CURRENT MEDICAL RESEARCH AND OPINION, 2017
http://dx.doi.org/10.1080/03007995.2017.1301903
Article FT-0081.R1/1301903

Taylor & Francis
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ORIGINAL ARTICLE

Impact of a multivariate serum-based proteomic test on physician treatment recommendations for advanced non-small-cell lung cancer

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ABSTRACT

Objective: The VeriStrat[1] (VS) test is intended to help guide treatment decisions for patients with advanced non-small-cell lung cancer (NSCLC) without an EGFR-sensitizing mutation, classifying patients into two categories. Patients classified as VSGood have a favorable prognosis and significant clinical response to EGFR tyrosine kinase inhibitors (TKIs). Patients classified as VSPoor have a less favorable prognosis and exhibit no significant response to *EGFR*-TKIs. The objective of this paper is to assess the real-world impact of VS test results on physicians' treatment recommendations including referrals for best supportive care (BSC).

Methods: Between 1 January 2012 and 1 November 2016, physician respondents were asked to complete standardized questionnaires before and after receiving VS results in patients meeting criteria for the intended use of the VS test. This study evaluated three endpoints: whether physicians followed VS test results in making treatment recommendations, the extent to which tests results changed these treatment recommendations, and the patterns of care subsequent to VS testing.

Results: Of the tests ordered by 989 physicians, 2494 VS tests had completed treatment recommendation questionnaires both prior to and after testing. Prior to VS testing, physicians were considering treatment with *EGFR*-TKIs for 2250 patients (90%). The VS test classified 1950 patients as VSGood and 544 patients as VSPoor. For patients classified as VSPoor, physicians recommended BSC for 25% of patients and standard systemic treatments such as chemotherapies for 65% of patients. Consistent with previous publications, physicians recommended *EGFR*-TKI therapy for only 10% of VSPoor patients but for 89% of VSGood patients. Overall, physician's treatment recommendations were consistent with test results in 98% of cases. Availability of test results decreased ineffective treatment recommendations by 89% for VSPoor patients.

Conclusions: Among physicians ordering VS, the test significantly influenced treatment recommendations for patients with NSCLC, reducing ineffective and expensive treatment at the end of life.

ARTICLE HISTORY
Received 7 February 2017
Revised 24 February 2017
Accepted 28 February 2017

KEYWORDS
Blood proteins; Hospice; Prognosis; Non-small-cell lung cancer; best supportive care

Introduction

Lung cancer is the third most common cancer in the United States and is the leading cause of cancer death[1]. In 2016, the number of new lung cancer cases was expected to exceed 224,000 with more than 158,000 deaths from the disease[1]. Over 79% of cases are diagnosed at advanced stages once the tumor has metastasized. About 85% of lung cancer cases are non-small-cell lung cancer (NSCLC). Five-year survival rates for patients with NSCLC are 28% and 4% for those with locally advanced and metastatic disease, respectively[2].

In advanced stages, treatment generally focuses on extending overall survival (OS), relieving symptoms and maintaining or improving quality-of-life (QOL). Best supportive care (BSC) is an option when subsequent chemotherapy regimens are viewed as no longer beneficial relative to the risks of adverse events. While the Medicare program provides hospice care benefits for patients with a prognosis of six months or less, the median duration of BSC is less than a month, with more than one third of patients referred to hospice within the last week of life[3]. One of the significant challenges of appropriate and timely BSC referrals is the difficulty in predicting the survival and the benefit to be derived from subsequent courses of therapy for an individual patient[4]. Without proper referrals, patients may miss out on the benefits of BSC: reduced pain, decreased hospitalization near end of life, decreased burden on family or caregivers, and the ability to die with dignity at home[5,6]. Knowledge of prognosis also has an impact on patient treatment preferences. Patients with poor prognosis may opt for less aggressive care, focusing on the reduction of symptoms and improvement of quality of life at the end of life[7]. One study showed that patients who expected only a 10% chance that they would live six months were more likely to favor comfort care over life-extending therapies compared with patients who expected to live to six months[8]. Despite this finding, a retrospective study of the cancer patients in the Veteran Administration care delivery system showed a recent increase

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in aggressive cancer care at the end of life, with more patients receiving late systemic therapies, higher rates of intensive care unit admissions, and long hospital stays within 30 days of death[9]. The lack of precision of current prognostic techniques compounded by the complexity of physician–patient end-of-life conversation creates the need for objective and actionable predictive and prognostic measures to guide treatment in the care of patients with cancer.

The VeriStrat[1] (VS) test is performed from a simple blood draw. It identifies patients with a poor prognosis who also do not benefit from certain therapies. The test is a serum-based, proteomic test that uses mass spectrometry and an advanced bioinformatics algorithm to stratify patients into two groups, VSGood and VSPoor. VS status is a significant predictor of survival outcomes independent of clinical factors previously used to guide prognosis, (ECOG performance status, smoking status, and histology)[10–18]. The predictive and prognostic value of the VS test has been demonstrated across a multitude of lines of therapy and therapies including standard chemotherapies, *EGFR*-TKIs and combination treatments[10,11,13–18]. Particularly, it is prognostic of outcomes in the first line. Grossi *et al.*[12] demonstrated that in non-squamous patients treated with standard chemotherapy in the front line setting, the VS test was prognostic. Patients classified as VSGood had significantly longer Progression Free Survival (PFS) and OS than those classified as VSPoor: 6.5 vs. 1.6 months, $p < .001$ and 10.8 vs. 3.4 months, $p < .001$ respectively. Additionally, the VS test identifies which patients will not benefit from *EGFR*-TKI therapies. Carbone *et al.* demonstrated that, for patients with tests results of VSPoor, treatment with an *EGFR*-TKI (erlotinib) was not significantly better than treatment with placebo ($p = .11$)[11]. Gregorc *et al.* reported in a prospective randomized phase III trial that patients classified as VSPoor had better median survival on chemotherapy rather than erlotinib (6.4 vs. 3.0 months, $p = .002$)[18].

These clinical results suggest that physicians can utilize the VS test results to assist in conversations about prognosis and optimize treatment goals and strategy for each individual patient. Patients with a test result of VSPoor have a poor prognosis: they should be considered for treatment with single-agent chemotherapy (if the patient can tolerate it) or best supportive care but given the inherent toxicity of treatment and lack of benefit, VSPoor patients should not be considered for treatment with *EGFR*-TKIs. On the other hand, patients classified as VSGood have a better prognosis, they benefit from standard systemic treatments as opposed to best supportive care. A prior study, Akerley *et al.*, assessed the impact of the VS proteomic test on treatment recommendations made by physicians. With a final analysis group of 403 tests, it found that 90.3% of patients with a test result of VSGood received erlotinib while only 9.6% of patients with test results of VSPoor received erlotinib. The remaining 90% of VSPoor patients were recommended alternative therapies such as chemotherapies. Physicians followed test results in making treatment recommendations 90% of the time[19].

The objective of this current study is to reassess the real-world clinical decision impact of the VS test in light of current utilization patterns in a large sample. Analysis will focus on treatment patterns following VS testing, including the extent to which treatment recommendations change after review of VS test results and whether physicians follow the test results in making treatment recommendations.

Patients and methods

Study design and population

The study is a pre/post observational analysis of treatment recommendations for VS tests ordered between 1 January 2012 and 1 November 2016 in adult patients diagnosed with NSCLC. Tests and associated recommendations were excluded from the study: (1) if the VS test result was indeterminate, (2) if the test was ordered for tumor types other than advanced NSCLC, (3) if VS was ordered alongside another test so that results for multiple tests were delivered at the same time, and (4) if the patient was known to harbor an *EGFR* mutation at time of VS testing.

Data collection

Data for this study was collected as an enumerated activity pursuant to the Health Insurance Portability and Accountability Act (HIPAA) regulations. The Quorum Review Institutional Review Board (IRB), Seattle, WA determined that the study did not constitute research involving human subjects as defined in Code of Federal regulation title 45 part §46.102 and therefore was exempt from IRB approval or a HIPAA waiver. Information required for ordering, processing and billing of the VS test was recorded on the test request form. This included international classification of diseases (ICD) codes to confirm location of tumor, *EGFR* mutation status, as well as patient demographics such as date of birth, date of service (combined to calculate age) and gender. Information on the ordering facility, physician name and address, and test results were also documented. Within the request form, physicians were given the option to report which of the following treatment options were being pursued as the primary consideration: pemetrexed, platinum doublet, docetaxel, bevacizumab, clinical study, radiation therapy (RT), afatinib, best supportive care/hospice, erlotinib, and other (with space for physicians to provide details of "other"). Following completion of the VS test and delivery of the test result, physicians were asked to voluntarily submit their final post-test treatment recommendation by choosing from the same list of options as the pre-test treatment considerations.

Data analysis

Treatment recommendations were assigned to one of three categories: (1) *EGFR*-TKIs as monotherapy or as part of a selection of treatments (e.g. adjunct to radiation therapy), *EGFR*-TKIs included any approved drug, such as erlotinib, afatinib, gefitinib; (2) best supportive care (BSC) (e.g. RT without adjunctive chemotherapy, no active treatment, supportive care/hospice); or (3) standard systemic therapy regimens, such as doublet and single agent chemotherapies,

clinical trials. Tests for which both pre- and post-treatment information was reported were included in the final analysis group.

All statistical analyses were carried out in R v3.2.2 software. Pearson chi-squared tests were used to evaluate the demographic differences between eligible tests and the analysis group. Changes in treatment recommendations were evaluated using McNemar's chi-squared tests. Confidence intervals around treatment recommendations and changes in treatment recommendations were elicited using exact methods. Linear multivariate regression analyses were used to evaluate the impact of physician and patient specific factors on referral to BSC, changes in treatment recommendations and concordance of final treatment recommendations with test results. Finally, treatment patterns were compared between large and small volume physicians (threshold set at the average number of tests per physician, 8.5 tests), and between above 65 and below 65 year old patients.

Results

Within the investigated time frame, 2411 physicians ordered 14,327 single VS tests. Of these, 241 were excluded because of indeterminate test results; tests for 226 non-lung tumor types were excluded; and 11 were excludes because the patient had a known *EGFR* mutation at time of VS testing. There were 13,849 eligible tests ordered by 2411 physicians eligible for this study. To observe changes in treatment considerations, physicians had to have voluntarily provided both a pre-test treatment consideration and a post-test treatment recommendation for each test. However, for most of the tests ($n = 11{,}355$) one or both of these data elements were not reported (Figure 1).

Both pre-test treatment consideration and post-test treatment recommendation data was provided for 2494 tests by 989 unique physicians. Demographics from the 13,849 eligible tests were compared to the 2494 tests in the analysis group to ensure that the study group was representative of real-world usage of the VS test (Table 1).

Eligible tests and the analysis groups were not significantly different in terms of patient age or gender. However, a slightly higher proportion of tests in the analysis group received VSGood results compared to the eligible group (78% and 76% respectively). In addition, a higher portion of tests in the analysis group were ordered by a physician serving in a community facility (95% and 92% respectively). Due to the large sample size of the eligible population, even small variances between groups are expected to be significant in binary variables. Tests in the final analysis group were ordered by physicians who on average ordered more tests than the total eligible group (8.4 versus 5.7 tests per physician); however, it is important to note that the majority of the 989 final physicians also ordered tests that were missing treatment recommendation information that could therefore not be included in the final analysis group. High volume

Table 1. Patient and physician demographics: eligible test group and analysis group.

	Eligible tests	Analysis group (complete pre and post data)	Pearson chi-square test, *p*-value
Tests (*N*)	13,849	2494	
Age (median years)	71.0	70.0	.818
Gender (% male)	51.8	51.6	.842
Test results (% VSGood)	75.5%	78.2	<.001***
Physician (*N*)	2411	989	
Facility type (% community)	92.3	94.9	<.001***

Confidence intervals: *90% CI, **95% CI, ***99% CI.

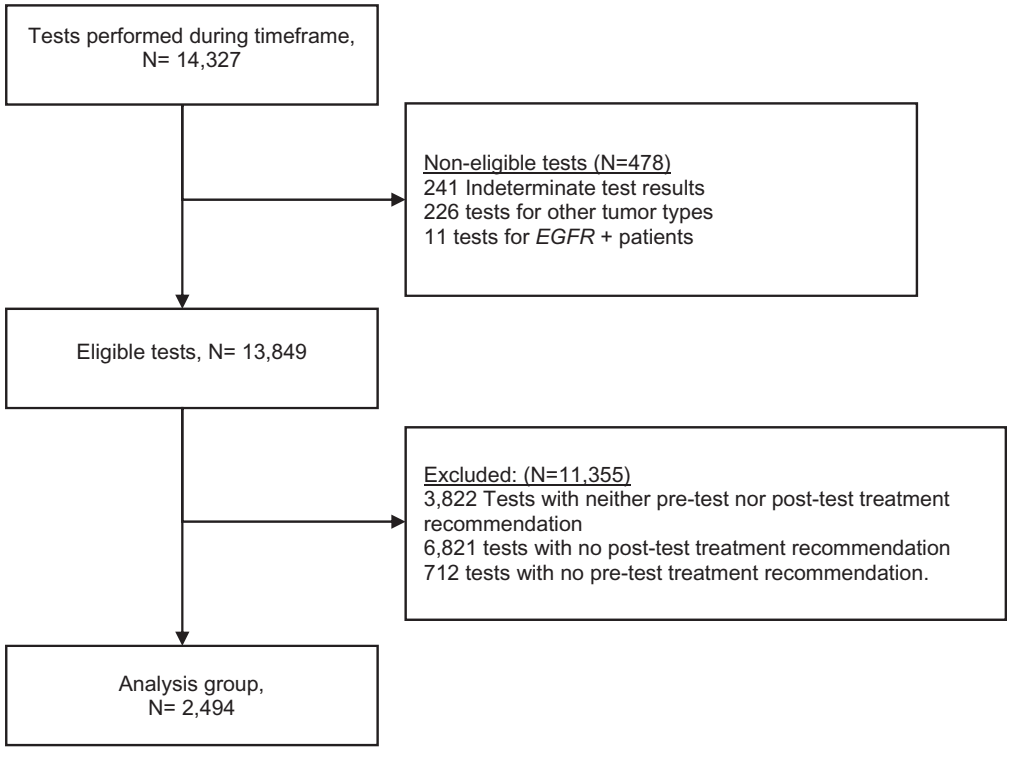

Figure 1. Inclusion and exclusion of tests from analysis.

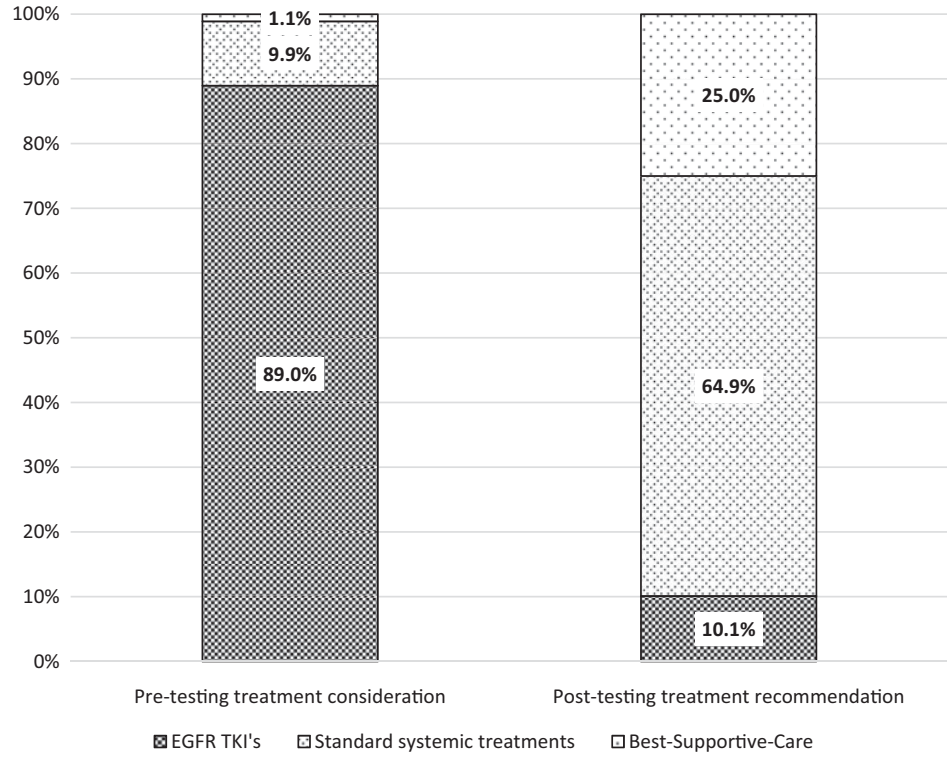

Figure 2. Changes in treatment recommendations for VSPoor patients.

Table 2. Changes in physicians' treatment recommendation with and without knowledge of VS test results.

Without test results (prior to testing)	Without test results (*N*)	With test results (post testing)	With test results, *N* (%)	95% CI
All patients combined				
EGFR-TKI	2250	EGFR-TKI	1675 (74.4)	[72.6–76.2]
		Other active treatment	430 (19.1)	[17.5–20.8]
		Best supportive care	145 (6.4)	[5.5–7.5]
Other active treatment	233	EGFR-TKI	114 (48.9)	[42.3–55.5]
		Other active treatment	109 (46.8)	[40.2–53.4]
		Best supportive care	10 (4.3)	[2.1–7.8]
Best supportive care	11	EGFR-TKI	3 (27.3)	[6.0–61.0]
		Other active treatment	4 (36.4)	[10.9–69.2]
		Best supportive care	4 (36.4)	[10.9–69.2]
VSGood				
EGFR-TKI	1766	EGFR-TKI	1626 (92.1)	[90.7–93.3]
		Other active treatment	122 (6.9)	[5.8–8.2]
		Best supportive care	18 (1.0)	[0.6–1.6]
Other active treatment	179	EGFR-TKI	108 (60.3)	[52.8–67.6]
		Other active treatment	66 (36.9)	[29.8–44.4]
		Best supportive care	5 (2.8)	[0.9–6.4]
Best supportive care	5	EGFR-TKI	3 (60.0)	[14.7–94.7]
		Other active treatment	2 (40.0)	[5.3–85.3]
		Best supportive care	0 (0.0)	[0.0–52.2]
VSPoor				
EGFR-TKI	484	EGFR-TKI	49 (10.1)	[7.6–13.2]
		Other active treatment	308 (63.6)	[59.2–67.9]
		Best supportive care	127 (26.2)	[22.4–30.4]
Other active treatment	54	EGFR-TKI	6 (11.1)	[4.2–22.6]
		Other active treatment	43 (79.6)	[66.5–89.4]
		Best supportive care	5 (9.3)	[3.1–20.3]
Best supportive care	6	EGFR-TKI	0 (0.0)	[0.0–45.9]
		Other active treatment	2 (33.3)	[4.3–77.7]
		Best supportive care	4 (66.7)	[22.3–95.7]

physicians, however, were more likely to have at least one test included in the analysis group.

In the analysis group, prior to receiving tests results, physicians were considering treatment with *EGFR*-TKIs for 2250 patients (90.2%), with systemic therapies other than *EGFR*-TKIs for 233 patients (9.3%), and BSC for 11 patients (0.4%). A total of 1950 patients received a classification of VSGood (78.2%) and 544 patients received a classification of VSPoor (21.8%).

Following receipt of the VS test results, physicians recommended BSC for 136 (25.0%) of the 544 patients classified as VSPoor, standard systemic therapies such as chemotherapies for 353 (64.9%) of patients and *EGFR*-TKIs in 55 patients or 10.1%. Figure 2 and Table 2 show the changes in treatment recommendations following the delivery of test results.

In the 1950 patients classified as VSGood, physicians recommended *EGFR*-TKIs for 1737 patients or 89.1%. Physicians recommended standard systemic treatments for 190 VSGood patients (9.7%) and BSC for the remaining 23 patients (1.2%).

Since VS is a negative predictor of response to *EGFR*-TKIs, we investigated post-test treatment recommendations in the subgroup considering *EGFR*-TKIs as a treatment prior to testing.

Physicians had been considering treatment with an *EGFR*-TKI in 484 of the 544 patients classified as VSPoor (89.0%) and in 1766 of the 1950 patients classified as VSGood (90.6%). Within the patients ultimately classified as VSPoor for whom physicians were considering treatment with an *EGFR*-TKI, only 49 (10.1%) were ultimately recommended *EGFR*-TKIs; instead, 127 (26.2%) were recommended BSC and 308 (63.6%) were recommended standard systemic treatments. In the 1766 patients considering treatment with *EGFR*-TKIs and classified as VSGood, physicians ultimately recommended *EGFR*-TKIs for 1626 (92.1%), standard systemic treatment for 122 (6.9%) and BSC for 18 (1.0%).

We evaluated changes in treatment recommendations and the extent to which physician ultimate treatment recommendations were consistent with VS test results. Given the results of Carbone *et al.*[11] (for patients with tests results of VSPoor, treatment with an *EGFR*-TKI is not significantly better than treatment with placebo, $p = .11$), in patients classified as VSPoor, we deem that treatment with an *EGFR*-TKI would be ineffective in improving OS or quality of life. However, in patients classified as VSGood, given the results of the PROSE study (similar outcomes on chemotherapy and *EGFR*-TKIs), all treatments recommendations were considered appropriate.

Table 3. Changes in treatment plan and test result application.

Treatment consideration changes	(% of group)
% change from initial treatment recommendation	28.2
% change when test result is VSGood	13.2
% change when test result is VSPoor	81.6
Treatment consideration follow test result	
% of post-test recommendations in concordance with test result	97.8
% following test result when test result is VSGood	100.0
% following test result when test result is VSPoor	89.9

Physicians followed test results in making treatment recommendations in 97.8% of all cases. In patients classified as VSPoor, physicians recommended treatments consistent with the test results (standard systemic therapies or BSC) in 89.9% of cases. Physician changed treatment recommendations to match test results in 81.6% of patients classified as VSPoor. As expected, the majority of treatment recommendation changes were made for patients with VSPoor test results. (Table 3).

While prior to testing 484 of 544 patients ultimately classified as VSPoor were being considered for an ineffective therapy (*EGFR*-TKI's), after testing, only 55 of 544 patients were recommended an ineffective therapy, an 88.6% decrease in ineffective treatment recommendations for patients classified as VSPoor.

Using linear multivariate models, we investigated the impact of test results, patient age and patient sex, as well as setting (academic or community), year of test, and physician familiarity with the test (high or low volume) on physician referral to BSC, on changes in treatment recommendations, and on concordance of final treatment recommendation with test result (Table 4). The VS test result was the only significant predictor of treatment recommendation to BSC in the multivariate model ($p < .001$). As expected, the VS test result was also the only significant predictor of change in treatment decision ($p < .001$). Finally, neither physician nor patient characteristics were significant predictors of concordance of treatment recommendation with test result in patients with a result of VSPoor. This suggests that physicians are not significantly influenced by patient factors to change their treatment recommendations following test results. Additionally, to ensure the lack of bias of our final data, we compared the treatment recommendations of all post-test treatment recommendations including the 712 that were excluded for missing pre-test information to the final analysis group. We found no significant difference between the groups in referral to BSC ($p = .691$), or in concordance of treatment decision with test results ($p = .999$).

Finally, there were no differences in test results or prescribing behavior for younger and older patients when defined at the Medicare eligibility threshold of 65 years. Test results were similar between the below 65 years and 65 and above age categories (% VSPoor: 21.3% versus 22.0% respectively, $p = .751$) and referral to BSC for patients with test results of VSPoor was also similar in the two age categories (24.4% and 25.3% respectively, $p = .607$). Additionally, familiarity with testing (based on volume of physician test orders) was not a significant factor in treatment decision or changes in treatment decisions.

Table 4. Multiple variable linear regression to estimate the impact of patient and physician characteristics on treatment recommendations.

	Post-test BSC recommendation		Change in treatment recommendation		Concordance of recommendation with test results (VSPoor only)*	
	Estimate	*p*	Estimate	*p*	Estimate	*p*
VSGood result	−0.243	<.001	−0.687	<.001	—	—
Year of test	−0.007	.136	−0.012	.123	0.016	.292
Age (above or below 65)	0.007	.505	−0.006	.703	0.014	.632
Gender (male)	0.002	.847	0.014	.350	0.029	.298
Academic setting	−0.003	.898	−0.034	.305	−0.102	.084
Physician order volume	−0.003	.777	−0.016	.277	−0.044	.115

*Concordance of recommendation with test results test results was only evaluated in VSPoor test results as all treatments were deemed appropriate for test results of VSGood.

Discussion

In 85% of cases, NSCLC is diagnosed at an advanced stage where it is incurable. Furthermore, NSCLC is most commonly diagnosed in the elderly, who are often frail or have significant comorbidities. Quality of life and overall survival should be significant factors in making treatment decisions. Tools that measure the aggressiveness of cancer or predict response to treatment are lacking, and prognostication using clinical factors can be difficult and unreliable. This uncertainty can decrease quality of life at end of life through overtreatment and use of ineffective therapies. While the low-toxicity profile and ease of administration of *EGFR*-TKIs offers potential benefit to patients who are unwilling or unable to undergo further rounds of chemotherapy, not all patients will benefit from therapy. The test's prognostic and predictive ability has been demonstrated in retrospective and prospective clinical trials[10–18]. Consistently, those trials demonstrate a statistically significant difference in outcomes between the VSGood and VSPoor populations. Patients with VSGood results benefit from *EGFR*-TKI therapy or standard chemotherapy while patients with VSPoor results have a poor prognosis and derive little to no benefit from *EGFR*-TKI therapy.

This study demonstrates that both the prognostic and predictive value of the VS test is used by physicians to help determine treatment recommendations for advanced NSCLC patients. Most significantly, for patients classified as VSPoor, a quarter are not recommended active treatment but instead are recommended for best supportive care to focus on quality-of-life care. The recommendation to forego treatment is consistent across patient demographics, with no statistical significance between the Medicare and under-65 patient populations.

In addition to the 25% recommendation to BSC, 64% of VSPoor patients were recommended standard systemic treatments. These results suggest that the VS test not only supports patient–physician conversations about prognosis and BSC but also helps physicians decide whether to treat with an *EGFR*-TKI. The VS test may allow for a reduction in aggressive end-of-life care and decrease costly, ineffective overtreatment in patients classified as VSPoor. These results are more pronounced in the subset of patients where physicians were considering *EGFR*-TKIs prior to testing. For this population, 26.2% of patients with VSPoor results are recommended BSC. This would indicate that some tested patients are unwilling or unable to undergo standard chemotherapies but would have elected treatment with less toxic *EGFR*-TKIs. In this patient population, the VS test is most likely to reduce ineffective overtreatment in favor of the quality of life gains that BSC can provide. On the other hand, patients with VSGood results were generally not referred to best supportive care.

Unsurprisingly, multivariate analysis found that patient demographics and physician characteristics were not significant predictors of treatment patterns or change in treatment decisions due to VS testing.

Due to its observational and voluntary nature, this study has several limitations. Because it is impossible to provide a control in a single patient to observe a change in treatment recommendations, we must rely on pre-testing treatment preferences as a proxy for non-tested treatment preferences in this patient group. Due to the voluntary nature of data submission, this study is based on a subset of eligible tests. However, demographic comparisons between the analysis group and the eligible population suggest that the observed outcomes are representative of real-world usage of the test. In addition, other clinical factors which may impact treatment decisions, such as patient performance status, patient and family preferences, and financial implications, were not available. Finally due to the nature of this study, compliance with the post-test treatment recommendation could not be observed within this study. The shift to BSC for patients with a poor prognosis (test result of VSPoor) is expected to create large cost savings to the system. Further studies evaluating the real-world health outcomes and cost–utility impact of these changes in treatment recommendations should be carried out.

Conclusion

The results of this study demonstrate that the VS test impacts physician treatment recommendations. After receipt of test results, physicians recommended best supportive care for 25% of patients with VSPoor test results and standard therapies for another 64% of patients. Physicians changed treatment recommendations for more than 80% of patients with a test result of VSPoor. VS testing reduced expensive ineffective treatment in VSPoor patients by 89%. In response to VSGood results, physicians overwhelmingly recommended *EGFR*-TKIs. This study suggests that, in clinical practice, physicians change treatment recommendations based upon the VS test, follow test results, and use the test to evaluate prognosis and avoid expensive ineffective therapies for their patients.

Note

1. VeriStrat is a registered trade name of Biodesix Inc., Boulder, CO, USA

Transparency

Declaration of funding

This work was supported by Biodesix Inc.

Declaration of financial/other relationships

W.L.A. has disclosed that he has previously received remuneration from Biodesix for advisory work but did not received payments for his work related to this study. A.M.A. has disclosed that she is an employee of Biodesix Inc. and owns stock options in Biodesix. B.R. has disclosed that he has previously received research funding from Biodesix Inc. for research unrelated to this current study but was not remunerated for his participation in this study.

R.D.P does not have relevant financial interests in the products discussed in this publication and was not remunerated for his participation in the study

CMRO peer reviewers on this manuscript have received an honorarium from *CMRO* for their review work, but have no relevant financial or other relationships to disclose.

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