Adherence to National Comprehensive Cancer Network ALK Testing Guidelines for Patients with Advanced Non-Small Cell Lung Cancer in U.S. Community Medical Centers

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Key Words. Real-world evidence • NCCN guidelines • ALK

ABSTRACT

Background. National Comprehensive Cancer Network (NCCN) guidelines recommend biomarker testing as the first step in the management of patients with advanced non-small cell lung cancer (aNSCLC). We assessed anaplastic lymphoma kinase (ALK) testing rates and factors related to underuse in community medical systems between 2012 and 2019 to understand guideline adoption.

Methods. A retrospective observational study using a nationwide electronic health record (EHR)-derived deidentified database was conducted. Patients with aNSCLC diagnosed in community medical centers from January 2012 to May 2019 were included to describe the ALK testing trend. This cohort was further restricted to patients diagnosed after 2015 to understand factors associated with testing underuse using mixed-effects multivariable logistic regression models.

Results. Trends for increased ALK testing rates by year were observed in both NCCN guideline-eligible patients (59.5% in 2012 to 84.1% in 2019) and -ineligible patients (15.6% to 50.8%) in a cohort of 41,728 patients. Histology type and smoking status had the greatest impact on test use. Compared with patients with nonsquamous histology and no smoking history, patients with squamous histology and no smoking history (adjusted odds ratio [aOR], 7.6; 95% confidence interval [CI], 5.6–10.4), NSCLC histology not otherwise specified (NOS) with smoking history (aOR, 3.4; 95% CI, 2.8–4.2), NSCLC NOS/nonsmoker (aOR, 1.8; 95% CI, 1.1–3.2), and nonsquamous/smoker (aOR, 1.5; 95% CI, 1.3–1.7) were less likely to be tested. Factors related to underuse also included Eastern Cooperative Oncology Group performance status, stage at initial diagnosis, and demographics.

Conclusion. This analysis of real-world data shows increasing test use by year; however, one fifth of patients eligible for ALK testing still remain untested and potentially missing therapeutic options.

Implications for Practice: Advancement in treatment of lung cancer is accompanied by an increasing number of tests that should be run to determine potential therapy options for each patient. This study assessed adoption of testing recommendations for anaplastic lymphoma kinase rearrangements in a national database. Although test use increased over the time period studied (2012–2019), there is still room for improvement. Efforts are needed to increase test use in undertested groups, thus enabling eligible patients to benefit from novel lung cancer therapies.

INTRODUCTION

Despite significant advances in targeted therapy and immunotherapy, lung cancer remains the leading cause of cancer-related mortality [1]. Formerly lumped under a broad histologic umbrella, lung cancer has been revealed by our current understanding of its molecular profiles to be a different number of disease entities often characterized by
targetable driver mutations [2]. The astonishing number of actionable mutations coupled with often well-tolerated oral therapies has transformed the care of patients with advanced lung cancer [3]. Guidelines have been published to provide high-level evidence of molecular testing [4]. However, owing to the persistent problem of limited tumor samples from small biopsies in patients often with significant underlying comorbidities, undertesting (and the related concept of undergenotyping) remains a significant concern for getting the broadest amount of information on a patient’s tumor to the treating physician. In addition, treating patients with immunotherapy prior to determining the patient’s genomic status can be problematic as the sequence of exposure (immunotherapy prior to targeted therapy) puts patients at risk for significant complications of pneumonitis or hepatitis [5]. Thus, careful consideration must be given to correctly using precious biopsy tissue to acquire the required genomic information [6].

Anaplastic lymphoma kinase (ALK) translocations have been described in approximately 4% of lung adenocarcinomas [7]. These tumors tend to arise in light or never-smokers who are younger, although these clinical features are not robust [7]. These tumors tend to arise in light or never-smokers who are younger, although these clinical features are not robust [7]. These tumors tend to arise in light or never-smokers who are younger, although these clinical features are not robust [7]. These tumors tend to arise in light or never-smokers who are younger, although these clinical features are not robust [7]. These tumors tend to arise in light or never-smokers who are younger, although these clinical features are not robust [7]. These tumors tend to arise in light or never-smokers who are younger, although these clinical features are not robust [7]. These tumors tend to arise in light or never-smokers who are younger, although these clinical features are not robust [7]. These tumors tend to arise in light or never-smokers who are younger, although these clinical features are not robust [7]. These tumors tend to arise in light or never-smokers who are younger, although these clinical features are not robust [7]. These tumors tend to arise in light or never-smokers who are younger, although these clinical features are not robust [7]. These tumors tend to arise in light or never-smokers who are younger, although these clinical features are not robust [7].

Guidelines for testing patients with lung cancer have provided direction for practitioners, but unfortunately, outside of individual institutions, it is difficult to evaluate how widely guidelines have been adopted in routine practice. Real-world databases and registries provide an opportunity to evaluate this question on a national scale. The purpose of this study was to obtain insights on ALK test use and alignment with current guideline recommendations at the community practice level through interrogation of a real-world database.

Materials and Methods

Study Design and Data Source
This retrospective observational study used Flatiron Health’s nationwide longitudinal, deidentified database derived from electronic health record (EHR) data from approximately 280 U.S. cancer clinics (~800 sites of care). The Flatiron Health database is composed of deidentified patient-level structured and unstructured data, curated via technology-enabled abstraction [13, 14], and the majority of patients in the database originate from community oncology settings; relative community/academic proportions may vary depending on study cohort. Institutional review board approval of the study protocol was obtained prior to conduct of the study and included a waiver of informed consent.

Study Population
Patients with advanced non-small cell lung cancer (aNSCLC; stage IIIb, IIIC, or IV by American Joint Committee on Cancer 7th edition) diagnosed from January 2012 to May 2019 were included. Eligible patients were also required to be ≥18 years of age at NSCLC diagnosis, have a follow-up visit ≥10 days from NSCLC diagnosis, and have at least one medical activity within 120 days of advanced NSCLC diagnosis. Patients were excluded from analysis for missing information (gender, region, stage, or smoking status) or potentially contradicted information (ALK TKIs treatment without evidence of ALK testing). The cohort was further limited to patients from community medical centers. This full cohort of patients (2012 patient cohort) diagnosed between January 2012 and May 2019 was analyzed to describe the trend of ALK test use (irrespective of test methodology) in the past 7.5 years.

A subcohort with patients diagnosed since January 2015 was analyzed to describe ALK testing use in the recent 5 years (2015 patient cohort). In this subcohort, we further restricted the analysis to patients who were eligible for ALK testing per NCCN guidelines (ALK eligible cohort) to understand the factors associated with ALK testing in ALK testing-eligible patients from 2015 to 2019.

Definitions of Key Variables
Per NCCN guidelines, a patient was eligible for ALK testing if they had an adenocarcinoma, large cell carcinoma, or NSCLC not otherwise specified (NOS); patients with squamous cell carcinoma with no history of smoking were also eligible. Although patients with small biopsy specimens or mixed histology and squamous histology type were also recommended as ALK testing eligible by NCCN guidelines, such data were not well-captured in the EHR and were not included as a criterion of ALK testing eligibility in this study. Those patients who had documented smoking history and squamous histology were defined as ineligible for ALK testing.

ALK testing information was obtained from biomarker reports (e.g., next-generation sequencing [NGS]), pathology reports/addendums, or physician notes. Testing methods included fluorescence in situ hybridization (FISH), immunohistochemistry, NGS, polymerase chain reaction, others, and unknown. ALK status is reported in the database as presence or absence of the rearrangement, pending results, unsuccessful or indeterminate test, or unknown status. Patients were considered ALK tested when there was documented evidence of ALK testing, including ALK testing-related dates or results.

Statistical Analysis
Descriptive statistics were used to describe patient baseline characteristics. Continuous variables were summarized with mean and SD. Frequency counts and the percentage of patients within each category were reported for categorical variables. In the ALK eligible cohort, bivariate logistic regression analysis was used to determine the association of patients’ demographic and clinical characteristics (individually) with ALK testing status. Mixed-effects multivariable logistic regression analysis (with hospital as a random effect) was used to identify factors associated with ALK testing status. Adjusted odds ratios (aOR) and 95% confidence intervals (CIs) were reported, and ORs greater than 1 indicated higher likelihood of being untested. For all analyses, significance levels were two-tailed, and aORs reported with 95% CIs that do not include one were considered statistically significant. All statistical analyses were performed by using R statistical package version 3.5.3 (R Foundation, Vienna) and
Table 1. Demographic and clinical characteristics of patients with aNSCLC diagnosed from 2015 to 2019

| Characteristics                  | All patients | NCCN ALK testing-eligible patients | NCCN ALK testing-ineligible patients |
|----------------------------------|--------------|-----------------------------------|-------------------------------------|
|                                  | n (%)        | ALK-tested, %                      | n (%)                               | ALK-tested, % |
| Total number of patients         | 26,617 (100.0) | 19,930 (100.0) 81.7 | 6,687 (100.0) 40.4 |
| Age at advanced NSCLC diagnosis, yr |              |                                  |                                     |
| Mean (SD)                        | 69.0 (9.8)   | 70.0 (15.0)                      | 71.0 (13.0)                         |
| 18–49                            | 789 (3.0)    | 681 (3.4)                        | 108 (1.6)                           | 50.9          |
| 50–64                            | 7,659 (28.2) | 5,995 (30.1)                     | 1,664 (24.9)                        | 42.2          |
| 65+                              | 18,169 (68.3)| 13,254 (66.5)                    | 4,915 (73.5)                        | 39.5          |
| Gender                           |              |                                  |                                     |
| Female                           | 12,476 (46.9)| 10,065 (50.5)                     | 2,411 (36.1)                        | 41.0          |
| Male                             | 14,141 (53.1)| 9,865 (49.5)                      | 4,276 (63.9)                        | 40.0          |
| Race                             |              |                                  |                                     |
| White                            | 18,096 (68.0)| 13,319 (66.8)                     | 4,777 (71.4)                        | 40.1          |
| Black                            | 2,286 (8.6)  | 1,716 (8.6)                       | 570 (8.5)                           | 37.7          |
| Asian                            | 769 (2.9)    | 673 (3.4)                         | 96 (1.4)                            | 45.8          |
| Other races                      | 2,745 (10.3) | 2,113 (10.6)                      | 632 (9.5)                           | 43.5          |
| Unknown                          | 2,721 (10.2) | 2,109 (10.6)                      | 612 (9.2)                           | 40.8          |
| Region                           |              |                                  |                                     |
| Midwest                          | 4,599 (17.3) | 3,382 (17.0)                      | 1,217 (18.2)                        | 32.0          |
| Northeast                        | 5,810 (21.8) | 4,441 (22.3)                      | 1,369 (20.5)                        | 38.0          |
| South                            | 11,744 (44.1)| 8,584 (43.1)                      | 3,160 (47.3)                        | 44.2          |
| West                             | 4,464 (16.8) | 3,523 (17.7)                      | 941 (14.1)                          | 41.9          |
| Insurance type                   |              |                                  |                                     |
| Commercial                       | 9,192 (34.5) | 7,064 (35.4)                      | 2,128 (31.8)                        | 43.0          |
| Medicare                         | 11,763 (44.2)| 8,652 (43.4)                      | 3,111 (46.5)                        | 40.1          |
| Medicaid                         | 1,068 (4.0)  | 788 (4.0)                         | 280 (4.2)                           | 41.4          |
| Assistance program               | 472 (1.8)    | 346 (1.7)                         | 126 (1.9)                           | 45.2          |
| Other payers                     | 3,231 (12.1) | 2,422 (12.2)                      | 809 (12.1)                          | 37.1          |
| Unknown                          | 891 (3.3)    | 658 (3.3)                         | 233 (3.5)                           | 28.8          |
| aNSCLC diagnosis year            |              |                                  |                                     |
| 2015                             | 5,991 (22.5) | 4,542 (22.8)                      | 1,449 (21.7)                        | 25.6          |
| 2016                             | 6,228 (23.4) | 4,712 (23.6)                      | 1,516 (22.7)                        | 32.4          |
| 2017                             | 6,339 (23.8) | 4,731 (23.7)                      | 1,608 (24.0)                        | 45.7          |
| 2018                             | 5,969 (22.4) | 4,414 (22.1)                      | 1,555 (23.3)                        | 52.7          |
| 2019<sup>a</sup>                 | 2,090 (7.9)  | 1,531 (7.7)                       | 559 (8.4)                           | 50.8          |
| Smoking status                   |              |                                  |                                     |
| Nonsmoker                        | 3,136 (11.8) | 3,136 (15.7)                      | NA                                  | NA            |
| Smoker                           | 23,481 (88.2)| 16,794 (84.3)                     | 6,687 (100.0)                       | 40.4          |
| Histology                        |              |                                  |                                     |
| Nonsquamous                      | 18,406 (69.2)| 18,406 (92.4)                     | NA                                  | NA            |
| NSCLC NOS                         | 1,262 (4.7)  | 1,262 (6.3)                       | NA                                  | NA            |
| Squamous                         | 6,949 (26.1) | 262 (1.3)                         | 6,687 (100.0)                       | 40.4          |
| Initial stage                    |              |                                  |                                     |
| Stage occult–IIIA                | 6,190 (23.3) | 4,260 (21.4)                      | 1,930 (28.9)                        | 42.2          |
| Stage IIIB–IIIC                  | 3,068 (11.5) | 1,733 (8.7)                       | 1,335 (20.0)                        | 31.0          |
| Stage IV                         | 17,359 (65.2)| 13,937 (69.9)                     | 3,422 (51.2)                        | 43.0          |

Data presented as n (%) or mean (SD) unless otherwise noted.
*2019 data are from January 1, 2019 to May 31, 2019.
Abbreviations: ALK, anaplastic lymphoma kinase; aNSCLC, advanced non-small cell lung cancer; NCCN, National Comprehensive Cancer Network; NOS, not otherwise specified; NSCLC, non-small cell lung cancer.
RESULTS

Patient Characteristics

An initial cohort of 41,728 patients with aNSCLC diagnosed from 2012 to 2019 was included. This cohort was used to assess trends in ALK test use. As routine ALK testing was first recommended in NCCN guidelines in late 2011, we chose January 2012 as the beginning time point to assess ALK testing trends [15]. Detailed analysis was then performed on patients (26,617) diagnosed with NSCLC from January 2015 to May 2019 (2015 patient cohort) who met the selection criteria (Table 1). This cohort was selected to allow time for practices to adopt the changes to NCCN guidelines and assess adherence to the recommendations. The mean age of patients was 69.0 years (SD, 9.8). Men composed 53.1% of the 2015 patient cohort and 68.0% of patients were White. The majority of patients had de novo NSCLC (76.7%) with nonsquamous histology as the predominant histology type (69.2%). A large percentage (88.2%) of the patients had a history of smoking.

In this 2015 patient cohort, 75% of patients were eligible for ALK testing per NCCN guidelines, whereas one quarter were ineligible (smokers with squamous histology).
ALK Test Methods

In this study, we observed a shift in test methodology over the time period. In 2012, FISH was the dominant method (1,730 out of 2,134 tests, or 81.07%). NGS gained over all the years studied. By the first half of 2019, 842 of 1,831 tests (45.99%) were performed by NGS compared with FISH, which was used in 690 of 1,831 tests (37.68%; Fig. 1).

ALK Test Use

With the analysis of the larger cohort of 41,728 patients diagnosed with NSCLC from 2012 to 2019 (2012 patient cohort), ALK test use rates in NCCN ALK testing-eligible patients rose from 59.5% in 2012 to 84.1% in 2019 (Fig. 2). This trend gradually increased until it reached a plateau at a rate above 84% after 2017. This increase in ALK testing was also observed in patients ineligible for testing, ranging from 15.6% in 2012 to 50.8% in 2019.

The rate of ALK testing varied by patients’ demographic and clinical characteristics (Table 1). It showed higher ALK testing rates in patients with younger age (<50 years), Asian race, insurance as patients’ assistance program, non-squamous histology type, nonsmokers, and initial stage as stage IV. When stratified by histology and smoking status (the two key elements that define testing eligibility), ALK testing rates were higher among nonsmokers and non-squamous histology types.

**Figure 3.** ALK testing rate stratified by histology and smoking status in patients with advanced non-small cell lung cancer diagnosed from 2015 to 2019 in U.S. community medical centers. Abbreviations: ALK, anaplastic lymphoma kinase; NCCN, National Comprehensive Cancer Network; NOS, not otherwise specified.

**Figure 4.** Factors associated with ALK testing in National Comprehensive Cancer Network ALK testing-eligible patients with advanced NSCLC diagnosed from 2015 to 2019 in U.S. community medical centers. Abbreviations: ALK, anaplastic lymphoma kinase; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio; NOS, not otherwise specified; NSCLC, non-small cell lung cancer.
testing rates were highest in nonsquamous histology type, followed by NSCLC histology nonspecific (NOS) and squamous type, and nonsmokers have a higher ALK testing rate than smokers within each histology type (Fig. 3). Among ALK testing-eligible patients, nonsmoker with squamous histology type has the lowest ALK testing rate (55.0%).

Factors Associated with ALK Testing

Among 19,930 patients with NSCLC diagnosed from 2015 to 2019 and eligible for ALK testing per NCCN guidelines, 16,284 patients (81.7%) received ALK testing. The association between demographic and clinical characteristics and ALK-tested status was examined with logistic regression analyses. In univariable analysis, histology type by smoking status, poorer Eastern Cooperative Oncology Group (ECOG) performance status (PS) score at diagnosis, earlier initial stage, advanced diagnosis year before 2016, older age (≥50 years), male sex, noncommercial insurance, race (other race vs. Asian) and region (other region vs. west) were associated with ALK undertesting status. After adjusting for covariates with mixed-effects multivariable logistic model, factors remaining statistically significant were histology type by smoking status, poorer ECOG PS score at diagnosis, earlier initial stage, year of advanced diagnosis before 2016, older age (≥50 years), male sex, and noncommercial insurance (Fig. 4). Compared with nonsmokers with nonsquamous histology type, patients with other histology types by smoking status were less likely to have been ALK tested, including squamous/nonsmoker (aOR, 7.6; 95% CI, 5.6–10.4), NSCLC NOS/smoker (3.4; 2.8–4.2), NSCLC NOS/nonsmoker (1.8; 1.1–3.2), and nonsquamous/smoker (1.5; 1.3–1.7). Compared with patients with an ECOG PS score of 0–1 at aNSCLC diagnosis, patients with poorer ECOG PS scores were less likely to be tested, including patients with ECOG PS score of 2 (1.4; 1.2–1.7) or 3+ (2.5; 2.0–3.1).

Discussion

This study of a large real-world database provides an overview of the frequency of ALK testing (regardless of methodology used) across the U.S. over a period of time when multiple drugs received U.S. Food and Drug Administration (FDA) approval for therapeutic use. Guidelines regarding testing and treatment have rapidly evolved to reflect the changes in therapeutic options. This database provided an opportunity to assess the adoption of guidelines in the real world. Although guideline adoption increased over the study period, there remains a significant number of patients eligible for testing that are not being tested for ALK rearrangements. Factors such as histology, ECOG status, insurance type, and smoking history were associated with undertesting.

We were interested in determining if patients were being tested in accordance with NCCN guidelines (adenocarcinoma, large cell carcinoma, NSCLC not otherwise specified, or patients with squamous carcinoma with no history of smoking). Testing in guideline-eligible patients reached a plateau (84%) by 2017 and remained constant through the first half of 2019. The rate of testing for NCCN guideline-eligible patients reached a peak in 2018 (52.7%) and appears to have plateaued. The average testing rate from the 2015 patient cohort, including both NCCN ALK testing-eligible and -ineligible patients (data not shown), was 71.3%, which is higher (53.1%) than reported in a similar database study from 2011 to 2017 [16], reflecting the trend that molecular testing is becoming more widely incorporated into routine practice. Despite gains in molecular testing and the ability to look at multiple driver mutations, there remain a significant number of eligible patients that are not being tested for actionable mutations.

Currently, testing rates are highest for patients with nonsquamous histology, as per guideline recommendations. However, limiting testing to patients with nonsquamous histology will miss a number of patients with the ALK translocation, denying them a chance to be treated with an oral, targeted therapy. In our previous published results [17], 3.3% of patients with squamous histology who were nonsmokers were found to be ALK positive and 6.3% of patients with NSCLC NOS were found to harbor the mutation. Disappointingly, in our study, among ALK testing-eligible patients, nonsmokers with squamous histology had the lowest ALK testing rate of 55.0%. Current guidelines do stress that in the case of a squamous result from a small biopsy or in a patient with a light or never smoking history, thought should be given to genomic testing, but it bears repeating that squamous and nonadenocarcinoma histologies are not reasons to forego biomarker testing. In addition, 1.7% of patients who were ALK positive were found in patients with nonsquamous histology who were tobacco users [17]—again emphasizing that the presence of tobacco exposure in patients who have an adenocarcinoma history does not preclude having the translocation.

It is not surprising that patients with poor ECOG performance status are undertested, especially if it is obvious that the patient has a high burden of disease and wants to focus on palliation. Nearly a quarter of the patients in our cohort were diagnosed at an early stage prior to disease advancement (Table 1), and these patients were less likely to be tested compared with those who were initially diagnosed at stage IV (Fig. 4). It is possible that this patient population was already receiving other types of treatment (e.g., chemotherapy) and decided against testing upon disease progression. The fact that noncommercially insured patients had lower testing rates raises the concern that testing disparities exist for patients with Medicare or Medicaid and needs to be studied in more detail. Although patients with noncommercial insurance had lower testing rates, there was no difference in terms of ethnicity. It is impossible to know from a retrospective study such as this one whether the reason for lower testing rates in noncommercially insured patients was owing to financial concerns of the expense of the testing, more significant comorbid conditions and worse performance status, or some combination of other factors. Further studies will need to examine coverage differences as well as geographic differences (rural vs. urban locations) to better understand disparities in biomarker testing. However, it is surprising and disappointing that tobacco history still seems to be a factor in the decision whether to test for genomic mutations, as it has been recognized for many years that smoking history should not be used as a discriminative factor in deciding on whether or not to test patients with advanced adenocarcinomas [18].
Our data suggest that nearly one in five patients are not being tested for ALK rearrangements, which is in alignment with other studies indicating that patients are being under-genotyped for the many other actionable mutations now with FDA approved therapies, which impacts their long-term survival [19]. Oncologists, pathologists, and pulmonologists need to work together in a multidisciplinary fashion to make sure that the maximal information can be obtained from often scant biopsies. Reflex upfront NGS panel testing holds the best chance to increase the yield of information and maximizing the number of patients tested according to current NCCN guidelines [6]. In addition, if the biopsy is small and the pathologist recognizes that there is not enough tissue for genomic testing, early use of circulating tumor DNA can often enhance the chance at finding driver mutations [20].

This is a large cohort across an extended period of time (7.5 years) with extensive collection of clinical variables and detailed biomarker testing data. We focused on community centers, where the majority of cancer care in this country is provided. Therefore, we believe this study provides a robust view of oncology practice in the real world and continues to advance the current knowledge around ALK testing patterns [21]. However, the standard limitations inherent to retrospective real-world data studies also apply to this study, such as the potential for coding errors in oncology practices and missing data if procedures or treatments occurred outside the specific oncology practice. As an example, patients’ ALK testing status might not be captured in the database if the testing was performed outside the Flatiron Health network or was not recorded in the EHR system. Although the accuracy of testing is of critical importance in assuring that patients receive the appropriate targeted therapy, it is beyond the scope of this study to assess the veracity of testing.

The assessment of guideline adoption is an important first step in understanding why testing for eligible patients is or is not occurring. The ability of real-world databases to capture details of testing, therapy, and outcomes provides promise of better understanding of these therapy decisions outside of a randomized clinical trial (RCT). Studies such as these are steps in understanding the information that is captured along with identification of information gaps. The hope is that as these databases mature, the information that is gleaned from real-world application of diagnostics and therapies will provide additional data to health regulatory authorities outside of RCT settings.

CONCLUSION
This study shows that, although the testing rates for ALK mutations have improved, it still falls short of maximally identifying patients who could benefit from therapy with a TKI. Patients deserve the opportunity for the best therapy for their disease. This paper affords community medical centers an opportunity to assess their adoption of guideline driven care. If they are undertesting patients, they should identify contributing factors in their population. Once factors have been identified, it is incumbent on the institution to mitigate undertesting. Failure to do so denies untested patients with lung cancer with actionable mutations the opportunity for their mutations to be identified, with the loss of their opportunity to receive targeted therapies that have shown to be of benefit. A multidisciplinary approach across the entire health care team is necessary to ensure that barriers to testing in patient groups that are currently undertested are removed and enable access to appropriate therapy for those whose tumors express an ALK rearrangement. Moreover, disparities in testing related to smoking status (possibly a residue of continuing stigma), region, age, gender, and insurance status need to be addressed and remedied.

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DISCLOSURES
Eric H. Bernicker: Novartis, Pfizer, AstraZeneca, Guardant Health (Other—personal fees); Yan Xiao: AstraZeneca, Roche Diagnostics Information Solutions (E); Anup Abraham: Genesis Research (E); Baiyu Yang: Roche Diagnostics Information Solutions (E); Denise Croix: Roche Diagnostics (E); Stella Redpath: Roche Diagnostics (E); Julia Engstrom-Melnyk: Roche Diagnostics, AstraZeneca (E); Roma Shah: Roche Diagnostics Information Solutions (E); Jaya Madala: Roche Diagnostics Information Solutions (E). The other authors indicated no financial relationships.

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