

Liquid Biopsy-based Precision Therapy in Patients with Advanced Solid Tumors: A Real-world Experience from a Community-based Oncology Practice

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Abstract

Background: Liquid biopsy testing offers a significant potential in selecting signal-matched therapies for advanced solid malignancies. The feasibility of liquid biopsy testing in a community-based oncology practice, and its actual impact on selecting signal-matched therapies, and subsequent survival effects have not previously been reported.

Patients and Methods: A retrospective chart review was conducted on adult patients with advanced solid cancer tested with a liquid-biopsy assay between December 2018 and 2019, in a community oncology practice. The impact of testing on treatment assignment and survival was assessed at 1-year follow-up.

Results: A total of 178 patients underwent testing. A positive test was reported in 140/178 patients (78.7%), of whom 75% had an actionable mutation. The actual overall signal-based matching rate was 17.8%. While 85.7% of patients with no actionable mutation had a signal-based clinical trial opportunity, only 10% were referred to a trial. Survival analysis of lung, breast, and colorectal cancer patients with actionable mutations who received any therapy ($n = 66$) revealed a survival advantage for target-matched ($n = 22$) compared to unmatched therapy ($n = 44$): patients who received matched therapy had significantly longer progression-free survival (PFS) (mPFS: 12 months; 95%CI, 10.6-13.4 vs. 5.0 months; 95%CI, 3.4-6.6; $P = .029$), with a tendency towards longer overall survival (OS) (mOS: 15 months; 95%CI, 13.5-16.5 vs. 13 months; 95%CI: 11.3-14.7; $P = .087$).

Conclusions: Implementation of liquid biopsy testing is feasible in a US community practice and impacts therapeutic choices in patients with advanced malignancies. Receipt of liquid biopsy-generated signal-matched therapies conferred added survival benefits.

Key words: liquid biopsy; precision oncology; neoplasm; survival benefit; biomarkers.

Implications for Practice

NGS-based liquid biopsy-driven targeted therapy is clinically feasible in a community-based oncology practice and allows matching of patients to appropriate target-selected therapy. Upfront testing with liquid biopsy allows early signal-based therapeutic matching, referral to appropriate signal-based clinical trials, and results in superior survival outcomes. The results of this study suggest a potential impact for incorporating liquid biopsy-based testing in current practice guidelines.

Introduction

Precision oncology relies on the identification of molecular abnormalities through molecular profiling of individual patient's tumor, and matching actionable mutations to specific target-based therapeutic agents when available.¹ While gold standard profiling has traditionally been based on resected or biopsied tumor material, recent years have witnessed the development of liquid biopsy (LBx) assays that allow early, timely, and minimally invasive testing for circulating genetic material in the blood including circulating tumor DNA (ctDNA).²⁻⁵

Compared to traditional cancer tissue biopsy, LBx is less invasive and more comprehensive to evaluate tumor heterogeneity because all tumor sites will release ctDNA into the blood.⁶ Facilitated by the rapid development of next-generation sequencing (NGS) technologies, ctDNA sequencing can achieve much higher sensitivity than tissue biopsy and can be used for different applications including early screening and diagnosis, treatment selection, and detection of residual disease and recurrent cancer.⁷⁻¹³

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In terms of enhancing molecular profiling and increasing target-matched therapeutic options, there is an evidence that higher matching results in improved disease control rates, progression-free survival and overall survival rates.¹⁴ LBx is uniquely placed to capture changes in the molecular landscape of a specific patient over time, and thus enhance molecular profiling and subsequently target-to-therapy matching rates. This is due to the capability of LBx to detect tumor heterogeneity within both primary and metastatic tumor sites, the high sensitivity of NGS, and the ease of access for potential serial assessments of a tumour's genomic landscape upon treatment failure.¹⁵

Herein, we report our experience using NGS-based LBx testing in a cohort of 178 patients with diverse, advanced solid tumors treated at a community-based oncology practice. We focus on testing utilization, LBx impact on molecular-based treatment selection, and the subsequent impact on patient's survival when actionable mutations are detected and targeted with precision therapy.

Materials and Methods

Patients

We retrospectively reviewed the clinicopathologic and outcomes data of 178 patients with advanced solid malignancies seen at the Cancer Center of Kansas, for whom molecular testing had been performed using LBx assay between December 2018 and December 2019. Survival analysis at 1-year post-testing was done (censor date: 01/06/2021). This study was performed in accordance with the Kansas University School of Medicine-Wichita Institutional Review Board guidelines.

Next-Generation Sequencing (NGS)-based Liquid Biopsy (LBx)

NGS-based LBx testing was performed by Guardant360[®] (Guardant Health, Redwood City, CA; <http://guardanthealth.com>), a blood-based liquid biopsy assay for comprehensive tumor mutation profiling approved by the US Food and Drug Administration (FDA) for use in all solid cancers. Guardant360[®] detects ct-DNA in blood specimens and evaluates exons from 73 genes, reporting point mutations (as a single-nucleotide variant—SNV), insertion/deletions (indels), copy number amplifications, and fusions/rearrangements. Upfront molecular testing was provided to patients as part of routine clinical care, and whole blood samples were collected, preserved, and sent for testing as per the manufacturer's instructions (<http://guardanthealth.com/Blood-Draw-and-Shipping-Instructions>).

Selection of Therapy

For each patient, potential molecular targets and therapies were reviewed based on the aberration(s) detected by the assay. The distinction was made between actionable mutations (aberrations amenable to targeted therapy with any FDA-approved agent) and non-actionable mutations. A test report with one alteration was considered a "positive" test, while the absence of any alteration was considered as a "negative" test result. Similarly, within the cohort of patients with a positive test result, a further distinction was made between those with non-actionable and those with actionable mutations who could benefit from target-specific FDA-approved agents (either within or outside current FDA indication/

off-label use). The availability of target-based clinical trial opportunities for patients with a positive test but no actionable mutation was also noted.

The choice of a therapeutic option was at the discretion of the treating oncologist, and was reviewed retrospectively: treatment was considered "matched" if the patient received at least one agent targeting at least one aberration, whether using an FDA-approved agent, an off-label agent, or through a signal-based clinical trial opportunity. Patients who received non-targeted therapy when an actionable mutation/signal was available, were considered "unmatched" and the reason for not matching was listed.

In patients who received signal-based targeted therapy, a "matching score" was used (described in¹⁶) whereby for each patient, the number of received matched drugs (numerator) was divided by the number of aberrations reported (denominator). For example, if a patient harboring 6 actionable mutations received 3 targeted therapies, the matching score would be 3/6 or 0.50. A cut-off value of 1.0 on the matching score was chosen for survival analysis according to the minimum *P* value criteria¹⁷.

Outcomes and Statistical Analysis

Endpoints of the study included: (i) LBx testing results including most commonly detected genetic alterations; (ii) matching rates (defined as the ratio between a total number of patients who received signal-based matched therapy, and the number of patients eligible for matched therapy based on LBx results) and determinants of non-matching (when available); (iii) Progression-free survival (PFS) after LBx results in a patient with lung, breast, and colorectal cancer, and (iv) overall survival (OS) after LBx results in patients with lung, breast, and colorectal cancer. PFS was defined as the time from the beginning of initial therapy (post LBx testing) to progression (as determined by treating oncologist and documented in patient's chart) or to last follow-up for patients who were progression-free. OS was defined as the time from the beginning of therapy to death or the time to last follow-up for patients who were alive. The cut-off date for the analysis was January 06, 2021; all patients who were progression-free (for PFS) or alive (for OS) at the date of analysis were censored on that date.

Simple descriptive statistics were used to determine baseline characteristics for patients, LBx testing results, and treatment allocation. Whenever appropriate, Chi-square (χ^2) tests were used to compare categorical variables, and the non-parametric Mann-Whitney *U* test to compare two groups on one continuous variable. PFS and OS were determined by Kaplan-Meier method, and the log-rank test was used to compare variables.

Results

Patient's characteristics and Liquid Biopsy Utilization

A total of 178 patients were referred for testing by 12 oncologists within a single community cancer center. Referral rates varied widely among oncologist (2.25%-22%). The majority of patients (98%) were tested upfront for molecular markers evaluation, in either newly diagnosed advanced cancer patients, or in recurrent patients who did not have enough tissue for testing. Other patients (2%)

were evaluated after the failure of first-line therapy to assess for acquired mutations. The mean age at diagnosis was 65 years. Median (m) Karnofsky Performance Scale was 90% and a majority of patients (89.9%) had ≥stage III-B disease. A total of 18 histological subtypes were tested including cancers of the lung (LCa), breast (BCa), colon (CRCa), kidneys (renal cell carcinoma), skin (melanoma), thyroid, head and neck, ovaries, uterus, smooth muscles (leiomyosarcoma), pancreas, unknown primary, esophagus, gastroesophageal junction, parotid glands, endothelial origins (angio-sarcomas), appendix, prostate, and rectum. LCa (50.56%), BCa (17.42%), and CRCa (7.87%) were the most common cancer types (Fig. 1).

Liquid Biopsy Testing Results and Potential for Matching

A positive test was reported in 140/178 patients (78.7%); of those, 105/140 (75%) had an actionable mutation, either with an FDA-approved target-matched therapy ($n = 32/105$; 30.5%) or with a therapy outside current FDA indication ($n = 73/105$; 69.5%). In patients with no actionable mutation ($n = 35/140$; 25%), 85.7% ($n = 30/35$) had a signal-based trial opportunity (Table 1).

The average number of alterations per LBx test was 3.1 (± 2.14 ; $n = 481$), and varied across subtypes: CRCa (4.36), prostate cancer (2.73), BCa (2.97), and LCa (2.59), had the highest average number of alterations per test. Similarly, LCa (48.44%), BCa (19.13%), and CRCa (12.68%), harbored most of the detected somatic alterations ($n = 481$). Of all the actionable mutations ($n = 457$), *TP53* (32.17%), *PIK3CA* (8.53%), *EGFR* (7.66%), and *KRAS* (7.22%) were the most commonly altered genes (Fig. 1). Supplemental Table S1 provides a listing of all the alterations of practical significance and their respective frequencies.

Impact of Liquid Biopsy Testing Results on Treatment Assignment

Of the 135 patients who were candidates for targeted therapy, 24 (17.8%) were treated with matched therapy based on LBx results, and 111 with an unmatched therapy (82.2%). The actual overall signal-based matching rate (24/135; 17.8%) included all candidates for matched therapy, either through an actionable mutation ($n = 105$) or via a signal-based clinical trial opportunity when an actionable mutation was not detected ($n = 30$) (Table 2). Within candidates for an FDA-approved treatment, 50% (16/32) received targeted therapy while only 6.9% (5/73) were treated with targeted agents outside current FDA indication. For those, the mean matching score (number of matched drugs/number of actionable mutations) was 0.6 (range: 0.33-2) and 0.8 (range: 0.17-2), respectively. Only 10% (3/30) were referred to signal-based clinical trials. Actual target-to-therapy matches are listed in Supplementary Table S2.

Table 1. Summary of liquid biopsy testing results in 178 tested patients with potential signal-based therapeutic opportunities. FDA: Food and Drug Administration

	Positive Test (n/N; %)	Negative Test (n/N; %)
Total tested patients: 178	140/178 (78.7)	38/178 (21.3)
Actionable mutation	105/140 (75.0)	-
<i>FDA-approved</i>	32/105 (30.5)	-
<i>FDA-off label</i>	73/105 (69.5)	-
Non-actionable mutation	35/140 (25.0)	-
<i>Clinical trial opportunity (%)</i>	30/35 (85.7)	-

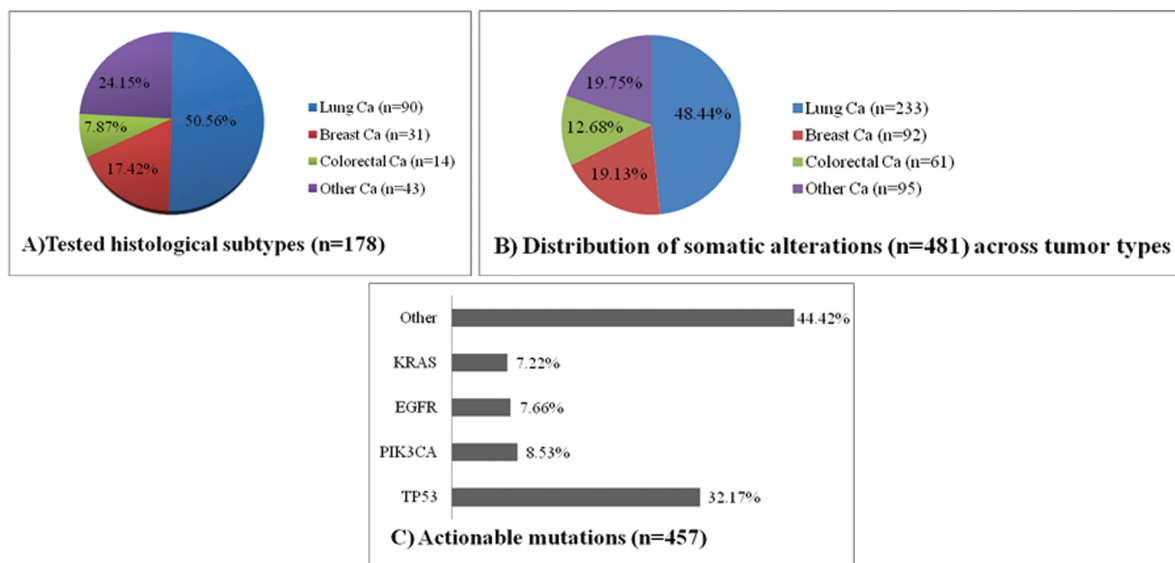


Figure 1. Liquid biopsy results: 18 histological subtypes were tested by LBx assays (A). This revealed a total of 481 somatic alterations across all tested patients (B). Of the overall detected actionable mutations (457), alterations in *TP53*, *PIK3CA*, *EGFR* and *KRAS* genes were the most common (C).

In patients with ≥ 1 actionable mutations who did not receive a signal-matched therapy (111/135; 82.2%), the reasons for not matching included: (i) the availability of a first-line, FDA-approved, non-targeted therapy (72.6% of unmatched cases), (ii) a decline in patient's status and/or death prior to assigning therapy (11.9%), and (iii) failure of targeted therapy to the detected signal in the past (2.4%), and patient's choice for end-of-life hospice/palliative care (2.4%) (Table 2).

Survival Analysis: Liquid Biopsy-based Matched versus Unmatched Therapy

A 1 year survival analysis was done in patients with LCa, BCa, and CRCa ($n = 66$) who received either matched ($n = 22$) or unmatched ($n = 44$) therapy. The main baseline characteristics were compared for matched and unmatched patients (Table 3). Mean age at diagnosis, performance status and stage at testing were similar across both groups. Overall, the cohort had more women (69.7%) than men (30.3%) but no gender difference was seen between matched and unmatched patients (women: 72.7% in matched vs. 68.2% in unmatched; $P = .7$). There was no statistically significant difference in the distribution of histological subtypes between matched and unmatched groups, but more patients with breast cancer (27.3% vs. 15.9%; $P = .27$) and fewer patients with lung (63.6%

vs. 72.7%; $P = .45$) and colorectal (9.1% vs. 11.4%; $P = 1$) cancer were found in the matched group.

The overall median OS for all patients ($n = 66$) was 13 months (95%CI, 11.4-14.6). The mOS was longer in the matched cohort ($n = 22$; mOS: 15 months; 95%CI, 13.5-16.5 vs. 13 months; 95% CI: 11.3-14.7; $n = 44$ in unmatched patients) but did not reach statistical significance ($P = .087$) (Fig. 2A). Median PFS was compared for matched versus unmatched patients (Fig. 2B). Patients who received a matched therapy following LBx testing had a significantly longer mPFS (12 months; 95% CI, 10.6-13.4) compared with patients who did not receive a matched therapy (5.0 months; 95% CI, 3.4-6.6), with $P = .029$.

In patients who received matched therapy ($n = 22$), implementation of the matching score (the higher the score, the better the match), showed no statistically significant difference in survival between patients with a matching score ≤ 1 and those with a score >1 . In terms of OS, patients with a low matching score (≤ 1) had a mOS of 14 months ($n = 19$; 95% CI, 11.11-16.89) compared to a mOS of 16 months in those with a higher matching score ($n = 3$; 95% CI, 12.36-19.64). Similarly, patients with higher matching scores (>1) had longer mPFS (14 months; $n = 19$; 95% CI, 5.51-22.49) than those with lower (≤ 1) matching scores (11 months; $n = 3$; 95% CI, 8.42-13.58). For both OS and PFS, the difference was not statistically significant.

Table 2. Summary of post-testing therapy assignment based on liquid biopsy signal generation

	Matching Rate (n/N; %)	Matching Score (mean; range)	Reasons for not matching signal to therapy when actionable mutation is available (%)
Overall match ^a	24/135 (17.8)	-	- 1st Line, non-targeted therapy available (72.6)
FDA-approved matched therapy	16/32 (50.0)	0.6 (0.33-2.0)	- Declining Status/Death prior to treatment (11.9)
FDA- off label matched therapy	5/73 (6.9)	0.8 (0.17-2.0)	- Prior Failure of targeted Therapy (2.4)
Signal-based clinical trial therapy	3/30 (10.0)	-	- Choice of Palliative Therapy (2.4)
Unmatched	111/135 (82.2)	-	- Unreported (1.2)

^aIncludes candidates with actionable mutation ($n=105$), and without actionable mutation but signal based RCT opportunity ($n=30$). Abbreviation: FDA, Food and Drug Administration.

Table 3. Comparison of baseline variables and survival outcomes for the matched vs. unmatched patients

Parameters	Total (n=66)	Matched (n=22)	Unmatched (n=44)	P
Age at diagnosis (Mean; 95% CI)	65.5 (62-69)	65.6 (59.6-71.6)	65 (60.8-69.2)	0.11
Gender, n (%)				0.7
Women	46 (69.7)	16 (72.7)	30 (68.2)	
Men	20 (30.3)	6 (27.3)	14 (31.8)	
KPS (%) at testing (Mean; 95% CI)	83.9 (81.5-86.3)	84 (79.9-88.1)	84.1 (81.2-87)	0.46
Tumor Type (n;%)				
Lung Cancer	46 (69.7)	14 (63.6)	32 (72.7)	0.45
Breast Cancer	13 (19.7)	6 (27.3)	7 (15.9)	0.27
Colorectal Cancer	7 (10.6)	2 (9.1)	5 (11.4)	1
Stage at testing (% \geq III-B)	65 (98.5)	22 (100)	43 (97.7)	1
Survival				
OS (median; 95% CI)	13 (11.4-14.6)	15 (13.5-16.5)	13 (11.3-14.7)	0.087
PFS (median; 95% CI)	10 (8.4-11.6)	12 (10.0-13.4)	5.0 (3.4-6.6)	0.029

Abbreviations: CI, confidence interval; KPS: Karnofsky Performance Scale; OS, overall survival; PFS, progression-free survival.

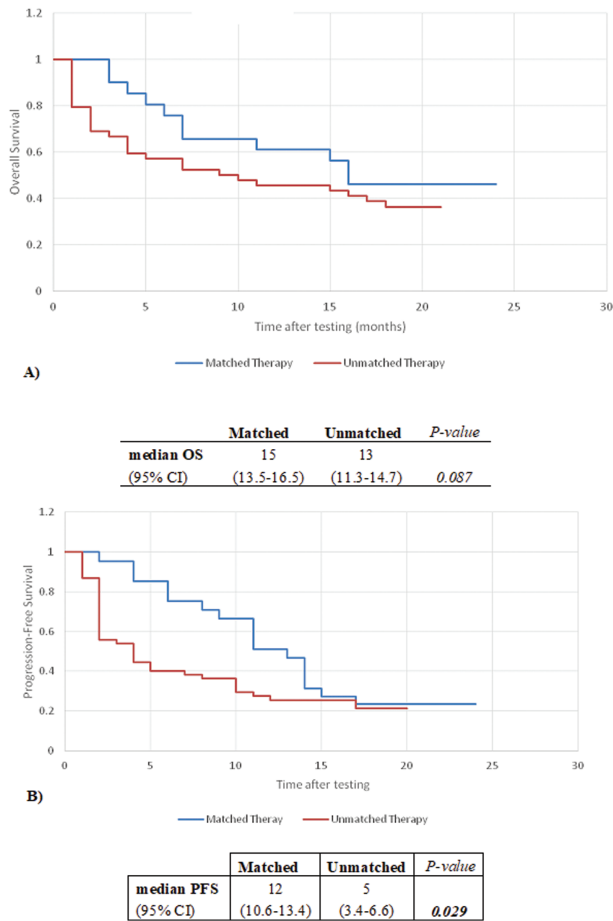


Figure 2. Kaplan-Meier survival curves comparing (A) OS and (B) PFS between matched (blue line) and unmatched (red line) patients following liquid biopsy testing. OS, overall survival; PFS, progression-free survival; CI, confidence interval.

Discussion

The application of precision oncology using biomarker-driven therapeutic agents is a complex process: the success of this targeted approach not only entails a definite “druggable” target with an effective and safe therapy but also depends on the safe, timely, and ease of access to tumor genomic material. Our results demonstrate the successful use of LBx based biomarker-driven therapy in patients with advanced cancer treated in a community-based oncology practice. Patients who were treated with matched therapy based on LBx test results had significantly longer PFS (median, 12.0 vs. 5.0 months; $P = .029$) than unmatched patients. OS was also longer in matched patients (median, 15.0 months vs. 13.0 months; $P = .087$) but the difference was not statistically significant. Several previous studies have demonstrated better survival outcomes when therapy was matched to specific molecular defects. While early studies had focused on specific driver mutations in specific tumor types,¹⁸⁻²¹ the development of multi-gene panel NGS technologies and the fast-paced development of targeted drugs, have allowed genome-wide biomarker identification and targeting across several cancer types.²² In an early multicenter study involving 1007 patients with metastatic lung adenocarcinoma, an oncogenic driver was identified in 64% of patients²¹. Patients with an oncogenic driver

who received genotype-directed therapy had significantly longer survival than those with an oncogenic driver who did not (median 3.5 vs. 2.4 years; $P = .006$).²¹ A study by Von Hoff et al was the first to expand the investigation of responses and outcomes of targeting multiple genes across different cancers. In this study, molecular profiling was used in patients who had progressed on prior lines of non-target matched systemic therapies, and patients were subsequently treated with drugs that matched their molecular aberrations.²³ Results revealed that patients treated according to molecular profiling results had longer PFS compared to their own prior PFS on prior therapy ($PFS_2/PFS_1 \geq 1.3$). Unlike our study, the study did not use NGS. Subsequent studies using comprehensive genomic profiling (CGP) have also demonstrated improved outcomes with the selection of therapy that is matched to patients’ tumor molecular profiles in patients with diverse cancers.^{16,22,24-27} Similar to these studies, our cohort of patients treated with matched therapy had significantly longer PFS. Although OS was also longer in the matched cohort, the difference was not pronounced enough to reach statistical significance and this can be attributed to the small sample size of the cohort (22 patients). Similar observations have been reported in the University of California San Diego PREDICT study,¹⁶ whereby matching patients with agents targeting specific genomic alterations was associated with better PFS but not with improved OS. In this study however, a subgroup analysis based on patients’ matching scores showed that within patients who received matched therapy, those with higher matching scores had significantly longer OS compared to lower scores (median, 15.7 vs. 10.6 months; $P = .04$).¹⁶ In our study, patients who received matched therapy with high matching scores (>1) had longer OS (median; 16.0 vs. 14.0 months) and longer PFS (median, 14 vs. 11 months). However, for both OS and PFS, the difference was not statistically significant, making the observation inconclusive given the small sample size. Yet, despite the small size, our observation echoes prior reports and highlights the potential positive implication of combining matched therapies (as opposed to monotherapy) on survival in patients with multiple target alterations. In fact, other studies have also suggested that treatment with single-agent matched therapy resulted in significantly lower response rates compared to combination therapy.²⁸

Overall, 140 patients (78.7%) had at least one molecular alteration. This detection rate is relatively similar to other studies that used LBx to detect ctDNA. In a recent study by Poh et al, 1338 samples from patients with solid malignancies underwent LBx testing and the detection rate of at least one alteration ranged between 44.2% and 74.6% depending on the tumor type.²⁹ This difference can be attributed to the inclusion of tumor types with lower genetic biomarkers prevalence such as nasopharyngeal cancer or tumors of unknown origin, while in our study lung, breast, and colorectal cancers, with well-characterized biomarkers, were the most common tumor types. Compared to tissue-based genomic profiling, our LBx-based detection rates are relatively lower: in the MD Anderson IMPACT trial, 82% of patients had at least one alteration,²⁴ compared to ~91% in the PREDICT study.¹⁶ In fact, detection rates in tissue-based genomic profiling assays have been reported as high as 95% in patients in whom adequate tissue was analyzed.^{16,21,22,27,30,31} This difference between our LBx assay detection rate and tissue-based assays is possibly attributed to the difference in patients’

populations as well as the size of the gene panels. Our patients' population was tested upfront at diagnosis or at first recurrence while patients in other studies were tested following failure of prior lines of the standard of care therapy. It is thus conceivable that receipt and failure of prior therapies is reflective of more resistance-generating somatic mutations, which eventually reflect in higher detection rates on CGP assays. The LBx assay used in our study evaluates exons from 73 cancer-related genes; this is in comparison to significantly larger gene panels used in the other studies: for example, the PREDICT study¹⁶ used an NGS panel that allowed the capture of exons from up to 236 cancer-related genes, and introns of up to 19 genes commonly rearranged in cancer. Panels of similar sizes were also reported in other studies^{22,25-27} and even larger in the IMPACT trial.²⁴ We thus propose that this difference is less attributed to the detection methods (liquid vs. tissue biopsy) but rather reflective of the patients population and the size of the gene panel used. In fact, LBx as a sampling and detection method potentially allows overcoming challenges associated with tissue-based biopsies such as accessibility to tumor genomic material and tumor heterogeneity, thus resulting in a more comprehensive capture of genomic information.^{32,33}

However, despite differences in crude detection rates seen in our study compared to tissue-based biopsy, 75% of patients with detected mutations had at least one actionable mutation. This is comparable to what was reported in the IMPACT study²⁴ whereby 77.5% of patients had actionable mutations. Similarly, the genomic profile was also comparable to other studies with *TP53*, *PIK3CA*, *EGFR*, and *KRAS* as the most commonly altered genes.^{24,29,34} More importantly, we report a signal-to-therapy matching rate of 17.8%, which is echoed by previously reported matching rates ranging between 17.5% and 27%.^{16,24,35} In terms of utilization of the technology, referral rates varied between the different oncologists, ranging between 2.25% and 22%. Although no direct comparison with referral rates to LBx testing is available in the literature, a national survey of oncologists in the US revealed that 34% of them referred patients with advanced solid tumors for NGS testing to specifically guide treatment decisions.³⁶ Our reported rates are lower and this can be attributed to the fact that current practice guidelines do not observe the use of LBx technology yet which is slowly gaining grounds in the practice of oncology, as more LBx assays are being approved as companion diagnostics in specific tumor subtypes. In our study, the result of testing did affect the treatment assignment whereby 50% of candidates for an FDA-approved targeted therapy received a matched agent, while only 6.9% were treated with targeted agents outside the current FDA indication. This can be explained by the setting of the study (private, community-based practice) that is often dependent on insurance approval to initiate therapy which can be challenging for off-label drug use. Only 10% of patients with non-actionable mutations were referred to signal-based clinical trials. A recent study done in Turkey revealed that results of CGP testing affected the treatment assignment in 48.3% of cases, whereby 42.1% of oncologists referred patients to on-label signal-based targeted treatment, compared to 52.6% of off-label treatment assignments and only 5.3% to signal-based clinical trials.³⁷ A direct comparison to our numbers is challenging given significant differences in healthcare models, practice settings, targeted agents availability, and accessibility to clinical trials.

However, this difference highlights the potential for further improvement in signal-based treatment assignment when an actionable alteration is available, and referral to signal-based trials, when not.

Our study thus establishes the clinical feasibility and usefulness of NGS-based LBx-driven targeted therapy that appears as effective at detecting significant alterations and matching patients to appropriate target-selected therapy, as tissue biopsy albeit in a less invasive and faster manner,³⁸⁻⁴⁰ and as we show in this study, testing results provide clinical benefit. Although our study focused on biomarker detection and selection of molecularly based targeted therapy, the potential clinical applications of LBx testing in oncology are numerous and include screening, the predication of recurrence, and early characterization of emerging resistance mechanisms, as well as longitudinal monitoring of disease progression.^{39,40}

Our study has several limitations. First, it was an observational, retrospective, non-randomized study. Second, the study was not controlled and the selection of therapy was left to the treating physician and the patient, meaning that a direct analysis between specific therapies and outcomes could not be done. However, this also implies a more genuine reflection of the currently ongoing real-world practice as well as the generalizable nature of our observations. Third, although statistical significance was obtained for PFS along with a trend toward significance in OS analysis, the overall sample size is small. This was even more pronounced in subgroup analyses rendering strong conclusions regarding the effect of matching scores, challenging to establish.

Conclusions

Our study demonstrates that LBx-based, biomarker-driven targeted therapy is feasible in a community practice setting and that it is associated with superior outcomes when compared with non-matched therapy in patients with advanced solid tumors. Our study evaluated patients who were tested upfront while prior studies had evaluated heavily pre-treated patients. While this is one of the few studies that specifically focus on LBx-based targeted therapy, large prospective and controlled clinical trials are needed to consolidate our findings. Whether LBx actually improves patients' quality of life, offers early detection of cancer, allows disease monitoring, or offers any cost benefits compared to tissue-based biopsies are all important future avenues for research.

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Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

Conception/Design: K.C., P.S.R. Provision of study material/patients: B.I.M., Q.V.T., T.K., P.V.T., C.D., M.W.C., S.J.P., J.M.D., E.C., D.F.M., N.H.N., S.R.D., P.S.R. Collection and/

or assembly of data: K.C. Data analysis and interpretation: K.C., K.J.K., P.S.R. Manuscript writing: K.C., K.J.K., P.S.R. Final approval of manuscript: All authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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