

Advancing Circulating Tumor Cell Analysis for Cancer Detection and Monitoring: NGRL's Approach and Innovations Using the Genesis System with Celselect Slides

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Executive Summary

NGRL has advanced the field of circulating tumor cell (CTC) research using the Genesis Cell Isolation System, the attributes of which aided NGRL's large-scale CTC enumeration study involving many external collaborators. The findings from this study involving over 2,000 individuals highlight both the potential and complexity of interpreting CTC signals in healthy and at-risk populations. By integrating CTC enumeration with cell-free DNA (cfDNA) analysis, NGRL is laying the foundation for a new generation of liquid biopsy strategies aimed at early detection, personalized therapy, and preventive oncology.

Introduction

CTCs are emerging as crucial players in liquid biopsy, offering visibility into early cancer detection, disease monitoring, and personalized treatment response. However, the rarity and fragility of CTCs present major challenges for reliable capture, enumeration, and downstream analysis. As a result, precision capture and high-dimensional characterization remain critical barriers to providing routine CTC analysis.

NGRL, together with 42 leading institutions across Japan, is redefining CTC potential (see [bulletin 3875](#) for more information on NGRL). In one of the world's largest prospective CTC studies, NGRL utilized the Genesis System with Celselect Slides™ to automate high-efficiency CTC capture, phenotyping, and enumeration at scale. As of 2025, this initiative has already profiled 2,157 individuals, including participants with an elevated cancer risk, providing an unprecedented view of baseline CTC biology within populations of people without cancer.

The following summary highlights NGRL's use of the Genesis System to advance cancer detection and prevention through a large-scale CTC enumeration study of healthy and high-risk individuals in Japan. NGRL's parallel investigations in CTC biology, ex vivo culture methods, and cfDNA integration demonstrate their potential for use in population monitoring and preventive oncology.

Why Innovation in CTC Detection Impacts Early Cancer Identification

Innovations that enable CTC detection in predisease or precancerous states could significantly expand the role of these molecules in cancer monitoring for oncology research. In clinical settings, CTC enumeration provides a minimally invasive alternative to tissue biopsy, offering insights into treatment response, minimal residual disease, and prognosis while reducing patient burden. Because it relies on simple blood sampling, CTC enumeration can be repeated, enabling longitudinal monitoring of treatment efficacy and disease recurrence.



Methodology of the Large-Scale CTC Enumeration Study Using the Genesis System and Celselect Slides

Table 1 describes the overall study methodology and some of its key findings. The results suggest that while occasional detection of low CTC counts may not necessarily indicate cancer onset, persistent or increasing counts may warrant closer monitoring.

Table 1. Study methodology and key findings.

Category	Details
Sample population	2,157 healthy and high-risk individuals
Collaborating sites	42 research facilities nationwide (Japan) Family history of cancer Current/former smoker
High-risk subject criteria	Long-term oral contraceptive use and hormone replacement therapy use in women Men aged 50+ years Medical conditions associated with elevated cancer risk
Marker strategy	CTCs identified as CD45-negative, cytokeratin-positive cells
Technology	Genesis System with Celselect Slides (140,800 microchambers, 8–30 µm pore size); automated capture-to-staining workflow within 3 hours
Method requirement	Routine incorporation in clinical research requires sensitive, accurate, and cost-effective methods
Volume requirement	Minimum 7.5 mL of blood for optimal recovery ≥1 CTC detected in 4.9% of subjects A single CTC detected in 4.4% of subjects
Key findings	0 CTCs detected at 6–12 months of follow-up in 10–20% of subjects with 1–2 CTCs Some subjects showed an increase to 3 CTCs over time

Select Study Findings

Healthy Populations Lack CTCs

In the study, NGRL established a verified background level of zero CTCs in healthy patients through CTC enumeration of liquid biopsy samples (Figure 1), applying CD45-negative and cytokeratin (CK)-positive immunophenotyping criteria. This finding is grounded in prior cell spike-in validation studies at NGRL demonstrating the sensitivity of the Genesis System and Celselect Slides to detect low levels of CTCs or their absence. The ability to detect states of no CTCs via patient monitoring has an immediate impact on broader population surveillance. It also sets the stage for future applications in preventative oncology, whereby baseline CTC profiles could support early determination of the presence or absence of cancer.

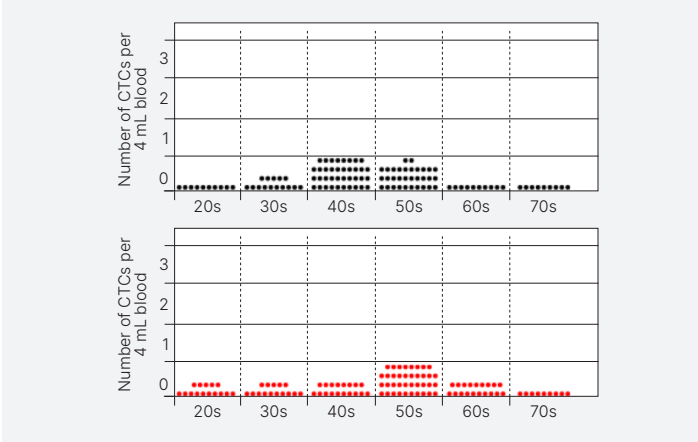


Fig. 1. Detection of zero CTCs in healthy individuals, 114 males and 114 females, through CTC enumeration, as based on CD45-negative and cytokeratin (CK)-positive criteria. Celselect Slides were used to enumerate CTCs in blood from healthy subjects. Blood was collected from 114 males (•) and 114 females (•), CK-/CD45+. Prior blood tests and lung computed tomography scans showed no abnormalities. (The x-axis shows age in decade of life; y-axis shows the number of CTCs detected.) Based on these criteria, the number of CTCs in all healthy control samples was zero. Each point represents the number of individual subjects in that age group, in whom no CTCs were detected.

Experimental Challenges Revealed by CTC Research

Capture Success Relies on Sufficient Blood Volume

NGRL research indicates that CTC capture performance relies mainly on the total volume of blood processed rather than on differences in sample type. For example, recovery from 4 mL of sample proved insufficient for reliable detection of rare CTCs, and a minimum input of 7.5 mL was required to consistently obtain sufficient CTC cells for analysis.

Size-Based CTC Capture Is Critical for Accurate Detection and Analysis

By enabling size-based capture of CTCs rather than relying on cell-surface antigens, Celselect Slides technology resolved a key challenge for NGRL. This approach preserves normal cellular states and broadens downstream analytical options. Moreover, it supports both epithelial marker assays and mesenchymal phenotyping using markers such as vimentin (Figures 2 and 3) to identify CTCs that have undergone the critical epithelial-to-mesenchymal transition (EMT). EMT is the process in which epithelial cells lose adhesion properties and gain mesenchymal traits. Such changes sharply increase motility, invasiveness, and metastatic potential, making EMT-associated CTCs especially important cells to detect and characterize in cancer progression.

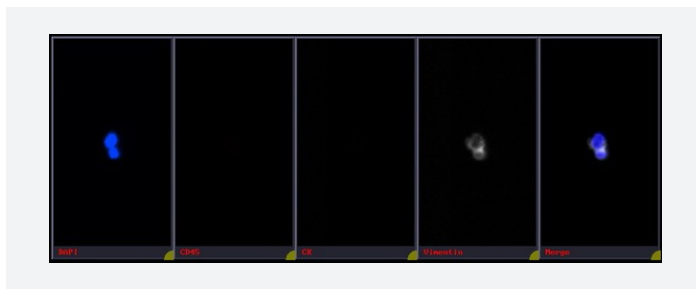


Fig. 2. Mesenchymal CTCs detected by cell enumeration using a Celsee Prep400 and scanned with a Celsee Analyzer. The NGRL study demonstrated successful detection of mesenchymal CTCs using size-based capture of CTCs. Following capture, CTC enumeration proceeds through a unified workflow applicable across diverse cancer types, utilizing antibody panels that include cytokeratin or EpCAM, DAPI, CD45, and vimentin. CTC, circulating tumor cell; DAPI, 4',6-diamidino-2-phenylindole; EpCAM, epithelial cell adhesion molecule.

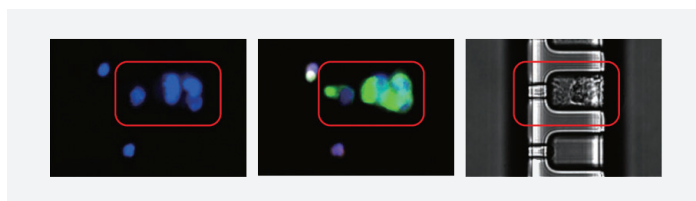


Fig 3. Detection of CTC clusters (indicated by a red box) on Celselect Slides and imaged using a BioView imaging system. The Genesis System with Celselect Slides platform supports the identification of multicellular CTC clusters, which are increasingly recognized as critical contributors to metastatic potential. CTC, circulating tumor cell.

Ensuring Culture of Fragile CTCs: The Brief Ex Vivo Life Span of CTCs

CTCs are inherently fragile during the processing of blood for liquid biopsy because they are vulnerable to hemolysis and the mechanical stress of high-speed centrifugation. Individual CTCs typically remain viable for only a few hours ex vivo, but CTCs that form clusters exhibit an extended lifespan, potentially due to intercellular support.

To evaluate their stability ex vivo, NGRL cultured CTCs isolated using the Genesis System and assessed their viability. Their results demonstrated that successful ex vivo culture requires prompt handling. Specifically, when blood samples were processed within 2 hr of collection, CTCs maintained viability and readily formed spheroid-like structures (Figure 4). Culture success declined afterwards, falling below 50% after 6 hr.

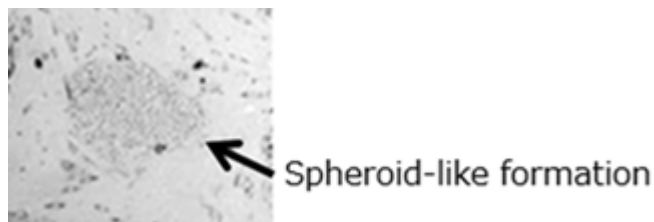


Fig. 4. CTC spheroid-like formation in culture. Successful CTC spheroid-like formation in culture is optimal within 2 hr post blood draw.

Applications of Cultured CTCs: Drug Sensitivity Testing

High-quality CTCs obtained using the Genesis System support robust ex vivo culture, enabling drug sensitivity testing and providing insights into individual therapeutic response. Beyond surveillance, ex vivo CTC culture has potential in a range of downstream applications. At NGRL, cultured CTCs are used to evaluate drug responses and guide experimental investigations, highlighting their value for future research and therapeutic development.

Genesis Celselect Utility for CTC Culture and Analysis

The Genesis Celselect platform facilitates rapid concentration and recovery of CTCs within a 2 hr window, aligning with the limited 2 hr viability timeframe of ex vivo CTCs. This feature makes the platform ideal for downstream CTC culture. Compared with other commercially available technologies, the Genesis System with Celselect Slides offers automated blood sample loading into microfluidic channels, and immunostaining is completed in under 3 hr, with high reproducibility.

Key Biological Questions to Evaluate with CTC Enumeration

Determining the CTCs That First Detach from the Tumor and Enter the Circulation

To advance CTC research, NGRL is investigating the mechanisms that govern how tumor cells first detach and enter the bloodstream. A central question is whether EMT initiates tumor cell detachment, producing the first CTCs, or whether epithelial CTCs are released first due primarily to shear forces from blood flow. Understanding this distinction is critical for defining the earliest steps of metastasis.

Additionally, the Genesis System with Celselect Slides technology enables the investigation of epithelial plasticity in CTCs (see [bulletin 3267](#)). As a result, the presence of intermediate hybrid states within tumors can be detected. These include epithelial-mesenchymal (metastable) phenotypes within tumors, which can be linked to the stem-like properties of CTCs and overall tumor heterogeneity. Such hybrid states can require detection assays beyond traditional epithelial markers and can be performed using the Genesis System.

These considerations highlight NGRL's emphasis that new approaches to CTC capture and analysis are needed, with the Genesis System with Celselect Slides offering a practical platform uniquely suited for inquiry into how tumor cells enter the circulation and initiate metastatic progression.

Liquid Biopsy of cfDNA: Sources of cfDNA in Blood and Its Role as a Metric for Tumor Growth or Inhibition

As illustrated in Figure 5A, variably sized extracellular DNA fragments called cfDNA exist in blood. Total cfDNA can be released from many different sources and includes not only tumor-derived cell-free tumor DNA (ctDNA) but also cfDNA derived primarily from white blood cells. Due to fragmentation patterns, ctDNA can show a slightly shorter average fragment length, often around 145–160 bp, than cfDNA from healthy cells, leading to a peak of approximately 166 bp. Figure 5B shows an analysis of how cfDNA concentration and length correspond to the source.

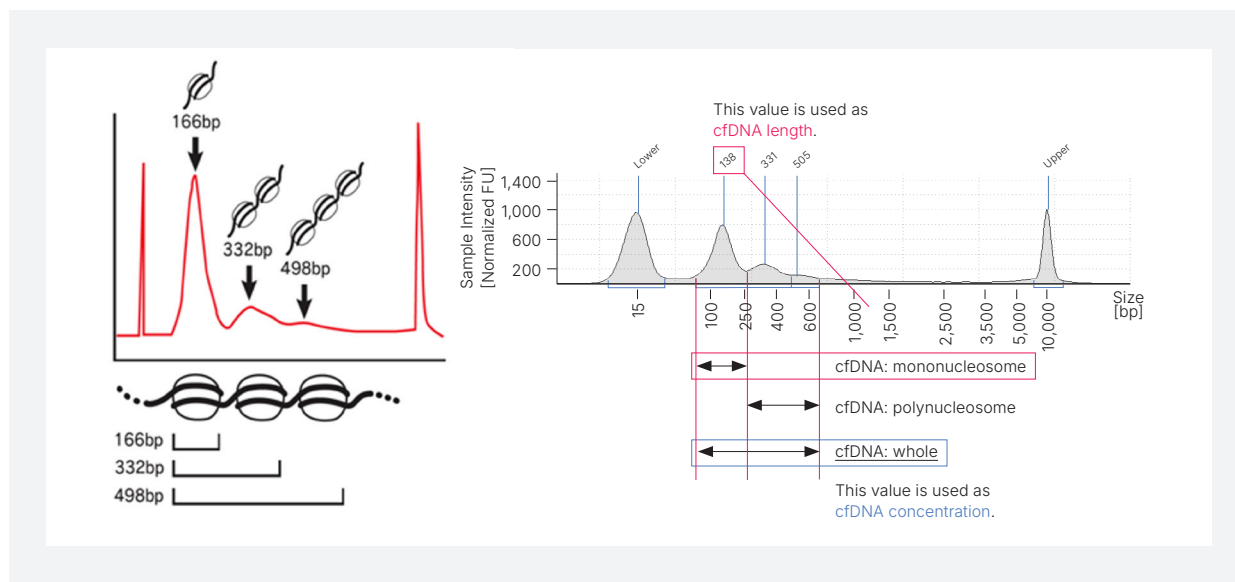


Fig. 5. cfDNA analysis. **A**, most tumor-derived cfDNA in blood arises from apoptotic cells, resulting in fragments predominantly around 166 bp (147-bp nucleosome plus a linker of ~20 bp). **B**, the portion corresponding to mononucleosomes is used for the cfDNA length, and the total concentration, including polynucleosomes, is used for the cfDNA concentration.

The Dynamics of cfDNA in Oncology and Integration with CTC Measurement

As a complement to CTC analysis, NGRL has shown that cfDNA profiling provides additional insights into tumor dynamics and treatment response. An analysis of cfDNA dynamics in oncology is summarized in Figure 6. In cancer patients, rising cfDNA concentrations correlate with increasing tumor burden and reduced treatment effectiveness. In contrast, a decline in cfDNA levels following surgery or chemotherapy (Figure 6A) indicates effective treatment. Cancer-derived cfDNA fragments also tend to be shorter than those found in healthy individuals (Figure 6B), reflecting underlying tumor biology.

Together, these findings support the integration of both CTC enumeration and cfDNA measurement as a dual-modality approach for early cancer detection and treatment monitoring and a guide for oncology intervention strategies.

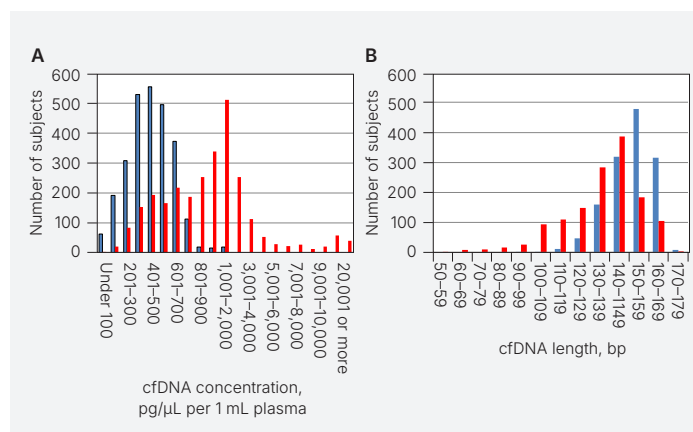


Fig. 6. Relationship between cfDNA concentration and treatment response and comparison of cfDNA fragment length in cancer patients versus healthy individuals. **A**, higher cfDNA levels correlate with increased tumor burden and reduced therapeutic efficacy, while decreasing cfDNA concentrations following surgery or chemotherapy are associated with effective treatment response. **B**, cfDNA fragments in cancer patients (■, n = 2,749) are generally shorter than those in healthy individuals (■, n = 2,679), reflecting tumor-derived DNA fragmentation patterns.

Conclusions on the Use of CTC Analysis with cfDNA

Through extensive collaboration, large-scale enumeration studies, and continuous innovation in capture technologies, NGRL has advanced the field of CTC research using the Genesis System, the attributes of which align well with NGRL's objectives (Table 2). The findings from their recent study of over 2,000 individuals emphasize both the potential and complexity of interpreting CTC signals in healthy and at-risk populations. By integrating CTC enumeration with cfDNA analysis, NGRL is laying the foundation for a new generation of liquid biopsy strategies aimed at early detection, personalized therapy, and preventive oncology.

Long-Term Vision of NGRL

- Application of CTC enumeration in minimal residual disease (MRD) detection, treatment monitoring, and recurrence checks
- Broader adoption in population monitoring and preventive medicine through integration of CTC measurement with cfDNA
- Implementation in precancer detection, enabling intervention at the earliest stages when treatment can be most effective

Table 2. Advantages of the Genesis System for CTC enumeration and analysis.

Feature	Description
Size-based capture	Enables isolation of CTCs independent of cell surface markers
Automated workflow	Full automation from sample input to immunostaining in under three hours
High reproducibility	Demonstrated consistency across multicenter studies
Assay versatility	Compatible with both epithelial and mesenchymal CTC assays
Rapid CTC recovery	Concentration and recovery of viable CTCs within two hours for downstream culture

Further Information

Genesis Cell Isolation System Brochure ([bulletin 3317](#)) describes capture efficiency, microfluidic design, and downstream applications.

[Antibody Selection and Preparation for Circulating Tumor Cell \(CTC\) and Rare Cell Isolation](#), which is helpful for understanding staining/identification workflows used in interlab studies.

[Maximizing Metastasis Insights with a Novel Integrated Workflow for CTC Enrichment and Enumeration webinar](#)

Bio-Rad offers a suite of products to facilitate the study of CTCs and other cell types in liquid biopsy:

- [Genesis System | Bio-Rad](#) – Learn more about the Genesis System with Celselect Slides technology and
- [Starbright Dyes & Kits for Flow Cytometry & Western Blotting | Bio-Rad](#) – Find out how StarBright Dyes can improve cell enumeration.

NGRL is a venture company established in 1994 as an R&D laboratory originating from Tohoku University. The company provides contract synthesis services for nucleic acids (DNA and RNA) in the field of organic synthesis, with expertise in the synthesis of complex and highly modified oligonucleotides. It also provides primers and probes for digital PCR using its original Hypercool Technology (Tm value adjustment mechanism), primers and probes for various diagnostics raw materials, oligonucleotides for click chemistry, and antisense oligos for nucleic acid therapeutics research. Additionally, the company provides chromosome analysis services for induced pluripotent stem cells and embryonic stem cells and contract research services related to CTC enumeration. See [Company outline - NGRL](#) for more information.

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