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"Plasma-first" approach for molecular genotyping in non-small cell lung cancer: A narrative review

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ABSTRACT

Molecular genotyping is essential for management of patients newly diagnosed with advanced non-small cell lung cancer (NSCLC). Plasma circulating tumor DNA (ctDNA) testing has emerged as a complement to tumor tissue genotyping for advanced NSCLC, especially when tissue or time are limited. The optimal way to integrate ctDNA testing into the diagnostic algorithm for patients with newly diagnosed NSCLC remains unclear. A "plasma-first" approach, using ctDNA genotyping for patients with suspected or confirmed advanced NSCLC before tissue genotyping, may shorten time to treatment and yield a higher rate of detection of actionable genomic alterations. In this review, we discuss current evidence exploring the "plasma-first" approach.

1. Introduction

Personalized medicine based on tumor genotyping for identification of actionable molecular drivers is essential in lung cancer management. Current guidelines recommend molecular genotyping for all patients newly diagnosed with metastatic non-squamous NSCLC, in addition to immunohistochemical assessment of programmed death ligand 1 (PD-L1), in order to guide treatment decisions [1–3]. Comprehensive genomic testing using next-generation sequencing (NGS) is recommended in order to simultaneously assess all relevant actionable targets [4,5].

Availability of molecular genotyping results before treatment initiation is crucial in NSCLC and can impact patient outcomes [6,7]. Genotyping of tumor tissue is considered the gold standard for molecular testing in NSCLC. However, there are inherent limitations to obtaining tissue for NGS, including difficult and/or unsafe biopsy locations and small sampling through minimally invasive techniques. In addition to limited tissue for NGS testing, many patients need to start treatment urgently, thus wait times for genotyping results are challenging in many jurisdictions [6,8,9]. Technological advances in genetic sequencing of cell-free (cf)DNA have enabled identification of actionable alterations in plasma ctDNA [10]. Plasma ctDNA testing is a practical alternative tool that has shown clinical utility as a complement to tissue genotyping in NSCLC [11–13]. Advantages of plasma ctDNA testing include its non-invasive nature, rapid turn-around time (TAT) and high concordance rate with tissue testing [14,15].

The integration of ctDNA testing in clinical practice has been increasingly investigated in NSCLC. This review highlights the clinical applications of ctDNA for molecular testing in advanced NSCLC with a focus on the "plasma-first" approach.

2. Plasma ctDNA testing for tumor genotyping of treatment naïve patients with advanced NSCLC

2.1. Sequential approach: ctDNA testing in patients with NSCLC and insufficient tumor samples for tissue genotyping

One possible strategy, as opposed to "plasma-first", is the sequential approach. In the sequential approach, liquid biopsy is performed after tissue biopsy in patients with confirmed advanced non-squamous NSCLC, but insufficient tumor samples or limited access to broad tissue testing [16,17].

It is estimated that up to 43% of patients have insufficient tissue for genotyping for several reasons including inability to undergo biopsy safely, failed biopsy and inadequate tissue sampling [18]. Several studies have explored the clinical utility of ctDNA testing in patients with NSCLC in the setting of unsuccessful NGS testing in tumor tissue. For example, Zugazagoitia et al. found that ctDNA testing in patients with NSCLC and insufficient tumor samples for tissue sequencing detected actionable

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genomic alterations variants, allowing initiation of genotype-matched therapies [16]. The main pitfall of the sequential approach is the long wait time for NGS results. A major barrier to personalizing cancer treatment and access to targeted therapy in NSCLC is delayed tumor genotyping.

A high proportion of patients do not have test results available at the time of first oncology consultation [9,19], which leads to prolonged wait times for results, inadequate treatment and inferior outcomes [6,20]. In some cases, patients are even required to undergo repeat tissue biopsy in order to achieve successful NGS testing in tissue, leading to further delay, increased cost and further risk of complications for patients [6]. Therefore, a different approach is warranted, aiming for faster molecular genotyping and shorter time to treatment initiation.

2.2. Concurrent approach: ctDNA testing after NSCLC diagnosis and simultaneously to tissue genotyping

The concurrent approach involves simultaneous initiation of molecular testing in both tumor tissue and plasma after pathologic confirmation of NSCLC.

Raez et al. conducted a retrospective study of 170 patients with advanced NSCLC who had concurrent tissue and plasma NGS testing at diagnosis. Treatment decisions were based mainly on plasma results (73.5%) versus tissue (25.9%), with a much shorter turnaround time (results were available on average 26.8 days faster than tissue), higher testing success, and high concordance with tissue for guideline-recommended biomarkers [21].

In a retrospective study performed by Aggarwal et al., 330 patients with non-squamous NSCLC diagnosed at the Hospital of the University of Pennsylvania underwent molecular testing and were included for analysis [22]. Testing with tissue NGS only was completed in 32.7% (108/330); 67.2% (222/330) underwent concurrent tissue and plasma NGS testing. The concurrent approach (tissue and plasma) was associated with a higher likelihood of comprehensive molecular genotyping, as well as improved availability of results. Importantly, patients with comprehensive genotyping have improved OS compared to patients with incomplete or no testing. In a recent update, Aggarwal and colleagues reported that patients with molecular test results available before first-line therapy had significantly longer OS relative to those without available testing [7]. While it is impossible to control for bias in retrospective comparisons, this study further supports the importance of a concurrent genotyping approach.

The prospective Non-invasive vs. Invasive Lung Evaluation (NILE) study demonstrated that plasma cfDNA testing was non-inferior to tumor tissue testing [11]. Among 282 patients with advanced non-squamous NSCLC, guideline-recommended actionable alterations were identified for 27.3% of patients using cfDNA versus 21.3% using standard of care tissue genotyping ($P < 0.0001$ for noninferiority). Concordance between cfDNA and tissue for approved biomarkers was >98.2%, with 80% clinical sensitivity and 100% positive predictive value for cfDNA versus tissue testing. In addition, median turnaround time for results was significantly faster (9 days with cfDNA versus 15 days with tissue, $P < 0.0001$). Complete biomarker testing was significantly increased with the use of cfDNA, 95% versus only 18% with tissue testing alone ($P < 0.0001$). Time to treatment was also faster using plasma testing, median 18 days versus 31 days with tissue genotyping alone ($P = 0.0008$) [23].

In a prospective real world study at the Royal Marsden Hospital in the United Kingdon, 311 consecutive patients with newly diagnosed, pathologically confirmed advanced NSCLC underwent concurrent plasma and standard of care tissue molecular testing [24]. Cui et al. reported that plasma testing increased the detection rate of tier 1 variants by 46% versus tissue alone with a sensitivity of 75% compared with tissue, acknowledging that comprehensive tissue NGS was not standard of care. Time from ordering to report was significantly shorter with plasma NGS versus tissue testing (8 versus 22 days; $p < 0.0001$). Median time from sampling to treatment initiation was also shorter for plasma NGS versus first tissue biopsy, 16 days versus 35 days, $p < 0.0001$). Additionally, 20% of patients started first-line systemic treatment based on plasma NGS results alone.

2.3. "Plasma-first" approach: pre-diagnostic ctDNA testing for suspected lung cancer

The "plasma first" approach involves plasma ctDNA testing before biopsy and pathologic diagnosis in patients with suspected advanced NSCLC. This approach may shorten current wait times for biomarker testing results and accelerate time to treatment for patients (Table 1). It is important to recall that this approach still includes the gold standard of tumor tissue biopsy and pathologic diagnosis, and does not mean "plasma only".

Cheng et al. prospectively tested the use of plasma NGS in the pre-diagnostic setting in a cohort of 20 hospitalized patients with suspected metastatic lung cancer prior to pathologic diagnosis [25]. The median time from pathologic diagnosis to plasma genotyping result was 3 days using the plasma-first approach. Using a concurrent plasma and tissue sampling approach, the median time to results was 18 days and 35.5 days for tumor NGS testing alone. Of note, 68% of patients went on to have pathologically confirmed metastatic NSCLC while 21% had cancer from a different primary (non-lung) site. Importantly, 45% of patients in the plasma-first cohort had an actionable or informative genomic variant in plasma, and 20% of patients received first-line targeted therapy based on the plasma NGS results.

Thompson et al. conducted a prospective cohort study of plasma NGS testing at the time of tissue biopsy in patients with suspected advanced lung cancer [26]. The primary endpoint was time to first-line systemic treatment initiation, compared with a retrospective cohort of consecutive patients with advanced NSCLC with reflex tissue NGS. In the plasma-first cohort, 65 patients with suspected advanced NSCLC had plasma NGS at the time of tissue biopsy. Of these, 55 (85%) had a pathologic diagnosis of NSCLC (48 non-squamous, 7 squamous). Results were compared with a reference group of 55 patients with advanced NSCLC who had tissue NGS only. In the "plasma-first" cohort, plasma NGS results were available before the first oncology visit in 85% of patients versus 9% in tissue NGS cohort ($p < 0.0001$). Time-to-treatment was significantly shorter in the plasma-first cohort (12 days versus 20 days, $p = 0.003$), along with a median shorter time-to-treatment in patients with specific driver alterations (10 days versus 19 days, $P = 0.001$).

In the pilot study conducted by Cui et al. at the Royal Marsden, pre-diagnostic plasma NGS testing was performed in 51 patients with radiologically suspected advanced lung cancer during the COVID-19 pandemic [27]. Of 49 evaluable patients, 41 underwent tissue biopsy and 31 (63%) had a pathologic diagnosis of NSCLC. Eleven patients (22%) started targeted therapy based on plasma NGS results without awaiting tissue molecular results. The median time to result was shorter for plasma NGS compared to standard-of-care tissue testing (9 versus 25 days, $P < 0.0001$).

Our group performed a prospective pilot study using a limited plasma DNA-based NGS panel in 20 patients with suspected advanced lung cancer and a smoking history of ≤15 pack-years [28]. Most, 85%, were diagnosed with NSCLC on biopsy. The mean time from referral to treatment initiation was significantly shorter in the plasma-first cohort compared to a contemporary cohort not enrolled in the study (32.6 versus 62.2 days, $p < 0.0001$), and also to an historical cohort referred to the rapid diagnostic program between 2018 and 2019 (32.6 versus 61.5 days, $p < 0.0001$).

In the prospective ACCELERATE study (NCT04863924) conducted at the Princess Margaret Cancer Centre, 150 patients with suspected advanced lung cancer underwent "plasma-first" NGS testing during initial diagnostic workup [ref 25]. Of these, 90 patients (60%) had final tissue confirmation of advanced non-squamous NSCLC. The median time to treatment for the "plasma-first" cohort was 39 days compared to 62

Table 1
Time to treatment (TTT) with plasma-first approach in patients with suspected lung cancer.

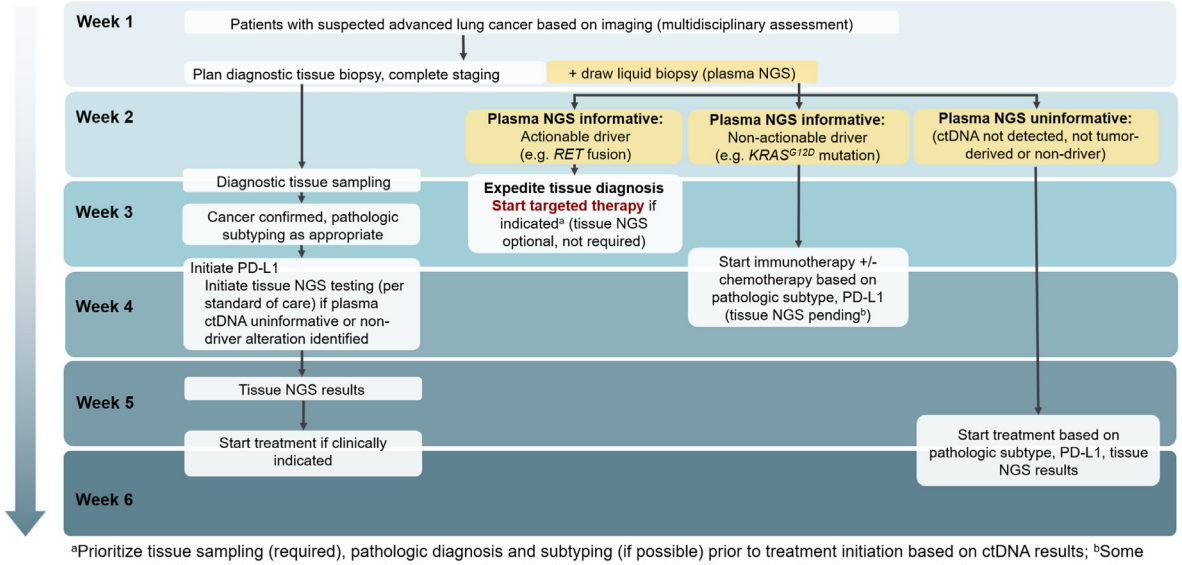
Study	N	Time (days) to molecular results plasma vs tissue	TTT (days) plasma vs tissue	TTT if actionable alteration	% NSCLC among all evaluable patients	% non-squamous among NSCLC
Cheng et al., Dana Farber [25]	20 hospitalized	3 vs 35.5	NA	NA	68%	NA
Cui et al., Royal Marsden [27]	49	9 vs 33	NA	NA	63%	NA
Thompson et al., University of Penn [26]	65 (55 control cohort)	8 vs 26	12 v 20 P = 0.003	10 v 19 P = 0.001	85%	74%
García-Pardo et al., Princess Margaret [28]	20 light/never smokers (41 control cohort)	17.8 vs 23.6	33 vs 62 P < 0.001	29 v 49 P < 0.001	85%	94%
García-Pardo et al., Princess Margaret [29]	150 (89 control cohort)	7 vs 23	39 v 62 P < 0.001	33 v 61 P < 0.001	60%	75%
Swalduz et al., multicenter randomized trial in France [30]	161 (158 control arm)	17.9 d vs 25.6	29 v 33.2 P < 0.001	21 v 37.4 P < 0.001	67.7%	80%

days for a reference cohort using tissue NGS only [29]. Median turnaround time from blood sample collection to plasma genotyping results was 7 days. Median turnaround time from biopsy to tissue NGS results was 23 days. Additionally, 21 of 90 patients with advanced non-squamous NSCLC (23%) started targeted therapy based on plasma results before tissue NGS results were available.

Finally, Swalduz et al. performed a multicenter, randomized study exploring the clinical utility of a plasma-first approach in 319 patients with suspected advanced lung cancer (LIBELULE, NCT03721120) [30]. Patients were randomized to either arm A (n = 161), with plasma testing performed at the first visit and arm B (n = 158), with tissue biopsy performed with genomic analysis as indicated per standard of care. In the plasma-first arm (A), investigators were to initiate treatment based on plasma results if an actionable driver alteration was found. Two thirds of patients had a pathologic diagnosis of NSCLC (57% adenocarcinoma, 11% squamous cell carcinoma). For patients that received treatment, the mean time to treatment initiation was 29.1 days in the plasma-first cohort versus 38.8 days in the reference group, ($P = 0.01$). The mean time to treatment was significantly shorter for patients with a tier 1 genomic alteration detected (21 days in Arm A vs 37.4 days in Arm B, $P = 0.004$). Time to molecular results was also shorter in the plasma first arm compared to the standard (17.9 days versus 25.6 days respectively, $p < 0.001$). In the plasma-first arm, only 7.4% of patient started treatment without genomic analysis available compared to 13.3% in the standard tissue-first arm.

Based on the consistent results across studies, our group has proposed a plasma-first approach for patients with suspected advanced lung cancer in order to accelerate time to complete biomarker results and initiation of treatment (Fig. 1). Treatment acceleration is greatest in patients with informative plasma NGS results that identify a treatable oncogenic driver. However, treatment can also be accelerated in patients with identification of unique oncogenic drivers, such as *KRAS* G12V, for which there are no current targeted therapies. For these patients, PD-L1 testing can be expedited and treatment initiated without awaiting tissue NGS results. One may even consider not performing tissue NGS in these cases in order to preserve tissue for future studies and to avoid the cost of NGS. Finally, there are 2 types of negative plasma ctDNA results. The first type is truly uninformative with insufficient ctDNA for testing. In these cases, tissue NGS testing is needed. The second type of negative ctDNA result may actually be informative, predicting the absence of targetable alterations in tissue as well.

Tumor fraction has been identified as a key determinant of whether or not negative plasma ctDNA results are informative. Using Foundation One Liquid CDx, Husain et al. examined data from plasma and tissue NGS from 1289 patients and found that if plasma samples had an elevated tumor fraction of ≥10%, (calculated based on tumor aneuploidy or non-germline variants), the detection of actionable alterations was nearly 100% compared to tissue testing [31]. In another study using the same assay, both the positive predictive association and negative predictive value of plasma ctDNA results was 96% compared to tissue profiling



[a]Prioritize tissue sampling (required), pathologic diagnosis and subtyping (if possible) prior to treatment initiation based on ctDNA results; [b]Some may consider tissue NGS testing optional in this scenario as the frequency of actionable co-alterations is uncommon in the presence of another driver alteration.

Fig. 1. Plasma-first approach proposed algorithm.

when the tumor fraction was ≥1% [32]. However, not all plasma ctDNA NGS assays report tumor fraction and these thresholds have not been validated across different platforms. Thus, the use of tumor fraction to predict informative negative ctDNA results is not yet ready for routine use in the clinic. However, with future validation of this approach, this may enter clinical use in the near future.

3. Upfront plasma ctDNA testing to identify resistance mutations

The first studies exploring a "plasma-first" approach stemmed testing for resistance mutations in patients with epidermal growth factor receptor (*EGFR*)-mutated NSCLC after failure of first- or second-generation tyrosine kinase inhibitors (TKIs). Guidelines endorse a "plasma-first "approach when testing for the *EGFR T790 M* resistance mutation in this patient population [33,34]. Multiple studies have validated this approach [35–37], recommending tumor biopsy for patients without evidence of the resistance mutation on ctDNA testing and for those in whom small-cell or other histologic tumor transformation is suspected. This scenario is becoming less frequent since third-generation *EGFR* TKIs are now used in first-line setting [38]. However, a "plasma-first" approach remains important given the challenges of repeat tumor biopsy in this population. For example, in a study of 50 patients with *EGFR* mutant advanced lung cancer with cancer progression on osimertinib, only 39% were able to undergo successful tumor biopsy and NGS testing [NCT03239340] [39].

Genomic assessment continues to play a key role in overcoming osimertinib resistance, including the identification of EGFR-dependent alterations (e.g. *EGFR*797S, G724S), mesenchymal epithelial transition (*MET)* amplification, and other targetable drivers [40,41].

4. Limitations

A plasma-first approach in patients with suspected advanced NSCLC can accelerate time to treatment and facilitate access to precision medicine. However, this strategy has some limitations. It is important to recall that plasma-first does not mean "plasma only", and that tumor tissue biopsy remains the gold standard for pathologic diagnosis and determination of cancer site of origin.

In the studies exploring a plasma-first approach, despite expert selection of patients with radiologic evidence of advanced lung cancer, only 63–85% of patients had biopsy-proven advanced NSCLC [25–27,29,30]. These results reinforce the need for tissue biopsy for lung cancer diagnosis and pathologic subtyping, as well as for PD-L1 assessment. Additionally, plasma NGS has lower sensitivity than tissue NGS, with low levels of ctDNA available for analysis in some scenarios (i.e. intrathoracic disease or brain only metastasis), as well as limited sensitivity for detection of fusions, and challenges in assessment of copy number variation [29]. As routine NGS testing moves into earlier stages of NSCLC, this may limit the application of existing plasma ctDNA NGS assays as their sensitivity is even lower in smaller non-metastatic tumors [42]. However, for patients with sufficient burden of disease to detect plasma ctDNA, and for whom tissue profiling results are expected to take several weeks, a plasma-first approach may yield faster diagnosis and shorter time to appropriate targeted treatment [15].

Recent developments in plasma methylation assays to detect tissue of origin [43] and detection of exosomal and methylation markers in plasma to differentiate between adenocarcinoma, squamous and small cell carcinoma [44,45] may soon move the field of lung cancer diagnosis beyond tumor biopsy as the only gold standard. Beyond plasma ctDNA, other body fluids in close contact with the tumor may provide an alternative approach; in other tumor types, cfDNA analysis from non-blood biological fluids such as urine, sputum, saliva, seminal fluid or breast milk may become relevant in the early detection and molecular profiling of patients with cancer [46,47].

Finally, despite the clinical benefits of liquid biopsy for molecular profiling in NSCLC, cost remains a potential barrier limiting its widespread use. In a cost-effectiveness analysis of concurrent plasma and tissue NGS in patients with newly diagnosed advanced non-squamous NSCLC, our group demonstrated that the addition of liquid biopsy did not increase overall treatment costs and led to more patients receiving appropriate targeted therapy in the publicly funded Canadian healthcare system [48]. However, the budget impact of the plasma-first approach remains to be defined. A key challenge will be to justify the cost of liquid biopsies in patients that later do not have pathologic confirmation of NSCLC. However, given the rapid progress in targeted therapies across cancer types, these results may be informative for patients with other cancers as well [5].

5. Conclusion

A plasma-first approach, using plasma NGS testing earlier in the diagnostic pathway of patients with suspected advanced NSCLC, can yield faster molecular results and accelerate time to treatment. This leads to increased access to precision medicine and the potential to improve patient outcomes. This strategy should be considered to improve the speed and accuracy of clinical decision-making in advanced NSCLC and to accelerate the time to treatment for patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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