DIAGNOSTICS

Turnaround Time of Plasma Next-Generation Sequencing in Thoracic Oncology Patients: A Quality Improvement Analysis

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abstract

PURPOSE Genomic analysis of plasma cell-free DNA has become a widespread tool for advanced non-small-cell lung cancer care. Whereas accuracy has been reported on widely, its usefulness is also tied tightly to its turnaround time (TAT), which is not well studied.

METHODS We studied the TAT of commercial plasma next-generation sequencing (NGS; Guardant360) for 533 results from 461 patients at our center between August 2016 and October 2019. The study received institutional review board approval as a quality improvement study; therefore, the results of the test and clinical setting were not analyzed.

RESULTS TAT from blood draw to result (median of 9 days) was slightly longer than the TAT from laboratory receipt to result, a median of 7 days. Testing volume at our center increased three-fold over the time of the study. During this period, clinical TAT decreased from an initial median of 12 days to a median of 8 days in 2018, but more recently the median increased slightly to 9 days. During the most recent 12 months, 231 (95%) of 247 cases resulted within 14 days from blood draw, with delayed results usually because of billing, whereas 44 cases (18%) resulted within 7 days of blood draw. Studying 92 cases drawn in the most recent 3-month period, the median time of result receipt was 4:01 PM Eastern Time/1:01 PM Pacific Time; 39 results (43%) were returned after 5:00 PM Eastern Time.

CONCLUSION In a large single-institution experience, we find that plasma NGS results can routinely be expected within 2 weeks, but uncommonly result within 1 week, supporting the need for new strategies to incorporate plasma NGS into the initial genotyping of advanced non-small-cell lung cancer.

JCO Precis Oncol 4:1098-1108. © 2020 by American Society of Clinical Oncology

INTRODUCTION

Genotyping of plasma cell-free DNA (cfDNA), also termed liquid biopsy, is a noninvasive diagnostic strategy with a growing range of applications across multiple cancer types.¹ The relative rapidity of cfDNA genotyping makes the approach especially valuable in advanced non-small-cell lung cancer (NSCLC) in which the detection of an actionable mutation is crucial for selecting a personalized therapy.^{2,3} The development of robust next-generation sequencing (NGS) panels for plasma cfDNA now allows for relatively complete genomic analysis using a blood test.⁴⁻⁶ Furthermore, plasma NGS for targetable driver mutations maintains the high positive predictive value of existing polymerase chain reaction (PCR)-based plasma genotyping approaches,⁷ allowing providers to confidently select a therapy given a positive result.⁸

However, plasma genotyping has a well-recognized limitation in that negative results, which can occur in the setting of low tumor DNA shed, cannot rule out the

presence of an underlying actionable tumor genotype, thereby necessitating reverting to standard-of-care tissue genotyping.^{8,9} Indeed, the US Food and Drug Administration approval of the first plasma genotyping test, the cobas epidermal growth factor receptor mutation version 2 real-time PCR assay, specifically states the expectation that when negative, there should be a reflex to confirmatory tissue-based epidermal growth factor receptor testing.¹⁰ Reflexing to tissue genotyping after negative plasma genotyping has the potential to prolong the overall time needed to complete testing.

Whereas results of PCR assays may be returned in a matter of days, results of plasma NGS has the potential to take weeks. This turnaround time (TAT) must be fully understood to determine the appropriate clinical application of plasma NGS. With a fast TAT, plasma NGS could be applied as a quick screening test before tumor genotyping. With a slower TAT, plasma NGS would have more value as a complement to tissue genotyping, as it has been shown that

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on July 31, 2020 and published at ascopubs.org/journal/po on September 21, 2020; DOI <https://doi.org/10.1200/P0.20.00121>

CONTEXT

Key Objective

We aimed to understand the turnaround time (TAT) of plasma next-generation sequencing (NGS) by studying 533 cases over 3 years to better understand the appropriate clinical application of this emerging diagnostic.

Knowledge Generated

TAT from blood draw to results initially decreased from a median of 12 days in the first 6 months to 8 days in 2018, rising slightly to 9 days in the final 6 months. Over the final 12 months studied, 97% of cases had plasma NGS results returned within 2 weeks, but only 18% had results returned within 1 week.

Relevance

Plasma NGS TAT has improved; however, these improvements have recently plateaued. Instead of demanding a shorter TAT, clinicians may need a diagnostic strategy that accommodates a 1- to 2-week TAT for plasma NGS, such as (when possible) planning first-line treatment 2 weeks after plasma NGS is sent to allow for consideration of these results.

a combination of plasma and tissue NGS improves mutation detection compared with tissue NGS alone.⁴ Understanding TAT also allows clinicians to plan appropriately for how long to wait for results before starting therapy.

METHODS

An institutional database was retrospectively reviewed for cases in which plasma NGS was ordered and results obtained for thoracic oncology patients at our center. Plasma NGS was ordered from a commercial vendor (Guardant360; Guardant Health, Redwood City, CA). A corresponding database of relevant testing dates (date of order, date of blood draw, date of shipment, date received, and date of result) was compiled. As a quality improvement study, protected patient health information, such as the clinical context and results of plasma NGS testing, was not studied. This project was reviewed and initiated as a quality improvement initiative at Dana-Farber Cancer Institute and as such was not formally supervised by the Dana-Farber Institutional Review Board, per their policies.

TAT was calculated four ways per case (Fig 1A). Clinical TAT 1 (TAT_{C1}) was defined as the interval between the date of order and the date of result. Clinical TAT 2 (TAT_{C2}) was defined as the interval between the date of blood draw and the date of result. Clinical TAT 3 (TAT_{C3}) was defined as the interval between the date of sample shipment and the date of result. Laboratory TAT (TAT_L) was defined as the interval between the date the sample was received by the laboratory and the date of result. For a subset of cases, the time results were released to the ordering physician via email notification was also abstracted.

RESULTS

We studied 533 results from 461 patients between August 2016 and October 2019. The volume of plasma NGS orders increased from 50 during the initial 6 months to 138 during the final 6 months. For 467 cases (88%), the date of order and the date of blood draw were the same, whereas for 66 cases (12%), the test was ordered in 1 to 51 days in

advance (Appendix Fig A1). Similarly, for 463 cases (87%), the date of blood draw and the date of shipment were the same, whereas for 70 cases (13%), blood was shipped 1 to 5 days after being drawn (Appendix Fig A2). It took a median of 1 day between the date of shipment and the date of receipt (range, 1 to 5 days; Appendix Fig A3).

There were small but consistent differences in TAT depending on the method of calculation. TAT_{C1} (order to result) was slightly skewed, with 11 cases (2%) having a TAT_{C1} of more than 21 days, likely because of a scheduled delay between the order and the blood draw (Appendix Fig A4). Because the date of blood draw and the date of shipment were often the same, TAT_{C2} (draw to result) and TAT_{C3} (ship to result) had a similar distribution (Appendix Fig A5). We therefore focused on comparing TAT_{C2} (date of blood drawn to result) with TAT_L (date of received to result) moving forward (Fig 1B). Over the time studied, clinical TAT (TAT_{C2} median of 9 days) was slightly longer than laboratory TAT (TAT_L median of 7 days) given the additional time needed for specimen handling and shipment.

Over the time period studied, our site has increased its volume of plasma NGS ordered (Fig 2A). TAT_{C2} initially dropped from a median of 12 days in the first 6 months to 8 days in 2018, rising slightly to 9 days in the final 6 months (Fig 2B). The time from blood draw to shipment (0 days median) and the time from shipment to laboratory receipt (1 day median) was stable over the study period (Appendix Figs A6 and A7), suggesting that variations in laboratory TATs were the primary contributors to variations in clinical TAT. Focusing on 247 cases from the most recent 12 months, a TAT_{C2} of more than 14 days was rare (Fig 2A), observed in only 6 cases (2%), such that 97% of cases had results returned within 2 weeks of blood draw. Upon review of these delayed cases, three were a result of billing, one had a Friday evening blood draw, and one required retest. A clinical TAT_{C2} of 7 days or fewer was observed in 45 cases (18%), suggesting that the return of results within 1 week of blood draw occurs occasionally but not routinely.

FIG 1. Measuring turnaround time (TAT) of plasma next-generation sequencing. (A) Clinical TAT 1 (TAT_{C1}) was defined as the interval between the date of patients' samples being ordered and the date of result. Clinical TAT 2 (TAT_{C2}) was defined as the interval between the date of patients' blood being drawn and the date of result. Clinical TAT 3 (TAT_{C3}) was defined as the interval between the date of the sample being shipped and the date of result. Laboratory TAT (TAT_L) was defined as the interval between the date of sample received by the laboratory and the date of result. (B) Over the time studied, clinical TAT (TAT_{C2} median of 9 days) was slightly longer than laboratory TAT (TAT_L median of 7 days) given the additional time needed for specimen handling and shipment.

Finally, we studied the time of day when results were received by the physicians in our group (in the Eastern Time Zone), noting that testing is performed in the Pacific Time Zone. Studying 92 cases from the most recent 3-month period, the median time of result receipt was 4:01 PM Eastern Time (interquartile range, 2:31 PM to 6:57 PM Eastern Time) or 1:01 PM Pacific Time (Fig 3). Thirty-nine results (43%) were returned after 5 PM Eastern Time on the day of receipt.

DISCUSSION

The performance of a diagnostic is usually evaluated on the basis of its accuracy—sensitivity, specificity, and concordance. Yet when applying a diagnostic to clinical practice, it must also be evaluated on the basis of practical considerations—feasibility and TAT. The accuracy of plasma genotyping is well described, and the logistical ease of using these blood tests is self-evident; however, the TAT of this testing approach is underreported, and there is

FIG 2. Monthly volume and turnaround time (TAT) over a 3-year period. (A) Volume of plasma next-generation sequencing orders have increased from August 2016 to October 2019. More recently, a greater number of cases have results returned within 7 days, whereas the majority have results returned within 14 days. (B) Median TAT_{C2} (clinical TAT 2 defined as the interval between the date of patients' blood being drawn and the date of result) each month initially dropped from 12 days in the first 6 months to 8 days in 2018, then increased to 9 days in the more recent 6 months.

variability in how TAT is reported. In one prospective pilot study of 210 patients with advanced lung cancer, a median TAT was found to be 9 days for plasma NGS calculated as blood draw to result, but was measured as 20 days for 106 patients undergoing tumor NGS, measured as specimen receipt to result.⁴ Such inconsistencies in calculating TAT can make it difficult to compare the resulting numbers. Whereas the TAT of plasma NGS has been described as part of prospective trials, here we review our institutional experience to assess for comparable TAT performance.

Our first finding is that it matters how TAT is calculated; any report must clearly specify the method for TAT calculation for it to be interpretable. We favor reporting the clinical TAT,

calculated as the interval between the date of blood sample collection and the date of result, because this reflects how long an ordering provider can expect to wait for a result, assuming a same-day blood draw. For plasma NGS, this clinical TAT tended to be 1 day longer than the laboratory TAT (date of receipt to date of result). This 1-day difference is remarkably short compared with the expected difference for tumor NGS, where specimen acquisition and handling can lead to weeks of delays before genomic testing is even started. Furthermore, there is some question as to the most meaningful way to assess TAT. Is the median TAT a meaningful measure if it fails to capture the TAT of 50% of patients whose results take longer than the median?

FIG 3. Time of day when plasma next-generation sequencing results are received. Across 92 cases from the most recent 3-month period, the median time of result receipt was 4:01 PM Eastern Time (1:01 PM Pacific Time). Thirty-nine results (43%) were received after 5 PM Eastern Time on the day of receipt.

FIG 4. Two strategies for incorporating plasma next-generation sequencing (NGS) into initial treatment planning. (A) In a patient with a lower symptom burden, treatment could be scheduled to start 2 weeks from the blood draw, and plasma NGS results would usually be available by then (or earlier). (B) In a patient with a higher symptom burden, you may not be able to wait 2 weeks; empirical treatment may need to be scheduled within a week, at which point plasma NGS results may not yet be available, but these results could be incorporated in cycle 2 or later lines of therapy.

A second important finding is that the TAT of plasma NGS has improved at our site since its introduction in 2016, although more recently TAT has largely plateaued. Over the most recent year, results were received within 2 weeks 95% of the time and within 1 week 18% of the time. Yet the time of day when results are released to providers may also need to be considered when calculating TAT. If results are released toward the end of business hours, it effectively adds an additional business day to the TAT. Thus, it may be more useful to note that results are returned within 13 days of blood draw 91% of the time and within 6 days 4% of the time. These intervals are important because patients with advanced NSCLC and high symptom burden may need to initiate systemic therapy within 1 or 2 weeks.

Unfortunately, our data do not point to a clear opportunity to shorten the TAT of plasma NGS. Most of our blood specimens were shipped the same day as the blood draw, and shipping took only a single day. The key contributor to TAT is the analysis at the laboratory, and as we mentioned, this

has plateaued over recent years. This suggests that, instead of demanding a shorter TAT, clinicians will need a diagnostic strategy that accommodates a 1- to 2-week TAT for plasma NGS. For a patient with advanced NSCLC in which genotype is unknown, we see two potential strategies with regard to the timing of treatment planning (Fig 4). In a patient with a lower symptom burden, empirical treatments, like chemotherapy, could be scheduled to start 2 weeks from the blood draw, and plasma NGS results would usually be available by then (or earlier), allowing for the switch to a targeted therapy before treatment begins. Alternatively, in a patient with higher symptom burden, clinicians may not be able to wait 2 weeks; empirical treatment may need to be scheduled within a week, at which point plasma NGS results may not yet be available. However, if plasma NGS points to a targeted therapy option, these results could be incorporated in cycle 2 or later lines of therapy. In this way, knowledge of the expected TAT is essential when integrating a new diagnostic test into the planning of cancer care.

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SUPPORT

G.R.O. is the Damon Runyon-Gordon Family Clinical Investigator supported by the Damon Runyon Cancer Research Foundation (CI-86-16). Supported in part by National Institutes of Health Grant No. R01-CA240592.

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Manuscript writing: All authors

Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Patents, Royalties, Other Intellectual Property: Dana-Farber Cancer Institute patents on microfluidic culture and analysis of organotypic tumor spheroids

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Research Funding: AstraZeneca, Astellas Pharma, Daiichi Sankyo, Eli Lilly, Boehringer Ingelheim, Puma Biotechnology, Takeda, Revolution Medicines

Patents, Royalties, Other Intellectual Property: Co-inventor on a Dana-Farber Cancer Institute-owned patent on EGFR mutations licensed to Lab Corp and receive postmarketing royalties from this invention

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Patents, Royalties, Other Intellectual Property: Dana-Farber Cancer Institute has a patent pending, titled "Non-invasive blood-based monitoring of genomic alterations in cancer," on which I am a co-author (Inst)

No other potential conflicts of interest were reported.

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APPENDIX

FIG A1. For the majority of cases (87%), the date of order and the date of blood draw were the same, whereas in a minority of cases (12%) the test was ordered in advance, ranging from 1 to 51 days.

FIG A2. For the majority of cases (87%), the date of blood draw and the date of shipment were the same, whereas for 13% of cases blood was shipped 1 to 5 days after being drawn.

FIG A3. Of cases, 75% took 1 day in transit (the date of shipment and the date of receipt). Median time was 1 day between the date of shipment and the date of receipt with the range being 1 to 5 days.

FIG A4. TAT_{C1} (order to result turnaround time [TAT]) was noted to be skewed, with 15 cases (3%) having a TAT_{C1} of more than 21 days, likely because of a planned delay between the order and the blood draw.

FIG A5. Date of blood draw and the date of shipment were often the same, TAT_{C2} (blood draw to result [TAT]) and TAT_{C3} (ship to result) had a similar distribution. TAT, turnaround time.

FIG A6. Time from blood draw to shipment. Over the time studied, it consistently took a median of 0 days from blood draw to specimen shipment, meaning the patients' samples were shipped on the same day.

FIG A7. Time from shipment to receipt of the specimen at the laboratory. In-transit time was consistently a median of 1 day over the period studied.