FRIENDS of CANCER RESEARCH

A FRIENDS OF CANCER RESEARCH WHITE PAPER

TRENDS IN THE MOLECULAR DIAGNOSIS OF LUNG CANCER

RESULTS FROM AN ONLINE MARKET RESEARCH SURVEY

INTRODUCTION

Beginning in 2015, Friends of Cancer Research (*Friends*) and the Deerfield Institute began a research collaboration to study trends in the use of molecular diagnostics in oncology. The goal of the partnership was to fill knowledge gaps regarding the type of molecular diagnostics that oncology practices in the United States use to guide treatment with targeted therapy. These gaps exist because prevailing data sources, such as claims data, lack the granularity necessary to conduct research into the use of molecular diagnostics. To address these gaps, *Friends* and the Deerfield Institute designed and implemented a direct-to-physician questionnaire and patient chart audit to characterize trends in the use of specific diagnostic tools that are used to deliver personalized cancer care.

The first output of this research collaboration was in 2016, when *Friends* and the Deerfield Institute jointly published a study in the journal *Personalized Medicine in Oncology*.[1] This study addressed a major policy issue, and contributed to the debate over the use of laboratory-developed tests in non-small cell lung cancer (NSCLC). Following publication of the study, *Friends* and the Deerfield Institute participated in a briefing on Capitol Hill to discuss policy implications of the work and educate the public about the US Food and Drug Administration's proposal [2] to extend oversight to laboratory-developed tests.

In this white paper, *Friends* and the Deerfield Institute are releasing additional data captured through the course of their research partnership. The data presented below characterize trends in the collection of tumor tissue to support molecular testing, as well as the impact of the timing of molecular testing on treatment decisions.

THE AUTHORS

Céline M. Audibert
Deerfield Institute

Michael B. Shea
Friends of Cancer Research

Daniel J. Glass
Deerfield Institute

Marina L. Kozak
Friends of Cancer Research

Alexis Cazé
Deerfield Institute

Ryan M. Hohman
Friends of Cancer Research

Jeff D. Allen
Friends of Cancer Research

Ellen V. Sigal
Friends of Cancer Research

Jonathan S. Leff
Deerfield Institute

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ABOUT FRIENDS OF CANCER RESEARCH

Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients.

ABOUT THE DEERFIELD INSTITUTE

The Deerfield Institute is the internal research group at Deerfield Management Company, a healthcare investment firm dedicated to advancing healthcare through investment, information and philanthropy.

BACKGROUND ON MOLECULAR TESTING IN LUNG CANCER

In the last fifteen years, the treatment of lung cancer has been transformed by the identification of genomic alterations that play a role in tumor growth and maintenance. Termed "oncogenic drivers," these alterations produce downstream effects that can be negated by targeted agents. In lung cancer, several drugs have been approved by the US Food and Drug Administration (FDA) that successfully target oncogenic drivers, and which have been shown to significantly improve patient outcomes compared to traditional cytotoxic chemotherapy. In response to this development, clinical guidelines began to strongly recommend molecular testing, a process in which a laboratory test is ordered to identify the presence of oncogenic drivers in tumor cells and thus determine eligibility for targeted therapy.

A range of technologies are employed to perform molecular testing, from sophisticated genomic sequencing platforms to simpler single-marker assays. These tests, broadly referred to as molecular diagnostics, have quickly become an essential component of the treatment of advanced lung cancer. The simpler tests, which identify the presence of a single molecular marker, are often called "companion diagnostics" because they are developed and tested alongside targeted therapies in clinical trials. The more complex tests, which use genomic sequencing technologies to detect alterations in tens to hundreds of genes simultaneously, have been made possible by next-generation sequencing (NGS), a collection of technologies that allow rapid sequencing of large segments of an individual's DNA and even an individual's entire genome.[3] While the use of NGS panels for prescreening patients for biomarker-targeted clinical trials has been well documented,[4] the utility of this technology in direct patient care has not been fully characterized.

Some have argued that, given the expanding number of oncogenic drivers for which testing is recommended, NGS panels represent a more cost-effective and straightforward means of performing molecular testing.[5] However, the ability of the average physician to correctly interpret the results generated from these tests remains a concern.[6] Enhanced communication between oncologists and pathology departments has been encouraged to alleviate these concerns. Single-marker assays, on the other hand, have easily interpretable results, but may exhaust available tumor tissue before a satisfactory number of tests have been performed. Current guidelines accept the use of both methodologies.[7]

Three oncogenic drivers are targets for approved therapies in lung cancer: epidermal growth factor receptor (EGFR) mutations, and anaplastic lymphoma kinase (ALK) and *ROS1* gene rearrangements. *EGFR* mutations were discovered in 2004, followed by *ALK* in 2007 and *ROS1* in 2008. In adenocarcinoma, a major subtype of non-small cell lung cancer where oncogenic drivers have been most successfully targeted, *EGFR* mutations occur in about 10% to 15% of patients, while *ALK* and *ROS1* rearrangements occur in less than 5% of patients. Drugs targeting each of these drivers have been demonstrated to be superior to chemotherapy in head-to-head studies.[8]

In 2016, studies estimated that between 70% and 95% of US oncology practices perform molecular testing in lung cancer, up from an estimated 20% of practices in 2010.[1,9-11] Despite these gains, concerns have been raised that process inefficiencies in clinical practice may be preventing molecular diagnostics from having their greatest possible impact on patient management. One concern is that a slow, disorganized testing process may drive patients to receive chemotherapy before the likelihood of their benefiting from less toxic targeted therapies is known.[12] Another is that shortcomings in the communication between the various specialties involved in the molecular testing process have led to delays and uncoordinated care, especially in the tissue collection process, where lack of sufficient tissue has been cited as an impediment to testing.[13] Strategies for process improvement and physician education have been undertaken to address these concerns.[14]

SURVEY GOALS

To better understand the challenges that practices face in testing patients for oncogenic drivers, as well as the uptake of various testing technologies, a questionnaire was developed to obtain the opinions and experiences of practicing medical oncologists regarding the molecular testing process. Numerous specialties are involved in decisions about when and how to test patients and rarely does a single individual have full knowledge of all the steps in the process. However, as the primary point of contact with the patient, the medical oncologist was identified as the person most likely to provide insight into the entire process, from diagnosis, to testing, to treatment. The setting of non-small cell lung cancer (NSCLC) was identified as an area of focus due to the presence of multiple known oncogenic drivers and approved targeted agents, as well as the existence of several approved molecular diagnostics in that setting.

CHARACTERISTICS OF RESPONDENTS

The final sample included 157 respondents who both met the eligibility criteria and completed the survey (Appendix Table 2, page 18). The clear majority of respondents were medical oncologists (148, 94%), with an additional 6% either nurses or physician assistants. More than half of respondents reported spending most of their time in a private practice (88, 56%), while the remaining were split between community (36, 23%) and academic settings (29, 18%). The region with the largest number of respondents was the southern United States (63, 40%), with an additional 24% (37) from the Northeast and 18% from the Midwest and West, respectively.

CHARACTERISTICS OF TREATED PATIENT POPULATIONS

Respondents reported diagnosing on average 63 patients with NSCLC in the past 12 months, with an average of 53% presenting with stage IV disease (Appendix Table 1, page 17). Among their patients with stage IV disease, respondents reported an average histology breakdown of 62% adenocarcinoma and 29% squamous cell carcinoma.

SURVEY RESULTS

A selection of survey questions is reproduced below.

What proportion of your stage IV NSCLC patients of the following subtypes received a genetic test?

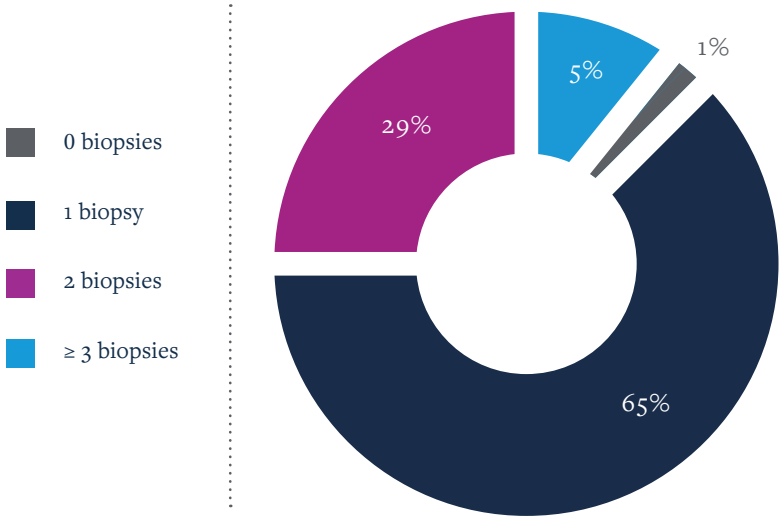
Proportion of Stage IV Patients Who Received Genetic Alteration Tests

		Type of setting				Region			
	Total n=157	Private Clinic n=88	Academic Center n=29	Community Based Center n=36	Other n=4	NE n=37	MW n=29	S n=63	W n=28
Squamous cell carcinoma	24%	20%	25%	29%	3%	28%	15%	25%	23%
Adenocarcinoma	87%	81%	96%	84%	94%	94%	88%	91%	62%
Large cell	68%	77%	71%	50%	70%	74%	44%	71%	78%
NSCLC not otherwise specified (NOS)	75%	75%	87%	43%	94%	85%	85%	67%	59%

The most common types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. Genetic alteration testing is recommended in adenocarcinoma, where *EGFR, ALK*, and *ROS1* alterations are most prevalent. At the time that this survey was implemented, clinical guidelines recommended against testing for squamous cell histologies. Since then, these restrictions have been loosened due to the presence of some positive cases and the possibility of incorrect histological classification.[5] In practice, 87% of stage IV adenocarcinoma patients in our sample received a genetic alteration test, although the testing rate was predictably higher at academic centers.

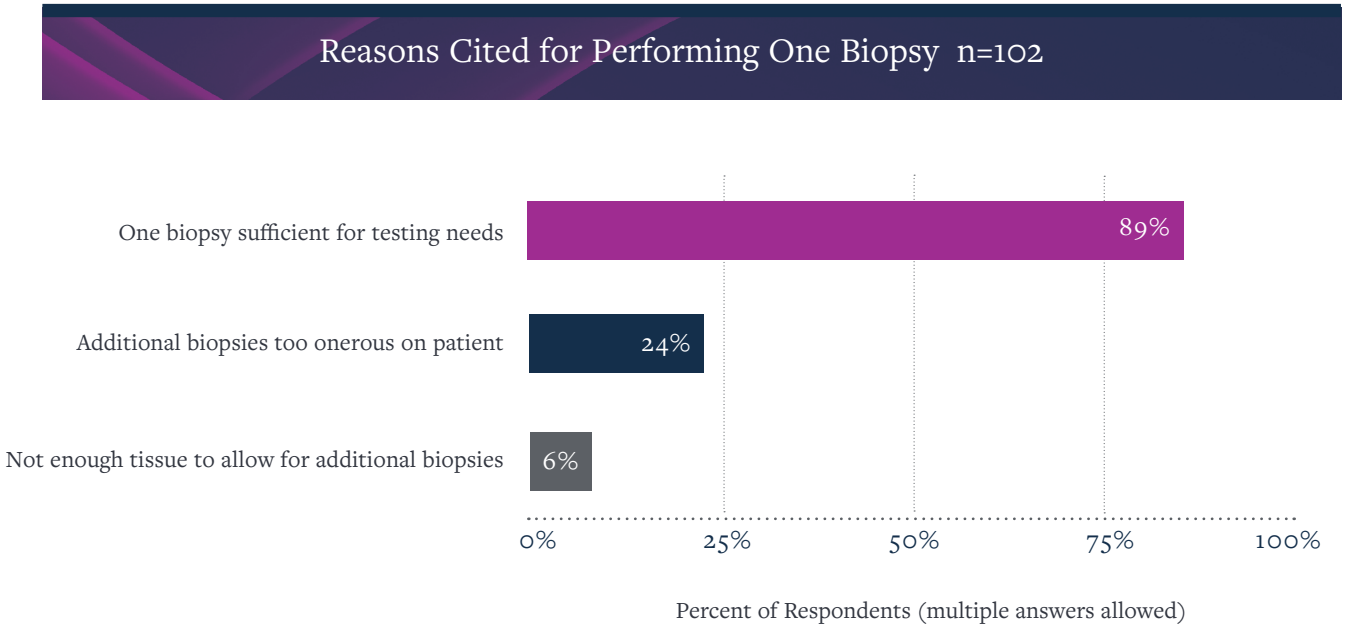
When testing for genetic alterations in NSCLC, how many separate tissue biopsies are typically performed per patient over the course of his/her disease progression?

Number of Separate Tissue Biopsies Performed n=157



As routine molecular testing began to pick up speed following the FDA approval of crizotinib (Xalkori) in 2011 for ALK-positive lung cancer and the narrowing of the approval of erlotinib (Tarceva) in 2013 for EGFR-positive lung cancer from a broader lung cancer indication, many observers pointed to acquisition of adequate tissue samples as a primary barrier to molecular testing. Many patients with lung cancer have small tissue specimens acquired through biopsies. Since some tissue is required initially to determine histology, there is sometimes limited tissue left over for use in molecular testing. There is often the possibility of performing additional biopsies, but these are invasive procedures and can be burdensome on patients. Thus, many observers have called for biopsy techniques that gather enough tissue for multiple purposes.

You mentioned one tissue biopsy is typically performed to support genetic alteration testing in NSCLC. Why is only one tissue biopsy typically needed?



The finding that most respondents in this survey perform only one biopsy coupled with their explanation that one biopsy was sufficient for testing needs can have two possible explanations. First, practices may be relying more heavily on techniques that collect more tissue, such as CT-guided lung biopsies using core biopsy needles, rather than fine-needle aspiration (FNA).[15] Another plausible explanation is that the widespread use of genomic sequencing, shown in the table below, has led to practices requiring less tissue to conduct molecular testing. Genomic sequencing using NGS has been shown to require substantially less tissue than first-generation genomic testing, allowing physicians to test for a range of markers using a small amount of tissue.[5]

What type of test is used when looking for genetic alterations?

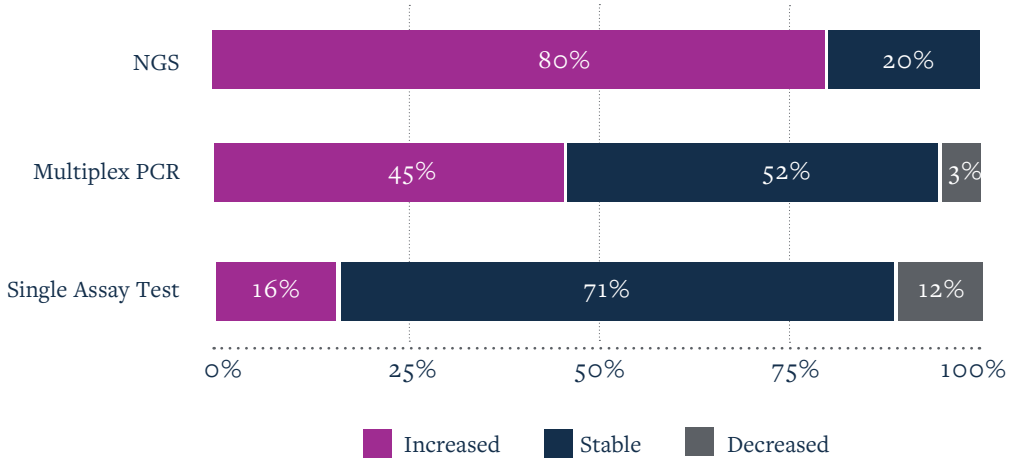
Type of Test Used Across Practice Setting and Region

		Type of setting				Region			
	Total n=157	Private Clinic n=88	Academic Center n=29	Community Based Center n=36	Other n=4	NE n=37	MW n=29	S n=63	W n=28
Single assay test	58%	52%	52%	78%	50%	57%	52%	59%	64%
Multiplex PCR	18%	17%	24%	17%	25%	11%	10%	17%	39%
Multi-gene panel sequencing	36%	33%	59%	28%	0%	32%	34%	32%	50%
Unsure / Info not available	21%	26%	10%	14%	50%	27%	17%	24%	11%

Single assay tests were used by 58% of respondents, with the remainder split between multi-gene panels using Next-Generation Sequencing (NGS) (36%) and multiplex PCR (18%). The use of NGS differed across practice settings, indicating a meaningful relationship between multi-gene panels using NGS use and practice setting (59% academic, 33% private, 28% community; p=.02). No similar relationship was observed between use of NGS across geographic region or hospital ownership category (p=.37, p=.53, respectively).

How has the utilization of the following test formats changed in the past year, if at all?

Changes in the utilization of the various test formats in the past year



Among the 56 respondents who reported using NGS-based panels to test patients for lung cancer mutations, 80% reported that the rate of test utilization increased in their practice during the past year. Among the 91 respondents who reported using single assay tests, 71% reported that usage of this testing technique was stable in the past year, suggesting that most practices are still heavily relying on single assay tests. Another popular category of tests called multiplex polymerase chain reaction (PCR) uses a methodology that can simultaneously determine the mutational status of a handful of genes using small tumor samples. Rather than identifying new or additional drug targets, multiplex PCR allows physicians to efficiently test for a series of known, or actionable targets.[3] Nearly half of the 29 respondents who reported using this type of test reported that usage has increased in the past year.

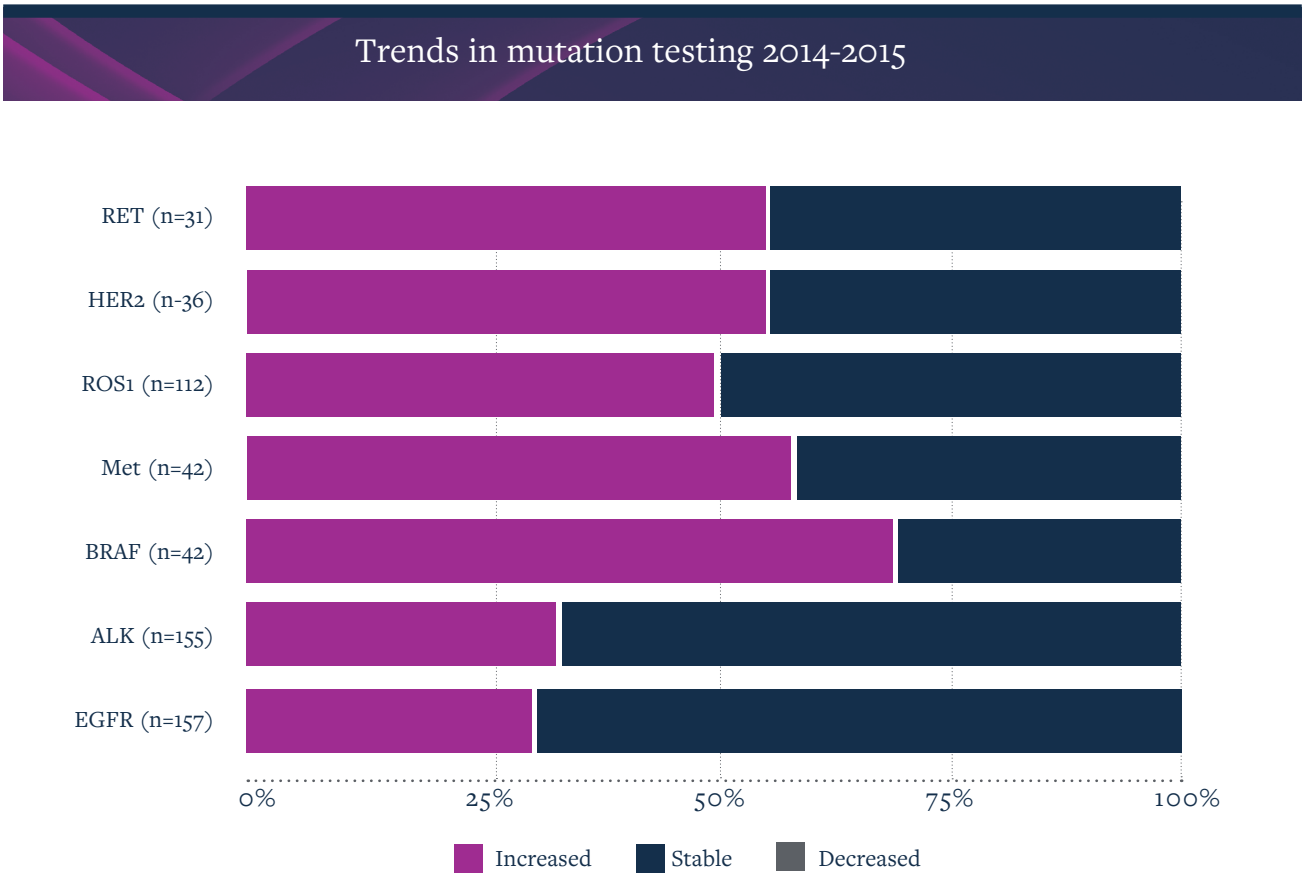
Of the patients you diagnosed with NSCLC in the past year, please indicate what proportion were screened for the following mutations.

Proportion of Newly-Diagnosed Patients who were Screened for the Following Genetic Alterations

		Type of setting				Region			
	Total n=157	Private Clinic n=88	Academic Center n=29	Community Based Center n=36	Other n=4	NE n=37	MW n=29	S n=63	W n=28
EGFR mutations	72%	76%	72%	68%	31%	79%	66%	67%	79%
ALK rearrangement	69%	71%	70%	67%	31%	75%	66%	63%	78%
BRAF V600E mutation	18%	8%	36%	12%	1%	11%	18%	25%	13%
MET amplification	17%	13%	31%	6%	1%	11%	19%	24%	11%
ROS1 rearrangements	38%	36%	45%	32%	4%	29%	39%	36%	57%
HER2 mutations	16%	7%	33%	9%	1%	14%	15%	20%	11%
RET rearrangements	14%	7%	28%	8%	0%	12%	15%	17%	11%
Other	2%	0%	5%	0%	0%	0%	10%	0%	0%

Testing for *EGFR, ALK*, and *ROS1* alterations, which are the only oncogenic drivers that are currently associated with approved drugs in lung cancer were tested at the highest rates. Testing for *EGFR* was the highest (72% overall) most likely due to the presence of three FDA-approved therapies targeting *EGFR* mutations, the high prevalence of *EGFR*-positive status in patients with adenocarcinoma (10%-15%), and the fact that many sequential testing algorithms recommended in the literature suggest testing for *EGFR* prior to other drivers if single assay tests are used.

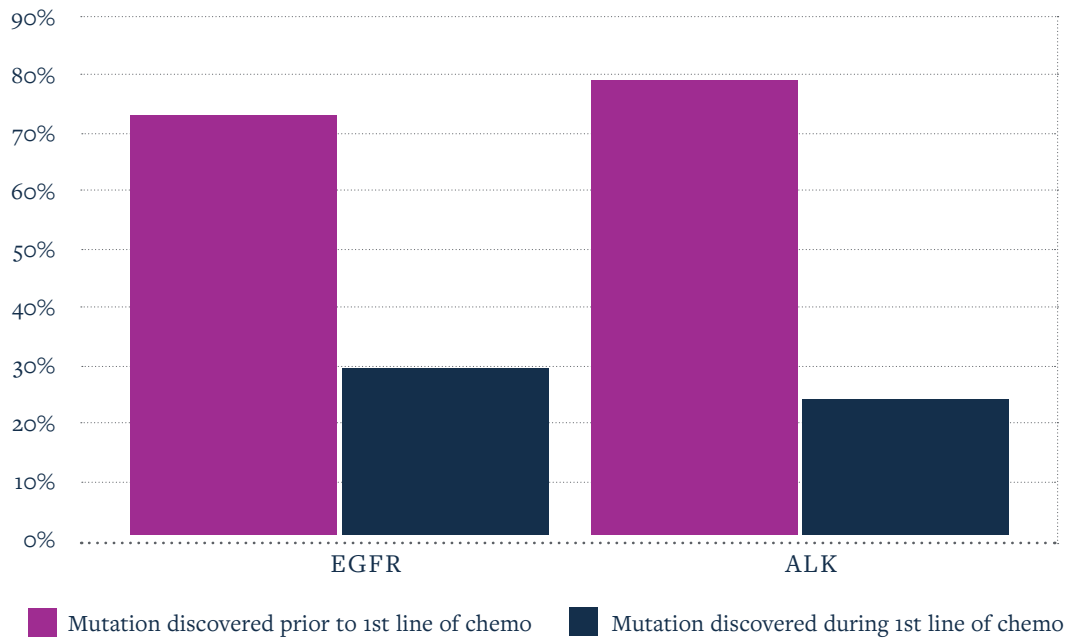
How would you describe the trend in genetic alteration testing for each of the following tests?



Mutation testing for *EGFR* and *ALK* was reported as stable between 2014 and 2015, while detection of other mutations increased. This is probably linked to an increase in use of multiplex *PCR* and *NGS*, which allows for more oncogenic drivers to be detected. Particularly sharp increases were reported for mutations associated with the *BRAF* and *MET* genes, which both occur in less than 5% of patients with adenocarcinoma, but which can be targeted with existing drugs. Dabrafenib (Tafinlar) was approved in 2013 for patients with metastatic melanoma with *BRAF* mutation, and early-stage trials testing the drug's effectiveness in lung cancer have been promising.[5] Crizotinib (Xalkori), which is already approved for several lung cancer indications, has been demonstrated to have activity in patients with *MET* amplification.

Thinking of your EGFR and ALK positive patients, what proportion had their mutation discovered prior to 1st line chemotherapy, and what proportion during 1st line chemotherapy?

Proportion of Patients who had Mutation Discovered Prior to 1st-Line Therapy



Respondents reported that among patients who tested positive for EGFR mutations and ALK rearrangements, 73% and 78%, respectively, had their mutation discovered prior to undergoing chemotherapy. Of the EGFR positive patients who were tested prior to undergoing chemotherapy, 81% received erlotinib and 17% afatinib. Of the ALK positive patients who were tested prior to undergoing chemotherapy, 95% received crizotinib and 4% ceritinib. For the patients who had their EGFR mutations discovered after treatment with chemotherapy had already begun, respondents reported that 71% completed chemotherapy prior to starting erlotinib or afatinib, 23% interrupted chemotherapy to start erlotinib or afatinib, and 6% added erlotinib or afatinib to current treatment. For the remaining ALK positive patients who had their mutation discovered during 1st line chemotherapy, 56% completed planned chemotherapy before starting crizotinib or ceritinib, 39% interrupted chemotherapy to start crizotinib or ceritinib, and 4% added crizotinib or ceritinib to current treatment.

DISCUSSION

In this survey, we asked oncologists to share their experiences and perspectives on how molecular diagnostics are used in the treatment of lung cancer. The role of molecular diagnostics in medical practice has changed rapidly in recent years, as have advances in the field of genomics. New targeted therapies and more sophisticated testing platforms have expanded the landscape of personalized medicine, particularly in lung cancer.

In developing this physician questionnaire, we sought to answer three questions about the use of molecular diagnostics:

1. **Is availability of adequate tissue samples a rate-limiting step in tumor molecular analysis?**

2. **What is the uptake of next-generation sequencing platforms across practice settings and regions?**

3. **How often is molecular testing performed too late to enable patients to be treated with a targeted therapy in the first-line setting?**

Broadly, these questions address whether practices are adapting to a changing environment to allow molecular diagnostics to have their greatest impact on patient management.

We found that most oncologists did not report that access to adequate tissue samples was a major impediment to molecular testing. Sixty-five percent of all respondents reported performing only one biopsy to support tumor molecular analysis, while also noting that it was sufficient for testing needs. Surprisingly, only 6% of respondents cited an inadequate amount of tissue in providing reasons for the number of tissue biopsies they typically perform. Despite these positive findings from physicians' self-reports, concern about adequate tissue remains high: 79% of respondents reported extreme to moderate concern about obtaining adequate tissue for molecular testing.

A second component of the questionnaire related to the methodology of the test that was used to perform molecular testing. Using three general categories of tests identified in NCCN guidelines—single gene assays, multiplex polymerase chain reaction (PCR) systems, and broad molecular profiling systems, such as next-generation sequencing (NGS)—we asked respondents to choose which test types they use. Respondents could choose multiple test types. Over a third (36%) of all respondents reported using NGS, with the largest number of users coming from academic settings. The finding that there existed a 31% difference in the proportion of respondents from academic centers who reported using NGS compared to respondents from community centers was unsurprising given that many academic centers have developed in-house NGS platforms for both routine patient care and research use.

Adequate tissue acquisition and uptake of new technologies are positive findings, although for these developments to have the greatest impact on patient care, testing needs to be timed so that patients can receive targeted therapy in place of less effective alternatives. Respondents reported that 27% and 22% of their EGFR and ALK patients had mutations discovered when patients had already begun treatment with a non-targeted agent. Furthermore, among these patients, 71% and 56%, respectively, completed chemotherapy before starting additional treatment with targeted therapy. It follows from this finding that nearly 20% of their EGFR positive patients and 12% of their ALK positive patients had targeted therapy delayed due to the timing of molecular testing. Testing at earlier stages of disease progression may prevent patients undergoing chemotherapy when they are eligible for targeted therapy.

This study has several limitations. First, a true response rate cannot be calculated for this survey. Physicians were invited by email or postal mail, and they voluntarily self-screened based on knowledge, interest, and experience level in treating this condition. They had the opportunity to respond to the survey invitation by logging on to the online survey. As it is unknown how many physicians successfully received, reviewed, and self-screened for this survey invitation, the true response rate cannot be calculated. Additionally, response to the survey was voluntary, which may introduce bias in the responses that were provided.

CONCLUSION

Despite widespread concerns regarding the adequacy of tissue samples to support molecular testing, we found that for most respondents, acquisition of adequate tumor tissue was not a rate-limiting step in molecular testing. However, timing of testing does appear to be preventing a sizable portion of patients from receiving targeted treatment prior to chemotherapy, highlighting the need for more early-stage testing. Finally, use of NGS is still primarily concentrated in academic research institutions, indicating that its use outside a research setting is not yet widespread.

FUNDING SUPPORT

Financial support for this research was provided by the Deerfield Institute, the internal research group at Deerfield Management Company, a healthcare investment firm dedicated to advancing healthcare through investment, information and philanthropy.

METHODS

Study sample design

A universe sample frame of NSCLC-treating oncologists was created by sourcing Symphony Health Analytics' 2014 insurance-claims activity for all oncologists in the United States for both the 162 series of lung cancer ICD9 codes as well as the claims-activity related to prescribing lung-cancer targeted therapies (Erlotinib, Afatinib, Crizotinib, and Ceritinib). By combining

both sources, we identified 10,184 oncologists with activity related to the care of lung cancer patients. In order to ensure that the physicians targeted for this research would have the required minimum number of patients to participate, we further limited this sample to those with at least three unique lung cancer patients in all of 2014. This reduced the list of oncologists to 8,129, all of which were invited to participate in the survey by e-mail or postal mail. Oncologists were eligible to participate if they personally managed at least 5 NSCLC patients per month, and diagnosed at least one NSCLC patient in the past 12 months. A total of 221 oncologists responded to the survey and 157 met eligibility criteria and completed the survey. Participants were offered an industry-standard honorarium as compensation for their time in completing the survey. The survey was administered online and was fielded from April 8, 2015 to September 14, 2015.

Data collection

A questionnaire was developed to assess current NSCLC treatment practices and level of use of molecular testing in the United States. We developed and pre-tested this instrument through interviews and consultations with 13 NSCLC-treating oncologists. The online questionnaire included both quantitative and qualitative questions, and covered the following topics: patients' characteristics such as disease clinical stages and stage IV histological subtypes, number of biopsies performed, proportion of patients who received a test, which genetic alterations was tested, what was the outcome of the test, what are the trends in genetic alterations testing, what type of test is used (single assay vs multiplex PCR vs next generation sequencing), sequencing of tests, detection of T790M mutation, management of EGFR positive and ALK positive patients.

Data analysis

All survey data were analyzed in aggregate and the individual identities of the survey respondents were blinded to the study authors. The planned analyses for quantitative data were descriptive and included means and percentages. Data were analyzed in total and split per type of practice and geographical location. Qualitative data were analyzed thematically and coded according to the main themes of the survey questions. Any response that addressed multiple themes was counted as multiple comments.

Statistical analyses

An analysis was conducted to determine if a relationship existed between test type and either practice setting, geographic region, or hospital ownership. For the purpose of the analysis, the test type variable was calculated to reflect the binary outcome of "Next-generation Sequencing" or "No Next-generation Sequencing". Chi-squared test of independence was conducted with the Python statistical library Scipy. Descriptive statistics were used to characterize aggregate responses to survey questions.

Ethics, consent, and permissions

By electing to complete the survey, respondents provided consent to use their anonymous responses to the survey questions. The study did not involve patients and data on patient characteristics within colonoscopy practices were provided only in the aggregate. As such, there was no institutional review board and/or licensing committee involved in approving the research and no need for informed consent from the participants per US regulations (§46.116 General requirements for informed consent. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.102).

APPENDIX

Table 1. Respondents' Report of Treated Patient Populations

CHARACTERISTICS		TOTAL SAMPLE N=157
MEAN NUMBER OF PATIENTS DIAGNOSED IN PAST 12 MONTHS		62.9
DISEASE STAGE	STAGE I	8%
	STAGE II	13%
	STAGE III	27%
	STAGE IV	53%
HISTOLOGIC SUBTYPE	SQUAMOUS CELL CARCINOMA	29%
	ADENOCARCINOMA	62%
	LARGE CELL	4%
	NSCLC NOT OTHERWISE SPECIFIED (NOS)	4%
	OTHER	0%

APPENDIX

Table 2. Characteristics of Survey Respondents

		TOTAL SAMPLE N=157	
CHARACTERISTICS		NO.	%
ROLE	ONCOLOGIST	148	94%
	NURSE	4	3%
	PHYSICIAN	5	3%
GEOGRAPHIC REGION	MIDWEST	29	18%
	NORTHEAST	37	24%
	SOUTH	63	40%
	WEST	28	18%
TYPE OF PRACTICE	ACADEMIC CENTER	29	18%
	COMMUNITY BASED CENTER	36	23%
	PRIVATE CLINIC	88	56%
	OTHER	4	3%
PRACTICE OWNERSHIP	PHYSICIAN-OWNED	91	58%
	HOSPITAL-OWNED	63	40%
	OTHER	3	2%
CENTER DESTINATIONS	CANCER CENTER	39	25%
	COMPRENSIVE CANCER CENTER	26	17%
	NCI COMMUNITY ONCOLOGY RESEARCH PROGRAM	13	8%
	NONE OF THE ABOVE	73	46%
	UNSURE	6	4%

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