Underutilization and disparities in access to EGFR testing among Medicare patients with lung cancer from 2010 – 2013

Julie A. Lynch1,7*, Brygida Berse2,3, Merry Rabb4, Paul Mosquin4, Rob Chew4, Suzanne L. West4, Nicole Coomer4, Daniel Becker5,6 and John Kautter2

Abstract

Background: Tumor testing for mutations in the epidermal growth factor receptor (EGFR) gene is indicated for all newly diagnosed, metastatic lung cancer patients, who may be candidates for first-line treatment with an EGFR tyrosine kinase inhibitor. Few studies have analyzed population-level testing.

Methods: We identified clinical, demographic, and regional predictors of EGFR & KRAS testing among Medicare beneficiaries with a new diagnosis of lung cancer in 2011–2013 claims. The outcome variable was whether the patient underwent molecular, EGFR and KRAS testing. Independent variables included: patient demographics, Medicaid status, clinical characteristics, and region where the patient lived. We performed multivariate logistic regression to identify factors that predicted testing.

Results: From 2011 to 2013, there was a 19.7% increase in the rate of EGFR testing. Patient zip code had the greatest impact on odds to undergo testing; for example, patients who lived in the Boston, Massachusetts hospital referral region were the most likely to be tested (odds ratio (OR) of 4.94, with a 95% confidence interval (CI) of 1.67–14.62). Patient demographics also impacted odds to be tested. Asian/Pacific Islanders were most likely to be tested (OR 1.63, CI 1.53–1.79). Minorities and Medicaid patients were less likely to be tested. Medicaid recipients had an OR of 0.74 (CI 0.72–0.77). Hispanics and Blacks were also less likely to be tested (OR 0.97, CI 0.78–0.99 and 0.95, CI 0.92–0.99), respectively. Clinical procedures were also correlated with testing. Patients who underwent transcatheter biopsies were 2.54 times more likely to be tested (CI 2.49–2.60) than those who did not undergo this type of biopsy.

Conclusions: Despite an overall increase in EGFR testing, there is widespread underutilization of guideline-recommended testing. We observed racial, income, and regional disparities in testing. Precision medicine has increased the complexity of cancer diagnosis and treatment. Targeted interventions and clinical decision support tools are needed to ensure that all patients are benefitting from advances in precision medicine. Without such interventions, precision medicine may exacerbate racial disparities in cancer care and health outcomes.

Keywords: Lung cancer, EGFR testing, Medicare, Hospital referral region, Billing code
Background
In 2017, approximately 222,500 patients within the United States (U.S.) will be diagnosed with lung cancer and 155,870 are expected to die from it [1]. The average age at lung cancer diagnosis is 70 years, and 68% of patients are 65 years or older and eligible for Medicare [2]. Lung cancer causes serious medical problems or death in 1.7% of Medicare beneficiaries [3]. Studying lung cancer molecular test utilization within Medicare claims provides a unique opportunity for a comprehensive, population-level analysis of precision medicine testing.

Over the last decade, molecular testing of lung tumors has become an essential component of diagnosis and treatment of advanced non-small cell lung cancer (NSCLC). Molecular testing facilitates targeted treatment directed at specific genetic alterations in tumors [4]. There are now multiple drugs approved by the Food & Drug Administration (FDA) to treat lung cancer patients with specific tumor alterations (see Additional file 1).

Mutations of the epidermal growth factor receptor (EGFR) gene and chromosomal rearrangement of the anaplastic lymphoma kinase (ALK) gene were among the first established molecular targets for therapy in lung adenocarcinoma. Testing for these two markers identifies a subset of patients for whom specific oral tyrosine kinase inhibitors (TKIs) are most effective. Because KRAS and EGFR mutations are mutually exclusive in greater than 99% of cases, analysis of KRAS mutational status has also been used to exclude sensitivity to EGFR inhibitors [5]. However, guidelines do not recommend use of KRAS testing in lung cancer.

Guidelines for EGFR testing and targeted treatment evolved gradually over the past decade, as illustrated in Additional file 2. The FDA approved erlotinib in 2004 for second-line therapy regardless of tumor histologic type or EGFR status. It was not until 2011, however, that clinical guidelines linked erlotinib treatment with EGFR testing [6–9]. From 2011 through 2013, EGFR testing was indicated for all patients with newly diagnosed metastatic adenocarcinoma of the lung being considered for first-line therapy with an EGFR tyrosine kinase inhibitor. This indication corresponded to approximately 35% of all new lung cancer cases [10, 11]. EGFR testing was also recommended for patients with recurrent metastatic disease. In 2013, FDA approved erlotinib as first line therapy for EGFR mutation-positive patients. According to Local Coverage Determinations by several Medicare contractors, reimbursement for the EGFR test applies to patients with clinical indications for testing [12].

The importance of EGFR testing for diagnosis and treatment of lung cancer is illustrated by its worldwide availability. EGFR testing is now available in 57 countries [13]. Test availability and cost are strongly correlated with the Human Development Index of a given country, underscoring the importance of bringing precision medicine to underserved populations.

The prevalence of EGFR mutations in lung adenocarcinomas differs by patient ancestry. Among patients of European descent, mutation prevalence is between 10% to 15%, and among Asians it can be as high as 50%, with higher frequency in women and non-smokers across all ethnicities [5]. Within populations, the EGFR mutation rate may differ among specific patient groups based on their history of smoking. Among U.S. veterans, mutation prevalence is lower (7%), likely due to the high number of veterans who smoke [11]. EGFR mutations are less frequent in squamous cell carcinomas therefore the guidelines suggest testing only those patients with squamous histology whose clinical or demographic characteristics (e.g., absence of smoking history, Asian descent) indicate an increased likelihood of mutations.

Assays used to detect EGFR mutations can be limited by the amount of tissue available from the biopsy specimen. Thus, patient-level differences in testing may be partially explained by the types of diagnostic procedures patients undergo. Two decades of research have demonstrated racial, regional, and socioeconomic differences in access to lung cancer surgical procedures [14–21]. Black patients and those of low socioeconomic status were less likely to receive surgery or biopsies that yield enough lung tumor tissue for identifying EGFR mutations. Disparities in treatment and outcomes of lung cancer were most pronounced among Black men, who are diagnosed an average of four years younger than Whites and who experienced a significantly lower five-year survival rate [22].

There were four objectives of this study: (1) Identify Medicare patients with newly diagnosed lung cancer who underwent molecular and proteomic testing. (2) Compare the proportion of patients tested to the expected rate of testing based on population-level statistics reported in cancer-registry data. (3) Identify patient-level and regional variations in access to EGFR and KRAS testing; and (4) Evaluate whether patient-level disparities in access to diagnostic procedures compound disparities in access to EGFR testing.

Methods
Data sources
We conducted a retrospective study using secondary data analysis methods. The primary data source was Medicare claims, including 2010–2013 100% inpatient MedPAR, Part B, and Outpatient files. Additional data sources included the Denominator file (100%), the Hierarchical Condition Categories (HCC) risk score file, Provider of Service file, Health Resources and Services Administration Area Health Resource File [23] and the Dartmouth Atlas Hospital Referral Region (HRR) database [24].
Our analytic sample consisted of patients who met the following criteria:

1. Were Medicare fee-for-service beneficiaries who had a diagnosis code for lung cancer (malignant neoplasm of trachea, bronchus, and lung, (International Classification of Disease (ICD-9) 162.0–162.9) in any diagnosis fields within MedPAR, Outpatient, or Part B files.
2. Had a short term or specialty hospital encounter in a physician office, inpatient or outpatient hospital, or ambulatory surgical center.
3. Sought lung cancer treatment from 2010 to 2013, defined as having a lung biopsy and/or a lung surgery, or lung surgical pathology analysis (ICD-9-CM and Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) codes in Table 3) claim in MedPAR, outpatient or Part B files.

We restricted our analysis to claims that had lung cancer listed as the line item or principal diagnosis code. MedPAR, outpatient, and Part B claims were rolled up to a patient-level analytic file that became the basis for the study. We used a validated algorithm to identify incident lung cancer cases in Medicare claims data [25–27]. This algorithm relied on identifying newly diagnosed cases by restricting analysis to patients who had a new claim for lung cancer diagnosis and twelve months of claims history without a previous indication of lung cancer. Most patients with lung cancer are diagnosed at an advanced stage of the disease, when symptoms have progressed and healthcare interventions are essential, which generates continuity in claims prior to and following a diagnosis of lung cancer.

Variables
The unit of observation was the patient. The outcome variable was whether the patient had a claim for a lung cancer molecular test. We created variables that allowed us to conduct analysis on the total population and a subset of the population. We identified the year of the first lung cancer claim and we identified whether a patient had a year of prior claims data. (Without access to 2009 claims, we had no method for differentiating incident versus prevalent cases in the 2010 claims data. Therefore, we reported molecular test claims for patients identified in 2010 but then dropped these patients from subsequent analysis.) The vast majority (93%) of patients identified in 2011–2013 claims represented newly diagnosed cases.

Lung cancer clinical procedures
Using the set of CPT codes listed in Table 3, we created dichotomous variables to identify whether a patient underwent specific lung cancer surgical procedures. Some of these procedures, such as fine-needle aspiration, are unlikely to general sufficient tumor cells for molecular testing. Patients who had a claim for surgical pathology procedures billed with CPT codes 88305, 88307, 88309, with a primary or line item diagnosis code of lung cancer, likely had sufficient lung tumor tissue for testing. These variables allowed us to restrict some analysis to only those patients who underwent a lung biopsy.

Patients who had a lung cancer molecular test were identified using different CPT codes, depending upon the year the claim was submitted. Years 2010–2012, molecular tests were billed with stacked methodology-based codes, which made it impossible to conclusively identify or distinguish EGFR or KRAS tests from other molecular tests. However, these were essentially the only genetic tests used for lung cancer during this time. Therefore, we identified patients who had a claim for code 83912 (Genetic examination), with line item diagnosis of lung cancer. This code was billed once per procedure and it was included in the stacks of codes used by major reference laboratories for EGFR and KRAS tests. Code 83912 was discontinued in 2013 and replaced by gene-specific CPT codes. For 2013 claims, we identified patients who had either an EGFR (81235) test or a KRAS codons 12 and 13 (81275) test. We also identified whether the patient had undergone a proprietary lung cancer proteomic test. This test was billed using a combination of the CPT code 84999 and the Clinical Laboratory Improvement Amendment (CLIA) number (06D1090464) for the laboratory that conducts the test (Biodesix Inc., Boulder, CO).

We also captured variables to identify patient demographics (age, gender, and race), Medicaid status, risk score, zip code of residence, distance to a National Cancer Institute (NCI) designated cancer center, and the HRR in which the patient lived.

Statistical analysis
We conducted univariate and bivariate analyses, including t-tests for continuous variables and χ2 for categorical variables. Statistically significant explanatory variables (P values < 0.05) were then included in logistic regression modeling. Statistical analysis was performed using Stata software (version 12.0; StataCorp, College Station, TX).

Results
Molecular testing from 2010 to 2013
We identified 1,178,293 Medicare beneficiaries who had a diagnosis code of lung cancer from 2010 to 2013. Among these patients, 62,955 (5%) underwent a molecular test over during that time period. There were 42,415 tests billed using 83912, 18,898 EGFR tests, and 8,066 KRAS tests. Patients identified in 2010 represented both incident and prevalent cases. Among patients identified with lung cancer in 2010, there were a total of 21,422
who received a molecular test from 2010 through 2013. Most patients (18,845) underwent a test billed with code 83912. There were 2,516 patients who underwent an EGFR test and 1,095 who underwent a KRAS test. There were 1,034 patients who had claims for multiple molecular tests. Patients identified in 2011 through 2013 represented mostly incident cases. There were 13,568 patients identified in 2011 and 14,302 patients identified in 2012 who underwent at least one molecular test. There were 12,433 patients identified in 2013 who underwent EGFR testing; 4,856 who underwent KRAS testing; and 3,626 who underwent both EGFR and KRAS testing.

All subsequent analysis was conducted on patients identified in 2011 through 2013. Table 1 illustrates the percentage of patients tested among newly diagnosed patients who had lung tissue available for analysis. There was a 19.7% increase testing from 2011 through 2013. In 2011, 7.8% of patients who underwent surgical pathology were tested. In 2013, this increased to 9.3%. The absolute number of claims for molecular testing decreased slightly in 2013. This decrease may be explained by limitations in the data. Patients diagnosed in December of 2013 may have been tested in January 2014 or there may be an expansion of next generation sequencing, which would not be billed with the gene-specific billing codes.

**Patient characteristics by lung tissue analysis and molecular testing**

Lung cancer diagnosis was associated with increasing age. In the overall Medicare population, 37% of beneficiaries are 75 years or older [28]. In our analysis, 298,829 (43.4%) of beneficiaries were 75 or older and the mean age was 72.9 (standard deviation (SD) 9.5). Lung cancer diagnosis was more common in White patients than among other racial groups. Whites represented 80.8% of all Medicare patients [28] but 85.1% of the cohort we examined. In contrast, Asian patients represented 2.1% of Medicare beneficiaries but only 1.5% of lung cancer patients.

Table 2 illustrates a bivariate analysis of patients by whether they had a claim for surgical pathology analysis and molecular testing. Among patients identified from 2011 through 2013, there were 465,168 (67.6%) who underwent surgical pathology analysis of lung tissue and 40,085 (8.6%) of those patients underwent a molecular test.

We observed significant racial differences in percentage of patients who underwent lung tissue analysis. Among North American Natives and Whites, 71% and 68.6%, respectively, had claims for surgical pathology analysis. Only 61.7% of Blacks had claims for lung tissue analysis. Identifying patient-level differences in access to surgical pathology is important because these patients will not have access to lung tissue molecular testing. Further, the denominator in the analysis of molecular testing was restricted to patients who had lung tissue available for analysis.

There were small but statistically significant differences by age, race, Medicaid status, and risk score and testing. Beneficiaries under age 55 were the least likely to be tested (5.9%), which may be explained by an earlier stage of diagnosis or by these patients being diagnosed and tested prior to enrolling in Medicare. Among racial/ethnic groups, a greater percentage of Asian/Pacific Islanders were tested (13.7%) compared to Whites (8.7%), Blacks (7.3%), Hispanics (6.5%), and North American Natives (7.1%). A greater percentage of non-Medicaid patients were tested than patients who received Medicaid (9.1% compared to 6.7%). Testing was also associated with patient comorbidity, as measured by the HCC risk score. The mean HCC risk score for all Medicare beneficiaries is 1. The mean risk score for lung cancer patients is 1.9. Lung cancer patients with low risk scores (below 1) were twice as likely to be tested compared to those with risk scores above the mean risk score (10.6% vs. 5.4%, respectively).

There were also regional differences in access to molecular testing. Testing was associated with living in closer proximity to an NCI designated cancer center and in a

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**Table 1** Claims for lung cancer molecular testing among all Medicare beneficiaries diagnosed with lung cancer

| By year and billing code | Molecular test a | EGFR | KRAS | Multiple | Total b |
|--------------------------|-----------------|------|------|----------|--------|
| Year diagnosed           | Code 83912      |      |      |          |        |
| 2010                     | 18,845          | 2,516| 1,095| 1,034    | 21,422 |
| 2011                     | 12,254          | 1,235| 655  | 576      | 13,568 |
| 2012                     | 11,316          | 2,714| 1,460| 1,188    | 14,302 |
| 2013                     | –               | 12,433| 4,856| 3,626    | 13,663 |
| Total                    | 42,415          | 18,898| 8,066| 6,424    | 62,955 |

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*Current Procedural Terminology (CPT) Healthcare Common Procedure Coding System (HCPCS) codes 83912 for years 2011–2012; 81235 (EGFR) and 81275 (KRAS) for 2013

*Total represents patients who had claims for 83912, 81235, and 81275

*Current Procedural Terminology (CPT) Healthcare Common Procedure Coding System (HCPCS) codes 88305, 88307, 88309

*Current Procedural Terminology (CPT) Healthcare Common Procedure Coding System (HCPCS) codes 83912 for years 2011–2012; 81235 and 81275 for 2013
| Total newly diagnosed patients 2011–2013 | Newly identified patients | Surgical pathology | Molecular test | Percent with surgical pathology | Percent tested |
|-----------------------------------------|--------------------------|-------------------|----------------|---------------------------------|----------------|
| Total                                   | 688,541                  | 465,168           | 40,085        | 67.6                            | 8.6            |
| Newly diagnosed                         | 642,570                  | 443,483           | 38,170        | 69.0                            | 8.6            |

Demographics characteristics

| Age group | Newly identified patients | Surgical pathology | Molecular test | Percent with surgical pathology | Percent tested |
|-----------|--------------------------|--------------------|----------------|---------------------------------|----------------|
| 0–54      | 24,567                   | 15,831             | 941            | 64.4                            | 5.9            |
| 55–59     | 24,598                   | 15,772             | 1,046          | 64.1                            | 6.6            |
| 60–64     | 59,883                   | 35,144             | 2,842          | 58.7                            | 8.1            |
| 65–69     | 141,033                  | 96,945             | 9,347          | 68.7                            | 9.6            |
| 70–74     | 137,641                  | 97,741             | 9,300          | 71.0                            | 9.5            |
| 75+       | 298,829                  | 203,120            | 16,571         | 68.0                            | 8.2            |
| Missing   | 1,990                    | 615                | 38             | 30.9                            | 6.2            |

| Gender    | Newly identified patients | Surgical pathology | Molecular test | Percent with surgical pathology | Percent tested |
|-----------|--------------------------|--------------------|----------------|---------------------------------|----------------|
| Male      | 363,596                  | 249,182            | 19,707         | 68.5                            | 7.9            |
| Female    | 322,955                  | 215,371            | 20,340         | 66.7                            | 9.4            |
| Missing   | 1,990                    | 615                | 38             | 30.9                            | 6.2            |

| Race/Ethnicity | Newly identified patients | Surgical pathology | Molecular test | Percent with surgical pathology | Percent tested |
|----------------|---------------------------|--------------------|----------------|---------------------------------|----------------|
| White          | 586,000                   | 401,995            | 34,808         | 68.6                            | 8.7            |
| Black          | 67,982                    | 41,922             | 3,071          | 61.7                            | 7.3            |
| Asian/Pacific Islander | 10,488       | 6,758              | 929            | 64.4                            | 13.7           |
| Hispanic       | 8,580                     | 5,301              | 342            | 61.8                            | 6.5            |
| North American/Native | 2,722       | 1,936              | 137            | 71.1                            | 7.1            |
| Other, unknown, or missing | 12,769    | 7,256              | 798            | 56.8                            | 11.0           |

| Medicaid Status | Newly identified patients | Surgical pathology | Molecular test | Percent with surgical pathology | Percent tested |
|-----------------|---------------------------|--------------------|----------------|---------------------------------|----------------|
| Medicaid        | 141,724                   | 94,771             | 6,324          | 66.9                            | 6.7            |
| No Medicaid     | 544,827                   | 369,782            | 33,723         | 67.9                            | 9.1            |
| Missing         | 1,990                     | 615                | 38             | 30.9                            | 6.2            |

| Clinical characteristics | Newly identified patients | Surgical pathology | Molecular test | Percent with surgical pathology | Percent tested |
|--------------------------|---------------------------|--------------------|----------------|---------------------------------|----------------|
| Risk score (Mean/SD)     |                           |                    |                |                                 |                |
| Less than or equal 1     | 322,995                   | 227,476            | 24,141         | 70.4                            | 10.6           |
| Between 1.0–1.9          | 194,281                   | 129,935            | 10,079         | 66.9                            | 7.8            |
| Greater than 1.9 (mean)  | 171,265                   | 107,757            | 5,865          | 62.9                            | 5.4            |

| Regional characteristics | Newly identified patients | Surgical pathology | Molecular test | Percent with surgical pathology | Percent tested |
|--------------------------|---------------------------|--------------------|----------------|---------------------------------|----------------|
| Distance to an NCI CC    |                           |                    |                |                                 |                |
| (Mean (SD) in miles)     | 85.5 (111.4)              | 86.5 (107.7)       | 82.4 (103.6)   |                                 |                |
| Metropolitan county      | 546,710                   | 362,381            | 32,100         | 66.3                            | 8.9            |
| Nonmetropolitan county   | 141,831                   | 102,787            | 7,985          | 72.5                            | 7.8            |
Table 2: Demographics of Lung Cancer Patients in Medicare Who Underwent Surgical Pathology Analysis and Molecular Testing for Lung Cancer in from 2011 to 2013 (Continued)

| Demographics characteristics | Newely diagnosed patients per year | 2011 | 2012 | 2011 | 2012 |
|------------------------------|-----------------------------------|------|------|------|------|
|                             | Surgical pathology | Molecular test | Percent tested | Surgical pathology | Molecular test | Percent tested |
| Total                        | 167,291 | 13,008 | 7.8 | 155,408 | 13,818 | 8.9 |
| Newly diagnosed              | 158,654 | 12,256 | 7.7 | 147,459 | 13,120 | 8.9 |
| Demographics characteristics |                                   |      |      |      |      |
| Age group                    |                                   |      |      |      |      |
| 0–54                         | 5,955 | 312 | 5.2 | 5,404 | 314 | 5.8 |
| 55–59                        | 5,628 | 323 | 5.7 | 5,294 | 374 | 7.1 |
| 60–64                        | 13,058 | 985 | 7.5 | 12,354 | 1,045 | 8.5 |
| 65–69                        | 34,591 | 3,085 | 8.9 | 32,582 | 3,217 | 9.9 |
| 70–74                        | 34,958 | 3,010 | 8.6 | 32,057 | 3,133 | 9.8 |
| 75+                          | 72,869 | 5,278 | 7.2 | 67,500 | 5,727 | 8.5 |
| Missing                      | 232 | 15 | 6.5 | 217 | 8 | 3.7 |
| Gender                       |                                   |      |      |      |      |
| Male                         | 88,082 | 6,193 | 7.0 | 83,098 | 6,804 | 8.2 |
| Female                       | 78,977 | 6,800 | 8.6 | 72,093 | 7,006 | 9.7 |
| Missing                      | 232 | 15 | 6.5 | 217 | 8 | 3.7 |
| Race/Ethnicity               |                                   |      |      |      |      |
| White                        | 144,973 | 11,342 | 7.8 | 134,110 | 11,969 | 8.9 |
| Black                        | 14,973 | 936 | 6.3 | 14,206 | 1,093 | 7.7 |
| Asian/Pacific Islander       | 2,336 | 330 | 14.1 | 2,293 | 313 | 13.7 |
| Hispanic                     | 1,961 | 105 | 5.4 | 1,739 | 123 | 7.1 |
| North American/Native        | 665 | 46 | 6.9 | 636 | 42 | 6.6 |
| Other, unknown, or missing   | 2,383 | 249 | 10.4 | 2,424 | 278 | 11.5 |
| Medicaid Status              |                                   |      |      |      |      |
| Medicaid                     | 33,488 | 1,988 | 5.9 | 32,024 | 2,238 | 7.0 |
| No Medicaid                  | 133,571 | 11,005 | 8.2 | 123,167 | 11,572 | 9.4 |
| Missing                      | 232 | 15 | 6.5 | 217 | 8 | 3.7 |
| Clinical characteristics     |                                   |      |      |      |      |
| Risk score (Mean/SD)         | 1.4 (1.1) | 1.1 (0.9) | – | 1.4 (1.2) | 1.1 (0.9) | – |
| Less than or equal 1         | 79,620 | 7,717 | 9.7 | 74,947 | 8,242 | 11.0 |
| Between 1.0–1.9              | 47,962 | 3,414 | 7.1 | 43,333 | 3,642 | 8.4 |
| Greater than 1.9 (mean)      | 39,709 | 1,877 | 4.7 | 37,128 | 1,934 | 5.2 |
| Regional characteristics     |                                   |      |      |      |      |
| Distance to an NCI CC (Mean SD in miles) | 86.5 (108.5) | 79.4 (104.8) | – | 86.2 (107.3) | 83.0 (101.5) | – |
| Metropolitan county          | 130,669 | 10,526 | 8.1 | 121,214 | 11,110 | 9.2 |
| Nonmetropolitan county       | 36,622 | 2,482 | 6.8 | 34,194 | 2,708 | 7.9 |


| Demographics characteristics | 2013 |
|------------------------------|------|
|                             | Surgical pathology | EGFR | KRAS | Both | Total tested | Percent tested |
| Total                        | 142,469          | 12,090 | 4,677 | 3,514 | 13,250 | 9.3 |
| Newly diagnosed              | 137,370          | 11,661 | 4,514 | 3,381 | 12,794 | 9.3 |

**Demographics characteristics**

**Age group**

| Age group | Surgical pathology | EGFR | KRAS | Both | Total tested | Percent tested |
|-----------|--------------------|------|------|------|--------------|----------------|
| 0–54      | 4,472              | 271  | 107  | 63   | 315          | 7.0            |
| 55–59     | 4,850              | 311  | 128  | 90   | 349          | 7.2            |
| 60–64     | 9,732              | 721  | 294  | 203  | 812          | 8.3            |
| 65–69     | 29,772             | 2,781 | 1,122 | 858  | 3,045        | 10.2           |
| 70–74     | 30,726             | 2,887 | 1,123 | 853  | 3,157        | 10.3           |
| 75+       | 62,751             | 5,105 | 1,895 | 1,434 | 5,566        | 8.9            |
| Missing   | 166                | 14   | 5    | 13   | 6            | 3.6            |

**Gender**

| Gender | Surgical pathology | EGFR | KRAS | Both | Total tested | Percent tested |
|--------|--------------------|------|------|------|--------------|----------------|
| Male   | 78,002             | 6,044 | 2,447 | 1,781 | 6710         | 8.6            |
| Female | 64,301             | 6,032 | 2,222 | 1,720 | 6,534        | 10.2           |
| Missing| 166                | 14    | 5    | 13   | 6            | 3.6            |

**Race/Ethnicity**

| Race/Ethnicity | Surgical pathology | EGFR | KRAS | Both | Total tested | Percent tested |
|----------------|--------------------|------|------|------|--------------|----------------|
| White          | 122,912            | 10,513 | 4,036 | 3,052 | 11,497       | 9.4            |
| Black          | 12,743             | 933   | 352  | 243  | 1,042        | 8.2            |
| Asian/Pacific Islander | 2,129 | 262 | 117  | 93   | 286          | 13.4           |
| Hispanic       | 1,601              | 98    | 46   | 30   | 114          | 7.1            |
| North American/Native | 635 | 45    | 15   | 11   | 49           | 7.7            |
| Other, unknown, or missing | 2,449 | 239 | 108  | 85   | 262          | 10.7           |

**Medicaid Status**

| Medicaid Status | Surgical pathology | EGFR | KRAS | Both | Total tested | Percent tested |
|-----------------|--------------------|------|------|------|--------------|----------------|
| Medicaid        | 29,259             | 1,885 | 722  | 509  | 2,098        | 7.2            |
| No Medicaid     | 113,044            | 10,191 | 3,947 | 2,992 | 11,146       | 9.9            |
| Missing         | 166                | 14    | 5    | 13   | 6            | 3.6            |

**Clinical characteristics**

| Clinical characteristics | Surgical pathology | EGFR | KRAS | Both | Total tested | Percent tested |
|--------------------------|--------------------|------|------|------|--------------|----------------|
| Risk score (Mean/SD)     | 1.2 (1.0)          | 1.0 (0.8) | 1.0 (0.9) | 1.0 (0.8) | 1.0 (0.8) | – |
| Less than or equal 1     | 72,909             | 7,501 | 2,883 | 2,202 | 8,182        | 11.2           |
| Between 1.0–1.9          | 38,640             | 2,783 | 1,028 | 788  | 3,023        | 7.8            |
| Greater than 1.9 (mean)  | 30,920             | 1,806 | 763  | 515  | 2,054        | 6.6            |

**Regional characteristics**

| Regional characteristics | Surgical pathology | EGFR | KRAS | Both | Total tested | Percent tested |
|--------------------------|--------------------|------|------|------|--------------|----------------|
| Distance to an NCI CC (Mean (SD) in miles) | 86.8 (107.2) | 85.3 (106.2) | 69.0 (78.25) | 66.1 (74.9) | 84.6 (104.6) |
| Metropolitan county      | 110,498            | 9,541 | 3,832 | 2,918 | 10,455       |                |
| Nonmetropolitan county   | 31,971             | 2,549 | 845  | 596  | 2,798        |                |

Source: RTI analysis of 2011–2013 Medicare

* As identified by HCPCS codes 88305, 88307
* As identified by HCPCS code 83912, 81235

There was essentially no difference in the age across years or by surgical pathology or testing status. Mean age was 72.9 with SD of 9.5
metropolitan county. Patients tested lived an average of 4 miles closer to an NCI cancer center than a non-tested patient. In 2013, the relationship between testing status and distance to an NCI cancer center was much stronger for KRAS testing than for EGFR testing. Patients undergoing both KRAS and EGFR testing lived an average of 66 miles away from an NCI cancer center compared to 85 miles for those undergoing EGFR testing.

**Regional differences in lung cancer molecular testing**

We analyzed the variability of testing across states and HRRs (See Additional file 3). The latter are areas served by individual referral centers [24]. Most Americans seek care from hospitals that are near their place of residence [24], therefore the beneficiaries’ zip codes provide statistically reliable information about the HRR. The upper left quadrant of Fig. 1 illustrates the percentage of patients in 2011, by HRR and by state, who had a claim for lung tissue surgical pathology and who underwent molecular testing. Testing by HRR ranged from no patients tested in Mason City, Iowa to 18.86% of patients testing in Salinas, California. Colorado was the state with the highest percentage of patients tested with 188 claims for lung cancer molecular tests, (12.40%) of patients who underwent lung tissue surgical pathology analysis. Utah had the lowest percentage of patients tested (4.23% or 19 tests). The upper right quadrant of Fig. 1 illustrates that in 2012 there was a 1% increase in percentage of patients tested, with some patients in every HRR being tested. In 2012, the range of patients tested was from 2.15% of patients testing in Rochester, Minnesota to 30.86% in Springdale, Arkansas. Wyoming had the highest percentage of patients tested (15.9% or 37 tests). Puerto Rico had the lowest percentage of patients tested (3.4% or 7 tests). In 2013, introduction of the gene specific CPT codes allowed us to distinguish between EGFR testing and KRAS testing. Figure 1c and d illustrate the percentage of patients in 2013 who underwent EGFR and KRAS testing, respectively. The overall percentage of patients who underwent EGFR testing was 8.5%, which was a decrease from 2012 but represents specific EGFR testing. The greatest percentage of patients tested (29%) remained those living in Springdale, Arkansas. The HRR with the lowest percentage of patients tested was in Covington, Kentucky (1.2%). The state with
the highest percentage of patients who underwent \textit{EGFR} testing was Vermont (18.9%, 44 tests). As discussed previously, \textit{KRAS} testing was closely associated with proximity to NCI cancer centers. The highest percentage of patients who underwent \textit{KRAS} testing was in Montgomery, Alabama (13.4%, 28 patients tested).

\textbf{Relationship between testing and type of biopsy or lung surgical procedures}

We then analyzed whether there was a relationship between testing and type of surgical procedure. These results are presented in Table 3. This analysis was restricted to those patients who underwent lung tissue analysis as indicated by codes 88305, 88307, and 88309. There were differences in the type of lung surgery performed and testing status. Among procedures that yield tumor tissue, the percentage of patients tested was highest among those who underwent video-assisted thoracoscopic surgery (16.9% of patients tested) followed by mediastinoscopy (16.6% of patients tested). The data point to a correlation between undergoing other types of surgical procedures and testing. Although a thoracentesis does not yield tumor tissue, the percentage of patients tested among those who underwent this procedure was still greater than among all patients with claims for surgical pathology (10.3% vs. 8.6%). However, these categories are not exclusive. Therefore, patients who underwent thoracentesis may have also had another procedure in which lung tissue was analyzed.

\textbf{Factors that predict utilization of lung cancer molecular testing}

The relationship between patient characteristics and odds to undergo testing persisted in multivariate logistic regression analysis (Table 4). A patient’s address had the greatest impact on testing status. Patients who lived in the Boston, Massachusetts HRR had an odds ratio (OR) of 4.94, with a 95% confidence interval (CI) of 1.67–14.62. Patients living in the Los Angeles, CA HRR were equally likely to be tested (OR 4.94, CI 2.08–11.71). Patients least likely to be tested lived in the Mason, Indiana HRR (OR 0.10, CI 0.04–0.30).

Clinical procedures had the next strongest correlation with testing. Patients who had a transcatheter biopsy were 2.54 times more likely to be tested (CI 2.49–2.60) than those who did not undergo this type of biopsy. This was followed by patients who had a transbronchial needle aspiration (TNBA, OR 1.53, CI 1.48–1.59). There was also a significant increase in odds to be tested by year diagnosed. Patients diagnosed in 2012 were more likely to be tested than patients diagnosed in 2011 (OR 1.09, CI 1.09–1.12). As patients’ level of comorbidities increased, their odds to be tested decreased. To interpret the OR of continuous

\begin{table}[h]
\centering
\begin{tabular}{lllll}
Procedure & HCPCS codes & Surgical pathology & Molecular test & Percent tested \\
\hline
Patients who underwent tissue analysis & 88305, 88307, 88309 & 465,168 & 40,085 & 8.6 \\
Fine-needle aspiration & 10021, 10022 & 48,901 & 5,789 & 11.8 \\
Lymph node biopsy & 38505 & 8,741 & 957 & 10.9 \\
Bronchoscopy & 31622, 31623, 31624, 31625, 31626, 31627 & 143,900 & 16,608 & 11.5 \\
Thoracentesis & 32421 & 25,854 & 2,675 & 10.3 \\
Endobronchial ultrasound & 31620 & 34,512 & 5,232 & 15.2 \\
Transbronchial needle aspiration & 31628, 31629, 31630, 31631, 31632, 31633 & 79,480 & 10,415 & 13.1 \\
Other bronchoscopies & 31635, 31636, 31637, 31638, 31640, 31641, 31643, 31645, 31646 & 16,365 & 1,668 & 10.2 \\
Transcatheeter biopsy & 32400, 32405 & 130,485 & 19,063 & 14.6 \\
Mediastinoscopy & 39400 & 21,654 & 3,603 & 16.6 \\
Video-assisted thoracoscopic surgery & 32663, 32665, 32666, 32667, 32668, 32669, 32670, 32671, 32672 & 24,739 & 4,173 & 16.9 \\
Open surgery & 32440, 32442, 32445, 32480, 32482, 32484, 32488, 32491, 32505, 32506, 32507 & 32,886 & 4,778 & 14.5 \\
Thoracotomy & 32096, 32097, 32098, 32110, 32120, 32124, 32140, 32141, 32486, 32501 & 5,594 & 704 & 12.6 \\
Thoracoscopy & 32601, 32602, 32603, 32604, 32605, 32606, 32650, 2651, 32652, 32653, 32654, 32655, 32656, 32657, 32658, 32659, 32660, 32661, 32662, 32663 & 34,496 & 5,315 & 15.4 \\
\end{tabular}
\caption{HCPCS and ICD9 procedure codes used to identify lung biopsies and surgeries in the Medicare Fee-for-Service Part B claims}
\end{table}

Abbreviations: HCPCS Healthcare Common Procedure Coding System, ICD-9 CM International Classification of Disease

Source: RTI analysis of 2011–2013 Medicare claims data
### Table 4 Characteristics that predict use of molecular tests among lung cancer patients

| Variable                                      | OR   | P Value | 95% CI  |
|----------------------------------------------|------|---------|---------|
| **Demographic characteristics**              |      |         |         |
| Age (per year)                               | 0.99 | 0.00    | 0.99–0.99 |
| Asian (vs. White)                            | 1.63 | 0.00    | 1.53–1.79 |
| Black (vs. Whites)                           | 0.95 | 0.05    | 0.92–0.99 |
| Hispanic (vs. Whites)                        | 0.87 | 0.03    | 0.78–0.99 |
| Female (vs. Whites)                          | 1.18 | 0.00    | 1.16–1.21 |
| Medicaid recipient (vs. all others)          | 0.74 | 0.00    | 0.72–0.77 |
| Distance to NCI Cancer Center (per mile)     | 0.99 | 0.01    | 0.99–0.99 |
| Number of lung cancers patient in HRR        | 0.99 | 0.01    | 0.99–0.99 |
| **Clinical characteristics (vs. all others)**|      |         |         |
| Transcatheter biopsy                         | 2.54 | 0.00    | 2.49–2.60 |
| TBNA                                         | 1.53 | 0.00    | 1.48–1.59 |
| Inpatient stay                               | 1.48 | 0.00    | 1.45–1.51 |
| Thoracoscopy                                 | 1.42 | 0.00    | 1.36–1.48 |
| Mediastinoscopy                              | 1.35 | 0.00    | 1.30–1.41 |
| EBUS                                         | 1.32 | 0.00    | 1.27–1.38 |
| Bronchoscopy                                 | 1.24 | 0.00    | 1.21–1.27 |
| Open surgery                                 | 1.17 | 0.00    | 1.13–1.22 |
| VATS                                         | 1.14 | 0.00    | 1.09–1.20 |
| Year identified                              | 1.09 | 0.00    | 1.09–1.12 |
| HCC risk score                               | 0.77 | 0.00    | 0.76–0.78 |
| **Regional characteristics**                 |      |         |         |
| Distance to NCI Cancer Center                | 0.99 | 0.00    | 0.99–0.99 |
| Number of lung cancers patient in HRR        | 0.99 | 0.01    | 0.99–0.99 |
| **20 HRRs with increased likelihood of testing** |      |         |         |
| Boston, MA                                   | 4.94 | 0.00    | 1.67–14.62 |
| Los Angeles, CA                              | 4.94 | 0.00    | 2.08–11.71 |
| East Long Island, NY                         | 4.25 | 0.00    | 1.92–9.43 |
| Manhattan, NY                                | 2.99 | 0.00    | 1.69–5.31 |
| Fort Lauderdale, FL                          | 2.89 | 0.00    | 2.12–3.95 |
| Philadelphia, PA                             | 2.67 | 0.00    | 1.50–4.76 |
| Camden, NJ                                   | 2.57 | 0.00    | 1.48–4.48 |
| Orlando, FL                                  | 2.25 | 0.01    | 1.21–4.20 |
| Anchorage, AK                                | 2.21 | 0.00    | 1.29–3.77 |
| Springfield, AR                              | 2.08 | 0.03    | 1.09–4.00 |
| Houston, TX                                  | 1.93 | 0.01    | 1.14–3.24 |
| Atlanta, GA                                  | 1.83 | 0.04    | 1.02–3.30 |
| St. Louis, MO                                | 1.71 | 0.03    | 1.04–2.79 |
| Pittsburgh, PA                               | 1.66 | 0.01    | 1.13–2.43 |
| Nashville, TN                                | 1.59 | 0.00    | 1.31–1.93 |
| Miami, FL                                    | 1.49 | 0.00    | 1.23–1.80 |
| Columbus, OH                                 | 1.44 | 0.00    | 1.17–1.76 |
| Seattle, WA                                  | 1.39 | 0.01    | 1.09–1.76 |

### Table 4 Characteristics that predict use of molecular tests among lung cancer patients (Continued)

| Variable                                      | OR   | P Value | 95% CI  |
|----------------------------------------------|------|---------|---------|
| **20 HRRs with lowest likelihood of testing** |      |         |         |
| Cape Girardeau, MO                           | 0.26 | 0.00    | 0.12–0.56 |
| Binghamton, NY                               | 0.25 | 0.00    | 0.12–0.54 |
| St. Cloud, MN                                | 0.25 | 0.00    | 0.10–0.61 |
| La Crosse, WI                                | 0.24 | 0.00    | 0.10–0.57 |
| Corpus Christi, TX                           | 0.24 | 0.00    | 0.11–0.51 |
| San Angelo, TX                               | 0.24 | 0.00    | 0.09–0.59 |
| Abilene, TX                                  | 0.23 | 0.00    | 0.10–0.51 |
| Covington, KY                                | 0.23 | 0.00    | 0.10–0.50 |
| Longview, TX                                 | 0.22 | 0.00    | 0.09–0.53 |
| Slidell, LA                                  | 0.21 | 0.00    | 0.09–0.53 |
| Grand Forks, ND                              | 0.21 | 0.00    | 0.09–0.53 |
| Tuscaloosa, AL                               | 0.21 | 0.00    | 0.09–0.48 |
| Wichita Falls, TX                            | 0.20 | 0.00    | 0.08–0.47 |
| Sayre, PA                                    | 0.18 | 0.00    | 0.07–0.46 |
| Texarkana, AR                                | 0.16 | 0.00    | 0.07–0.38 |
| Idaho Falls, ID                              | 0.16 | 0.00    | 0.05–0.48 |
| Alexandria, LA                               | 0.15 | 0.00    | 0.06–0.34 |
| Rochester, MN                                | 0.15 | 0.00    | 0.06–0.35 |
| Rome, GA                                     | 0.12 | 0.00    | 0.05–0.28 |
| Mason City, IA                               | 0.10 | 0.00    | 0.04–0.30 |

Abbreviations: VS versus, OR Odds ratio, CI Confidence Interval, HCC hierarchical condition categories, HRR Hospital referral regions, TBNA transbronchial needle aspiration, VATS video-assisted thoracic surgery, EBUS endobronchial ultrasound

Source: RTI analysis of 2011–2013 Medicare claims data

Reference groups: Race/ethnic groups, Medicaid status, and clinical characteristics were dichotomous variables

Reference group for HRR is Birmingham, Alabama which had the median percentage of patients tested (8%)

variables such as HCC risk score (which is measured in increments of 0.001), we obtained the logit coefficient and multiplied by a factor. There was a 23% decreased odds of testing for a 1 unit increase in risk score.

Patient demographics also had an impact on likelihood to be tested. Asian/Pacific Islanders were most likely to be tested (OR 1.63, CI 1.53–1.79). Minorities and Medicaid patients were less likely to be tested. Medicaid recipients had an OR of 0.74 (CI 0.72–0.77). Hispanics and Blacks were also less likely to be tested (OR 0.97, CI 0.78–0.99 and 0.95, CI 0.92–0.99), respectively. Females were more likely to be tested (OR 1.18, CI 1.16–1.21).

The number of lung cancer patients in each HRR and the distance from an NCI cancer center had an inverse relationship on likelihood to be tested. For each
Discussion
This analysis illustrated underutilization of EGFR testing. It also demonstrated regional and patient-level differences in access to guideline-recommended lung cancer molecular testing. Based on population-level cancer registry data, guidelines recommend EGFR testing for approximately 75,000 patients. We identified 12,433 patients diagnosed and tested in 2013. As illustrated in other studies, Asian women are most likely to be tested, which suggests that physicians’ decisions to test are influenced by the probability of finding a mutation [29].

Analysis of access to testing among most minority groups illustrated that there exists a compounded disparity. Fewer Black and Hispanic patients undergo lung cancer biopsies that produce enough tissue for molecular analysis, which automatically impedes access to tumor tissue analysis. Even among those Black and Hispanic patients who did undergo lung tumor surgical pathology, they were less likely than Asians or Whites to undergo EGFR and KRAS testing.

Clinical guidelines recommended testing patients who may have specific mutations that can influence the choice of treatment. It has been well documented that EGFR mutations are very common in lung cancer patients of East Asian descent (up to 35%) [30], so higher likelihood of testing among Asian patients was expected. In contrast, Black race was a negative predictor. In 2010, there were conflicting reports on the frequency of EGFR mutations in Black populations [31]. However, subsequent research discouraged use of patient race in evaluation of ordering a test.

Our own research on EGFR testing among U.S. veterans indicated that Black veterans were more likely to have an EGFR mutation than Whites [11]. Results presented here suggests that unequal access to surgery contributed to differences in testing frequency between White and Black Medicare beneficiaries. This disparity was compounded by differences in direct access to lung tumor molecular testing. Racial disparities in access to lung cancer molecular testing may be decreased as technologies that measure circulating tumor DNA in peripheral blood become commercially available. These tests, referred to as liquid biopsy tests, offer a noninvasive alternative to tissue biopsy for therapeutic decisions and clinical prognosis in patients with lung cancer. During the time of this study, a serum-based proteomics test, brand name VeriStrat was commercially available. This test was validated in clinical trials [32–36], and in 2013 it was approved for Medicare coverage [12, 37]. Among the 2,488 patients who underwent the proteomic test from 2011 to 2013, 257 (10%) of those tested had no lung biopsy or tumor tissue available for EGFR testing, which illustrates the capacity for liquid biopsy tests to improve access to lung cancer molecular testing. Analysis of physician uptake demonstrated that the proteomic test significantly influenced therapy recommendations in NSCLC [38].

The observation that oncologists practicing in Boston are most likely to order lung cancer molecular tests was consistent with the fact that EGFR mutations conferring responsiveness to EGFR inhibitors were discovered in the Boston-based Harvard Comprehensive Cancer Centers [29, 39, 40]. Harvard’s Massachusetts General Hospital was also the site of the first study demonstrating the effect of the ALK TKI crizotinib [41].

Clinical reasons may explain variation in testing by age and level of comorbidities. A suspected lung cancer diagnosis can be made by a combination of imaging techniques and sputum cytology [5], solid tissue biopsy may not be performed if the patient’s clinical condition or patient’s decision preclude treatment. These factors may account for some patient-level differences in biopsy and testing. Beneficiaries who were enrolled in Medicare prior to age 65 have disabilities, including end-stage renal disease, that may influence treatment decisions. Likewise, beneficiaries over 75 years old may decline treatment for lung cancer. If test results will not influence the treatment decision, there is limited utility of testing.

However, the strongest negative predictor was Medicaid status, which suggests less access to lung cancer molecular testing for low-income beneficiaries. Certain clinical factors that are not reported in claims, such as stage at presentation or smoking status for patients with squamous carcinoma, may explain some of the differences in rates of testing among Medicaid patients.

Our analysis indicated that for a substantial fraction of lung cancer patients, EGFR testing was not performed immediately after diagnosis. For some patients, this delay may have corresponded to their progression to the metastatic stage, when testing was recommended, but it also reflected the changes in clinical guidelines for lung cancer during the time studied. Although the evidence linking EGFR mutations and responsiveness to TKIs was established in 2004, the specific recommendations for EGFR testing were not issued until 2011 by the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO). Based on the 2011 ASCO opinion, initial Local Coverage Determinations were made by several Medicare contractors [12]. The first FDA approval of a companion diagnostic test for EGFR took place in 2013 [42]. This evolving clinical and regulatory landscape may partially explain why the
utilization of EGFR testing was low during the time covered by our study.

Our analysis has several limitations related to the data analyzed. Medicare claims provide an opportunity to evaluate health care interventions in a national cohort of patients. However, claims data do not contain clinical information that is relevant to eligibility for EGFR testing, such as the date of diagnosis, cancer stage, histological subtype of disease, and tissue availability. We were able to demonstrate that 95% of the patients analyzed represented newly diagnosed cases and we identified those patients with tissue available for analysis through surgical pathology codes. However, other clinical characteristics were not available. To provide comprehensive analysis of precision medicine, claims data need to be reconciled with cancer registry data and patients’ clinical records. However, if we limited our analysis to Surveillance, Epidemiology, and End Results (SEER) linked Medicare data, it would have represented only 28% of the US lung cancer population. Our goal was to provide a population-level analysis.

Until 2013, most molecular tests were billed using methodology-based, stacked codes and there was no direct way to relate the number of codes billed to the number of tests performed. In our investigation of 2011–2012 claims, we treated code 83912 in the combination with diagnosis codes for lung cancer as a proxy for EGFR/KRAS testing, but this type of analysis can only yield approximate numbers. We believe that our analysis of 2013 claims data is more accurate, as it is based on unique billing codes. Introduction and further expansion of gene-specific Tier1 codes will allow researchers to determine accurately the utilization of specific biomarkers.

Conclusion
The number of molecularly targeted drugs to treat lung cancer continues to expand, which increases the importance of providing all patients access to molecular testing. In October 2017, FDA awarded breakthrough therapy designation to osimertinib for first-line treatment of patients with metastatic EGFR mutation-positive NSCLC. Only patients with known mutation status will be eligible for osimertinib treatment. Our study demonstrated an overall increase in EGFR testing from 2010 to 2013. However, there was widespread underutilization of guideline-recommended testing. We observed racial, income, and regional disparities in testing. Precision medicine has increased the complexity of cancer diagnosis and treatment. Targeted interventions and clinical decision support tools are needed to ensure that all patients are benefitting from advances in precision medicine. Without such interventions, precision medicine may exacerbate racial disparities in cancer care and health outcomes.

Additional files

**Additional file 1:** FDA-Approved Molecularly Targeted Treatments for Lung Cancer. (XLSX 9 kb)

**Additional file 2:** Timeline of selected clinical guidelines and regulatory decisions. (XLSX 12 kb)

**Additional file 3:** Number and percentage of lung cancer patients who underwent tumor molecular testing. (XLSX 60 kb)

**Abbreviations**
ALK: anaplastic lymphoma kinase; CPT: Current Procedural Terminology; EGFR: epidermal growth factor receptor; FDA: Food & Drug Administration; HCC: Hierarchical Condition Categories; HCPCS: Healthcare Common Procedure Coding System; HRR: Hospital Referral Region; ICD-9: International Classification of Disease; NCI: National Cancer Institute; NSCLC: non-small cell lung cancer; TKI: tyrosine kinase inhibitors; TNBA: transbronchial needle aspiration; US: United States

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**Availability of data and materials**
The data used in this study are available from Research Data Assistance Center (https://www.resdac.org/).

**Authors’ contributions**
All authors read and approved the final manuscript. JA Lynch was the author mainly responsible for conception, design, analysis, and interpretation of these data. All other authors made substantial contributions acquisition of data, drafting the manuscript or revising it critically for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Ethics approval and consent to participate**
This study was approved by the Centers for Medicare & Medicaid Services and the RTI International Institutional Review Board, HHS-500-2005-00029I.

**Consent for publication**
Not applicable

**Competing interests**
All authors report no conflict of interest.

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**Author details**
1Department of Veterans Affairs Salt Lake City Health Care System, Salt Lake City, UT, USA. 2RTI International Waltham, Waltham, MA, USA. 3Boston University School of Medicine, Boston, MA, USA. 4RTI International, Research Triangle Park, Durham, NC, USA. 5Veterans Health Administration, New York, NY, USA. 6New York University, New York, NY, USA. 7Veterans Health Administration, 200 Springs Road, Building 70, Bedford, MA 01730, USA.

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