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ORIGINAL ARTICLE

The impact of a fourteen-gene molecular assay on physician treatment decisions in non-small-cell lung cancer

Shane Dormady · Michael S. Broder · Girish V. Putcha · Robert H. Dumanois · Alison H. DeCristofaro · Eunice Chang · Paul R. Billings · Thierry Jahan

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Abstract
Background Five-year survival in early–stage, non-squamous, non-small-cell lung cancer (NSCLC) remains poor compared with other solid tumors, even after complete resection. Post-operative management depends on prognostic staging to identify individuals at highest risk for death, and therefore with the greatest need for further intervention. A 14-gene quantitative RT-PCR test successfully differentiates stage I–III NSCLC patients who are at high-, intermediate-, or low-risk for 5-year mortality. This study assesses the impact of the assay's prognostic information on physician decisions regarding adjuvant chemotherapy.
Methods We invited 115 physicians who ordered the test to participate in an on-line survey. The primary outcome measure was the proportion of patients with different pre- and post-test chemotherapy recommendations.
Results Fifty-eight physicians (50 %) completed the survey on 120 stage I or II NSCLC patients. Ninety-one patients (76 %) had stage I lung cancer; 27 (23 %), 39 (33 %), and 54 (45 %) patients had low-, intermediate-, and high-risk scores, respectively. Physicians' chemotherapy recommendations were changed post-testing in 37 patients (30.8 %, 95 % CI 22.7–39.9 %). High-risk patients were more likely to have a change in treatment recommendation (44.4 %, 95 % CI 30.9–58.6 %) than low risk patients (3.7 %, 95 % CI 0.1–19.0 %); a substantial number of changes were observed in both stage I (33.0 %, 95 % CI 23.5–43.6 %) and stage II (24.1 %, 95 % CI 10.3–43.5 %).
Conclusions Our data show that the assay resulted in a significant impact on physician treatment decisions in early-stage NSCLC, and that the nature of treatment changes generally correlated with the test's assessment of risk.

Keywords Lung cancer · Chemotherapy · Medical decision-making

Introduction

Each year, more than 200,000 Americans are diagnosed with, and more than 150,000 die of, non-small-cell lung cancer (NSCLC) [1]. According to the National Cancer Institute's SEER data, overall 5-year survival for lung cancer from 2003 to 2009 was 16.6 % [2]. Five-year survival was only 3.9 % for patients with metastatic cancer at diagnosis, but survival even for patients with localized disease at diagnosis was still only 53.5 %. Since many of these patients die with distant metastasis even after successful resection of their primary tumors at a localized stage, very early, undetectable metastasis must be present in a large percentage of these patients despite early staging by the conventional TNM system [3].

S. Dormady
Valley Medical Oncology Consultants, 2940 Whipple Ave., Redwood City, CA, USA

M. S. Broder · A. H. DeCristofaro (✉) · E. Chang
Partnership for Health Analytic Research, LLC, 280 South Beverly Drive, Suite 404, Beverly Hills, CA 90212, USA
e-mail: alisonde@pharllc.com

G. V. Putcha · R. H. Dumanois · P. R. Billings
Life Technologies Corporation, 5791 Van Allen Way, Carlsbad, CA 92008, USA

T. Jahan
Helen Diller Family Comprehensive Cancer Center, University of California at San Francisco, Box 1724, San Francisco, CA 94143-1724, USA

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In contrast to the average improvement in survival of only several months with chemotherapy for stage IV NSCLC [4], post-operative adjuvant chemotherapy has been shown to improve long-term survival in stages II and III [5–7]. Taken together, these observations suggest that early occult metastasis is present in many patients within stages I–III, and that these patients may be managed more effectively with systemic therapy at these stages than with application of the same therapy in later-stage or recurrent disease, when more extensive, detectable metastasis is present. Furthermore, the degree of benefit in these adjuvant chemotherapy studies generally increased with increasing stage, suggesting that, as the risk of occult metastasis of NSCLC increases, so does the benefit of adjuvant chemotherapy. A better means of discriminating risk among early-stage NSCLC patients may therefore provide useful information to clinicians who need to make difficult decisions, together with their patients, regarding the interpretation of population-based guidelines on an individual basis. This may be particularly true in stage I NSCLC, in which definitive data demonstrating a benefit of adjuvant therapy have been elusive. Despite the absence of such evidence in stage I, even guidelines published by the National Comprehensive Cancer Network (NCCN) indicate a need to identify the highest risk patients so that early intervention can be attempted to mollify an otherwise very high risk of death [8].

Pervenio™ Lung RS (Life Technologies Corporation, Carlsbad, CA, USA), a 14-gene quantitative RT-PCR assay was demonstrated to successfully differentiate stage I–III NSCLC patients who were either at high, intermediate or low risk for 5-year mortality in two large-scale, blinded, independent studies that involved ~1,500 patients [9, 10]. The assay has now been validated in a clinical laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA), is commercially available, and can be used on commonly available formalin-fixed paraffin-embedded tissue samples. The assay identifies high-risk patients in stage I better than the criteria suggested by the NCCN to identify these same "high-risk" patients from stage IB alone [9]. The current study was designed to document how physicians currently use the prognostic information provided by this test in making patient management decisions.

The primary objective of this study was to evaluate the manner and extent to which physicians' treatment decisions were changed as a result of the multi-gene assay in a sample of Stage I or II lung cancer patients whose physicians ordered the test. The secondary objectives were to: analyze the direction of the treatment change (e.g., from chemotherapy to no chemotherapy or vice versa) stratified by patient characteristics including lung cancer stage I or II and test result (e.g., low, intermediate or high risk for death based on the test result), and to describe factors that influenced physicians' decisions to order the test.

Materials and methods

United States physicians who ordered the multi-gene assay between November 20, 2012 and February 26, 2013 were eligible to participate in the survey. One hundred and fifteen physicians who had ordered the test for at least one patient with stage I or II lung cancer were contacted and asked to complete a web-based survey about the impact of the assay on their chemotherapy treatment decision-making process. Physicians were each given a unique URL through which they could enter data about themselves and their patients into a secure database. Verification of receipt of a valid assay result was undertaken prior to analysis of the survey results.

The survey was developed through cognitive interviews with two physicians who had ordered the assay. They were asked why they had ordered the test, whether or not particular patient characteristics influenced their decision, and questions about the perceived usefulness of the test. Based on responses to these interviews, a survey, which consisted of a maximum of 32 items per physician/patient dyad was developed, tested and refined by senior researchers at the Partnership for Health Analytic Research (PHAR) with the assistance of clinical experts. (See "Appendix A").

The primary outcome measure for this analysis was the proportion of patients whose physicians' pre-test recommendation about chemotherapy treatment was different from his/her post-test recommendation. To evaluate this, we asked physicians what their chemotherapy recommendation was before and after performing the test. Physician-level variables included physician specialty, years in primary specialty, number of new lung cancer patients in a typical year, percentage of patients with stage I and II lung cancer seen, the number of times the physician had ordered the assay, and assessment of predictors of high recurrence risk. Patient-level variables included gender, age, comorbidities, assay risk score, clinical stage, and the importance of clinical and pathological factors in ordering the assay. Since the survey did not involve direct contact with human subjects, did not involve an intervention, and did not involve collection of any identifiable patient information, Institutional Review Board (IRB) approval was not required.

Statistical analyses were performed using SAS® version 9.3 (SAS Institute, Cary, NC). Descriptive statistics, such as mean, standard deviation (SD), median, range, frequency, and percentage, were reported for all physician- and patient-level measures whenever it was applicable. We

estimated the proportion of patients with changes to their chemotherapy treatment recommendation and the associated 95 % confidence intervals. The change in treatment recommendation analyses were further stratified and presented by assay risk score (low, intermediate, and high risk score). We used the McNemar's pre–posttest to assess the statistical significance of the impact of the risk assay results in terms of change in treatment recommendation. In some situations when the cell count was <5, the exact method was used to estimate the 95 % confidence interval and McNemar's test. For our secondary analysis, we reported all patient measures stratified by clinical stage of lung cancer (stage I and II).

Results

Receipt of a valid assay result was verified among 61 physicians who initiated the survey as of the date of survey closure (February 26, 2013). Of these, one physician did not enter any data and two provided information on patients with stage III or IV NSCLC. These three physicians were excluded from the analysis. The primary analytical data set therefore contained 58 physicians (response rate 50 %) with 120 stage I or II NSCLC patients.

Twenty-seven physicians (47 %) had ordered the assay once, 7 (12 %) twice and 24 (41 %) ordered the assay 3 or more times. Among the 58 respondents, 32 (55 %) were medical oncologists and 20 (35 %) were thoracic surgeons; the remainder were internal medicine or other specialties. Respondents had been in practice for a mean of 14.7 years (range 1–36 years). Most respondents practiced in a community single-specialty group (47 %), academic medical center (24 %), or community multi-specialty group setting (21 %). Respondents reported seeing an average of 88 newly diagnosed lung cancer patients per year (range 6–500).

Among the 120 eligible lung cancer patients for whom surveys were completed, 49 (41 %) were male, 91 (76 %) had stage I lung cancer, 29 (24 %) had stage II lung cancer, and the median age was 67 years (Table 1). Twenty-seven (23 %) patients had low-risk scores, 39 (33 %) had intermediate scores, and 54 (45 %) had high scores. The distribution of scores in other populations in which the assay was administered was similar to that found in this study. In the Kaiser Permanente cohort, which included patients in stage I and II according to the 7th edition of the NSCLC TNM staging system, risk distribution was 20 % low risk, 28 % intermediate risk, and 51 % high risk; in the Chinese cohort the distribution among Stage I and II patients was 24 % low risk, 18 % intermediate risk, and 58 % high risk [10]. Physicians cited their "desire to have quantitative, individualized recurrence risk information" as "very important" to their decision to order the assay in 100 (83 %) patients. Among the clinical and demographic predictors of lung cancer recurrence risk that physicians used to risk stratify, the physicians we studied cited tumor size greater than 4 cm, vascular invasion and visceral pleural invasion as "very important" or "somewhat important".

Physicians responded that their recommendation about chemotherapy treatment was changed by the assay results in 37 patients (30.8, 95 % CI 22.7–39.9 %; Table 2).

Table 1 Patient characteristics ($n = 120$)

	No. of patients (%)		
	All patients $n = 120$	Stage I $n = 91$; 75.8 %	Stage II $n = 29$; 24.2 %
Patient gender			
Male, *n* (%)	49 (40.8)	39 (42.9)	10 (34.5)
Female, *n* (%)	71 (59.2)	52 (57.1)	19 (65.5)
Patient age (years)			
Mean ± SD	66.8 ± 10.1	66.8 ± 10.5	67.0 ± 8.8
Median (range)	67 (29–88)	67 (29–88)	66 (47–85)
<55, *n* (%)	13 (10.8)	11 (12.1)	2 (6.9)
55–64, *n* (%)	31 (25.8)	24 (26.4)	7 (24.1)
65–74, *n* (%)	45 (37.5)	31 (34.1)	14 (48.3)
75+, *n* (%)	31 (25.8)	25 (27.5)	6 (20.7)
Comorbidities present			
Diabetes, *n* (%)	14 (11.7)	8 (8.8)	6 (20.7)
Uncontrolled hypertension, *n* (%)	5 (4.2)	3 (3.3)	2 (6.9)
Stroke, other cerebrovascular disease, *n* (%)	3 (2.5)	2 (2.2)	1 (3.4)
Congestive heart failure, chronic heart disease, *n* (%)	11 (9.2)	10 (11.0)	1 (3.4)
Pulmonary fibrosis, chronic lung disease, *n* (%)	15 (12.5)	12 (13.2)	3 (10.3)
Chronic renal insufficiency, *n* (%)	7 (5.8)	7 (7.7)	0 (0)
Peripheral neuropathy, *n* (%)	1 (0.8)	1 (1.1)	0 (0)
Cytopenias, *n* (%)	3 (2.5)	2 (2.2)	1 (3.4)
Assay risk score			
Low, *n* (%)	27 (22.5)	24 (26.4)	3 (10.3)
Intermediate, *n* (%)	39 (32.5)	34 (37.4)	5 (17.2)
High, *n* (%)	54 (45.0)	33 (36.3)	21 (72.4)
Pre-assay chemotherapy recommendation			
Yes, *n* (%)	34 (28.3)	14 (15.4)	20 (69.0)
No, *n* (%)	86 (71.7)	77 (84.6)	9 (31.0)
Post-assay chemotherapy recommendation			
Yes, *n* (%)	57 (47.5)	34 (37.4)	23 (79.3)
No, *n* (%)	63 (52.5)	57 (62.6)	6 (20.7)

Table 2 Chemotherapy recommendations by assay risk score ($n = 120$)

	Post-assay chemotherapy recommendation, *n*		Total	*P* value[a]	Any treatment change		
	Yes	No			*n*	%	95 % CI[b]
All patients ($n = 120$)							
Pre-assay chemotherapy recommendation				<0.001			
Yes	27	7	34		7	(20.6)	
No	30	56	86		30	(34.9)	
Total	57	63	120		37	(30.8)	22.7–39.9 %
Low risk score ($n = 27$)							
Pre-assay chemotherapy recommendation				0.999			
Yes	1	1	2		1	(50.0)	
No	0	25	25		0	(0.0)	
Total	1	26	27		1	(3.7)	0.1–19.0 %
Intermediate risk score ($n = 39$)							
Pre-assay chemotherapy recommendation				0.146			
Yes	3	3	6		3	(50.0)	
No	9	24	33		9	(27.3)	
Total	12	27	39		12	(30.8)	17.0–47.6 %
High risk score ($n = 54$)							
Pre-assay chemotherapy recommendation				<0.001			
Yes	23	3	26		3	(11.5)	
No	21	7	28		21	(75.0)	
Total	44	10	54		24	(44.4)	30.9–58.6 %

CI Confidence interval

[a] Exact McNemar's pre-posttest

[b] Exact Clopper–Pearson CI

Table 3 Chemotherapy recommendations by lung cancer stage ($n = 120$)

	Post-assay chemotherapy recommendation, *n*		Total	Any treatment change	
	Yes	No		*n*	%
Stage I ($n = 91$)					
Pre-assay chemotherapy recommendation[a]					
Yes	9	5	14	5	(35.7)
No	25	52	77	25	(32.5)
Total	34	57	91	30	(33.0)[a]
Stage II ($n = 29$)					
Pre-assay chemotherapy recommendation[a]					
Yes	18	2	20	2	(10.0)
No	5	4	9	5	(55.6)
Total	23	6	29	7	(24.1)[b]

[a] 95 % exact Clopper–Pearson confidence interval: 23.5–43.6 %

[b] 95 % exact Clopper–Pearson confidence interval: 10.3–43.5 %

Among 86 patients for whom no chemotherapy was recommended initially, 30 (34.9 %) had chemotherapy recommended post-assay. Among 34 patients for whom chemotherapy was recommended initially, the recommendation was changed to "no chemotherapy" in 7 patients (20.6 %). Patients with high-risk scores were more likely to have a change in treatment recommendation (44.4, 95 % CI 30.9–58.6 %) than were low-risk patients (3.7, 95 % CI 0.1–19.0 %; Table 2).

Among 91 Stage I patients, 30 (33.0, 95 % CI 23.5–43.6 %) had a change in chemotherapy recommendation (Table 3). Fourteen Stage I patients had a pre-assay recommendation for chemotherapy. Physicians changed their recommendation to no chemotherapy in 5 of those patients (35.7 %). Chemotherapy was not recommended initially for 77 Stage I patients; 25 of those patients' (32.5 %) recommendations were changed to chemotherapy. Treatment recommendations were changed more often in high-risk Stage I patients (57.6 %) than in intermediate- (32.4 %) and low-risk patients (0.0 %).

Treatment recommendations were also changed among patients in Stage II. Seven Stage II patients had their recommendation changed (24.1 %; exact Clopper–Pearson CI 10.3–43.5 %; Table 3). Chemotherapy was recommended pre-assay in 20 of the 29 Stage II patients in the sample (68.9 %). Of these, two (10.0 %) were changed to no chemotherapy post-assay (Table 3).

Discussion

After tumor resection for NSCLC, the primary clinical goal is prevention of recurrence and subsequent death. Despite this important goal, post-operative management of many

patients is still limited to observation alone, even though data from prospective randomized studies indicate that some patients with a high risk of recurrence (i.e. stage II or stage III) can derive long-term survival benefit from systemic chemotherapy [5–7].

Reliable clinical indicators of increased risk in stage I NSCLC have been sought for some time now. To date, tumor size >4 cm is the only indicator of high risk in stage I NSCLC for which there is any clinical evidence of a benefit from adjuvant chemotherapy. Furthermore, there are still many patients with stage II NSCLC who disregard published recommendations for potentially life-saving chemotherapy. Although the data for stage II and III patients suggests that patients at the highest risk derive the greatest benefit from adjuvant therapy, traditional staging does not allow one to differentiate risk within stage II patients when making these difficult decisions.

There remain today many clinical scenarios, particularly in oncology, with a dearth of prospective data to guide clinical decision-making. Indeed, the majority of NCCN recommendations in the management of NSCLC are based on Level II, not Level I, data [8]. When patients face high mortality, as is the case in early stage NSCLC, clinicians and patients must synthesize the best available data in an attempt to optimize the chances for survival. Recognizing this situation in stage I NSCLC, for example, NCCN guidelines already recommend adjuvant chemotherapy for stage I patients if they are felt by their clinicians to be at the highest risk based on clinical prognostic factors. Factors suggested by the NCCN for consideration of stage I risk are TNM stage IB, which is by definition higher risk than IA, when combined with one or more of six clinicopathological criteria (i.e., poor differentiation, vascular invasion, wedge resection, tumors greater than 4 cm, visceral pleural involvement, and incomplete lymph node sampling), despite the absence of prospective randomized data documenting any survival benefit with chemotherapy in that group, and despite any large-scale validation that those criteria reliably identify "high risk" stage I patients [5]. The large-scale validation of the 14-gene prognostic assay indicates that the assay provides better risk discrimination in stage I patients than either tumor size greater than 4 cm, or the group with "high risk" criteria suggested by the NCCN. It could therefore be argued that the results of this assay provide a more rigorous means of implementing the existing NCCN recommendations.

The survival of NSCLC patients has not changed much over the past 40 years. Given the unmet need for better management of these patients, and in light of the clinical evidence that a high risk of occult metastasis is associated with a survival benefit from adjuvant chemotherapy, it is important to understand how clinicians are integrating novel molecular risk discrimination into their management decisions.

The 14-gene prognostic assay studied here is a well-validated method of stratifying the stage I and II lung cancer population that identifies patients at the highest risk of 5-year mortality. This clinical validity has been demonstrated in a cohort of 433 resected stage I NSCLC patients from the Northern California Kaiser Permanente network of hospitals, for whom the hazard ratio (HR) for death was 2.04 (95 % CI 1.28–3.26) based on a high-risk molecular categorization, compared with HR 1.10 (95 % CI 0.73–1.66) based on tumor size >4 cm, a commonly used criterion to guide the use of chemotherapy at the present time. In a cohort of 1,006 patients who underwent resection of non-squamous NSCLC in China, multivariate analysis demonstrated that a high risk score on the assay was a better predictor of mortality (HR 2.37; 95 % CI 1.63–3.43) than was lung cancer TNM stage (HR 1.43; 95 % CI 1.33–1.53). Among patients with T1a node-negative cancer, a high risk score on the assay was highly predictive of mortality in both younger patients (age <65, HR 2.82; 95 % CI 1.15–6.94) and older patients (age ≥65, HR 4.64; 95 % CI 2.01–10.73) [9]. Xie and Minna [11] have described the assay as "a molecular prognostic signature that seems ready for widespread use". Our survey data show that the 14-gene test was useful to physicians in making clinical decisions and that it resulted in clinically rational changes in treatment decisions.

In interpreting these results, a number of limitations must be considered. The study employed a cross-sectional, non-randomized design to survey a sample of physicians. Respondents received compensation of $250 for each completed survey. As with any survey, physicians who responded to the survey invitation may have had systematically different impressions of the clinical utility of the assay than non-respondents; the unusually high response rate to our survey invitation, however, may mitigate this concern to some extent. American Society for Clinical Oncology data suggest that, at least in terms of the practice setting, the respondents in our study were similar to the population of oncologists in general: with 68 % of the study population based in community settings versus 57 % of the general oncology population [12].

Documentation of an increase in long-term survival with adjuvant chemotherapy has been elusive for stage I NSCLC, in which more of the target patients are cured by surgery, but in which a substantial number still harbor occult metastatic disease that might also be susceptible to systemic treatment. There does not appear to be any fundamental difference in the biology of stage I vs. stage II/III NSCLC or in the biology of metastatic disease in these

patients that would render them more resistant to chemotherapy; rather, the fundamental difference between stage II/III and stage I NSCLC is the higher risk of recurrence and death in the former, very likely a reflection of a higher rate of occult metastasis. Previous studies have reported a greater degree of benefit from adjuvant therapy among patients with a higher risk of death [5, 6]. Since many stage I patients have undetectable but, ultimately, fatal metastasis after resection, better discrimination of those at higher risk would enable much more informed risk:benefit analysis of early intervention based on existing data, even prior to additional prospective studies that will take many years in this population.

In this study, a substantial impact was made by a 14-gene molecular assay on physician management decisions in early stage NSCLC. As described above, better risk stratification in stage I and stage II NSCLC patients represents a significant unmet need. The results from this study indicate that physicians find molecular prognostic information, like that provided by the 14-gene assay described herein, to be meaningful and useful in their patient management decisions, even as future prospective studies are underway to demonstrate chemotherapy benefits. The test is an objective, quantitative, and biologically driven prognostic measure that is accurate, reproducible, easy to use, and provides a practical mechanism for implementing current guidelines.

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Conflict of interest Robert Dumanois, Paul Billings and Girish Putcha are employed by Life Technologies Corporation (LTC), which sponsored this research. Michael Broder, Alison DeCristofaro, and Eunice Chang are employed by PHAR, LLC, which received funding from LTC to conduct the study. Shane Dormady and Thierry Jahan have no conflicts to report. The authors have full control of all primary data and we agree to allow the journal to review the data if requested.

Appendix A. Survey instrument

The full physician survey, programmed and administered in SurveyGizmo©, is shown below. Note, this version of the survey does not show programming logic (e.g., looping, skip patterns, etc.) that were part of the web-based version of the survey.

Pervenio™ assay in lung cancer

This brief survey, sponsored by Encore Clinical and Life Technologies and conducted by the Partnership for Health Analytic Research, examines physician practices with regard to the Pervenio™ Lung RS, a risk stratification assay for patients with early stage non-small cell lung cancer. The survey asks about how the results of the assay have affected your treatment recommendations.

About this survey and your participation

Participation in this study is strictly voluntary, but your participation will help to increase the study's validity.

Your individual survey responses will be kept confidential, and results will only be reported in aggregate.

Neither your name nor any identifying information obtained in connection with this research will be disclosed without your permission. Only the research team will have access to these data.

Below are a few important points about completing this survey:

- If you have any questions or concerns, please contact {removed} by email at {removed} or by phone at {removed}
- If you cannot complete the survey in one sitting, select 'Save & continue survey later' at the top of the page and enter your email address. Re-click on the link provided in your email at a later time to resume your survey session.
- The study has two parts. The first part asks about you, the respondent: your specialty, practice and experience. The second part of the study asks about patients with stage I or II lung cancer for whom you ordered the Pervenio assay and reviewed the results.
- You must have the medical record(s) of patients about whom you are responding available to you as you complete the items.
- If you need a prompt to remember the name of patients for whom you ordered the assay, please contact {removed} by {removed} or by phone at {removed}.

SCREENING

What is your primary specialty?
( ) Thoracic surgery
( ) General surgery or other surgical specialty
( ) Medical oncology
( ) Internal medicine or other medical specialty
( ) Other: _____

How many times have you ordered the Pervenio assay for a stage I or II lung cancer patients?
( ) 0
( ) 1
( ) 2
( ) 3
( ) 4
( ) 5
( ) 6
( ) 7
( ) 8
( ) 9
( ) 10

You will be asked 5-8 questions per patient. Completing the survey will take 10-15 minutes per patient. You will receive an honorarium of $250 for each completed medical record for stage I or II lung cancer patients for whom you *ordered the Pervenio assay and reviewed the results.*

How many patient records will you input?

You *must* have the medical record(s) of patient(s) about whom you are responding available to you as you complete the items.
( ) 1
( ) 2
( ) 3
( ) 4
( ) 5
( ) 6
( ) 7
( ) 8
( ) 9
( ) 10

We will start with a few questions about your practice.

What is your primary practice setting?
( ) Academic medical center
( ) Health maintenance organization
( ) Community multi-specialty group
( ) Community single-specialty group
( ) Community solo practitioner
( ) Other: _____

For approximately how many years have you been practicing in your primary specialty?
_____

In a typical year, approximately how many newly diagnosed lung cancer patients do you see either as a consultant or for ongoing care?

_____

In a typical year, how many of the newly diagnosed patients have stage I or II disease?

_____

The following question is about your risk assessment of stage I or II lung cancer patients.

Please rate the following clinical and pathological features in terms of their importance as predictors of high recurrence risk for Stage I and II lung cancer patients:

	Very important	Somewhat important	Not important
Size >4 cm	( )	( )	( )
Vascular invasion	( )	( )	( )
Visceral pleural invasion	( )	( )	( )
Poorly-differentiated histology	( )	( )	( )
Wedge resection	( )	( )	( )
Number of positive lymph nodes	( )	( )	( )
Age >65	( )	( )	( )
Past or current smoker	( )	( )	( )

For the remaining questions, we would like you to recall the clinical characteristics of all of the stage I or II lung cancer patients for whom you ordered the Pervenio assay and reviewed the results.

Please have as many of these patients' medical record(s) available as possible when you complete this survey. We will ask a brief series of questions about each patient.

Please complete the following questions for each patient for whom you have ordered the Pervenio assay.

What is the patient's gender?
( ) Male
( ) Female

How old was the patient when you ordered the assay?

_____

Had the patient been diagnosed with any of the following comorbidities? (If the patient was diagnosed with any other comorbidities that limit suitability for chemotherapy, specify in the blank field below.)

	Yes	No	Don't Know
Diabetes mellitus	( )	( )	( )
Uncontrolled hypertension	( )	( )	( )
History of stroke or other cerebrovascular disease	( )	( )	( )
Congestive heart failure or other chronic heart disease	( )	( )	( )
Pulmonary fibrosis or other chronic lung disease	( )	( )	( )
Chronic renal insufficiency	( )	( )	( )
Peripheral neuropathy	( )	( )	( )
Cytopenias	( )	( )	( )
	( )	( )	( )

What was the patient's clinical stage when you ordered the assay?

( ) I
( ) II
( ) III
( ) IV

How important were each of the following factors in your decision to order the test for this patient?

	Very important	Somewhat important	Not important	Not applicable
Desire to have quantitative, individualized recurrence risk information	( )	( )	( )	( )
Conventional clinical and pathological risk factors not sufficiently informative for making adjuvant treatment recommendation	( )	( )	( )	( )
Recommendation by colleague(s) or expert(s)	( )	( )	( )	( )

What was the patient's Pervenio risk score?

( ) Low
( ) Intermediate
( ) High

Before the Pervenio assay results were known, was chemotherapy recommended?

( ) Yes
( ) No

After the assay results were known, was chemotherapy recommended?

( ) Yes
( ) No

Press next to continue to the next patient record.

If this is your last patient record, press next to end the survey.

CONTACT INFORMATION

Thank you for completing this important survey!

Your individual survey responses will be kept confidential, and results will only be reported in aggregate.

Neither your name nor any identifying information obtained in connection with this research will be disclosed without your permission. Only the research team will have access to these data.

Please enter your contact information so that we can send your honorarium. You will receive a $250 honorarium per completed patient medical record for stage I or II patients for whom the Pervenio assay was ordered.

First: _____
Last: _____
Address: _____
City: _____
State

( ) AK
( ) AL
( ) AR
( ) AS
( ) AZ
( ) CA
( ) CO
( ) CT
( ) DC
( ) DE
( ) FL
( ) FM
( ) GA
( ) GU
( ) HI
( ) IA
( ) ID
( ) IL
( ) IN
( ) KS
( ) KY
( ) LA
( ) MA
( ) MD
( ) ME
( ) MH
( ) MI
( ) MN
( ) MO
( ) MP
( ) MS
( ) MT
( ) NC
( ) ND
( ) NE
( ) NH
( ) NJ
( ) NM
( ) NV
( ) NY
( ) OH
( ) OK
( ) OR
( ) PA
( ) PR
( ) PW
( ) RI
( ) SC
( ) SD
( ) TN
( ) TX
( ) UT
( ) VA
( ) VI
( ) VT
( ) WA
( ) WI
( ) WV
( ) WY

Zip code: _____

Thank You!

Thank you! Your responses have been recorded.

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