

Evaluating the Prognostic Value of a Pan-Cancer Circulating Tumor DNA Next-Generation Sequencing Panel in Advanced Cancer Patients

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Purpose: This study aimed to evaluate the clinical utility of a pan-cancer circulating tumor DNA (ctDNA) next-generation sequencing (NGS) panel for predicting treatment response and progression-free survival (PFS) in patients with advanced solid tumors.

Patients and Methods: A total of 41 patients with advanced solid tumors, including gastric cancer (n=13), non-small cell lung cancer (n=10), head and neck cancer (n=9), esophageal cancer (n=7), breast cancer (n=1), and colon cancer (n=1), were prospectively enrolled and included in the analysis. ctDNA was analyzed at three time points: pretreatment (41 patients), post-treatment evaluation (37 patients), and follow-up (18 patients).

Results: Among 41 patients analyzed at pretreatment, 35 (85.4%) exhibited tier 1 or 2 somatic variants in ctDNA, with TP53 being the most frequently mutated gene. At the post-treatment evaluation, ctDNA was assessed in 37 patients (3 with rapid deterioration and 1 lost to follow-up were not evaluable). Newly emerging variants after treatment were strongly associated with poor clinical outcomes. Consistent with the Kaplan-Meier analysis, Cox proportional hazards regression confirmed that post-treatment ctDNA positivity was significantly associated with inferior PFS (HR 10.5, 95% CI 1.4–80.0, P=0.024). At follow-up, 18 patients were evaluable, while the others were not due to follow-up loss, rapid deterioration, or study termination. ctDNA positivity at post-treatment evaluation was significantly associated with shorter PFS (median PFS, 5.0 months [95% CI: 2.0–12.0] vs not reached; HR, 4.87; 95% CI: 1.69–14.09; P = 0.0035).

Conclusion: Longitudinal monitoring of ctDNA using a pan-cancer NGS panel provides meaningful prognostic information in patients with advanced cancers. Post-treatment ctDNA dynamics may better reflect disease progression than baseline ctDNA status alone, highlighting the need for further validation in larger cohorts, particularly in gastric, lung, head and neck, and esophageal cancers.

Plain Language Summary: Cancer cells can release small fragments of their DNA into the bloodstream, known as circulating tumor DNA (ctDNA). These fragments can be detected through a blood test, often called a “liquid biopsy.” By monitoring changes in ctDNA over time, doctors can better understand how a patient’s cancer is responding to treatment. In this study, we analyzed blood samples from 41 patients with advanced cancers, including stomach, lung, and esophageal cancers. Using a genetic test called next-generation sequencing (NGS), we examined cancer-related DNA changes at three time points: before treatment, after the first round of treatment, and during follow-up care. We then assessed how these changes related to the time patients lived without their cancer worsening, a measure known as progression-free survival (PFS). We found that over 85% of patients had significant cancer-related DNA changes before starting treatment. After treatment, many patients developed new mutations, which were associated with shorter PFS. In contrast, patients without new ctDNA changes after treatment generally had better outcomes. These results suggest that ctDNA monitoring after treatment may provide better information about a patient’s status than testing before treatment alone. Ongoing blood-based monitoring could help guide future treatment decisions. However, larger studies are needed to validate these findings.

Keywords: circulating tumor DNA, next-generation sequencing, liquid biopsy, prognostic biomarker, longitudinal monitoring

Introduction

The accurate prediction of the prognosis of solid cancers remains a critical challenge in oncology. Traditional approaches relying solely on pathological staging often fail to capture the complexity of tumor biology and its dynamic response to treatment. Circulating tumor DNA (ctDNA), a minimally invasive biomarker, has emerged as a promising tool for the real-time monitoring of tumor dynamics and prognosis prediction. ctDNA derived from primary, metastatic, or circulating tumor cells can be analyzed through liquid biopsy, offering several advantages over traditional tissue biopsies. These include applicability to tumors in hard-to-reach locations, repeatability of longitudinal monitoring, and reduced patient burden.¹

Circulating tumor DNA (ctDNA) is not only a prognostic biomarker but also provides clinically actionable information that can support treatment decisions, such as early identification of treatment resistance, detection of minimal residual disease, and timely switching of therapeutic strategies. By offering dynamic, real-time insights into tumor evolution, ctDNA complements conventional imaging and pathology, enabling more precise and personalized clinical decision-making.

Advancements in ctDNA analysis, particularly through next-generation sequencing (NGS), have enabled the detection of a wide range of genetic alterations. Compared to polymerase chain reaction (PCR), NGS provides a broader and more detailed mutational landscape, making it particularly valuable for evaluating the prognosis of advanced cancers. However, despite these advancements, further data are required to validate the utility of ctDNA NGS in specific cancer types, such as head and neck, esophageal, and gastric cancer.^{2–4}

This study evaluated the clinical utility of a pan-cancer ctDNA NGS panel in patients with advanced cancers, including head and neck, esophageal, gastric, and lung cancer. By analyzing ctDNA variants longitudinally, we aimed to assess their value in monitoring treatment response and predicting outcomes, thereby providing insights into the feasibility of integrating pan-cancer ctDNA NGS into routine oncology practice. Given the potential of ctDNA, this study focuses on its utility across various advanced cancers, including but not limited to head and neck, esophageal, and gastric cancers. Unlike previous studies that primarily investigated single tumor types or baseline ctDNA status, our study employed a pan-cancer NGS panel across multiple advanced cancers and implemented longitudinal monitoring at pretreatment, post-treatment, and follow-up. This design allowed us to demonstrate that ctDNA dynamics after treatment, rather than baseline ctDNA alone, provide stronger prognostic information for progression-free survival. By combining a pan-cancer scope with sequential sampling, this study offers novel insights into the clinical feasibility of ctDNA-based prognostic monitoring in real-world oncology practice.

Materials and Methods

Ethics Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients. This study was approved by the Institutional Review Board of the Catholic University of Korea School of Medicine (XC21TIDI0130).

Subjects and Study Design

We prospectively recruited patients diagnosed with advanced cancer between December 2021 and August 2022 in Incheon St. Mary's Hospital. Eligible patients provided written informed consent and agreed to participate in this study. Patients with impaired decision-making capacity and those who opted for palliative care were excluded. The participants received appropriate treatment, including chemotherapy (CTx), radiotherapy (RTx), immunotherapy, or surgical resection, as determined by their physicians. ctDNA NGS testing was performed up to three times: at pretreatment, six weeks post-treatment for response evaluation, and during follow-up - except in cases of progressive disease (PD), where follow-up testing was omitted. PD was defined according to RECIST version 1.1. The patient enrollment and analysis process is summarized in [Figure 1](#).

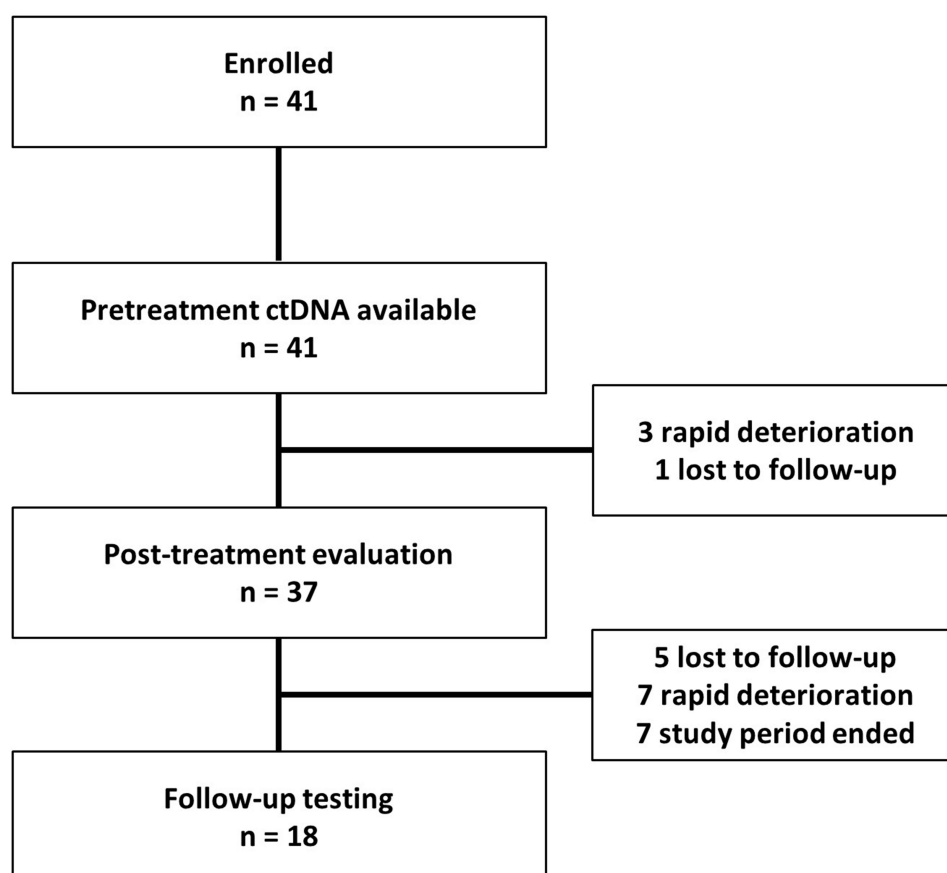


Figure 1 Flow diagram of patient enrollment and analysis. A total of 41 patients with advanced solid tumors were prospectively enrolled and included in the initial analysis. At the post-treatment evaluation, 37 patients were evaluable (3 patients experienced rapid deterioration and 1 was lost to follow-up). At the follow-up assessment, 18 patients remained evaluable, while the others were not due to follow-up loss, rapid deterioration, or study termination.

ctDNA Analysis

Peripheral blood was collected in cfDNA-preserving tubes (DxTube™, Dxome, Sungnam, Korea), and plasma was separated by sequential centrifugation. cfDNA was extracted using the Dxome circulating DNA Maxi Reagent, and germline DNA from PBMCs was obtained using the QIAamp DNA Mini Kit (QIAGEN). DNA quality and quantity were assessed with Qubit (Invitrogen) and TapeStation (Agilent).

Libraries were prepared from 5 - 30 ng of cfDNA or 200 ng of matched gDNA using the DxSeq ctDNA Pan100 Kit and DxLiquid Pan100 panel (Dxome), targeting 100 cancer-related genes. The targeted gene list of the DxLiquid Pan 100 panel is provided in [Supplementary Table 1](#). Paired-end sequencing (2×151 bp) was performed on an Illumina NovaSeq 6000 platform, achieving mean depths of $>30,000\times$ for cfDNA and $>1,000\times$ for gDNA. The analytical sensitivity (limit of detection) was 0.25% variant allele frequency (VAF).

Sequencing reads were aligned to GRCh37 (hg19) with BWA, and variants were called using the PiSeq algorithm (Dxome), with cross-validation by ExomeDepth for CNVs and Delly for structural variants. Variants were annotated with DxSeq software. Quality control thresholds included cfDNA yield ≥ 5 ng/mL, minimum mean depths $\geq 30,000\times$ for cfDNA and $\geq 1,000\times$ for gDNA, and visual confirmation of all tier I/II or pathogenic variants using Integrative Genomics Viewer (IGV). The variants were classified as pathogenic, likely pathogenic, or of unknown significance based on the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines [5], or categorized into tiers 1, 2, or 3 according to standards from the Association of Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO), and College of American Pathologists (CAP) [6]. Germline and CHIP-related variants were excluded by comparing cfDNA findings with matched PBMC DNA; variants detected in both cfDNA and PBMC DNA were considered germline or CHIP-derived and were not included in ctDNA analysis.

Statistical Analysis

Given the exploratory design of this study, the sample size was not predetermined. We planned to study all eligible patients without follow-up loss. The primary endpoint was PFS according to ctDNA dynamics after appropriate treatment. The cutoff for statistical significance was set at $P = 0.05$. The primary outcome measure was PFS according to RECIST. Statistical analyses were performed using the MedCalc v.20.

Results

Patient Characteristics

A total of 41 patients with advanced solid tumors were prospectively enrolled and included in the initial analysis. At the post-treatment evaluation, 37 patients were evaluable (3 with rapid deterioration and 1 lost to follow-up). At the follow-up assessment, 18 patients remained evaluable, while the others were not due to follow-up loss, rapid deterioration, or study termination ([Figure 1](#)). The most common cancer types were advanced gastric cancer (AGC) and non-small cell lung cancer (NSCLC), followed by head and neck cancer (HNC), esophageal cancer (EC), breast cancer, and colorectal cancer ([Table 1](#)). Detailed information on systemic treatment distribution, including chemotherapy, radiotherapy, surgery, and targeted therapy, is provided in [Supplementary Table 2](#).

Table 1 Characteristics of Enrolled Participants

Characteristics	Values
Age	
Median (range)	65 (45–81)
Sex	
Male	28
Female	13
Tumor	
Advanced gastric cancer	13
Non-small cell lung cancer	10
Head and neck cancer	9
Esophageal cancer	7
Breast cancer	1
Colon cancer	1
Concurrent Tumor	
Thyroid papillary carcinoma	1
Pheochromocytoma	1
Relapsed case at enrollment	2
Past history of cancer	3
Metastasis at enrollment	19
Family history	0

ctDNA Variant Detection Before Treatment

All 41 patients had pretreatment ctDNA results; among them, 35 patients (85.4%) had detectable tier 1 or 2 somatic variants, while 6 patients had no detectable variants. The gene with the highest number of variants was *TP53*, followed by *PIK3CA*, *APC*, *ARID1A*, and *ERBB2*. Of these, actionable tier 1 single-nucleotide variants (SNVs) were identified in 9 patients. Germline pathogenic/likely pathogenic variants were observed in 6 patients. Gene-level CNVs were observed in 7 patients, and chromosome-level CNVs were suspected in 7 patients. Among the patients with gene-level CNVs, three also showed results suggesting chromosome-level CNVs, and in the case of chromosome-level CNVs, six patients were suspected to have complex karyotypes. The results of observing tier 1 or 2 somatic SNV in patients are summarized in [Supplementary Table 2](#). The gene with the highest variant frequency, regardless of the cancer type, was *TP53*. Excluding *TP53*, frequent variants were observed in *APC* and *PIK3CA* in AGC, *PIK3CA* and *DNMT3A* in EC, and *PTEN* and *CHEK2* in HNC. *KRAS*, *EGFR*, and *ARID1A* variants were commonly detected in NSCLC ([Figure 2A](#)).

Post-Treatment Evaluation

In the post-treatment phase, ctDNA tests were performed in 37 patients. After the initial evaluation, 3 patients discontinued the study due to rapid deterioration and 1 patient was lost to follow-up. Among these 37 patients, 35 had detectable tier 1 or 2 somatic variants at pretreatment, whereas 6 had no detectable variants. In those with variants, the variant allele frequency (VAF) was generally low, with a maximum observed value (VAFmax) below 3%. Notably, three of the six initially variant-negative patients showed newly detected somatic variants during post-treatment evaluation or follow-up, all of whom exhibited progressive disease (PD) at the time of observation.

There were 18 patients with newly observed variants in the post-treatment evaluation. Of these, two were lost to follow-up before the follow-up examination, and 12 showed PD or died. There were 16 patients with no newly observed variants at the same time point, of which one died and the rest showed improvement.

Follow-Up ctDNA Testing

A total of 18 patients underwent follow-up examinations, while follow-up ctDNA testing could not be performed in the remaining 19 patients due to loss to follow-up ($n = 5$), termination of the study period before follow-up testing ($n = 7$), or rapid clinical deterioration ($n = 7$). Among the 18 patients who underwent follow-up, 9 experienced PD or death. Newly detected variants were observed in 8 of these patients (2 during the post-treatment evaluation and 6 during the follow-up phase), whereas 1 patient showed no newly detected variants at either time point.

Among the 9 patients who showed improvement during the follow-up phase, two had no newly detected variants in both the post-treatment evaluation and follow-up phases. Newly detected variants were observed in three patients during the post-treatment evaluation phase and in four patients during the follow-up phase.

When comparing VAFmax values at the follow-up stage, patients with PD or who had died exhibited a higher median VAFmax and interquartile range (IQR) compared to those who showed improvement (median: 7.9 vs 0.7; IQR: 2.7500–17.6750 vs 0.3750–3.1250). This difference was statistically significant ($P = 0.0272$).

Among the newly detected tier 1 or 2 variants observed in both the post-treatment evaluation and follow-up phases, *TP53* was the most frequently detected gene, followed by *DNMT3A* and *SMAD4* ([Figure 2B](#)).

Clinical Correlation with ctDNA Findings

Forty-one patients with advanced cancer were analyzed for clinical changes based on ctDNA NGS results. The group included patients with gastric, lung, esophageal, head and neck, breast, and colorectal cancer. Before treatment, 85.4% of the patients had tier 1 or 2 somatic variants in ctDNA. CNVs were found at the gene level in seven patients, chromosome level in seven, and common denominator in three.

The positivity rate of the ctDNA NGS was 64.9% during the post-treatment evaluation phase and 94.4% during the follow-up phase. Among the 20 patients who showed clinical improvement during the post-treatment evaluation, 45% had tier 1 or 2 somatic variants. In contrast, 88.2% of the 17 patients without improvement tested positive for these variants, showing a significant difference ($P=0.0068$).

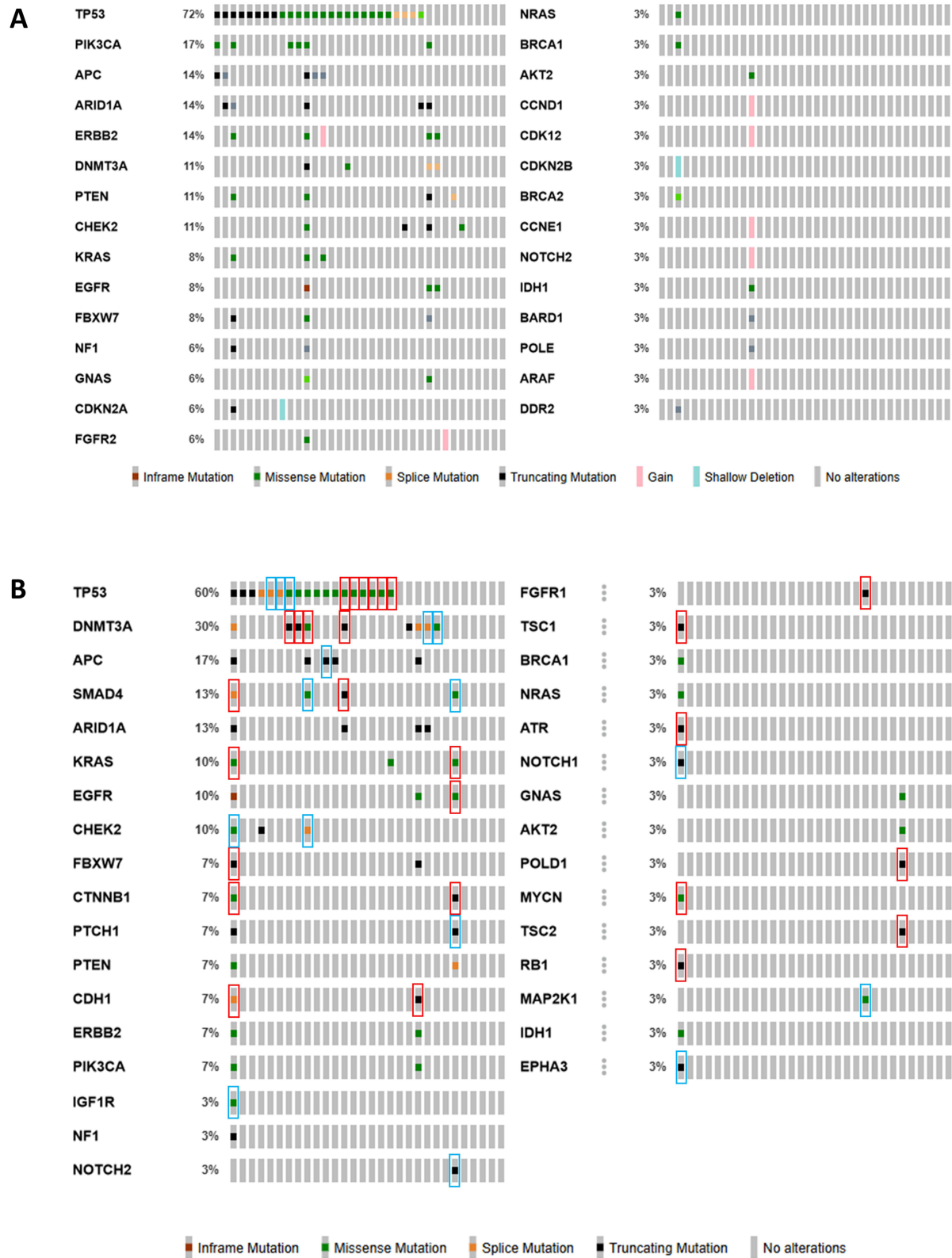


Figure 2 Tier 1 and 2 variants detected before and after treatment. Oncoplot of tier 1 and 2 variants detected before treatment (**A**) and newly detected tier 1 and 2 variants after treatment (**B**). Red box, variants newly detected at post-treatment evaluation; Blu box, variants newly detected at follow-up evaluation.

Four initially negative patients who developed new variants experienced PD, and six out of 8 with newly detected variants at follow-up showed no clinical improvement. Among patients with tier 1 or 2 somatic variants identified in pretreatment testing, 51.4% (18/35) experienced disease progression. Similarly, 50.0% (3/6) of patients without detectable somatic variants in pretreatment testing also showed disease progression. No statistically significant difference in prognosis was observed based on the presence or absence of initial variants ($P = 0.9491$).

Additionally, 60.0% (6/10) of patients with an initial VAFmax $\geq 20\%$ experienced disease progression, which was higher than the 48.4% (15/31) observed in patients with a lower initial VAFmax. However, this difference was not statistically significant ($P = 0.5280$).

In the post-treatment evaluation, patients with somatic variant positivity (66.7%, 22/33) exhibited a shorter PFS than those with somatic variant negativity, with the difference being statistically significant ($P=0.0035$, Figure 3).

At the post-treatment evaluation, patients with ctDNA positivity ($n=22$) showed significantly shorter PFS compared to those with ctDNA negativity ($n=11$). The median PFS was 5.0 months (95% CI: 2.0–12.0) in the ctDNA-positive group, while the median PFS was not reached in the ctDNA-negative group. The hazard ratio for progression in the ctDNA-positive group was 4.87 (95% CI: 1.69–14.09, $P=0.0035$). In Cox proportional hazards regression, post-treatment ctDNA positivity was also significantly associated with inferior PFS (HR 10.5, 95% CI 1.4–80.0, $P=0.024$), reinforcing the prognostic impact of residual ctDNA after treatment. In addition, longitudinal analysis of VAF was performed using pre-treatment, post-treatment, and follow-up samples. As summarized in [Supplementary Table 2](#) and [Supplementary Figure 1](#), patients who achieved ctDNA clearance after treatment exhibited substantially lower VAF levels during follow-up compared with those with residual ctDNA positivity. These findings suggest that post-treatment VAF dynamics may provide additional prognostic information beyond baseline measurements.

Among the ten patients with NSCLC, only one patient exhibited no genetic variants during the pretreatment phase. However, ctDNA variants coinciding with disease progression were detected during the follow-up testing. Except for

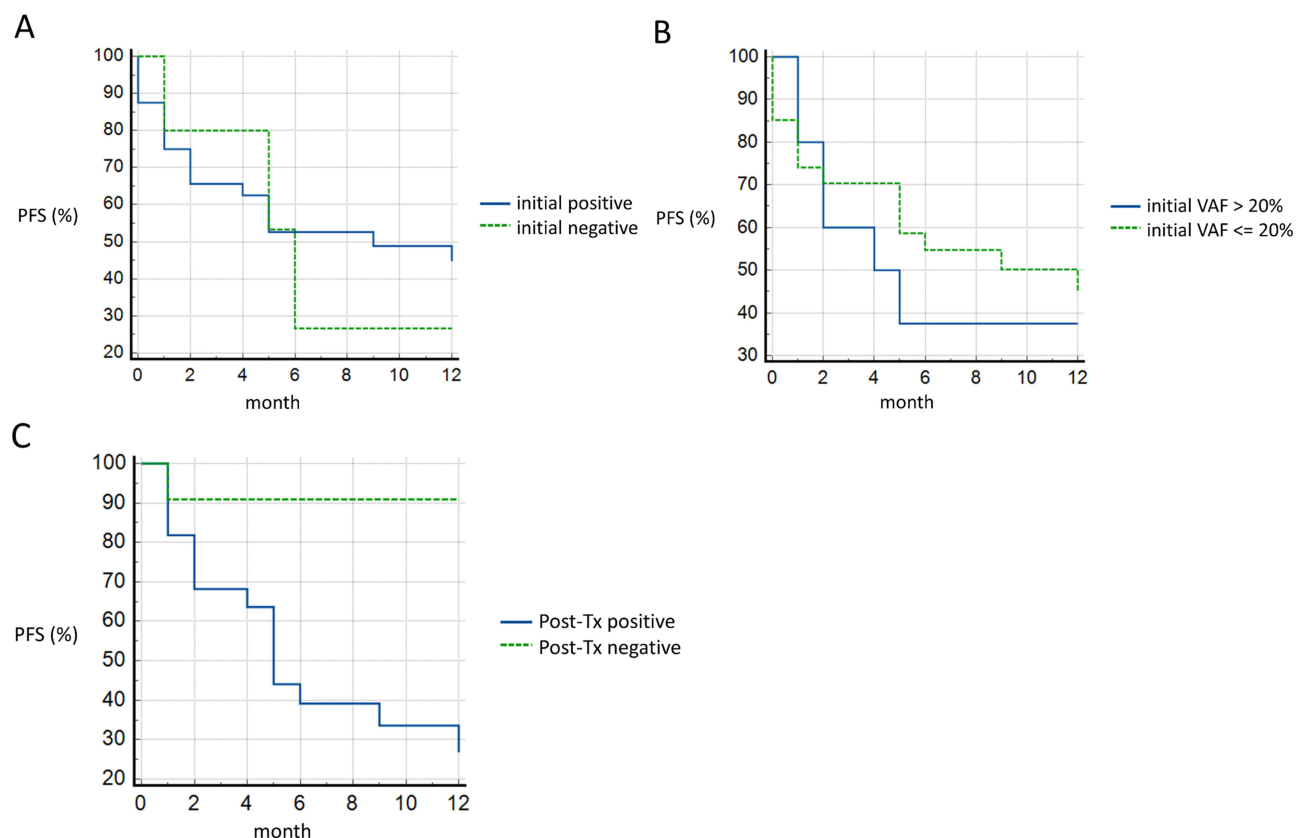


Figure 3 Kaplan-Meier survival curves showing PFS stratified by ctDNA variant status. (A) PFS according to ctDNA variant presence at pretreatment, (B) PFS by VAFmax at pretreatment, (C) PFS according to ctDNA variant detection at post-treatment evaluation.

Patient 38, no representative *EGFR* gene target variants were identified in NSCLC cases. Among the three patients without disease progression, ctDNA variants significantly decreased after treatment and did not reappear during subsequent evaluations.

Discussion

This study evaluated the clinical utility of a pan-cancer ctDNA NGS panel in patients with advanced solid tumors, with the aim of predicting post-treatment and PFS. Our findings support the prognostic value of ctDNA dynamics, particularly the emergence or persistence of somatic variants after treatment, in identifying patients at risk of disease progression.

Newly detected ctDNA variants during follow-up were strongly associated with poor clinical outcomes, emphasizing the role of post-treatment ctDNA monitoring in assessing clonal evolution. This finding reinforces the clinical utility of ctDNA as a real-time biomarker for guiding treatment decisions, even in patients initially negative for detectable variants.

Although the diversity of tumor types in this study presents a challenge, the use of a pan-cancer ctDNA panel reflects real-world clinical settings. The use of pan-cancer ctDNA panels offers a practical and efficient strategy for non-invasive tumor monitoring across multiple cancer types, as ctDNA has been shown to reflect dynamic tumor evolution, treatment response, and resistance across various malignancies.⁵ A unified panel allows efficient testing across various cancer types and may be more practical for laboratories without access to tumor-specific assays. Despite the heterogeneity and limited sample size, consistent trends across different tumor types suggest the panel's potential generalizability. We have provided additional justification for the pan-cancer approach in the Discussion.

Additionally, our results challenge the common assumption that the absence of ctDNA variants in pretreatment testing predicts a better prognosis. In our cohort, patients with undetectable pretreatment variants had outcomes comparable to—or in some cases worse than—those with variant-positive ctDNA.^{3,4,6} This finding may be explained by biological or technical factors. Some tumors may shed ctDNA at very low levels or not at all, resulting in false-negative results. Alternatively, variant-negative status may reflect aggressive tumor biology that is not captured by the current panel. Indeed, the absence of detectable ctDNA does not necessarily indicate the absence of disease, particularly in early-stage or biologically indolent tumors, which are known to release little or no ctDNA into circulation.⁷ Our findings are consistent with previous studies demonstrating that dynamic changes in ctDNA levels closely correlate with tumor burden and treatment response. Notably, longitudinal ctDNA monitoring using patient-specific mutation tracking has been shown to outperform conventional biomarkers in predicting disease recurrence.⁸ These insights underscore the importance of enhancing assay sensitivity and incorporating complementary biomarkers for comprehensive risk stratification.

Accurate interpretation of ctDNA results requires the exclusion of germline and CHIP-associated variants, particularly in genes frequently affected by CHIP such as *DNMT3A*.⁹ To enhance analytical specificity, we performed parallel sequencing of PBMC-derived DNA for all patients. However, the impact of this approach on variant classification was not quantitatively assessed in this study. Future research should aim to systematically evaluate the contribution of parallel PBMC analysis and establish cost-effective protocols for CHIP and germline discrimination. Standardized frameworks for distinguishing germline variants and CHIP-related alterations from true tumor-derived mutations have been proposed,¹⁰ but clinical implementation remains challenging.

Consistent with previous reports,^{11,12} we observed that ctDNA variant positivity following treatment was significantly associated with worse PFS. However, we also found that dynamic changes—such as emergence of new variants or increasing VAF—were more predictive of prognosis than baseline ctDNA status alone. This underscores the value of longitudinal ctDNA testing as a tool for monitoring disease trajectory. The predictive value of longitudinal ctDNA dynamics was also demonstrated in a prospective study of resected colorectal cancer, where ctDNA positivity following treatment was strongly associated with relapse and preceded radiologic recurrence by a median of 8.7 months.¹³

In the NSCLC subgroup, although classic *EGFR* variants were mostly absent, dynamic changes in ctDNA correlated with clinical outcomes. Patients with good prognosis showed marked decreases in ctDNA burden post-treatment, whereas those with progression exhibited newly detected variants during follow-up. These findings support the role of ctDNA as a prognostic tool even in the absence of canonical driver variants.

Beyond its prognostic significance, longitudinal ctDNA monitoring has potential clinical applications. For instance, detection of newly emerging variants after treatment could support tailoring surveillance intervals, enabling earlier intervention for patients at high risk of relapse. In addition, persistent ctDNA positivity may identify patients who could benefit from treatment intensification or alternative therapeutic strategies. Furthermore, ctDNA dynamics could help stratify patients for enrollment in clinical trials, particularly those evaluating novel targeted or immunotherapies. While these implications remain exploratory, our findings highlight the potential role of ctDNA in guiding individualized treatment approaches.

This study has some limitations. While we observed that the emergence of new ctDNA variants after treatment was strongly associated with poor clinical outcomes, these findings should be interpreted with caution. The relatively small sample size and inclusion of heterogeneous cancer types reduce the statistical power and limit meaningful subgroup analyses. In addition, variation in treatment regimens across patients may have introduced potential confounding effects. In this study, we primarily evaluated progression-free survival as the clinical endpoint, and overall survival (OS) could not be systematically analyzed due to the limited follow-up duration and small sample size. Nevertheless, given the well-established prognostic relevance of OS, future studies with larger cohorts and longer follow-up periods should investigate the association between ctDNA dynamics and OS to validate and extend our findings. In addition, the wide confidence intervals observed in the Cox regression analyses reflect the limited sample size, which reduces the precision of hazard ratio estimates. Larger studies are needed to obtain more reliable effect size estimates and validate these findings. Therefore, validation in larger, tumor-specific cohorts will be required to confirm the robustness and generalizability of our results. Nevertheless, our findings provide valuable preliminary evidence supporting the clinical relevance of pan-cancer ctDNA monitoring in advanced solid tumors.

Conclusion

Our findings suggest that a pan-cancer ctDNA NGS panel has potential clinical implications for post-treatment monitoring and prognosis in advanced solid tumors. Longitudinal assessment of ctDNA variants, particularly the emergence or persistence of tier 1 and 2 variants after treatment, may help inform personalized management strategies. However, these observations remain preliminary, and validation in larger, tumor-specific cohorts with longer follow-up is required before clinical implementation can be fully realized.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request. Due to licensing restrictions, the data are not publicly available. However, de-identified data may be shared by the corresponding authors (J.H.B. and M.K.) on reasonable request for academic purposes.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Seung Jung Han and Youjin Jung are employees of Dxome Co., Ltd., which developed the ctDNA NGS panel utilized in this study. All other authors declare that they have no conflicts of interest related to this work.

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