution of tumor types in the cancer cohort (N=496).

Tumor Type	n	%
Lung adenocarcinoma	36	7.3
Lung squamous cell carcinoma	21	4.2
Ovarian serous carcinoma	29	5.8
Breast cancer ER/PR+ HER2 -	55	11.1
Breast cancer Triple Negative	47	9.5
Breast cancer ER/PR - HER2+	18	3.6
Osteosarcoma	11	2.2
Hepatocellular carcinoma	27	5.4
Cholangiocarcinoma	11	2.2
Pancreatic ductal adenocarcinoma	29	5.8
Colon adenocarcinoma	41	8.3
Rectal adenocarcinoma	19	3.8
Cervical squamous cell carcinoma	17	3.4
Endometrial adenocarcinoma	22	4.4
Esophageal squamous cell carcinoma	7	1.4

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Esophageal adenocarcinoma	11	2.2
Gastric adenocarcinoma	19	3.8
Gastric signet -ring cell carcinoma	14	2.8
Neuroendocrine tumors	23	4.6
Renal clear cell carcinoma	24	4.8
Leiomyosarcoma	15	3.0

2.2. Cisterna Chyli Markedly Enriches CTC Counts

Across all tumor types, mean CTC counts in cisterna chyli were 12–15-fold higher than in peripheral blood or peripheral lymph (Figure 1; Table 3). This enrichment was observed consistently across carcinomas and sarcomas, supporting a compartment-driven amplification rather than tumor-type restriction.

In peripheral blood and peripheral lymph, mean CTC burdens were similar, indicating that the cisterna chyli represents a distinct high-yield reservoir rather than a simple reflection of circulating load.

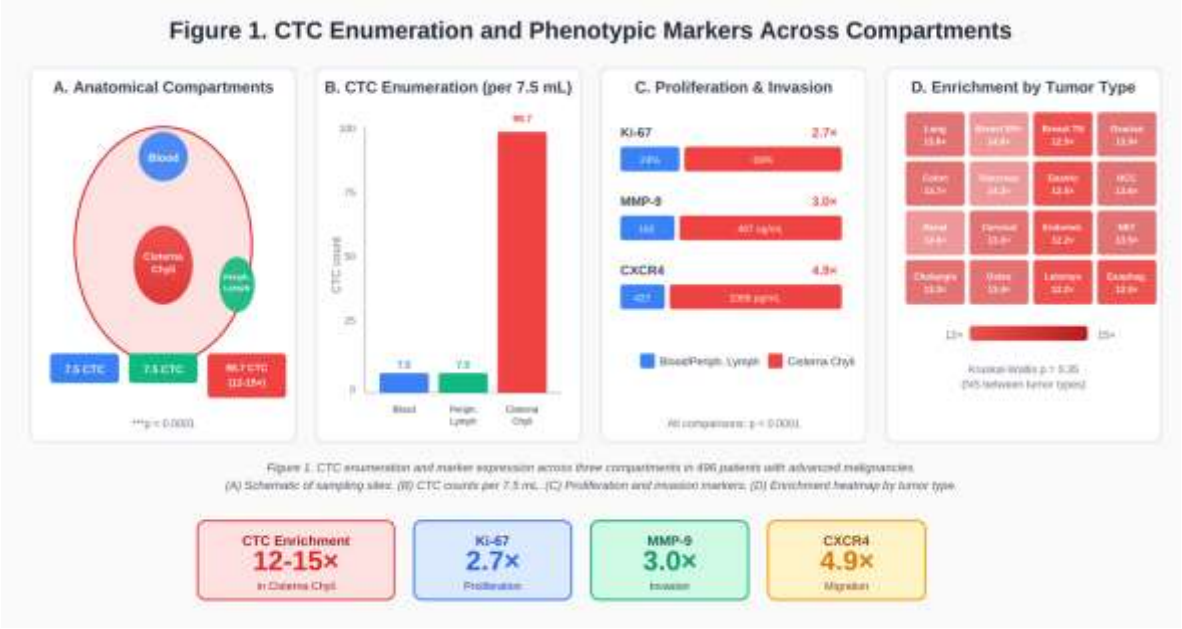

Figure 1. CTC enumeration across matched compartments. CTC counts (per 7.5 mL) in peripheral blood, peripheral lymph and cisterna chyli for N = 496 cancer patients, demonstrating 12–15× enrichment in cisterna chyli. All comparisons: cisterna chyli vs. blood/lymph, $p < 0.0001$.

Table 3. (CTC enumeration by tumor type) is provided in the accompanying Excel file due to its size, and summarized in Figure 1.

2.3. Proliferation, Invasion and Migration Phenotypes Are Elevated in Cisterna Chyli CTCs

Cisterna chyli CTCs displayed increased proliferative activity (Ki-67) [55], enhanced invasive protease expression (MMP-9) [56], and elevated CXCR4 levels consistent with chemokine-driven trafficking (Table 4; Figure 2). The magnitude of enrichment was greatest for CXCR4 (~5×), implicating CXCR4/CXCL12 signaling as a potential mediator of lymphatic and nodal tropism [57,58].

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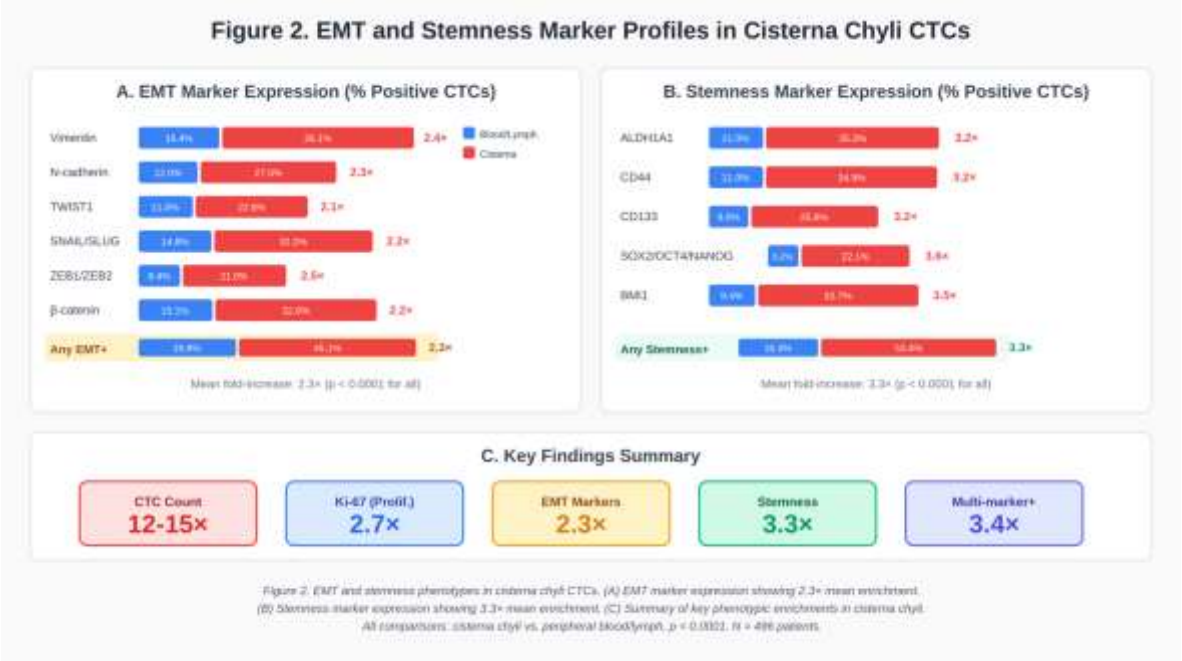

Figure 2. EMT and stemness marker profiles in cisterna chyli CTCs. (A) EMT marker expression (% positive CTCs) showing ~2.3× enrichment in cisterna chyli. (B) Stemness marker expression showing ~3.3× enrichment in cisterna chyli. (C) Summary of key phenotypic enrichments in cisterna chyli. N = 496.

Table 4. Proliferation and invasion/migration markers in CTCs (all tumor types pooled).

Marker	Blood	Peripheral lymph	Cisterna chyli	Fold
Ki-67 (%)	24.2 ± 4.6	23.9 ± 4.7	68.9 ± 15.2	2.7×
MMP-9 (ng/mL)	162.4 ± 33.8	161.7 ± 33.2	487.3 ± 102.1	3.0×
CXCR4 (pg/mL)	426.8 ± 89.2	424.1 ± 88.6	2089.4 ± 428.6	4.9×

2.4. EMT and Stemness Programs Are Enriched in Cisterna Chyli

Compared with blood/lymph CTCs, cisterna chyli CTCs showed increased expression of EMT markers (vimentin, N-cadherin, TWIST1, SNAIL/SLUG, ZEB1/2, nuclear β-catenin) and higher rates of multi-marker EMT positivity (Table 5; Figure 2). In parallel, cisterna chyli CTCs exhibited enrichment of stemness markers (ALDH1A1, CD44, CD133, SOX2/OCT4/NANOG, BMI1) and greater multi-marker stemness positivity (Table 6; Figure 2). These findings align with established links between EMT-like plasticity and cancer stem cell states [34–47].

Table 5. EMT marker expression in CTCs (all tumor types pooled).

Marker	Blood	Peripheral lymph	Cisterna chyli	Fold
Vimentin (VIM)	16.4 ± 2.8	16.2 ± 2.7	39.1 ± 5.0	2.4×
N-cadherin (CDH2)	12.0 ± 1.3	12.0 ± 2.3	27.5 ± 3.3	2.3×
TWIST1	11.0 ± 1.6	11.2 ± 2.0	22.8 ± 4.5	2.1×
SNAIL/SLUG	14.8 ± 2.9	14.6 ± 1.8	32.2 ± 5.1	2.2×
ZEB1/ZEB2	8.4 ± 0.9	8.4 ± 1.5	21.0 ± 3.2	2.5×

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β-catenin (nuclear)	15.1 ± 2.9	15.3 ± 2.3	32.8 ± 3.4	2.2×
Any EMT marker+	19.8 ± 2.6	19.8 ± 2.3	45.1 ± 6.1	2.3×
≥3 EMT markers	5.4 ± 0.7	5.5 ± 0.8	13.5 ± 1.9	2.5×

Table 6. Stemness marker expression in CTCs (all tumor types pooled).

Marker	Blood	Peripheral lymph	Cisterna chyli	Fold
ALDH1A1	11.0 ± 1.6	11.1 ± 1.4	35.3 ± 3.7	3.2×
CD44 (high)	11.0 ± 2.1	11.3 ± 1.4	34.9 ± 4.4	3.2×
CD133	8.0 ± 1.6	7.9 ± 1.5	25.8 ± 4.7	3.2×
SOX2/OCT4/NANOG	6.2 ± 1.0	6.3 ± 1.1	22.1 ± 2.3	3.6×
BMI1	9.4 ± 1.5	9.4 ± 1.2	32.7 ± 3.4	3.5×
Any stemness marker+	16.3 ± 2.2	15.9 ± 2.1	53.4 ± 9.3	3.3×
≥2 stemness markers	7.7 ± 1.0	7.6 ± 1.2	26.1 ± 3.6	3.4×

2.5. cfDNA and ctDNA Levels Are Similar Across Compartments

Despite large differences in CTC burden and phenotype, cfDNA and ctDNA levels were comparable across cisterna chyli, peripheral lymph and peripheral blood (Table 7). This supports the concept that cellular (CTC) and acellular (cfDNA/ctDNA) compartments may capture distinct biological information and that cisterna chyli sampling preferentially augments cellular yield.

Table 7. cfDNA/ctDNA levels across compartments (all tumor types pooled).

Parameter	Blood	Peripheral lymph	Cisterna chyli
cfDNA (ng/mL)	30.2 ± 5.7	29.8 ± 5.5	30.4 ± 5.9
ctDNA fraction (%)	1.22 ± 0.26	1.23 ± 0.25	1.21 ± 0.26
cfDNA fold vs Blood	1.00	0.99	1.01
ctDNA fold vs Blood	1.00	1.01	0.99

Table 8. Control cohort summary.

Metric	Value
Control cohort (non-oncological trauma surgery)	118
CTC-positive controls (any compartment)	23
CTC positivity rate (%)	19.5
Reported distribution	CTCs identified with comparable frequency in cisterna chyli, peripheral lymph, and peripheral blood
Identification method	CellSearch + ICC panel (same as cancer cohort)

Control cohort details are provided as reported by investigators.

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3. Discussion

This study provides evidence that the cisterna chyli is a high-yield compartment for CTC recovery and that cisterna-derived CTCs are enriched for proliferative, invasive, EMT-like and stem-like features. The observed 12–15× increase in cisterna chyli CTC counts across 21 tumor types suggests that lymphatic convergence and reservoir physiology concentrate tumor cells before venous entry. Importantly, phenotypic enrichment (Ki-67, MMP-9, CXCR4, EMT and stemness markers) indicates that cisterna chyli CTCs may represent a biologically selected subpopulation rather than a passive accumulation.

Mechanistically, lymphatic transport and nodal/cisternal microenvironments can impose unique selective pressures, including variable shear, intermittent flow, lipid-rich substrates, hypoxia-related signaling, and immune and stromal interactions [6–8,26–33,48–53]. CTC cluster biology and CTC–immune cell interactions may further support survival and metastatic competency [19–21]. The enrichment of EMT and stemness programs is consistent with models of metastasis requiring phenotypic plasticity and tumor-initiating capacity [34–47].

The control cohort yielded CTC-like events in ~20% of trauma-surgery patients without compartmental enrichment. Although the clinical meaning of these rare events remains uncertain in the absence of longitudinal follow-up, the lack of cisterna enrichment in controls supports that the marked cisterna signal in cancer participants is disease-associated.

Clinically, cisterna chyli sampling may serve as a superior intraoperative liquid biopsy site when feasible, enabling improved CTC enumeration and molecular profiling for prognosis, treatment resistance assessment, and investigation of metastatic potential. Therapeutically, the cisterna chyli and central lymphatic conduits could be explored as regional targets for drug delivery or for strategies aimed at limiting dissemination of highly plastic CTC states.

Chronobiology-related pathways, including melatonin signaling, may modulate oxidative stress, metabolic programming and metastatic behavior and therefore represent testable adjunct hypotheses for targeting metastatic traits [59–67].

Limitations include the intraoperative nature of sampling, heterogeneity in tumor types and prior therapies, and incomplete demographic characterization of the control cohort in the current dataset. Future work should integrate longitudinal outcomes, single-cell multi-omics, and standardized control phenotyping to better define the clinical significance of cisterna-derived CTCs.

4. Materials and Methods

4.1. Study Design and Participants

A prospective observational study was conducted over 7 years at the Institute for Personalized Medicine of Georgia. The cancer cohort included 496 adults with stage III–IV solid tumors undergoing surgery or diagnostic procedures allowing access to the cisterna chyli. Tumor types are listed in Table 2. The control cohort included 118 non-oncological patients undergoing surgery after trauma.

4.2. Sample Collection

Matched samples (7.5 mL each) were obtained intraoperatively from peripheral blood, peripheral lymph, and the cisterna chyli using sterile technique and processed immediately.

4.3. CTC Enumeration and Phenotyping

CTCs were enumerated using the CellSearch system (EpCAM enrichment with cytokeratin positivity and CD45 exclusion) [13,14,23,24]. For tumors with reduced epithelial marker expression (e.g., sarcomas or EMT-high phenotypes), immunocytochemistry panels including vimentin and additional lineage markers were used for phenotypic classification. Phenotyping assays targeted proliferation (Ki-67), invasion/migration (MMP-9, CXCR4), EMT markers (VIM, CDH2, TWIST1,

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SNAIL/SLUG, ZEB1/2, nuclear β-catenin), and stemness markers (ALDH1A1, CD44, CD133, SOX2/OCT4/NANOG, BMI1). Negative controls were included for each staining run.

4.4. cfDNA/ctDNA Quantification

cfDNA and ctDNA were quantified from matched plasma/lymph/cisternal fluid using standardized extraction and quantification workflows.

4.5. Statistics

Continuous variables are reported as mean ± SD. Comparisons between cisterna chyli and peripheral compartments used paired tests as appropriate; significance was set at $p < 0.05$. Where multiple comparisons were made across marker panels, results were interpreted with attention to overall effect sizes.

5. Conclusions

The cisterna chyli is a central lymphatic reservoir that concentrates CTCs and enriches for aggressive phenotypes characterized by proliferation, invasion, EMT and stemness. Cisterna chyli sampling may provide a high-yield intraoperative liquid biopsy and highlights the central lymphatic system as a potential therapeutic and diagnostic target in metastasis.

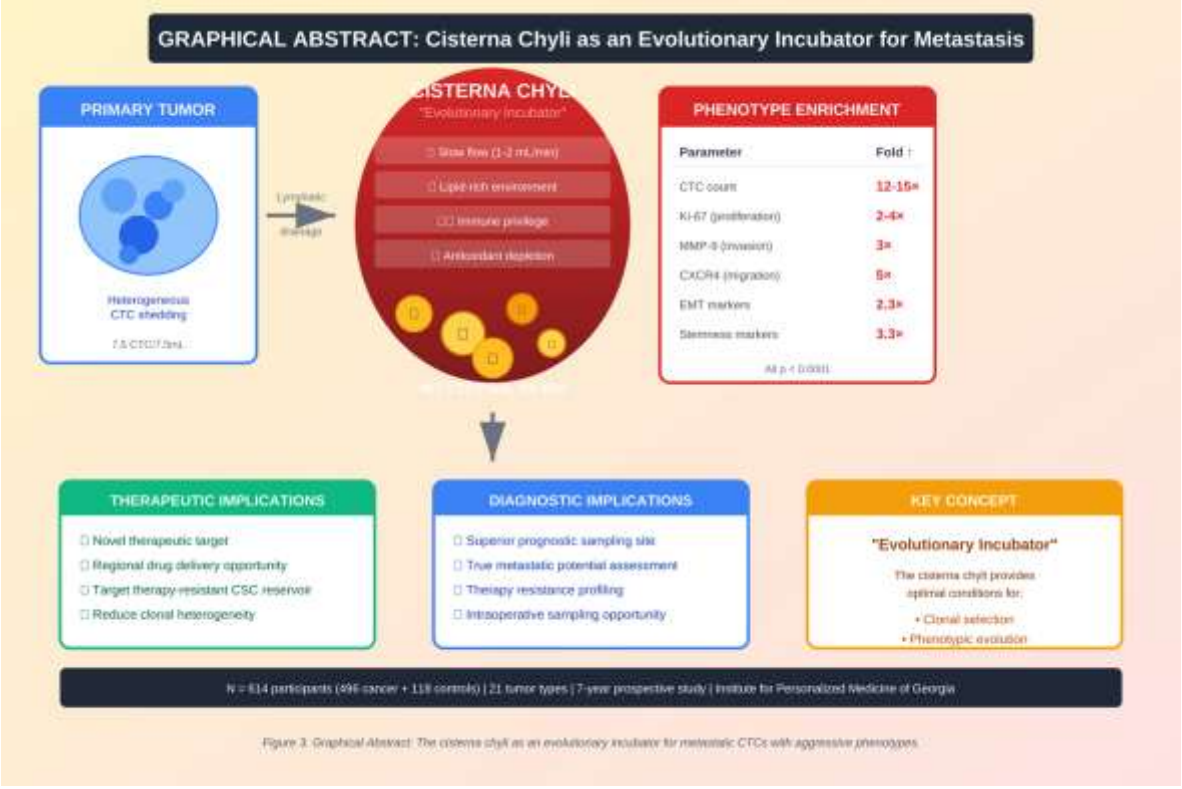

Figure 3. Graphical abstract. Proposed model of the cisterna chyli as an "evolutionary incubator" that concentrates CTCs and enriches aggressive phenotypes, with diagnostic and therapeutic implications. N = 614 participants.

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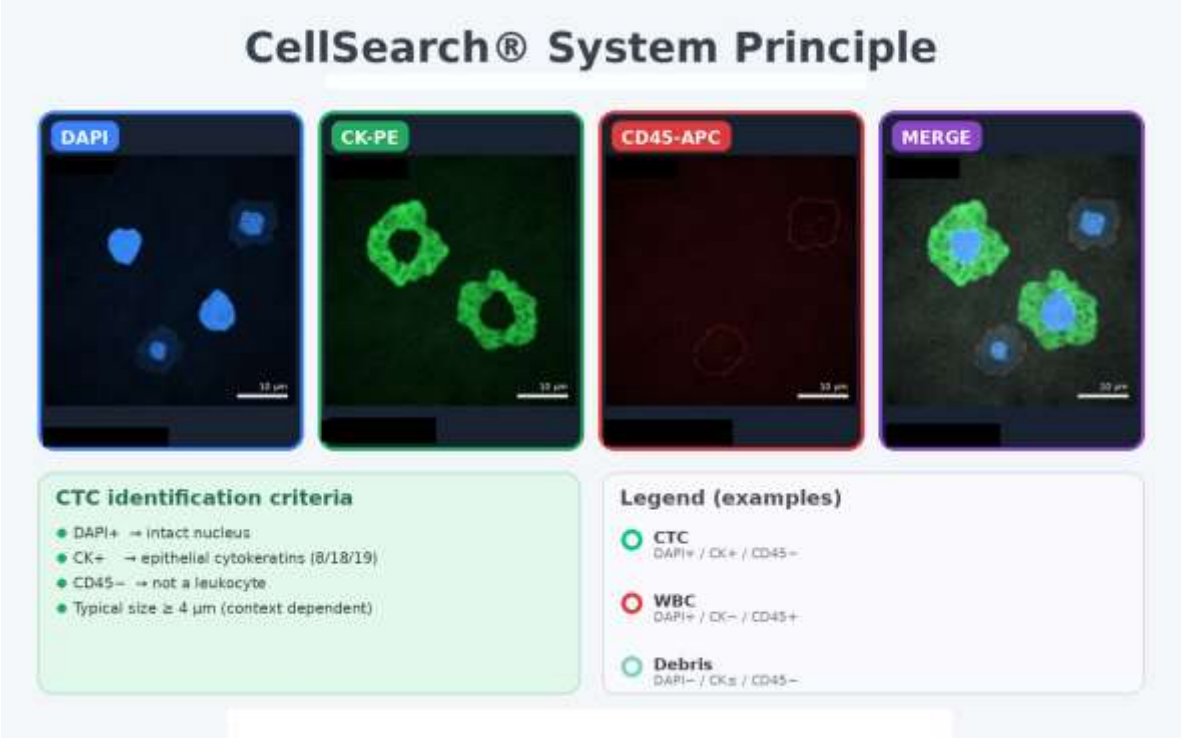

Figure 4. CellSearch system principle. Schematic overview of EpCAM-based immunomagnetic enrichment, fluorescent labeling (CK/DAPI/CD45) and automated imaging used for CTC enumeration.

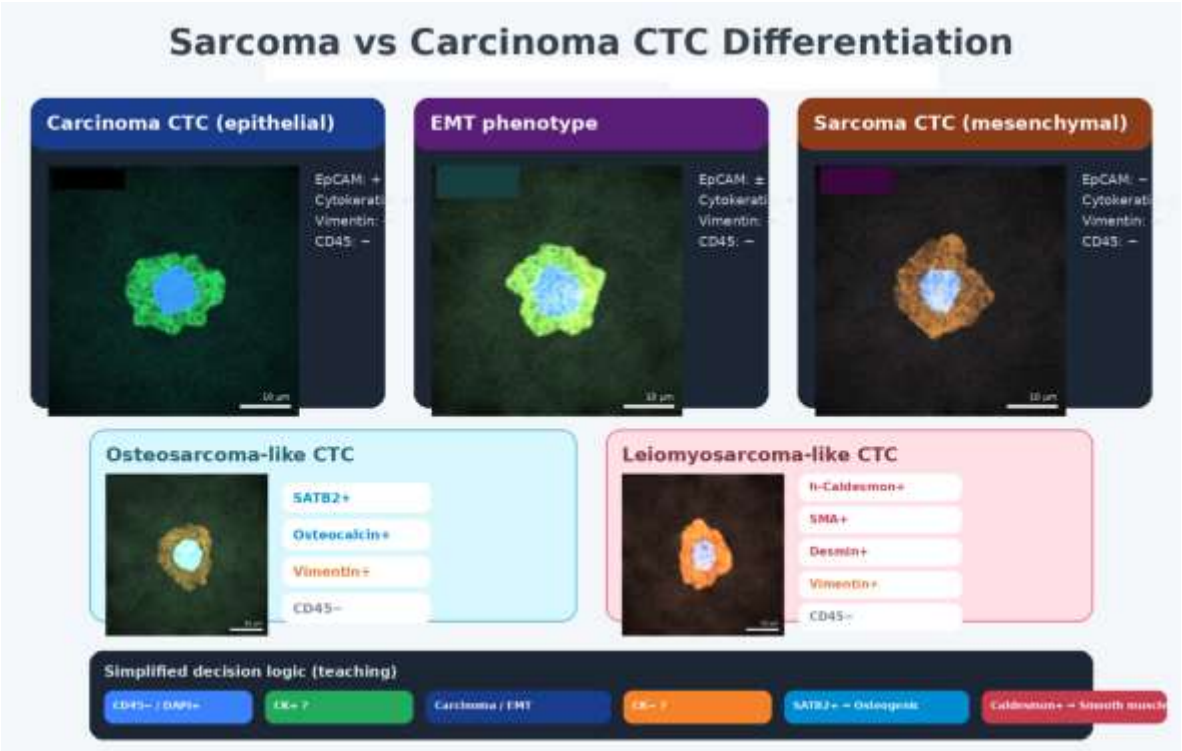

Figure 5. Decision logic for differentiating carcinoma- vs sarcoma-like CTC phenotypes. Representative immunophenotyping patterns and simplified classification logic applied to epithelial and mesenchymal CTC states.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. The Excel file provided with this submission contains full Table 3 (tumor-type-specific enumeration) and the complete set of tables used in this study.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board/Ethics Committee of the Institute for Personalized Medicine of Georgia (Approval ID: insert).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: De-identified data are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest. Update if applicable.

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