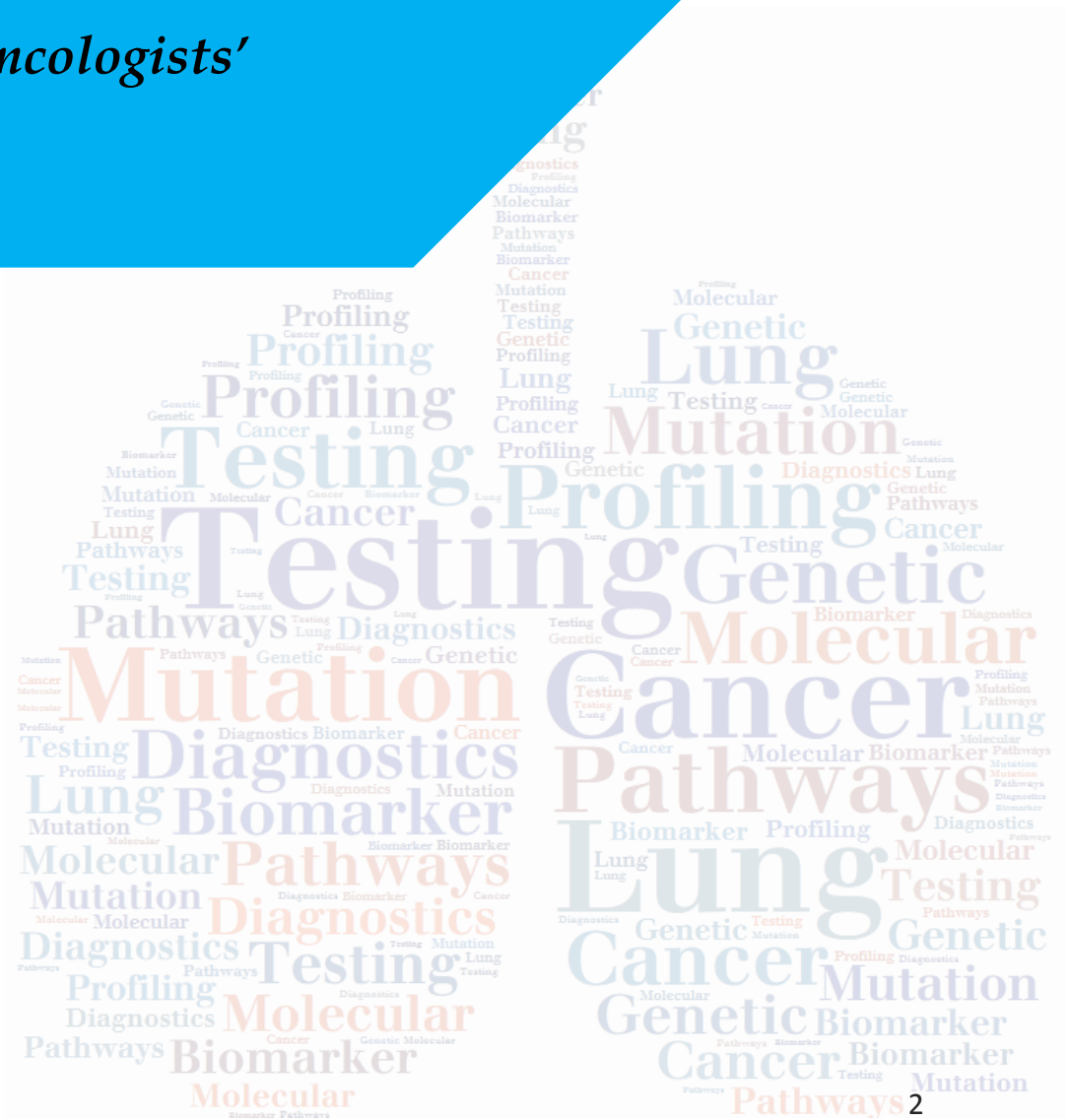
Willingness to perform multiple biopsies to improve quality of lung cancer care:

Understanding the oncologists' perspective



ACKNOWLEDGMENTS

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EXECUTIVE SUMMARY

Background: Biomarker testing of advanced-stage non-small cell lung cancer (NSCLC) at the time of diagnosis is required to determine if a patient will benefit from a targeted therapy or immunotherapy. A patient may, however, need additional biopsies (rebiopsies) if the cancer recurs, to determine the next line of therapy or eligibility for a new drug or participation in a clinical trial. A LUNGevity study, conducted with 340 patients, revealed that patients were willing to undergo rebiopsies if that meant access to additional treatment options at the time of recurrence. However, only 36% of patients reported that their doctors recommended repeat biopsies at progression.

Methods: To understand this patient-physician communications gap, we conducted an IRB-approved semi-structured survey-based study of 130 U.S. oncologists from academic research centers, community cancer centers, and private practice.

Results: Of the 130 oncologists surveyed,

- Ninety percent of oncologists reported recommending a rebiopsy to their patients. However, when stratified by advanced-stage patient volume, oncologists with higher advanced-stage patient volumes reported higher rebiopsy and testing rates than those with lower volumes (95% vs. 78%, $p<0.05$).
- Only 29% of the oncologists prescribed a rebiopsy in the past one year
- Major barriers to rebiopsy reported by oncologists included cost/reimbursement of a rebiopsy and treatment delay for 2nd- or subsequent lines of therapy
- Among the types of biomarker testing performed at the time of progression, oncologists were more likely to prescribe testing for biomarkers with approved treatments (driver mutations—94%, PD-L1—85%) than for biomarkers for treatments in clinical development (43%) ($p<0.05$)
- A forward linear regression analysis revealed that positive predictors of rebiopsy included treatment at an NCI Designated Cancer Center, while treatment at a community cancer center or private practice, presence of driver mutations at the time of diagnosis, and performance status of patient were negative predictors of rebiopsy
- When presented with specific treatment scenarios for biomarkers (EGFR and ALK) that have 2nd-line treatment options, oncologists differed in their approach, suggesting a need for oncologist education about rebiopsying and subsequent biomarker testing

Conclusions: Our study demonstrates that rebiopsy practices vary by practice settings and volume of advanced-stage lung cancer patients. Even when rebiopsies are prescribed, a comprehensive biomarker profile of the tumor may not be obtained, due to variations in tests requested. A major implication is the need for appropriate education for oncologists to ensure practice change for delivery of optimal care to lung cancer patients.

INTRODUCTION

Lung cancer is one of the most common malignancies in the United States and globally.[1] The American Cancer Society estimates that there will be 234,030 news cases of lung cancer in the US in 2018.[2] Globally more than two million people will be diagnosed with lung cancer in 2018.[3] Non-small cell lung cancer (NSCLC) is the more common type of lung cancer, diagnosed in about 85 percent of people with lung cancer.[2,4,5] The other type of lung cancer is small cell lung cancer (SCLC). NSCLC is further subdivided into adenocarcinoma, squamous cell lung cancer, and large cell lung cancer.

The complex and heterogeneous nature of lung cancer requires personalized management plans for patients.[5] Since the discovery of the first epidermal growth factor receptor (EGFR) mutation in lung cancer in 2004, targeted therapies have become a major component of the treatment arsenal of NSCLC patients.[6-10] Now, at least 10 driver mutations in adenocarcinoma have been identified (EGFR, ALK, ROS, RET, ERB2/HER2 mutations, ERB2/HER2 amplifications, MET amplifications, MET mutations, NTRK, BRAFV600E, and KRAS).[9-12] In concert with the identification of an increasing number of targetable mutations is the development of novel, potent, and specifically targeted therapies. For example, at present, 3rd-generation EGFR [13] tyrosine kinase inhibitors (TKIs) and anaplastic lymphoma kinase (ALK) TKIs[14] are used in clinical practice for the treatment of advanced-stage adenocarcinoma patients. In addition, targeted agents for two additional mutations (ROS1 and BRAF) and biomarker-driven immunotherapies such as Keytruda (pembrolizumab) are currently approved for use in the 1st-line setting.[9] With the increased use of targeted agents has come the problem of acquired resistance, where cancer cells inevitably develop resistance to the targeted agent. The EGFR T790M is an excellent example of a resistance mutation that develops in patients treated with 1st- and 2nd-generation EGFR TKIs. The problem of acquired resistance is also being observed for immune checkpoint inhibitors.[15] Lung cancer is now leading the field of precision medicine where research is rapidly progressing to develop (1) better targeted therapies that combat mechanisms of resistance and (2) new biomarker-driven therapies for actionable mutations and immunotherapy biomarkers.[9,16]

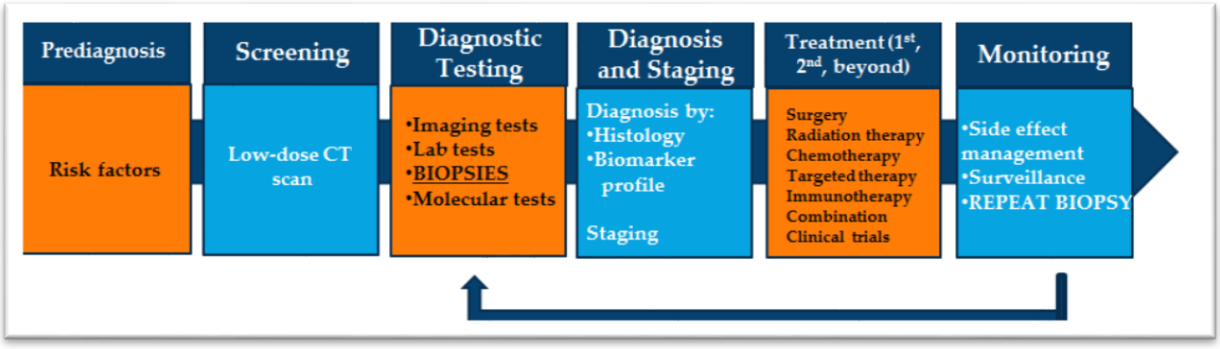


Figure 1: Journey of a typical lung cancer patient, at diagnosis and at recurrence or progression. The arrow at the bottom indicates rebiopsy and treatment decision-making at recurrence or progression

Typically, patients suspected with lung cancer undergo a sequence of diagnostic testing, such as a chest computed tomography (CT) scan, followed by a biopsy of the lesion. This biopsy is known as the **diagnostic** biopsy and is necessary for the histological typing of the cancer (NSCLC or SCLC).[17] Based on the location of the tumor, the biopsy is conducted either through bronchoscopy (for central and endoscopically visible lesions) or through percutaneous means, such as transbronchial needle aspiration (for peripheral lesions).[18] Other imaging modalities such as total body CT scan and position emission tomography (PET) scans inform whether the patient requires additional biopsies, such as sampling of the surrounding lymph nodes. This additional biopsy, also referred to as the **staging** biopsy, is required for the accurate staging of the disease, as lung cancer stage informs treatment decision and prognosis.[17] Typically, tumor tissue obtained during a **diagnostics** biopsy of advanced-stage NSCLC patients is tested for the presence of biomarkers at the time of diagnosis, which in turn, determines 1st-line treatment option for advanced-stage NSCLC patients. The National Comprehensive Cancer Network (NCCN) and the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association of Molecular Pathologists (AMP) recommend broad biomarker profiling for advanced-stage NSCLC patient using a multi-analyte approach such as next-generation sequencing (NGS).[19-22] This is independent of the clinical characteristics of the patient. Patients whose tumors have either a targetable mutation or a specific immunotherapy biomarker are prescribed the appropriate biomarker-driven therapy.

Following the prescription of a biomarker-driven therapy, if the cancer progresses or recurs after 6 to 12 months (or later) after treatment commencement, a **progression/recurrence biopsy** (also referred to as a **repeat biopsy** or **rebiopsy** in this white paper) is advised for the following reasons:

1. ***Determine the 2nd- and subsequent-line treatment options***: This is especially true for patients who have been treated with 1st- or 2nd-generation EGFR tyrosine kinase inhibitors (TKIs) and develop the T790M mutation[23,24]
2. Identify actionable mutations that have corresponding drugs in clinical trials.[18] In fact, several clinical trials have mandatory repeat biopsy requirements
3. Catalog mechanisms of acquired resistance to better understand the evolution of the tumor during the course of 1st-line treatment[16-18]
4. Characterize rare changes of histology from NSCLC to SCLC, in EGFR-positive lung cancer treated with 1st- and 2nd-generation EGFR TKIs[25]

Currently, biomarker testing at progression or recurrence is required for the following U.S. Food and Drug Administration (FDA)-approved therapies.

Drug [26-30]	Associated biomarker	Subtype of NSCLC
Tagrisso (osimertinib)	EGFR T790M mutation	Adenocarcinoma
Alunbrig (brigatinib)	ALK rearrangements	Adenocarcinoma
Lorbrena (lorlatinib)	ALK rearrangements and ROS1 fusions	Adenocarcinoma
Vitrakvi (larotectinib)	NTRK gene fusions	Adenocarcinoma
Keytruda (pembrolizumab)	PD-L1 protein	Adenocarcinoma and Squamous Cell Lung Cancer

Anecdotal evidence suggests that clinicians do not always recommend a rebiopsy at progression or recurrence, because they believe that patients will not want to undergo a biopsy procedure again. However, in a study conducted by LUNGevity Foundation in 2016, three-quarters of the lung cancer patients surveyed indicated their willingness to have an additional biopsy regardless of whether they reported any pain or complications from their initial biopsy—especially if a rebiopsy meant being matched to a new treatment option at a new decision point in their lung cancer journey.[31] The patient-facing research indicated there might be a mismatch in communications between patients and physicians. In order to understand the perspective of lung cancer oncologists on prescribing rebiopsy for their patients, LUNGevity surveyed oncologists from different practice settings. Specifically, LUNGevity was interested in documenting:

1. Whether oncologists were prescribing rebiopsies to advanced-stage lung cancer patients
2. Patient-specific factors that influence rebiopsy practices
3. How oncologists are using rebiopies to determine treatment in the 2nd- and subsequent-line setting for EGFR- and ALK-positive adenocarcinoma patients for whom a clear 2nd-line treatment option exists

APPROACH

LUNGevity, in collaboration with EdgeResearch, surveyed 130 oncologists from five different practice settings: NCI Designated Cancer Center (N = 15), Community Cancer Center (N = 22), Academic/ Research Hospital (N = 39), Non-Academic/Non-Research Hospital (N = 5), and private practice (N = 67). Basic demographic characteristics of the oncologists are described in **Appendix A.** These five practice settings were selected to understand how they each influence an oncologist's knowledge, attitude, and practice of rebiopsies. The recruitment and surveying were completed by EdgeResearch through an online platform. The study was IRB-approved by Advarra (previously known as Schulman) IRB (Protocol # 201706543).

MAJOR FINDINGS

Lung cancer patient characteristics and biomarker testing before 1st-line treatment

Characteristics of patient volume and characteristics of the practice setting of the surveyed oncologists are described in the following table. On average, oncologists prescribe biomarker testing to 72% of their advanced-stage lung cancer patients before commencing 1st-line treatment. As expected, a lower percentage (only 50%) of oncologists prescribe biomarker testing for advanced-stage (extensive-stage) SCLC, given that SCLC does not have any biomarker-driven FDA-approved drugs in the 1st-line setting. Of note is the fact that the volume of advanced-stage lung cancer patients seen in a specific setting is a determinant of 1st-line biomarker testing: **only 63% of oncologists who saw a low volume of advanced-stage lung cancer patients (50% or less of annual patient volume) prescribe biomarker testing, as against 77% of oncologists with a high advanced-stage lung cancer patient volume (76%-100% of annual patient volume)** ($p < 0.05$ by t-test). Variations (by practice setting) in biomarker testing in the 1st-line setting are highlighted in the following table.

		Private practice	NCI Designated Cancer Center	Community Cancer Center	Academic/ Research Hospital	Non-Academic/ Non-Research Hospital
Annual volume of lung cancer patients	1-5	-	13%	-	13%	-
	6-10	3%	-	-	8%	-
	11-20	3%	-	-	15%	20%
	21-49	25%	20%	27%	23%	20%
	50-99	33%	13%	50%	13%	20%
	100 or more	36%	53%	23%	28%	40%
Percentage of oncologists who treated specific histology of lung cancer commonly seen in practice	Adenocarcinoma	100%	93%	100%	95%	100%
	Squamous cell lung cancer	100%	100%	95%	92%	80%
	Large cell lung cancer	88%	93%	95%	79%	80%
	Small cell lung cancer (SCLC)	99%	87%	95%	90%	80%
	Carcinoid or neuroendocrine tumor	82%	73%	82%	74%	40%
	Other, please specify:	-	7%	-	-	-
Percentage of advanced-stage lung cancer seen in practice	<25%	3%	7%	5%	10%	40%
	25%- 49%	13%	7%	23%	21%	20%
	50%- 74%	39%	40%	23%	33%	40%
	75%+	45%	47%	50%	36%	-
	Mean	66.97	67.67	64.00	58.54	38.00
	Median	70	70	72	70	25
Percentage of advanced-stage lung cancer patients prescribed biomarker testing (driver mutations and PD-L1) done before 1st-line treatment?	<25%	6%	7%	5%	8%	20%
	25%- 49%	10%	-	14%	13%	-
	50%- 74%	15%	27%	27%	23%	40%
	75%+	69%	67%	55%	56%	40%
	Mean	76.16	75.33	70.45	67.21	54.00
	Median	86	80	78	75	55
Percentage of oncologists	Adenocarcinoma	98%	100%	95%	95%	80%

who report prescribing biomarker testing for specific histology of advanced-stage lung cancer patient	Squamous cell lung cancer	94%	93%	82%	92%	80%
	Small cell lung cancer	48%	50%	45%	57%	40%
Point of first encounter with lung cancer patient	Right at diagnosis	84%	93%	95%	77%	100%
	Before they have begun a treatment	64%	40%	68%	67%	80%
	After they have begun a treatment	37%	20%	50%	59%	80%
	Other point in their treatment journey, please describe:	1%	-	5%	13%	-

Oncologists-reported rebiopsy practices

When asked about rebiopsy practices, 90% (N = 117) of the oncologists reported that they prescribed a rebiopsy for their advanced-stage lung cancer patients at the time of recurrence or progression in the past year (**Figure 2**). As expected, two important determining factors of rebiopsy were: ***volume of lung cancer patients treated annually*** and ***volume of advanced-stage lung cancer patients treated annually***. The 13 oncologists who reported not rebiopsying their patients cited various barriers to not prescribing it (**Appendix B**).

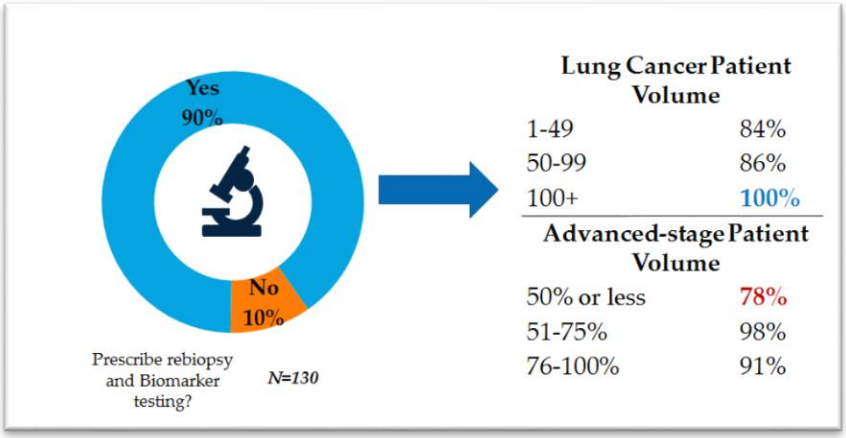


Figure 2: Rebiopsying practices of surveyed oncologists (N = 130). Table on right indicates variation by patient volume and advanced-stage patient volume. Colored values indicate differences.

Of the oncologists who reported prescribing rebiopies, the presence of driver mutations at the time of diagnosis as well as the performance status of the patient were important determinants (**Figure 3**). Interestingly, presence of a KRAS mutation in the tumor at the time of diagnosis wasn't a predictor of rebiopsies. Given that presence of a KRAS mutation predicts sensitivity to EGFR TKIs[32], it would be interesting to evaluate how liquid biopsies are current being used to evaluate KRAS mutation status.

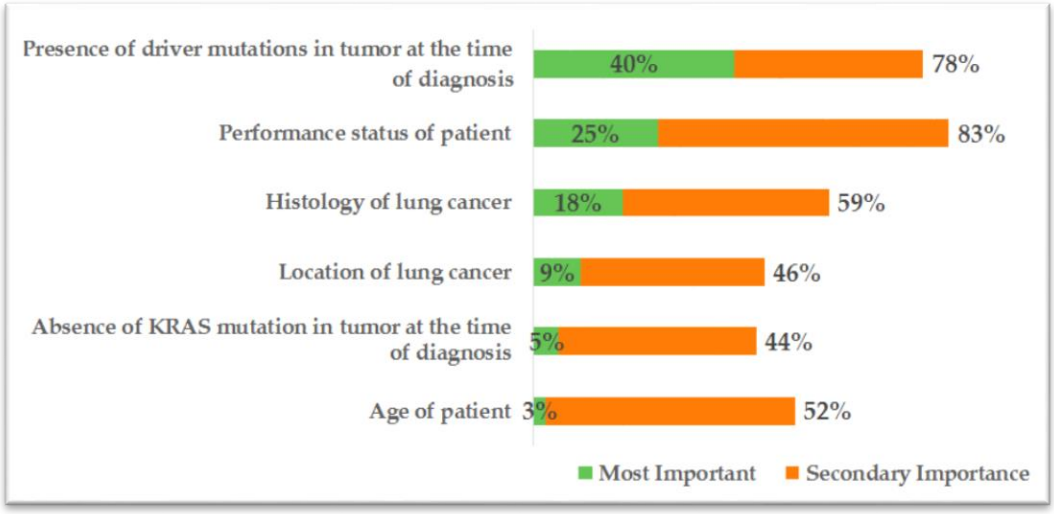


Figure 3: Important factors in prescribing rebiopsies to advanced-stage lung cancer patients, as reported by surveyed oncologists (N = 117)

Notably, when oncologists who reported prescribing rebiopsies (N = 117) were asked specifically about what percentage of advanced-stage patients were prescribed rebiopsies annually, they reported prescribing rebiopsies to only a third of their advanced-stage lung cancer patients, of whom 64% reportedly underwent the rebiopsy procedures (**Figure 4**).

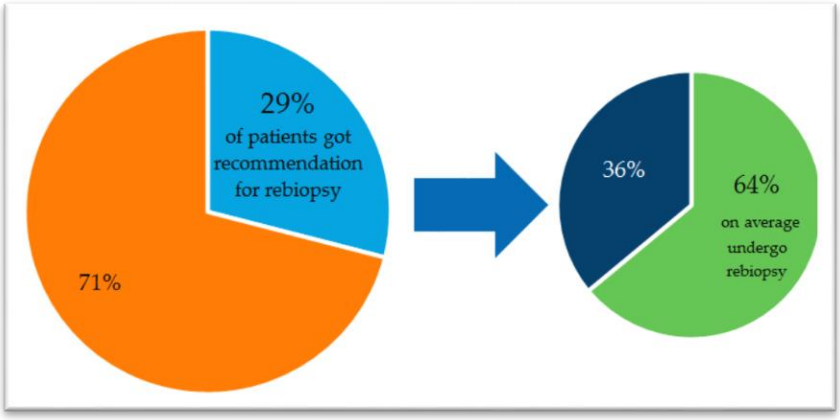


Figure 4: Prescription (left pie chart) and uptake (right pie chart) of rebiopsies to advanced-stage lung cancer patients (N = 117)

This suggests that while oncologists may report prescribing rebiopsies, the actual practice may vary (as indicated by the data presented in Figure 4). Therefore, factors other than lung cancer patient volume and advanced-stage patient volumes contribute to the determination of rebiopsy practices. In order to identify factors that may contribute to variation in rebiopsy practices, we conducted a forward linear regression with **"Percentage of advanced-stage lung cancer patient referred for rebiopsy**" as a dependent variable, with "**Practice Settings**" and "**Patient-Specific Factors**" as independent variables. The following table lists the coefficients of regression. As shown in the table below, both practicing in a ***private setting*** (10 times less likely) or at a ***community cancer center*** (8 times less likely) are negative predictors of rebiopsying amongst oncologists, whereas oncologists practicing in an NCI-designated comprehensive cancer center are 10.5 times more likely to predict rebiopsying to their advanced-stage lung cancer patients. Patient-specific factors such as ***higher age*** and ***higher performance status*** were both negative predictors of rebiopsying.

Practice Setting	**Coefficient of Regression**
Private Practice	-9.909
NCI-designated Comprehensive Cancer Center	10.597
Community cancer Center	-8.421
Patient-specific factors	**Coefficient of Regression**
Higher patient age	-17.738
Higher performance status of patient	-14.672

Rebiopsy practices and clinical decision-making reported by oncologists

Tumor recurrence or progression after treatment is typically determined by chest CT scans. Increased tumor growth is often referred to as radiological progression. When oncololgists were asked **how** they prescribed rebiopsies to their advanced-stage lung cancer patients, there was significant variation in practice (**Figure 5**).

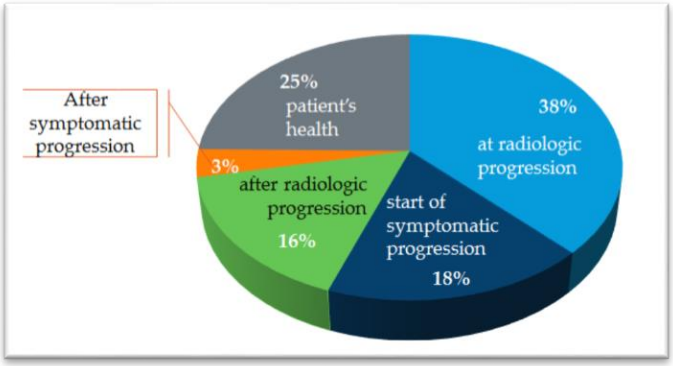
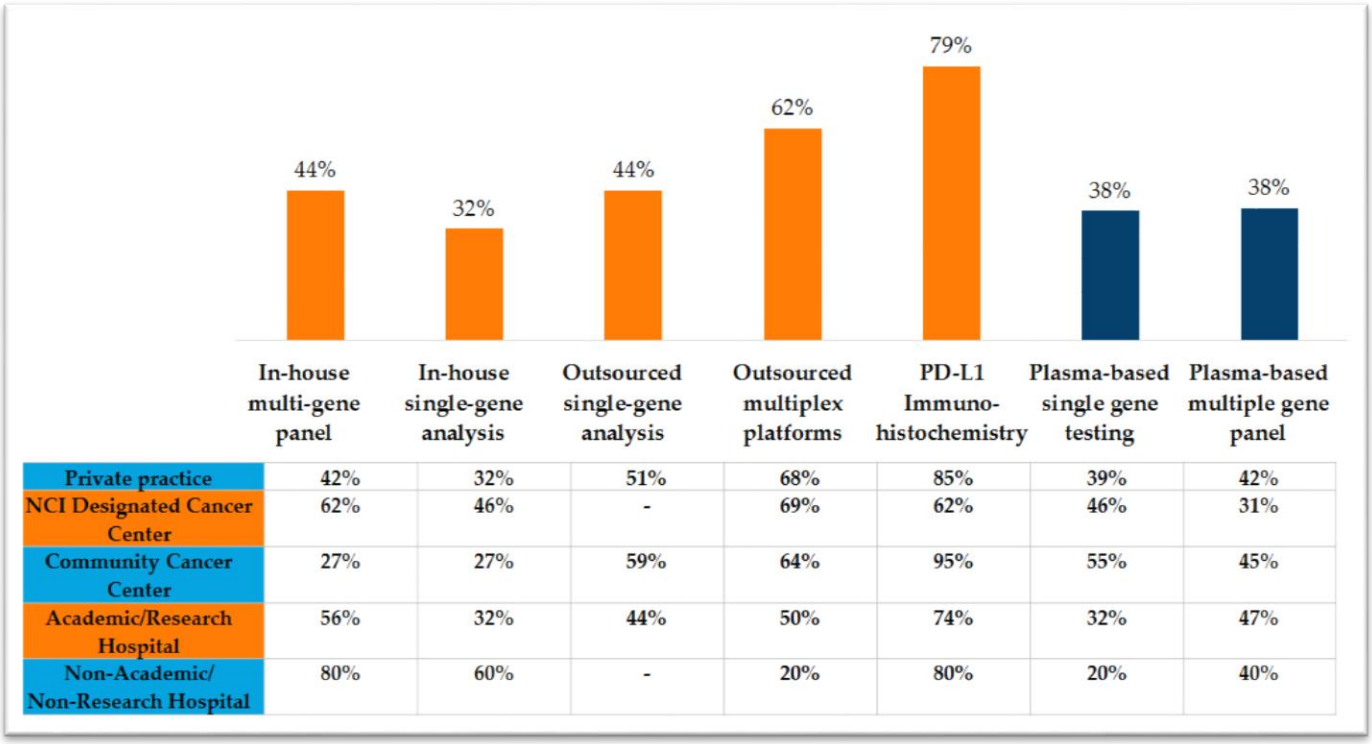


Figure 5: Oncologist-reported practice of how rebiopsying is determined (N = 117)

Fifty-four percent of oncologists prescribed a rebiopsy based on radiologic findings, whereas 21% of oncologists surveyed relied on their patient's symptoms to prescribe a rebiopsy. Of note is the finding that 25% of oncologists used their patient's health status to decide whether a rebiopsy was indicated. This behavior was especially common among those oncologists (37%) who treat a low volume of patients (1-49 patients annually).



	In-house multi-gene panel	In-house single-gene analysis	Outsourced single-gene analysis	Outsourced multiplex platforms	PD-L1 Immuno-histochemistry	Plasma-based single gene testing	Plasma-based multiple gene panel
Private practice	42%	32%	51%	68%	85%	39%	42%
NCI Designated Cancer Center	62%	46%	-	69%	62%	46%	31%
Community Cancer Center	27%	27%	59%	64%	95%	55%	45%
Academic/Research Hospital	56%	32%	44%	50%	74%	32%	47%
Non-Academic/ Non-Research Hospital	80%	60%	-	20%	80%	20%	40%

Figure 6: Oncologist-reported practice of testing platforms used after rebiopsying. Blue bars indicated liquid biopsy-based approaches (N = 117)

When asked about specific platforms or types of tests oncologists prescribe to the pathologists when recommending rebiopsies, 4-in-5 oncologists reported that PD-L1 immunohistochemistry was the most frequently described test. (**Figure 6**). This may be due to the fact that several clinics have in-house immunohistochemistry platforms. Oncologists also reported that they frequently outsourced the testing to multiplex platform companies such as FoundationOne (reported by 3-in-5 oncologists). We also asked oncologists whether they prescribed plasma-based testing. Around 2-in-5 oncologists report use a plasma-based platform for testing at the time of progression or recurrence (either a single-analyte or a multi-gene panel, such as Guardant).

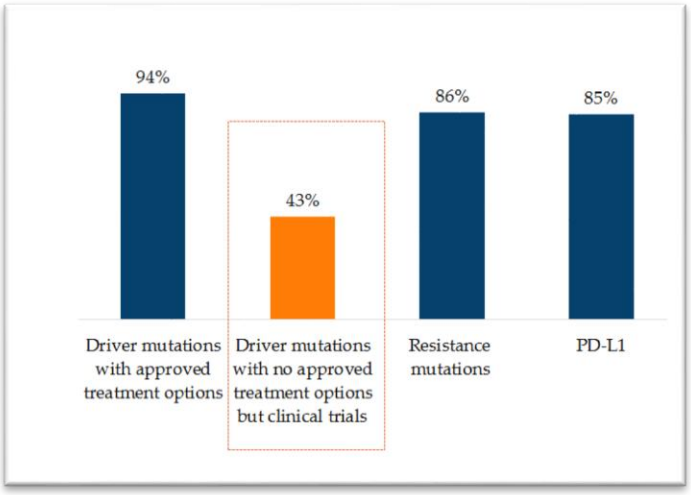


Figure 7: Specific biomarker groups tested at the time of rebiopsying (N = 117)

We also asked oncologists about specific types of biomarkers that were tested for after their patients were rebiopsied (**Figure 7**). Almost all oncologists (94%) reported testing for driver mutations with FDA-approved 2nd- and subsequent-line treatment options; this was, followed by testing for mutations associated with acquired resistance (86%) and PD-L1 (85%). However, only 43% of the oncologists surveyed reported testing for mutations that had associated drugs in clinical development. This is a point of education for oncologists, as both the NCCN and the American Society of Clinical Oncology (ASCO) recommend clinical trials as a part of routine care for advanced-stage lung cancer patients.[22,33] Clinical trials for biomarker-driven agents have mandatory rebiopsy and testing requirements.

To understand how oncologists are using information from rebiopsies to inform treatment decisions for their patients, we specifically asked them how rebiopsy testing was used to decide 2nd- and subsequent-line treatment options for EGFR- and ALK-positive advanced-stage NSCLC patients (Figure 8). These two scenarios were selected for the following reasons:

1) Both the NCCN and CAP/AMP/IASLC guidelines recommend a plasma-based testing for patients who had been on 1st- or 2nd-generation EGFR TKIs to determine whether patients have developed the T790M mutations. The guidelines further recommend a tissue-based rebiopsy only if the plasma test is negative.[19-22]
2) For ALK-positive lung cancer, there is no clear consensus on how to determine the appropriate line of treatment in the 2nd- and subsequent-line setting, because of the fact that mechanisms of resistance to ALK inhibitors are highly variable.[34]

Therefore, the two situations provide a clear understanding of how oncologists are using rebiopsies to guide treatment decisions.

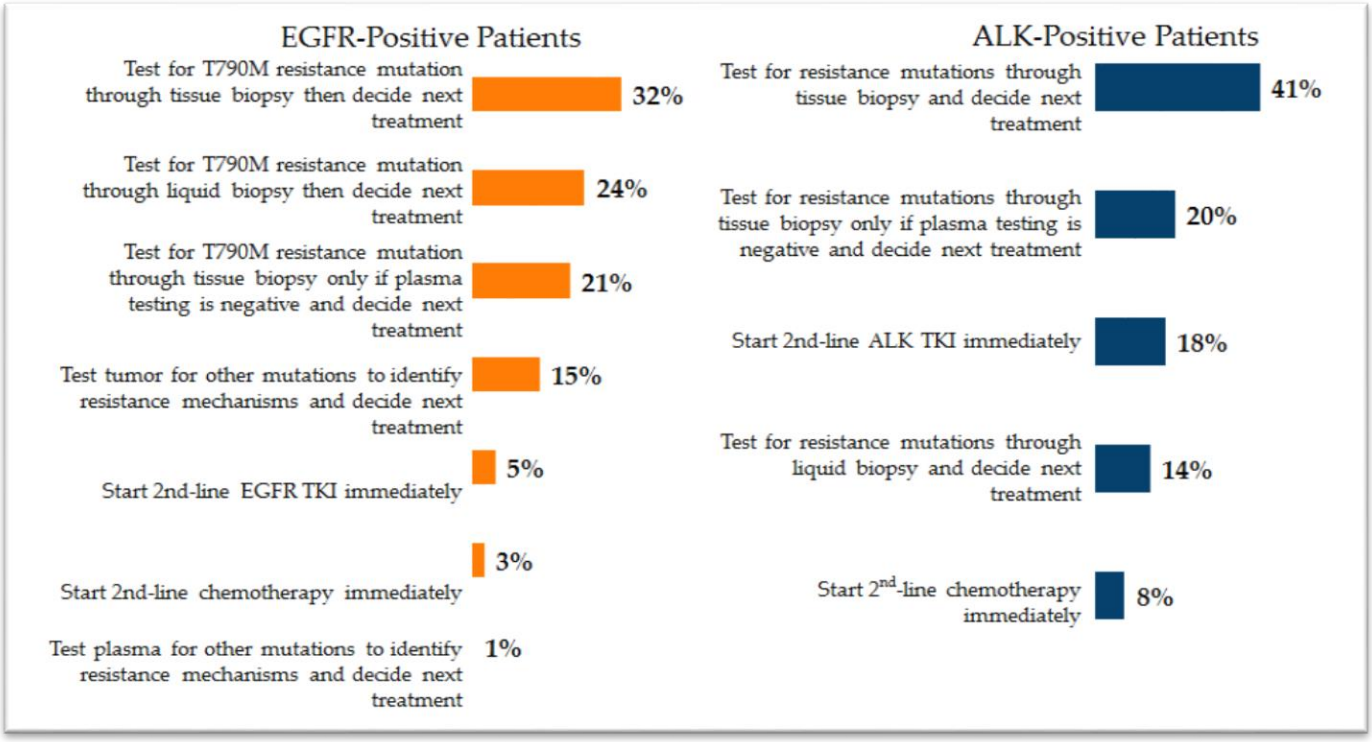


Figure 8: Use of rebiopsies for 2nd- and subsequent-line treatment decision-making in EGFR- and ALK-positive advanced-stage NSCLC (N = 117)

As seen in **Figure 8**, there is considerable variation in how oncologists approach 2nd-line treatment decision-making, especially for EGFR-positive lung cancer. Only 45% of the oncologists surveyed reported using a guidelines-consistent approach in treatment decision-making: testing for T790M mutation using a plasma test. As expected, there is no clear consensus on how oncologists use rebiopsies to determine the next course of treatment for ALK-positive lung cancer.

Importance of patient communication in decision-making about rebiopsies

In the patient-facing survey conducted by LUNGevity, almost all of the patients surveyed (82%) would undergo rebiopsies if it would help their health care team better match treatment to their specific cancer and personalize their care, versus just being told the test was to look for mutations. In other words, understanding the end benefit of having the test is an important piece of communication. Furthermore, if the doctor were to recommend an additional biopsy or a biopsy after the start of treatment, nearly half would definitely undergo one. About two-thirds of those surveyed felt that their doctor explained the reason for getting their initial biopsy really well. Both these findings highlight that patients value their doctor's opinion and rely on being educated by them.

We therefore sought to understand whether doctors are explaining the importance of rebiopsies to their patients. Of the 130 oncologists surveyed, 76% reported always explaining the reasons behind a rebiopsy procedure to their patients. Importantly, almost 80% of the oncologists reported that their patients were willing to undergo the procedure, when the importance of rebiopsies was explained to them. These findings reiterate the importance of patient-physician communication in treatment decision-making.

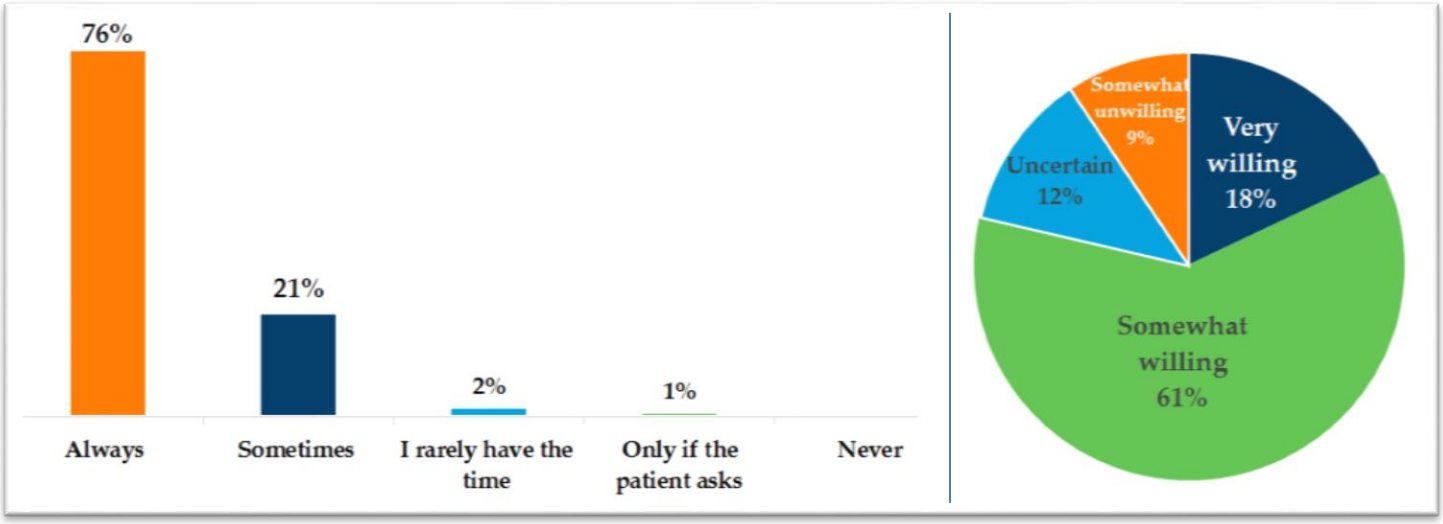


Figure 9: Oncologist-reported frequency of patient communication before rebiopsy procedures (left bar graph) and patient willingness to under rebiopsy procedure (right pie chart) (N = 117)

We also asked oncologists how they were explaining the importance of rebiopsies to their patients (**Figure 10**). Oncologists are more likely to position the need for rebiopsy as a way to provide more personalized or targeted treatment.

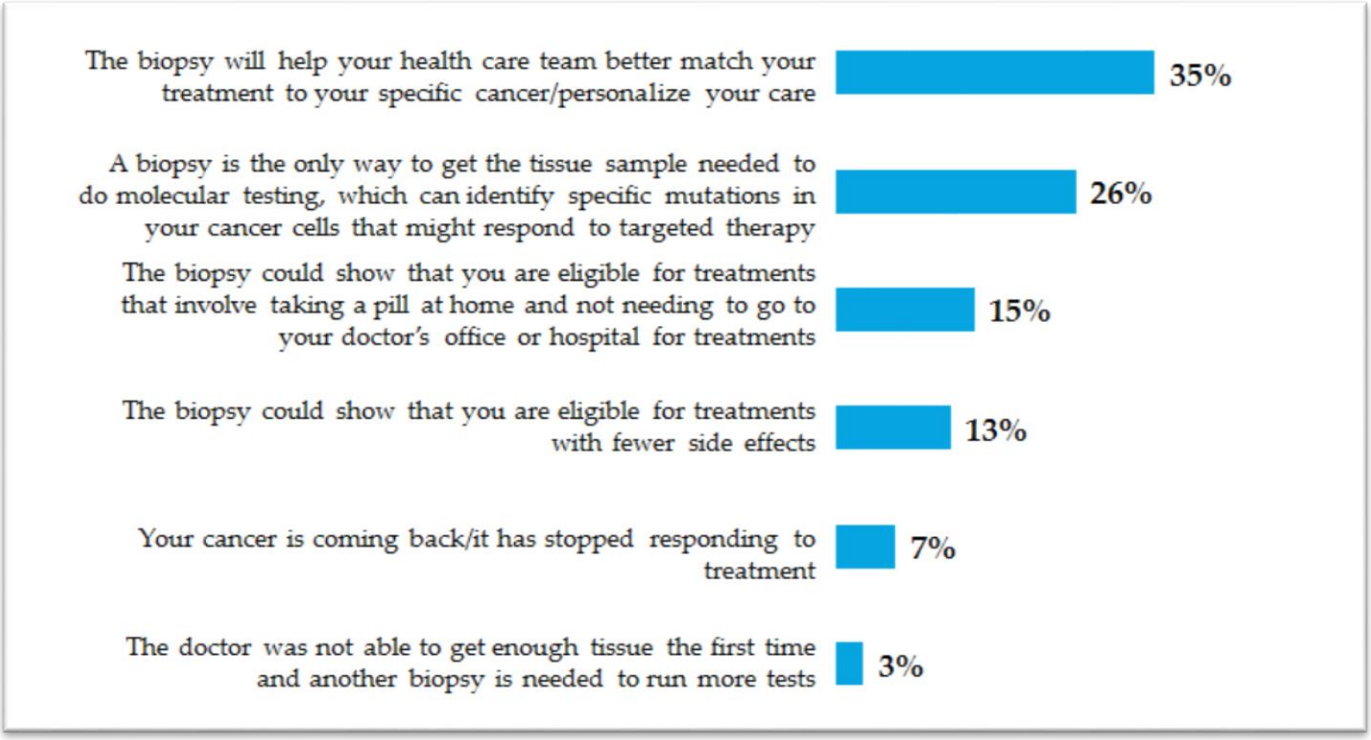


Figure 10: Top explanations cited by oncologists in patient-physician communication on the importance of rebiopsies (N = 117)

CONCLUSIONS AND IMPLICATIONS

Our study demonstrates that there is significant variation in rebiopsy practices among oncologists in the U.S.. While most oncologists report prescribing rebiopsies to their advanced-stage patients, practice setting (practicing in an NCI-designated comprehensive cancer center, community cancer center, and private practice) influences the actual rebiopsy behavior. This finding highlights the need for targeted oncologist education and tumor boards in different clinical settings. The education should not only include the importance of rebiopsies in clinical decision-making, but also about types of biomarkers that need to be tested. We found that only 43% of oncologists surveyed prescribed the testing of biomarkers for therapies in clinical development, suggesting that advanced-stage patients who have relapsed or exhausted existing treatment options may not be eligible for clinical trials that have mandatory biomarker-testing requirements at progression.

Our study relies on self-reported rebiopsy practices of oncologists. It is important to point out that the Patient Attitudes towards Rebiopsy study found that only 36% of the patients were recommended a rebiopsy by their physicians.[31]. Nine-in-ten oncologists participating in this study reported prescribing a rebiopsy. This discrepancy may be due to the fact that that the area of tissue rebiopsies and reliance on blood-based liquid biopsies as an alternative (discussed below) remains an area of scientific investigation. Several experts suggest that blood-based biopsies may provide a better snapshot of tumor heterogeneity; therefore, individual preferences of oncologists may vary significantly.[35]

Whether a rebiopsy is useful for deciding treatment strategy for a lung cancer is contingent on several factors. The lung is a vital organ, and biopsy of the lung is associated with potential complications such as pneumothorax, hemoptysis, air embolism, seeding of the biopsy tract, and death.[36] Furthermore, the patient's health status or lung function may not allow for additional biopsies. In a study by Yoon et al that documented rebiopsy procedures in lung cancer patients who had relapsed after chemotherapy, the authors reported a 100% success rate in patients who underwent the rebiopsy procedure. The authors noted that patient selection was based on imaged-guide location of tumors and also reported that size of the lesion (>5 mm had higher success rate) was a determinant of rebiopsy success.[37] It is also necessary to point out that lesions other than lung lesions, such as those in the adrenal gland and liver, may also be rebiopsied at the time of progression, in patients who present with metastatic disease.[38]

In summary, a rebiopsy is often necessary to decide the best course of treatment for an advanced-stage lung cancer patient. The decision to undergo one should be made jointly by the patient and the oncologist, and take into account factors such as patient health, tumor location, and availability of other options for gaining information on the patient's tumor.

LIMITATIONS OF THE CURRENT STUDY

We noted the following limitations of the study:

1) **Sample size and demographics of study population**: The sample size of the study (N = 130) may not represent the perspective of thoracic and general oncologists in the United States. We also note that our study over-sampled oncologists engaged in private practice, suggesting a bias from this group of oncologists. It is necessary to note that our study sampled 15 oncologists from the 49 NCI-designated comprehensive cancer centers.

2) **Evolution of clinical care paradigms for advanced-stage lung cancer**: The Patient Attitudes towards Rebiopsy study was conducted in 2015 and 2016.[31] Since the conclusion of the study, liquid biopsies have become more mainstream in the clinical care of lung cancer patients. [39,40]. Therefore, the role and need for tissue-based rebiopsies needs to be re-evaluated constantly and on a patient case-by-case basis. Though our survey was not intended to capture information on how clinical care is changing with progress in liquid biopsy technologies, we cannot exclude the possibility that the respondents of the survey may, in fact, be using both tissue-based and liquid biopsies at progression or recurrence.

Despite these limitations, our study uncovers existing gaps in oncologists' knowledge, attitude, and practice of rebiopsies in the treatment of advanced-stage lung cancer patients and opportunities for physician training and education.

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APPENDIX A

Variable	Options	Private practice	NCI Designated Cancer Center	Community Cancer Center	Academic/ Research Hospital	Non-Academic/ Non-Research Hospital
Numbers of years in clinical practice (excluding training)	0-5 years	6%	20%	-	21%	-
	6-10 years	21%	27%	27%	36%	20%
	11-20 years	39%	27%	45%	23%	80%
	20+ years	34%	27%	27%	21%	-
Age	Less than 35	1%	20%	5%	26%	-
	35 to 44	25%	40%	23%	41%	80%
	45 to 54	40%	13%	41%	21%	20%
	55 to 64	24%	7%	27%	10%	-
	65 or older	9%	20%	5%	3%	-
Gender	Male	81%	67%	86%	64%	100%
	Female	18%	33%	14%	26%	-
	Other	-	-	-	-	-
	Prefer not to say	1%	-	-	10%	-
Location of practice	Northeast	21%	53%	27%	41%	20%
	Midwest	24%	20%	14%	18%	-
	South	33%	13%	32%	18%	20%
	West	22%	13%	27%	23%	60%

Appendix B

Barriers cited for not prescribing rebiopsies (N is too small to report percentages)

Barrier	Number saying "very" or "somewhat" significant
Risk/Complications of a new tissue biopsy outweigh the benefits	10
Tissue biopsy is offered but patient declines	10
Patients are not likely to want a new tissue biopsy upon progression	10
Cannot allow delay for 2nd-line patients	10
Cost of a new plasma-based liquid biopsy is a barrier to a patient	9
Reimbursement for a new plasma-based liquid biopsy	9
Tissue biopsy procedure is too difficult for patients to endure upon progression	8
Cost of a new tissue biopsy is a barrier to a patient	8
Reimbursement for a new tissue biopsy is a barrier	8
Rebiopsy is not necessary because biomarker testing was already done on the initial biopsy	8
Unsure how to get/order a new tissue biopsy	5
Unsure how to get/order a new plasma-based liquid biopsy	5