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Original Research

Up-front cell-free DNA next generation sequencing improves target identification in UK first line advanced non-small cell lung cancer (NSCLC) patients

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Abstract ***Background:*** Genomic sequencing is necessary for first-line advanced non-small cell lung cancer (aNSCLC) treatment decision-making. Tissue next generation sequencing (NGS) is standard but tissue quantity, quality, and time-to-results remains problematic. Here, we compare upfront cell-free-DNA (cfDNA) NGS clinical utility against routine tissue testing in patients with aNSCLC.

Methods: cfDNA-NGS was performed in consecutive, newly identified aNSCLC patients between December 2019–October 2021 alongside routine tissue genotyping. Variants were interpreted using AMP/ASCO/CAP guidelines. The primary endpoint was tier-1 variants detected on cfDNA-NGS. cfDNA-NGS results were compared to tissue results.

Results: Of 311 patients, 282 (91%) had an informative cfDNA-NGS test; 118 (38%) patients had a tier-1 variant identified by cfDNA-NGS. Of 243 patients with paired tissue-cfDNA tests, 122 (50%) tissue tests were informative; 85 (35%) tissue tests identified a tier-1 variant. cfDNA-NGS detected 39 additional tier-1 variants compared to tissue alone, increasing the tier-1 detection rate by 46% (from 85 to 124). The sensitivity of cfDNA-NGS relative to tissue was 75% (25% tissue tier-1 variants were not detected on cfDNA-NGS); 33% of cfDNA tier-1 variants were not identified on tissue tests. Median time from request-to-report was shorter for cfDNA-NGS versus tissue (8 versus 22 days; $p < 0.0001$).

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A total of 245 (79%) patients received first-line systemic-therapy: 49 (20%) with cfDNA-NGS results alone. Median time from sampling-to-commencement of first-line treatment was shorter for cfDNA-NGS blood draw versus first tissue biopsy (16 versus 35 days; $p < 0.0001$).

Conclusions: cfDNA-NGS increased the tier-1 variant detection rate with high concordance with tissue, and halves time-to-treatment. 'Plasma-first' upfront cfDNA-NGS use should be considered routinely for aNSCLC.

1. Introduction

The increasing availability of first-line oncogene-targeted therapies for advanced non-small cell lung cancer (aNSCLC) means rapid and accurate genotyping is fundamental for therapeutic decision-making. Despite the predictive importance of genetic sequencing, real-world studies show that a significant proportion of patients with aNSCLC do not undergo adequate genotyping [1–3]. In the United States (US), contemporaneous real-world studies reported that as low as 18% of patients with aNSCLC underwent tissue testing for the National Comprehensive Cancer Network (NCCN) guideline-recommended [4] biomarkers [3]. Similar findings are also observed in Europe, where next generation sequencing (NGS) implementation has been slower, fundamentally driven by lack of clear funding channels between differing countries [5]. While NGS on tissue is optimal, barriers to tissue genotyping include availability of sufficient tissue samples, cost and delay in obtaining genotype results.

Currently, in the United Kingdom (UK), the process for tumour genotyping of NSCLC is often long, resulting in the potential for delayed treatment. Because of the COVID-19 pandemic, there are added delays in obtaining tumour material for genotyping, further delaying treatment commencement. Indeed, this is reflected in only 68% of UK patients with lung cancer receiving treatment within 62 days of referral in 2020/2021, far below the National Health Service (NHS) Cancer Waiting Times standard of 85% [6,7]. These delays are likely to continue in the years following COVID-19 and are unlikely to be restricted to the United Kingdom alone.

Cell-free (cf) DNA NGS allows sequencing of small tumour DNA fragments shed from the tumour, identifiable in patients' plasma [8] and can largely overcome the challenges posed by traditional tissue genotyping [9]. Current recommendations suggest using cfDNA-NGS to complement tissue testing in patients with aNSCLC [9,10]. However, in Europe, front-line cfDNA-NGS testing is generally unfunded through routine healthcare commissioning, resulting in a reliance on tissue testing since clinical benefits of cfDNA-NGS for target identification in routine practice over tissue testing have been poorly documented in government-funded healthcare settings.

Guardant360™ CDx (Guardant Health, Redwood City, California) is one of two FDA-approved plasma-based NGS assays commercially available [11,12]. Our study prospectively describes the clinical utility of cfDNA-NGS in real-world UK patients with newly identified aNSCLC enrolled in the Guardant360™ global access program (GAP) at a single academic cancer centre.

2. Material and methods

2.1. Population

Consecutive patients with pathologically confirmed aNSCLC who had not previously received treatment for advanced disease (newly diagnosed or relapsed previously radically treated NSCLC), and consented to their blood samples being sequenced through GAP, were enrolled at the Royal Marsden Hospital.

2.2. Study procedures

NSCLC patients unselected by histology underwent cfDNA-NGS using the Guardant360™ 74 gene assay (genes tested listed in Appendix Table A.1) [13]. cfDNA-NGS tests were funded by Guardant Health Inc. through GAP, which was supported by Blueprint, Janssen and TP Therapeutics and provided compassionate access to Guardant360™ cfDNA-NGS tests to patients with aNSCLC. Patients underwent tissue molecular testing as per local standards (standard-of-care tissue tests), as commissioned by NHS England [14]. A proportion of patients had additional tissue NGS testing through clinical trial screening programs or self-funded commercial platforms. Tissue tests performed are listed in Appendix Table A.2A, and the genes tested in the standard-of-care and additional tissue NGS panels are listed in Appendix Table A.2B.

Variants were tiered using the Associated of Molecular Pathology (AMP), American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) joint guidelines [15]. Each tier-1 variant was also classified as actionable (defined as available FDA licensed targeted drug treatment for NSCLC) or not. An informative cfDNA-NGS result was defined as detecting any genomic variant.

2.3. Data analysis

The primary endpoint was the proportion cfDNA-NGS tests that identified an AMP/ASCO/CAP tier-1 genetic variant in patients with newly identified aNSCLC. Secondary endpoints included the proportion of informative cfDNA-NGS tests, the concordance between cfDNA-NGS and tissue molecular tests, and the turnaround times for cfDNA-NGS versus standard-of-care tissue tests and treatments received. Variants detected on cfDNA-NGS were compared to variants detected on all tissue tests performed at time of identification of aNSCLC (both standard-of-care and additional non-standard tissue tests). Turnaround time for cfDNA-NGS was defined as the date of blood draw to the date stated on the cfDNA-NGS report. Turnaround time for tissue tests was only evaluated for standard-of-care tissue tests (turnaround time for additional non-standard tissue tests were not included) and was defined as the date of first biopsy at the time of identification of aNSCLC to the date stated on the last published standard-of-care tissue molecular test report (immunohistochemistry (IHC), fluorescence-in-situ-hybridisation, polymerase chain reaction (PCR) and/or DNA and/or RNA NGS) for sequentially evaluated biomarkers. The time from sampling to first-line treatment for aNSCLC was defined as the date of blood draw for cfDNA-NGS to the date of commencement of first-line systemic anticancer treatment (SACT) and the date of the first tissue biopsy at the time of identification of aNSCLC to the date of commencement of first-line SACT, respectively.

Demographic, radiological, pathological and treatment data were prospectively collected and described, including variables describing age, gender, smoking status, registered ethnicity, performance status, time-point of cfDNA sampling, sites of metastases, histology, dates and modes of tissue sampling, treatment received and dates, cfDNA and tissue biomarker results and dates. The Mann–Whitney U test was used to assess the significance of differences in turnaround time between cfDNA and tissue molecular tests and time from cfDNA and tissue testing to SACT commencement. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using GraphPad Prism version 9.1.0 software.

This study was ethically approved by the Royal Marsden Hospital Clinical Research Committee (SE0923).

3. Results

3.1. Study population

Between December 2019 and October 2021, 375 patients were enrolled. Sixty-four patients were excluded due to cfDNA-NGS not being performed, not having a diagnosis of lung cancer or not having a newly identified aNSCLC (Fig. 1). Overall, 311 patients met the eligibility criteria. Patient characteristics are summarised in Table 1.

3.2. Variants detected in cfDNA-NGS

Overall, 282 (91%) cfDNA-NGS tests were informative. An ASCO/AMP/CAP tier-1 variant was detected on cfDNA-NGS in 118 (38%) of 311 patients (Fig. 2); 67 (22%) were actionable. Tier 1 variants based on the European Society of Medical Oncology Scale for Clinical Actionability of Molecular Targets (ESMO-ESCAT) tiering guidelines [16] are described in Appendix Figure A.1 (n = 70, 23%). The majority of ASCO/AMP/CAP tier-1 variants were detected in patients with non-squamous subtype NSCLC (94%); but ASCO/AMP/CAP tier-1 variants were also identified in seven (6%) patients with squamous-cell subtype NSCLC (Appendix Table A.3).

3.3. Variants detected in tissue testing

Of 311 patients included, 291 patients had tissue molecular tests performed at any stage. Forty-eight patients with relapsed radically treated NSCLC had tissue tests performed at the time of diagnosis of early stage disease, and tissue tests were not performed at the time of identification of advanced disease. Overall, 243 (78%) patients had paired tissue tests performed at the time of identification of aNSCLC (Fig. 1).

Of the 291 tissue molecular tests performed overall, standard-of-care tissue tests were performed contingent on hospital of diagnostic tissue sampling and included local multi-gene NGS panels ($n=179$, 62%), *EGFR* single-gene assay ($n=105$, 36%), ALK IHC ($n=222$, 76%) and ROS1 IHC ($n=179$, 62%). Additional non-standard tissue tests were performed in 39 (13%) patients (Appendix Table A.2A shows all tissue molecular tests performed). *EGFR, ALK* and *ROS1* were tested in 249 (86%) patients overall, and the NCCN-recommended genetic biomarkers were tested in 185 (64%) patients. NCCN-recommended biomarkers were tested in both patients with squamous-cell (44/61, 72%) and non-squamous subtype NSCLC (141/230, 61%).

Of the 243 patients with tissue molecular tests performed at the time of identification of aNSCLC, standard-of-care tissue tests performed included local multi-gene NGS panels in 163 patients (67%); additional non-standard tissue NGS tests were performed in 29 of 243 (12%) patients. In patients with paired tissue-cfDNA tests, *EGFR, ALK* and *ROS1* were tested on tissue in 219 (90%) patients, and the NCCN-recommended biomarkers were tested on tissue in 163 (67%) patients. Of 243 patients with paired cfDNA-tissue tests, 122 (50%) tissue

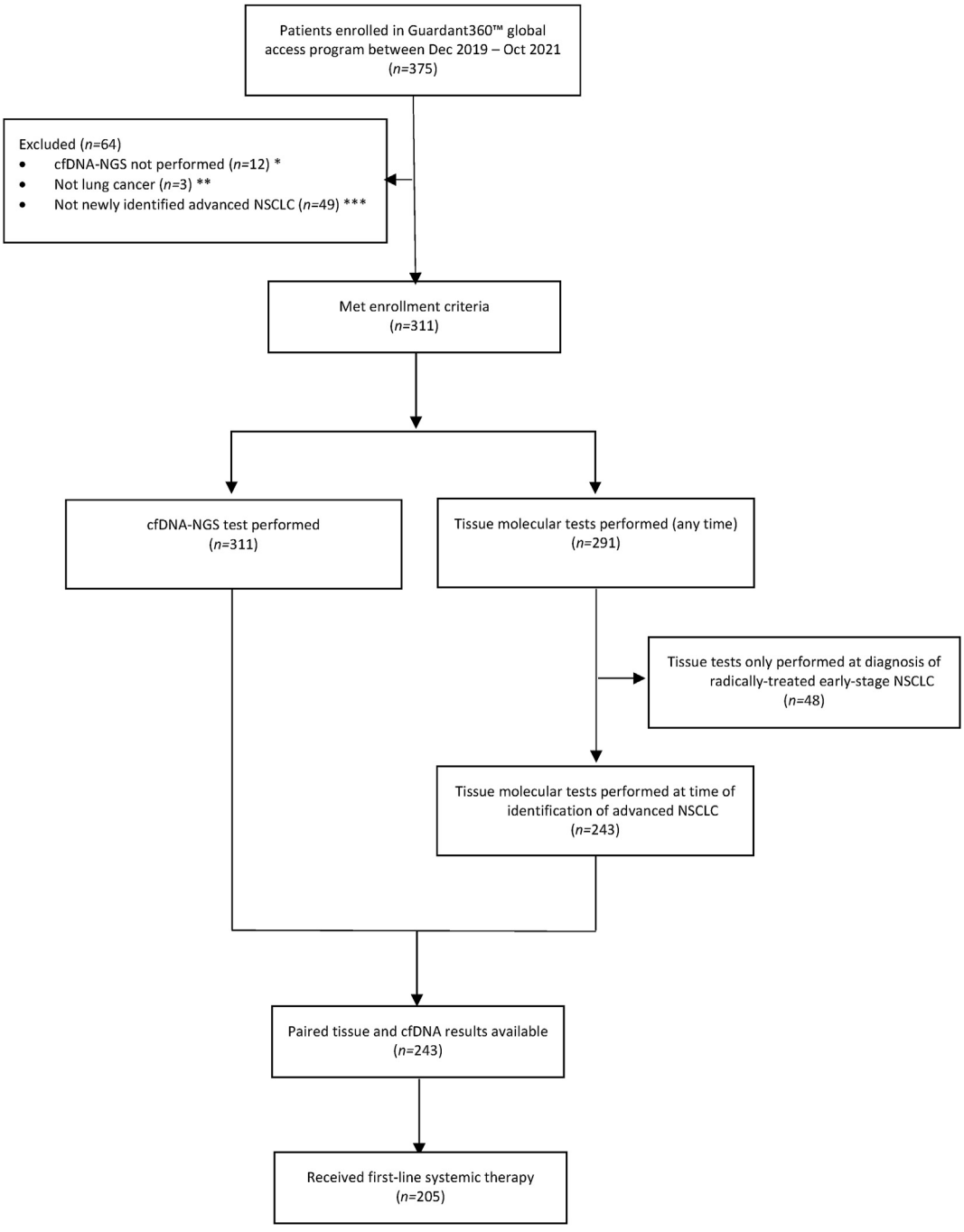

Fig. 1. **CONSORT diagram of eligible patients**. * Reasons for cfDNA-NGS not being performed included labelling errors, use of expired blood tubes, and blood test couriering errors. ** 3 patients had a change in diagnosis upon pathology review to testicular cancer ($n = 1$), lymphoma ($n=1$), carcinoma of unknown primary likely prostate cancer ($n = 1$). ***; Between April 2020 and August 2020, relapsed patients who had progressed on prior systemic treatment for advanced NSCLC were also allowed on the GAP program.

tests were informative. Standard-of-care tissue tests identified 80 tier-1 variants. Additional five tier-1 variants were detected on non-standard tissue testing through clinical trial screening programs or self-funded commercial platforms: a total of 85 (27%) tier-1 variants were detected by all tissue tests, of which 55 (18%) were actionable. No tier-1 variants were detected on any tissue tests in patients with squamous-cell subtype NSCLC.

3.4. Concordance between cfDNA-NGS and tissue molecular tests

Concordance between cfDNA-NGS and tissue molecular tests was assessable in 243 patients who had paired tissue tests (both standard-of-care and additional non-standard tests) performed at the time of cfDNA-NGS (Fig. 3).

Table 1
Patient characteristics.

	Study population (No prior treatment for advanced NSCLC) N (%) ($N=311$)
Age	
Median (range)	71 (33–97)
Sex	
Male	179 (58%)
Female	132 (42%)
Smoking	
Never	41 (13%)
Ex/current	268 (86%)
NA	2 (1%)
Median pack years (range)	30 (0–150)
Ethnicity	
Caucasian	281 (90%)
Asian	17 (5%)
Other	13 (4%)
ECOG	
0 to 1	235 (76%)
2	56 (18%)
3 to 4	16 (5%)
NA	4 (1%)
Disease time point at time of cfDNA-NGS test	
Newly diagnosed advanced NSCLC	235 (76%)
Metastatic relapse of previously radically treated NSCLC	76 (24%)
Sites of metastases	
Thorax only disease (lung, thoracic LN and pleural metastases only)	104 (33%)
Intracranial metastases only	11 (4%)
Bone metastases only	29 (9%)
Histology	
Adenocarcinoma	212 (68%)
Squamous cell	73 (23%)
Adeno-squamous	3 (1%)
Other (NOS, large cell, pleomorphic, sarcomatoid, small cell)	24 (8%)
PDL1	
<1%	87 (28%)
1–49%	104 (33%)
≥50%	93 (30%)
NA	27 (9%)
Tier-1 somatic variants previously known prior to GAP360 cfDNA-NGS	
Yes	6 (2%)[a]
No	305 (98%)

Abbreviations: ECOG: Eastern Cooperative Oncology Group performance status; NA: not available; NOS: not otherwise specified; PDL1: programmed death ligand-1.

[a] Sixty-eight of the 76 patients with relapsed previously radically treated NSCLC had molecular tests performed at the time of diagnosis of early stage disease. Of these patients, 6 patients had tier-1 variants detected on previous tissue molecular tests; these variants were: *EGFR* G719X ($n=1$), *EGFR* exon 20 insertion ($n=2$), *EGFR* exon 19 deletion ($n=1$), ALK IHC positive ($n=2$).

Of the 85 patients with a tier-1 variant detected on any tissue test, the tier-1 variant was identified in tissue alone in 21 patients (25%) or concordant with cfDNA in 64 patients (75%), demonstrating a sensitivity of cfDNA-NGS relative to tissue of 75% and a specificity of 75%. Of the 21 patients where tier-1 variants were detected on tissue alone, cfDNA-NGS was informative in 15 patients and non-informative in six patients (Appendix Table A.4A).

In the 158 tissue-negative patients, cfDNA-NGS detected 39 additional tier-1 variants that were not detected by paired tissue tests, increasing the detection rate of tier-1 variants by 46%, from 85 patients with tissue alone to 124 with tissue and cfDNA-NGS. Of the 39 additional variants detected by cfDNA-NGS alone 17 were actionable. In the 39 patients where tier-1 variants were detected on cfDNA-NGS alone, these variants were untested in tissue in 20 patients as testing was outside the scope of standard care. However, in 19 of 39 patients (49%), the cfDNA-NGS tier-1 variant was tested on the tissue molecular assay but was not identified (Appendix Table A.4B).

3.5. Test turnaround time

The median turnaround time for cfDNA-NGS tests was eight days. The median tissue testing turnaround time was 22 days. cfDNA-NGS test turnaround time was significantly shorter than tissue testing ($P < 0.0001$) (Fig. 4).

3.6. Treatment

The majority of patients (245 of 311, 79%) received first-line SACT after cfDNA-NGS testing (Appendix Table A.5). Thirty-five patients (11%) received first-line targeted therapy, and 17 (5%) patients received subsequent-line targeted therapy after disease progression (Appendix Table A.6).

Of the 245 patients who received first-line SACT, 126 (52%) commenced SACT after both tissue and cfDNA test results, 49 (20%) commenced SACT after cfDNA-NGS results alone, 35 (14%) commenced SACT with tissue results alone, and 35 (14%) commenced SACT without any molecular test results. Of the 49 patients who commenced SACT after cfDNA-NGS results alone, 12 (24%) patients had a tier-1 variant, of which 5 received first-line targeted therapy. Similarly, 9 of the 35 (26%) patients who commenced SACT with tissue results alone had a tier-1 variant, of which five received first-line targeted therapy.

In the 245 patients who received first-line SACT, 205 patients had undergone paired cfDNA-tissue testing. The median time from blood sampling for cfDNA-NGS to commencement of first-line SACT was 16 days. The median time from tissue biopsy to SACT commencement was 35 days. Time-to-treatment was significantly shorter for blood draw compared to tissue biopsy ($P < 0.0001$) (Fig. 5).

4. Discussion

In this real-world prospective UK study, cfDNA-NGS identified a tier-1 genomic variant in 38% of patients

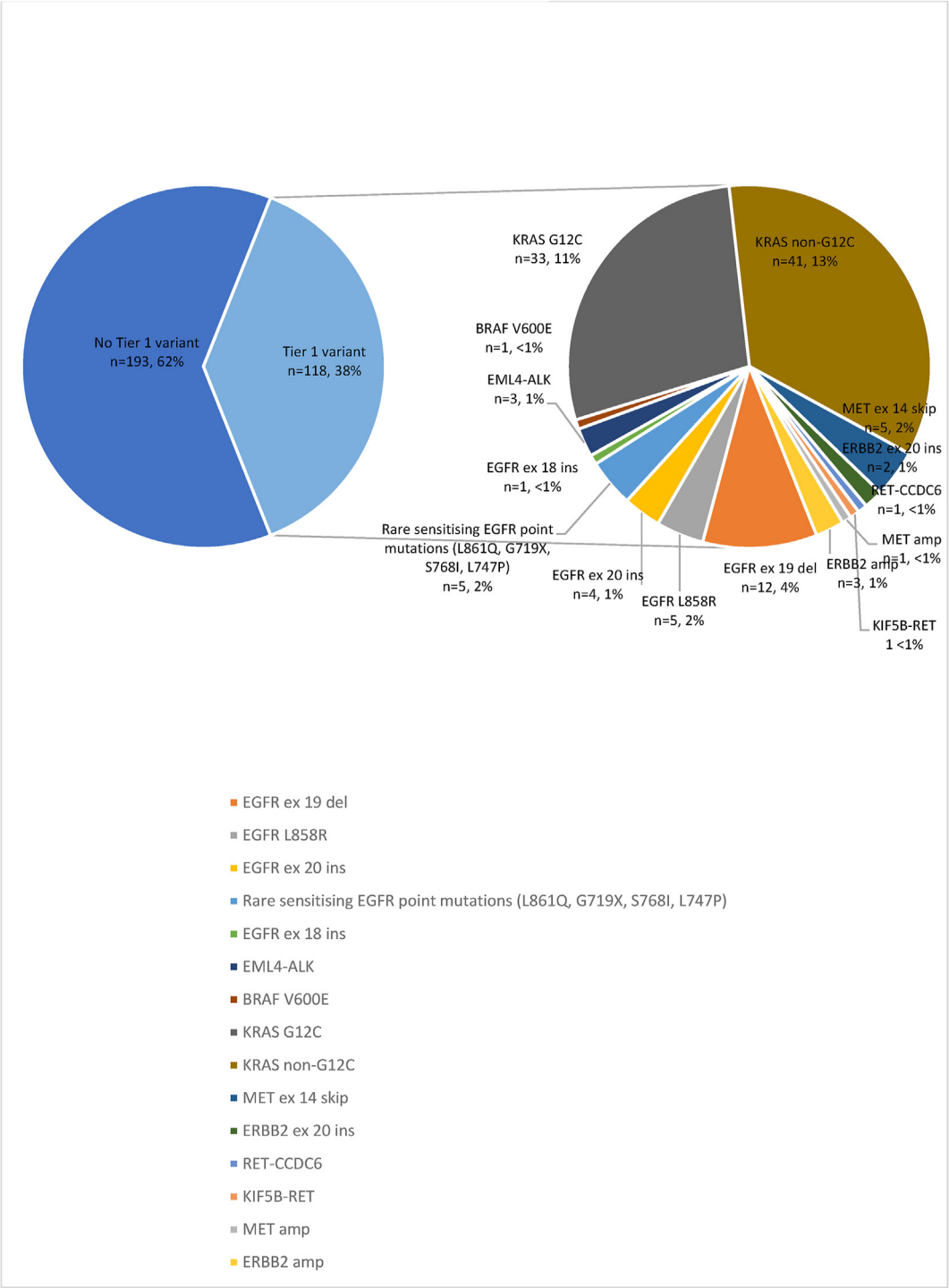

Fig. 2. Tier-1 variants detected on cfDNA-NGS (n = 311).

with newly identified aNSCLC, and increased the detection rate of tier-1 variants by 46% compared to tissue alone. Comparable to other series [3,17], the rate of informative cfDNA-NGS tests and concordance between cfDNA-NGS and tissue tests were high. In addition, the turnaround times for cfDNA-NGS tests were faster than standard-of-care tissue tests, and 20% of patients were able to commence first line SACT with cfDNA-NGS results alone without waiting for tissue results. These data demonstrate the clinical utility of concurrent plasma-based comprehensive genotyping parallel to standard tissue tests, emphasising their complementary nature.

A major barrier to personalising cancer treatment is inadequate and delayed tumour genotyping. We have demonstrated that in a UK cohort, where only front-line

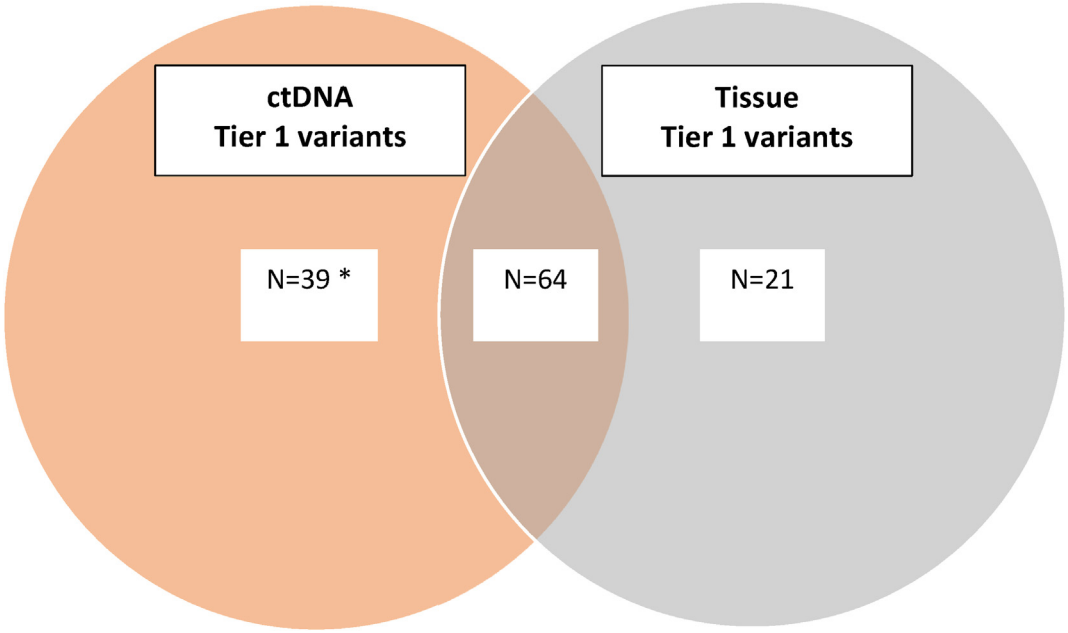

Fig. 3. **Concordance between cfDNA-NGS and all (standard-of-care and non-standard additional) tissue molecular tests in treatment-naïve patients with paired cfDNA and tissue tests**. * Seventeen of the 39 additional variants detected by cfDNA-NGS alone were actionable (*KRAS* G12C [n = 9], *MET* exon 14 skipping [n = 3], *ERBB2* exon 20 insertion [n = 2], *EGFR* exon 20 insertion [n = 2], *EGFR* exon 18 deletion [n = 1]); 22 were not actionable (*KRAS* non-G12C [n = 19], *ERBB2* amplification [n = 2], *MET* amplification [n = 1]).

tissue molecular testing is funded through routine government-funded healthcare commissioning, cfDNA-NGS identified a clinically meaningful genomic variant in more than one-third of patients, and importantly, a druggable variant in 22% of patients. Moreover, in our study, cfDNA-NGS increased the detection rate of tier-1 variants above that of tissue tests alone, even factoring in patients who had additional non-standard

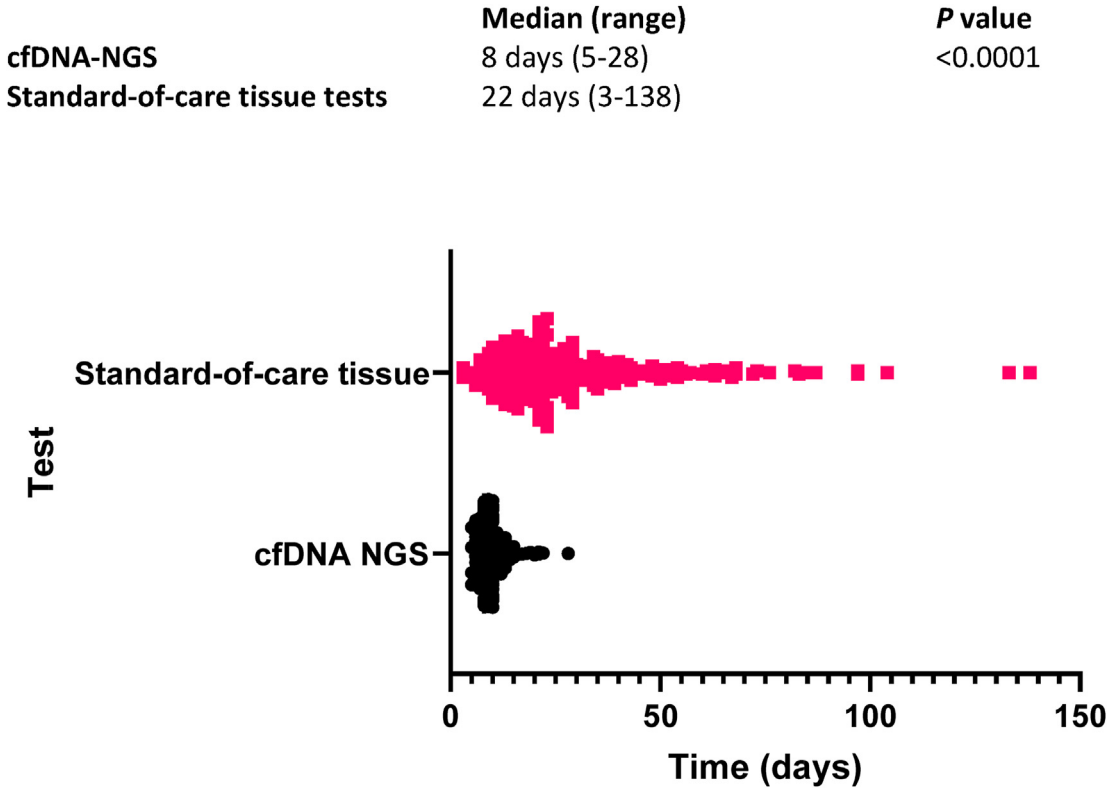

Fig. 4. Test turnaround times (n=243).

	Median (range)	*P* value
Blood sampling for cfDNA-NGS	16 days (0 to 98) *	<0.0001
Paired tissue biopsy	35 days (3 to 179)	

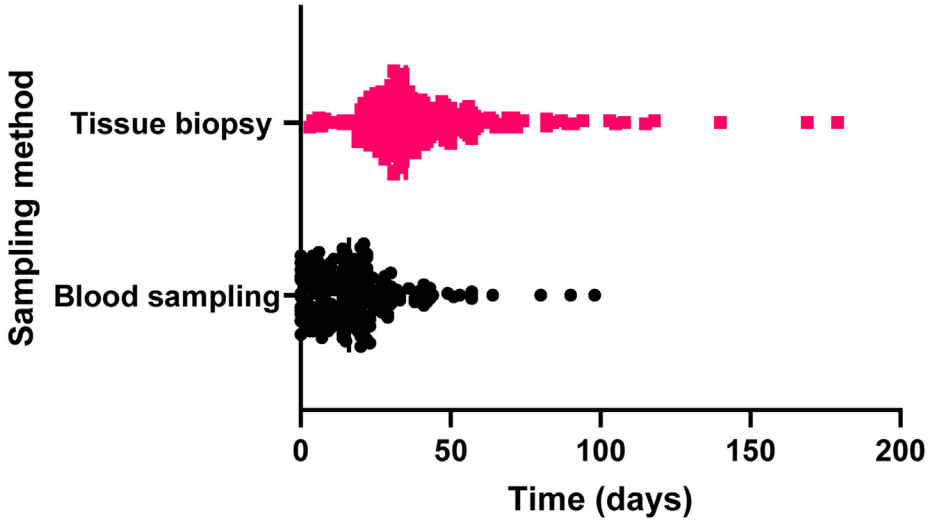

Fig. 5. **Time from sampling to commencement of first-line systemic treatment ($n = 205$).** * Eighteen patients commenced systemic treatment on the day of cfDNA-NGS blood sampling: eight had paired tissue molecular test results available, six were relapsed patients had prior tissue molecular results available from the previous diagnosis of radically treated early stage NSCLC, four did not have any molecular tests results.

tissue genotyping, allowing more patients to receive targeted therapy. These findings are similar to that seen in other large, predominately United States, real-world series of patients with aNSCLC, which report that cfDNA-NGS can increase the detection rate of clinically relevant somatic variants by 15–65% versus tissue only [3,17,18].

Another challenge of tissue genotyping is adequate gene coverage to detect all clinically significant variants. In our study, only 67% of patients underwent tissue testing for the NCCN-recommended biomarkers, despite the inclusion of results from additional tissue genotyping performed through clinical trials or self-funded platforms. These challenges can be largely overcome with the use of a comprehensive cfDNA-NGS approach [9].

Indeed, in our study, we have demonstrated that the turnaround time from sampling to results was markedly shorter for cfDNA-NGS compared to standard tissue tests, analogous to previous series [3,17], and this is likely an underestimate of the true magnitude of time saved as we did not include the time taken to schedule the tissue sampling procedure. This time-to-result benefit from cfDNA-NGS is particularly pertinent during and following the COVID-19 pandemic, where delays to diagnosis, and thus, treatment [7], are likely to persist in the coming years.

Furthermore, according to some government-funded treatment algorithms (e.g. NHS NICE guidelines [19]), targeted therapy may only be funded for use in untreated patients (e.g. first-line osimertinib [20]), and thus, patients who have already commenced other SACT and are later found to have a targetable variant, may no longer be eligible to receive such treatments. Our study has demonstrated that the time from sampling-to-treatment for cfDNA-NGS was significantly shorter than for tissue sampling, and patients were able to commence SACT after cfDNA-NGS results alone without waiting for tissue results. Although some of these patients received targeted therapy, many others received immunotherapy and/or chemotherapy, demonstrating the ability of cfDNA-NGS to not only promptly match patients with oncogene-addicted tumours to targeted therapies but also identify patients for whom there is no targeted option. There is clear and consistent clinical benefit, taken together, in performing concurrent cfDNA-NGS and tissue testing in patients with aNSCLC.

While it is well-documented that cfDNA NGS has high concordance with orthogonal tissue genotyping [3,17], also confirmed in our study, a proportion of patients may not shed detectable levels of cfDNA (9% in our study), such as those with lower tumour burden, lung-limited disease, or slowly proliferating tumours [21,22]. Furthermore, defining an informative cfDNA NGS sample can be challenging as cfDNA is not always tumour derived; non-tumour derived age-related clonal haematopoiesis variants (CHIP) can be detected in plasma, especially in those of older age; a target age overlapping with that typical in NSCLC [23,24]. Therefore, concurrent plasma and tissue testing would be the ideal scenario to maximise the identification of clinically relevant genomic variants or leukocyte genotype subtraction, but these both come at a substantial financial cost. Nevertheless, minimising potential false-positive variant calls and correctly identifying clonal hematopoietic variants from cfDNA NGS results can be established by implementing genotyping results review through an experienced genomic tumour advisory board, and some of our cases were reviewed in this manner. Moreover, Guardant360™ can identify potential CHIP variants using a statistical filter: alterations occurring in a gene known to be potential CHIP (such as *KRAS*) with a discordant variant allele frequency compared to the other somatic alterations detected on cfDNA-NGS are highlighted in the test report.

One strategy to optimise sequential testing in NSCLC may be a plasma-first approach followed by subsequent tissue testing in those with non-informative cfDNA-NGS, especially in patients where there is insufficient tissue or lack of access to upfront tissue NGS. Certainly, this approach was taken by two small studies where selected patients with suspected aNSCLC underwent cfDNA-NGS while awaiting tumour biopsy; these studies demonstrated that 20–22% of patients were able to receive targeted therapy after cfDNA results without tissue results [25,26]. This approach may counteract treatment delays for patients with aNSCLC, especially while potential delays are further intensified by COVID-19.

This study was performed at a single UK academic cancer centre, a limitation of this study. Patients were referred from a variety of diagnostic services with different tissue molecular ordering methods and timelines to our centre; therefore, in order to minimise unquantifiable bias, the tissue test turnaround time was calculated from the date of biopsy rather than the date of tissue molecular test request as this could not be accurately ascertained. Furthermore, in this real-world study, the tissue testing methods were heterogenous, reflecting our standard referral pathways and use of sequential hierarchical single-gene testing at some sites could bias the comparisons between cfDNA-NGS and tissue testing times. Nevertheless, our comparisons do reflect real-world testing scenarios and are, therefore, clinically relevant. Moreover, our results are based on a healthcare model of government-funded genotype testing, identifying the potential challenges and benefits of implementing cfDNA-NGS in this setting.

5. Conclusion

cfDNA-NGS performed at the time of aNSCLC diagnosis increased the detection of clinically meaningful variants, with high concordance to tissue testing in a government-funded healthcare setting, allowing more patients to be treated with upfront targeted therapies. Time from sampling to treatment was significantly shorter for cfDNA-NGS compared to tissue tests, and patients were able to commence SACT without needing to await tissue genotyping results. Concurrent tissue and plasma testing in the diagnosis of NSCLC is ideal, and both technologies are complementary, but this comes at a cost. Given the ability of cfDNA-NGS to rapidly detect clinically relevant genomic variants, a plasma-first, tissue-next (if no relevant variants are detected on plasma) testing approach could improve the speed and accuracy of therapeutic decision-making and should be considered a key strategy to increase adequacy and timeliness of target identification and treatment for all patients with aNSCLC.

Author statement

Wanyuan Cui: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing – original draft; Writing – review and editing. Charlotte Milner-Watts: Data curation; Writing – review and editing, Hazel O'Sullivan: Data curation; Writing – review and editing, Hannah Lyons: Data curation; Writing – review and editing, Anna Minchom: Writing – review and editing, Jaishree Bholse: Writing – review and editing, Michael Davidson: Writing – review and editing, Nadia Yousaf: Writing – review and editing, Sophie Scott: Funding acquisition; Writing – review and editing, Iris Faull: Funding acquisition; Writing – review and editing, Marina Kushnir: Funding acquisition; Writing – review and editing, Rebecca Nagy: Funding acquisition; Writing – review and editing, Mary O'Brien: Writing – review and editing, Sanjay Popat: Supervision; Conceptualization; Formal analysis; Methodology; Validation; Writing – review and editing.

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Conflict of interest statement

WC: WC reports honoraria from AstraZeneca, Janssen, Merck, and Pfizer; research grant funding from the Breast Cancer Trials group; and the Australian Government Research Training scholarship outside of the submitted work.

CWM: CWM reports honoraria from AstraZene ca outside of the submitted work.

HO: None.

HL: None.

AM: Has served on advisory boards for Janssen Pharmaceuticals, Merck Pharmaceuticals, Takeda Pharmaceuticals and Genmab Pharmaceuticals. Has received honoraria from Chugai Pharmaceuticals, Novartis Oncology, Faron Pharmaceuticals, Bayer Pharmaceuticals and Janssen Pharmaceuticals. Has received expenses from Amgen Pharmaceuticals and LOXO Oncology.

JB: None.

MD: None.

NY: NY reports honoraria from AstraZeneca outside of the submitted work.

SS: SS is an employee and stockholder at Guardant Health Inc.

IF: IF is an employee and stockholder at Guardant Health Inc.

MK: MK is an employee and stockholder at Guardant Health Inc.

RN: RN is an employee and stockholder at Guardant Health Inc.

MOB: reports personal fees from MSD, Amgen, Pierre Fabre and iTeos outside of the submitted work.

SP: SP reports personal fees from AstraZeneca, Roche, Boehringer Ingelheim, Pfizer, Novartis, Takeda, BMS, MSD, EMD Serono, Bayer, Blueprint, Daiichi Sankyo, Guardant Health, Janssen, GSK, BeiGene, Incyte, Eli Lilly, Amgen outside of the submitted work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.05.012.

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