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ORIGINAL ARTICLE

Impact of lung cancer screening on stage migration and mortality among the national Veterans Health Administration population with lung cancer

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Abstract

Background: Despite randomized trials demonstrating a mortality benefit to low-dose computed tomography screening to detect lung cancer, uptake of lung cancer screening (LCS) has been slow, and the benefits of screening remain unclear in clinical practice.

Methods: This study aimed to assess the impact of screening among patients in the Veterans Health Administration (VA) health care system diagnosed with lung cancer between 2011 and 2018. Lung cancer stage at diagnosis, lung cancer–specific survival, and overall survival between patients with cancer who did and did not receive screening before diagnosis were evaluated. We used Cox regression modeling and inverse propensity weighting analyses with lead time bias adjustment to correlate LCS exposure with patient outcomes.

Results: Of 57,919 individuals diagnosed with lung cancer in the VA system between 2011 and 2018, 2167 (3.9%) underwent screening before diagnosis. Patients with screening had higher rates of stage I diagnoses (52% vs. 27%; $p \leq .0001$) compared to those who had no screening. Screened patients had improved 5-year overall survival rates (50.2% vs. 27.9%) and 5-year lung cancer–specific survival (59.0% vs. 29.7%) compared to unscreened patients. Among screening-eligible patients who underwent National Comprehensive Cancer Network guideline–concordant treatment, screening resulted in substantial reductions in all-cause

The first two authors contributed equally to this article.

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mortality (adjusted hazard ratio [aHR], 0.79; 95% confidence interval [CI], 0.67–0.92; $p = .003$) and lung-specific mortality (aHR, 0.61; 95% CI, 0.50–0.74; $p < .001$). **Conclusions:** While LCS uptake remains limited, screening was associated with earlier stage diagnoses and improved survival. This large national study corroborates the value of LCS in clinical practice; efforts to widely adopt this vital intervention are needed.

KEYWORDS
cancer outcomes, early detection of cancer, lung cancer screening, lung neoplasms

INTRODUCTION

Lung cancer remains the leading cause of cancer deaths worldwide, and the majority of lung cancer is diagnosed at an advanced stage.[1] Among patients with non–small cell lung cancer (NSCLC), the most common form of lung cancer, 5-year survival for early stage I disease is approximately 68%, compared to a rate of 5.8% for metastatic disease.[2] Thus, prompt detection of early-stage disease is paramount to improving outcomes. The US Preventive Services Task Force (USPSTF) currently recommends annual low-dose computed tomography (LDCT) screening for adults between the ages of 50 and 80 years with at least a 20-pack-year smoking history who currently smoke or have quit within the past 15 years. This recommendation is based on randomized trial evidence of a mortality benefit and stage migration effect with screening. The National Lung Screening Trial (NLST) demonstrated that the use of annual lung cancer screening (LCS) compared to chest x-rays in high-risk patients resulted in a relative reduction of 20% in lung cancer mortality.[3] In the Dutch-Belgian Randomized Lung Cancer Screening Trial lung screening trial, high-risk patients who underwent LCS with CT imaging every 1–2.5 years (baseline and 1, 3, and 5.5 years) similarly had decreased lung cancer mortality. Notably, a higher proportion of screening-detected lung cancers were stage I compared to non–screening-detected cases (58.6% vs. 14.2%).[4] Presumably, the concept of stage migration, or the shift in identifying more earlier stage cancers at the time of diagnosis before progression to advanced disease, contributed to the mortality benefit in these trials.

However, the mortality benefits of screening shown in these trials can only be realized with broad implementation of screening into clinical practice, and there remains a need to demonstrate the real-world effectiveness of LCS. There are patient-, provider-, and system-specific challenges to the implementation of screening,[5] which have resulted in the slow adoption of screening in clinical care. Rates of adherence to screening, which were upward of 90% in both randomized trials, are lower in real-world settings,[6] particularly among Black patients[7] and current smokers as well as younger or less educated patients.[8] A recent analysis from the LCS registry demonstrated that only 1.9% of 7.6 million eligible smokers per NLST criteria underwent screening in 2016.[9] Variations in patient characteristics of those undergoing screening in practice have the potential to affect the effectiveness of screening. Participants of randomized controlled trials are often more educated or healthier than the general population, and such disparities in real-world patients from trial patients may raise concern over the applicability of trial results to the general population, who are often more elderly or frail or have more medical comorbidities.[6] It is also possible that the implementation of screening into practice has been affected by provider concern for overdiagnosis and the treatment of cancers that would have otherwise remained indolent.[4,10,11] Additional concerns involve adequate infrastructure available to support comprehensive screening programs, as noted in a survey of pulmonologists in the Veterans Health Administration (VA) system.[12]

The VA is the largest integrated provider of cancer care in the United States, and cares for approximately 6.7 million veterans a year system-wide.[13] There is a heightened prevalence of smoking among veterans with military service,[14–16] which results in an estimated 76% higher age-specific incidence of lung cancer than the general population.[17] The Lung Cancer Screening Demonstration Project via the VA estimated that nearly 900,000 patients out of a population of 6.7 million VA patients would be eligible for LCS.[13] However, there are limited VA data beyond single-site reports[18,19] to assess the effectiveness of LCS in diagnosing cancer at an earlier stage. In this study, we performed a retrospective analysis of 57,919 veterans in the national VA lung cancer registry diagnosed with lung cancer between 2011 and 2018 to assess whether LCS influences the outcomes of veterans with lung cancer.

MATERIALS AND METHODS

Study design

The national VA lung cancer registry was retrospectively reviewed to identify patients diagnosed with lung cancer between the years 2011 and 2018. This time period was chosen to encompass the years during which time we would expect to see screening become more used in clinical practice, after publication of the NLST. Demographic and clinical variables were extracted from the lung cancer registry at the time of diagnosis. Cancer stage was determined on the basis of the American Joint Committee on Cancer system currently in use at

the time of diagnosis, and patients with stage 0 lung cancer were excluded from the analysis because of their small numbers. Staging from the lung cancer registry was confirmed by manual chart review in a subset of 50 patients to ensure consistency between the registry and electronic medical record (EMR). The diagnosis of lung cancer included all primary lung cancers, such as adenocarcinoma, squamous cell carcinoma, and small cell lung cancer. Information on smoking history was obtained via a natural language processing algorithm to identify smoking pack-years and quit date status that were then manually verified. The main exposure variable of interest was LCS, and patients were considered to have had screening if they had at least one LDCT screening before the date of their lung cancer diagnosis identified on the basis of *International Classification of Diseases* (ICD), *Ninth and Tenth Revision* codes. The outcome of overall survival was obtained from the date of diagnosis until death or the last known follow-up in the EMR. Lung cancer–specific mortality was then extracted from the cancer registry and merged with National Death Index data via the ICD-coded lung-specific cause of death (C33 or C34). This study was reviewed and approved by the institutional review board (IRB) of the Veterans Affairs Ann Arbor Healthcare System.

Statistical analysis

Statistical analyses were performed via R (version 4.1.2) and GraphPad Prism. Comparisons in baseline characteristics between the LCS and no-LCS cohorts were made via χ^2 and Wilcoxon tests. To account for the lead time bias resulting from earlier disease detection by screening, an estimated correction time was subtracted from each patient's observed survival time. The expected additional survival time observed solely as a result of lead time in the screened patients was estimated according to the method in Duffy et al.[20] Survival functions were estimated with the Kaplan–Meier method and compared between the LCS and no-LCS cohorts via the log-rank test. We also defined a separate subset of patients from the overall cohort to be screening eligible. Screening-eligible patients were defined as those between the ages of 50 and 80 years, who were smokers with a pack-year history of ≥20 years or former smokers who quit within 15 years, and who underwent guideline-concordant treatment within 12 months of diagnosis. Multivariate Cox modeling was performed with this screening-eligible subset of patients. To estimate the effect of screening on eligible patients, inverse probability treatment weighting (IPTW) analysis was performed in a Cox regression. To do this, we developed a propensity scoring model to predict prior LCS exposure via age, gender, race, ethnicity, smoking status, pack-years, and comorbidity score. For each patient, we estimated their propensity score for LCS and computed IPT weights for LCS exposure status. Standardized mean differences before and after IPTW indicated that any covariate imbalances between the screened and unscreened groups had been eliminated by the weighting. The mean sojourn time for lung cancer required for this method was estimated from a meta-analysis by Chien et al.[21]

Patient and public involvement

The research questions addressed in this study directly reflect our goal to improve the outcomes of patients with lung cancer. It is known that despite randomized trial evidence and USPSTF recommendations, LCS has not been widely adopted. We hope that this study will inspire patients, physicians, hospital administrators, and policymakers alike to improve implementation of this intervention and save more lives with early cancer detection. Patients were not directly involved in the study design, and all data were retrospectively acquired with IRB approval from the VA (IRB 1638998).

RESULTS

A total of 57,919 individuals were diagnosed with lung cancer in the VA system between the years 2011 and 2018. Of these patients, 2167 (3.9%) underwent screening, with at least one LDCT before their lung cancer diagnosis. Baseline characteristics of the patients and characteristics of the diagnosed lung cancers are shown in Table 1, Table 2, and Table S1.

There were no significant differences in age, gender, or race among patients who had prior screening (LCS cohort) and those without prior screening (no-LCS cohort) (Table 1). There were more non-Hispanic patients ($p = .002$) and fewer nonsmokers ($p < .001$) among patients who were screened compared to unscreened. Additionally, there were more adenocarcinomas and fewer squamous cell carcinoma diagnoses in the screened group compared to those diagnosed without screening ($p < .001$). An uptake in screening was particularly noted after 2014, with an increasing proportion of patients diagnosed with lung cancer after screening over time; for example, 2.9% of the total screened cohort in 2014 increased to 44% by 2018 (Figure S1).

We explored whether prior LCS exposure would correlate with a stage shift and earlier diagnosis of lung cancer. Screened patients had double the rate of stage I diagnoses compared with unscreened patients (52% vs. 27%; $p \leq .0001$) as well as a lower proportion of stage IV diagnoses (11% vs. 32%; $p \leq .0001$) (Table 2; Figure 1; Table S2). The incidence of each stage of lung cancer (I–IV) by year among screened and unscreened patients is shown in Figure S2, and the trend toward a higher incidence of stage I lung cancers and lower incidence of stage IV cancers among screened patients is consistent, particularly in the years 2014–2018, in which an uptake in screening in this cohort is most notable (Figure S1).

Corresponding to the heightened incidence of stage I lung cancers in the screened cohort, we also observed improved overall survival among patients who received screening before their cancer diagnosis (Figure 2A). The 1-, 2-, and 5-year overall survival rates were 81.2%, 69.9%, and 44.9%, and 56.6%, 41.1%, and 22.3% for the screened cohort and unscreened cohort, respectively ($p < .0001$). Lung cancer–specific survival is similarly heightened among those undergoing screening (Figure 2B). The 1-, 2-, and 5-year lung cancer–

TABLE 1 Patient characteristics in the VA cancer registry from 2011 to 2018.

Patient characteristics	All patients (n = 57,919)	Cohort 1: LCS (n = 2167)	Cohort 2: no LCS (n = 55,752)	p (cohort 1 vs. cohort 2)
Age, years				.603
Median (range)	69 (64–75)	69 (66–73)	68 (64–75)	
Gender, No. (%)				.175
Female	1550 (2.7)	68 (3)	1482 (2.7)	
Male	56,369 (97.3)	2099 (97)	54,270 (97.3)	
Race, No. (%)				.381
Asian	144 (0.2)	7 (0.3)	137 (0.3)	
Black	9506 (16.4)	342 (15.7)	9164 (16.4)	
Native American	302 (0.5)	9 (0.4)	293 (0.5)	
Pacific Islander	338 (0.6)	11 (0.5)	327 (0.6)	
White	45,333 (78.3)	1709 (78.9)	43,624 (78.2)	
Other	378 (0.7)	21 (1)	357 (0.6)	
Unknown	1918 (3.3)	68 (3.1)	1850 (3.3)	
Ethnicity, No. (%)				.002
Non-Hispanic	54,942 (94.9)	2087 (96.3)	52,855 (94.8)	
Hispanic	1343 (2.3)	29 (1.3)	1314 (2.4)	
Unknown	1634 (2.8)	51 (2.4)	1583 (2.8)	
Smoking status, No. (%)				<.001
Nonsmoker	7054 (12.2)	222 (10.2)	6832 (12.3)	
Former smoker	12,262 (21.2)	504 (23.3)	11,758 (21.1)	
Current smoker	24,497 (42.3)	1124 (51.9)	23,373 (41.9)	
Unknown	14,106 (24.4)	317 (14.6)	13,789 (24.7)	
Alive, No. (%)				<.001
	13,464 (23.3)	1235 (57.0)	12,229 (21.9)	
Follow-up time, years				<.001
Median (Interquartile range)	2.22 (0.41–3.34)	2.48 (1.49–3.37)	1.34 (0.39–3.34)	

Abbreviations: LCS, lung cancer screening; VA, Veterans Health Administration.

specific survival rates were 82.5% versus 58.7%, 74.3% versus 44.4%, and 59.0% versus 29.7% for the screened versus unscreened cohorts, respectively ($p < .0001$).

We further explored the impact of screening within a defined subset of patients deemed screening eligible. This subset of our entire cohort was defined as those patients between the ages of 50 and 80 years, who were smokers with a pack-year history of ≥20 years or former smokers who quit within 15 years, and who underwent guideline-concordant treatment within 12 months of diagnosis. Of our total cohort of 57,919 patients, 10,075 (17.4%) were determined to be screening eligible. Multivariate Cox modeling of this subset showed that screening was associated with a sizeable decrease in all-cause mortality (adjusted hazard ratio [aHR], 0.46; 95% confidence interval [CI], 0.4–0.54; $p < .0001$) and lung cancer–specific death (aHR, 0.37; 95% CI, 0.31–0.45; $p < .0001$) (Figure 3). Cox modeling with an IPTW approach showed similar results (Figure S3). Finally, as a further sensitivity analysis, we also incorporated the IPTW with a lead time bias adjustment as described in our methodology and observed continued association of screening with an improvement in all-cause mortality (aHR, 0.79; 95% CI, 0.67–0.92; $p = .003$) and lung-specific mortality (aHR, 0.61; 95% CI, 0.50–0.74; $p < .001$).

Propensity score modeling of the screening-eligible subset further revealed that patients who had a smoking history (adjusted odds ratio [aOR], 1.26; 95% CI, 1.09–1.47; $p = .002$) or were Black (aOR, 1.2; 95% CI, 1.04–1.43; $p = .016$) were more likely to have been screened, whereas Hispanic patients (aOR, 0.56; 95% CI, 0.3–0.93; $p = .0391$) and patients with more comorbidities (aOR, 0.87; 95% CI, 0.83–0.91; $p \leq .0001$) were less likely to have had screening (Table S3).

TABLE 2 Cancer characteristics among patients in the VA cancer registry from 2011 to 2018.

Cancer characteristics	All patients (n = 57,919)	Cohort 1: LCS (n = 2167)	Cohort 2: no LCS (n = 55,752)	p (Cohort 1 vs. Cohort 2)
Stage, No. (%)				<.001
I	16,570 (28.6)	1136 (52.4)	15,434 (27.7)	
II	5279 (9.1)	185 (8.5)	5094 (9.1)	
III	10,594 (18.3)	292 (13.5)	10,302 (18.5)	
IV	18,281 (31.6)	250 (11.5)	18,031 (32.3)	
Unknown	7195 (12.4)	304 (14)	6891 (12.4)	
Histology, No. (%)				.002
Adenocarcinoma	24,662 (42.6)	993 (45.8)	23,669 (42.5)	
Squamous cell carcinoma	19,844 (34.3)	674 (31.1)	19,170 (34.4)	
Other	13,123 (22.7)	495 (22.8)	12,628 (22.7)	
Unknown	290 (0.5)	5 (0.2)	285 (0.5)	

Abbreviations: LCS, lung cancer screening; VA, Veterans Health Administration.

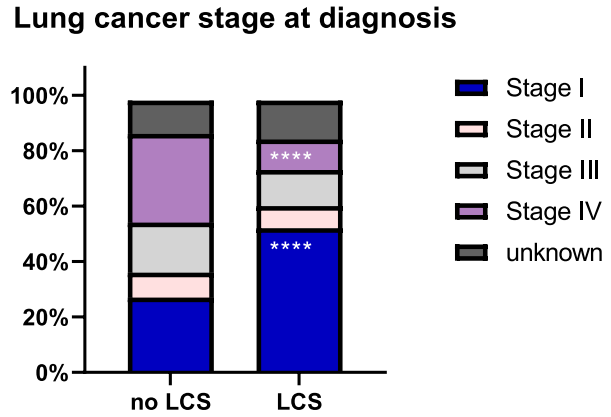


FIGURE 1 Stage migration of lung cancer diagnoses between 2011 and 2018 among screened and unscreened patients. ****$p < .0001$ via the χ^2 test. LCS indicates lung cancer screening.

DISCUSSION

Despite robust randomized clinical trial data demonstrating a mortality benefit to LCS,[3,4] we observed that only a small minority of veterans with lung cancer (3.9%) obtained an LDCT before their lung cancer diagnosis, similar to other reported rates.[22] However, the use of screening in this small subset of veterans was associated with a compelling stage migration effect as well as an improvement in overall survival and lung cancer–specific survival, presumably due to cancer diagnosis and intervention at an earlier stage of disease. Multivariate Cox modeling of the screening-eligible population subset showed that use of screening was strongly associated with decreased overall mortality as well as lung-specific mortality. To our knowledge, this is the largest retrospective cohort of patients with lung cancer quantifying the real-world impact of LCS among veterans, a population enriched in smokers at high risk of developing lung cancers.[16]

Our results are in line with other studies that have similarly highlighted the value of implementation of screening into routine clinical care. A US National Cancer Database and Surveillance, Epidemiology, and End Results database analysis showed a population-level increase in diagnosis of stage I NSCLC in the years 2014–2018, which coincided with recommendations for LCS.[23] Additionally, Robertson et al.[24] used a transportability analysis in a comparative effectiveness study to estimate the effects of LCS on a national population of NLST-eligible US adults and estimated a persistent lung cancer mortality benefit to screening in this target population. Our data similarly capture the benefit of LCS in a high-risk patient population that differs in baseline covariates from clinical trial participants. Vachani et al. also noted in a multicenter retrospective cohort of over 3000 patients that among those who underwent screening before a diagnosis of lung cancer there was a stage migration to detecting more early-stage lung cancers.[25] Our analysis builds on and corroborates these previous studies at a patient level, and our work is unique in that we have been able not only to assess the differences in outcomes between patients with lung cancer who did and did not undergo screening but also to quantify the impact of screening among screening-eligible patients who subsequently received lung cancer–directed therapy, the most relevant population for clinical practice.

This study has its limitations, namely the retrospective and correlative nature of the design. We used robust statistical methods such as IPTW with lead time bias adjustment to minimize otherwise unmeasured confounding. Additionally, approximately 10% of patients in the screened cohort were classified as nonsmokers. We suspect that this may reflect misclassification in the EMR, and thus these data are limited in scope for understanding the impact of smoking status on outcomes. We were also unable to assess whether LCS contributed to more subsequent procedures in screened patients compared to unscreened patients because of the complexity in capturing the range of relevant procedures, such as bronchoscopy or

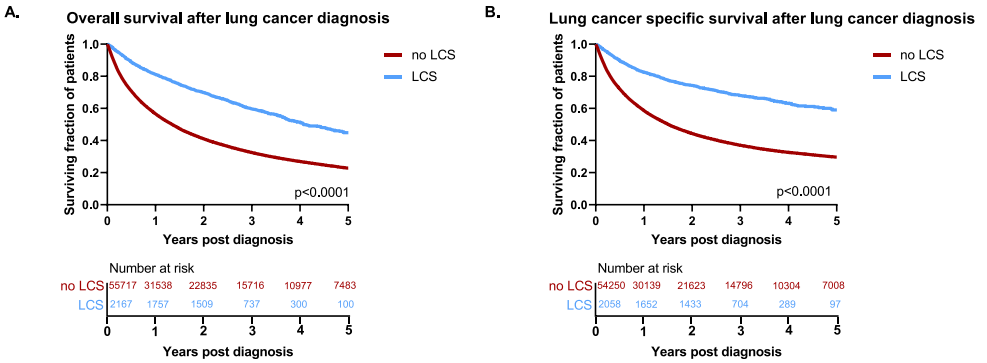


FIGURE 2 (A) Overall survival of patients with lung cancer who received LCS compared to those who did not receive screening before diagnosis. Overall survival was calculated from the date of diagnosis to the date of death or censoring at the last known follow-up. (B) Lung cancer–specific survival between patients with lung cancer who did and did not undergo screening before diagnosis. Data were censored after 5 years post diagnosis. LCS indicates lung cancer screening.

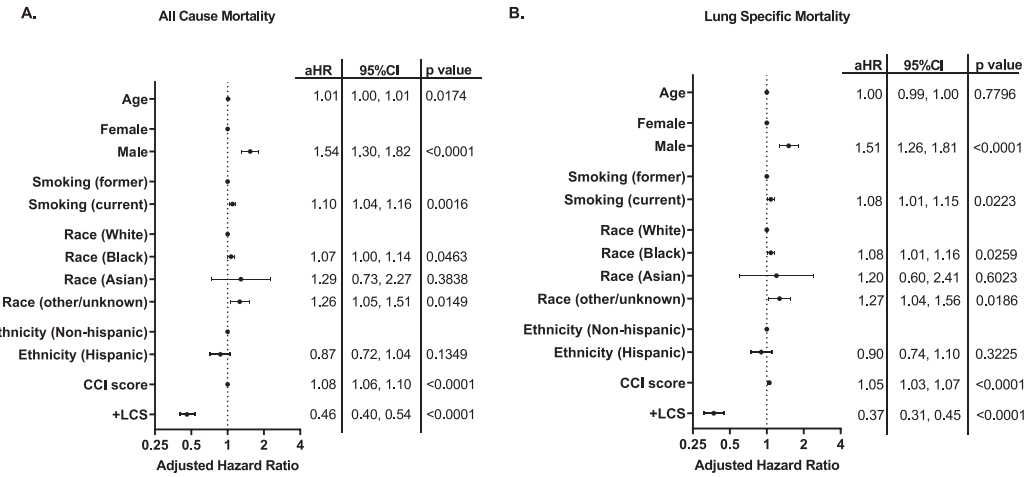


FIGURE 3 Cox modeling of baseline factors associated with all-cause mortality (A) and lung-specific mortality (B) among screening-eligible patients. aHR indicates adjusted hazard ratio; CCI, Charlson Comorbidity Index; CI, confidence interval; LCS, lung cancer screening.

CT-guided biopsy, and the inability to assess for potential confounding by patients for whom diagnosis triggered empiric treatment rather than additional procedures. Capturing such data would be an important goal for future study to fully appreciate the impact of LCS in clinical practice.

These findings provide corroboration of the results of randomized LCS trials in clinical practice. We hope that the striking association between LCS, earlier stage diagnosis of lung cancer, and improved mortality spurs a more robust uptake of this life-saving intervention into clinical practice.

AUTHOR CONTRIBUTIONS

Donna M. Edwards: Conceptualization, investigation, formal analysis, methodology, visualization, writing–original draft, and writing–review and editing. **Mina Pirzadeh**: Conceptualization, investigation, formal analysis, methodology, visualization, writing–original draft, and writing–review and editing. **Tony Van**: Conceptualization, data curation, formal analysis, investigation, and methodology. **Ralph Jiang**: Conceptualization, data curation, formal analysis, investigation, and methodology. **Akshay Tate**: Data curation. **Grace Schaefer**: Data curation. **Jadyn James**: Data curation. **Caroline Bishop**: Data curation. **Cydnee Wilson**: Data curation. **Nicholas Nedzesky**: Data curation. **Aaren Alseri**: Data curation. **Anthony Leveque**: Funding acquisition. **Amanda Malus**: Project administration. **Akbar Waljee**: Project administration. **David A. Elliott**: Project administration. **Jane Deng**: Project administration. **Ann Schwartz**: Supervision. **Matthew Schipper**: Conceptualization, data curation, formal analysis, methodology, and software. **Alex K. Bryant**: Conceptualization, data curation, formal analysis, methodology, and software. **Nithya Ramnath**: Conceptualization, funding acquisition, and supervision. **Michael D. Green**: Conceptualization, funding acquisition, and supervision.

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Donna M. Edwards affirms that the article is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained. All data were retrospectively acquired with institutional review board approval from the Veterans Health Administration. This work was supported by the institutionally approved use of resources and facilities at the Veterans Affairs Ann Arbor Healthcare System, as well as the LUNGevity Foundation (principal investigators [PIs], Alex K. Bryant and Michael D. Green), National Cancer Institute (CA252010; PI, Michael D. Green), Veterans Affairs (I01 BX005267; PI, Michael D. Green), Melanoma Research Alliance (MRA 689853; PI, Michael D. Green), and Lung Precision Oncology Program (VA 150CU000182; PI, Nithya Ramnath).

CONFLICT OF INTEREST STATEMENT

Matthew Schipper has been a consultant for Innovative Analytics. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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