Disparities and Trends in Genetic Testing and Erlotinib Treatment among Metastatic Non–Small Cell Lung Cancer Patients

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Abstract

Background: Despite reports of socioeconomic disparities in rates of genetic testing and targeted therapy treatment for metastatic non–small cell lung cancer (NSCLC), little is known about whether such disparities are changing over time.

Methods: We performed a retrospective analysis to identify disparities and trends in genetic testing and treatment with erlotinib. Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, we identified 9,900 patients with stage IV NSCLC diagnosed in 2007 to 2011 at age 65 or older. We performed logistic regression analyses to identify patient factors associated with odds of receiving a genetic test and erlotinib treatment, and to assess trends in these differences with respect to diagnosis year.

Results: Patients were more likely to receive genetic testing if they were under age 75 at diagnosis [odds ratio (OR), 1.55]

independent of comorbidity level, and this age-based gap showed a decrease over time (OR, 0.93). For untested patients, erlotinib treatment was associated with race (OR, 0.58, black vs. white; OR, 2.45, Asian vs. white), and was more likely among female patients (OR, 1.45); for tested patients, erlotinib treatment was less likely among low-income patients (OR, 0.32). Most of these associations persisted or increased in magnitude.

Conclusions: Race and sex are associated with rates of erlotinib treatment for patients who did not receive genetic testing, and low-income status is associated with treatment rates for those who did receive testing. The racial disparity remained stable over time, while the income-based disparity grew larger.

Impact: Attention to reducing disparities is needed as precision cancer treatments continue to be developed.

Introduction

Lung cancer, the most common cause of cancer-related death in the United States, is projected to account for 25% of cancer-related mortality in 2018 (1). Fewer than 10% of those with stage IV cancer survive longer than 5 years (2), and the majority of patients with non–small cell lung cancer (NSCLC), the most common lung cancer subtype, have stage IV disease at time of diagnosis (3). Since the late 1990s, the development of targeted cancer therapy has appreciably altered the landscape of lung cancer treatment by becoming a routine element of care for late-stage NSCLC (4).

Targeted therapy drugs inhibit specific molecular pathways associated with cancer growth, for example, the pathway driven by the epidermal growth factor receptor (EGFR) tyrosine kinase. Approximately 3 in 10 patients with NSCLC possess an EGFR mutation, with prevalence varying based on patient factors such as ethnicity (5, 6), and patients with certain types of EGFR mutation (i.e., exon 19 deletion or L858R mutation in exon 21) have better

outcomes when treated with an EGFR tyrosine kinase inhibitor (TKI) than with standard chemotherapy (7). Reports from as early as 2004 first indicated that EGFR mutations were associated with responsiveness to EGFR TKIs (8). NCCN guidelines encouraged genetic testing in 2007, but it was not definitively recommended due to lack of consensus until 2011 (9, 10), at which point it was recommended for all patients with advanced NSCLC considered for first-line EGFR targeted therapy regardless of patient characteristics such as age and sex (10). EGFR TKIs are currently only one of several precision treatment options available for NSCLC. In recent years, lung cancer immunotherapies, including programmed death-1/programmed death ligand-1 (PD-1/PD-L1) inhibitors, have also shown promising results (11). Biomarker testing more generally—including genetic testing for EGFR mutations and testing for elevated PD-L1 expression levels—is currently recommended for patients with NSCLC to determine eligibility for lung cancer precision treatments (12, 13).

Although precision treatments have yielded promising advancements in NSCLC treatment, utilization of some of these therapies is disproportionate across strata defined by race and socioeconomic status (SES). A reduced likelihood of receiving EGFR mutation testing is associated with factors suggesting lower socioeconomic status, including status as a Medicaid beneficiary (8) and patient residence in a relatively low-income area. The latter is also associated with lower rates of treatment with erlotinib, an EGFR TKI (14). Hospitals located in areas with more high-income or more highly educated residents are more likely to order EGFR testing for patients (9). A recent study also showed that blacks and Hispanics were less likely

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and Asians more likely than whites to receive EGFR testing (8). Racial disparities in cancer treatment have been well documented (15–18); with respect to targeted therapy treatments in particular, it has been found that black patients are less likely than white patients to receive HER2-targeted therapies for breast cancer (19), and black patients with renal cancer show worse survival than whites even after the advent of targeted therapy based on VEGF inhibition (20, 21). Despite these studies on disparities in cancer treatment, little is known about whether such discrepancies are stable, growing, or shrinking over time within the context of the rapidly evolving and relatively new field of precision cancer treatment.

We performed a retrospective study to investigate disparities in biomarker testing and precision treatment for NSCLC, and how the disparities changed over time. We analyzed genetic testing and erlotinib treatment among patients with late-stage NSCLC diagnosed in 2007 to 2011 to discern patterns that may apply to current developments in targeted therapy and immunotherapy for cancer. By studying these disparities and trends, clinicians and other healthcare providers can be more aware of how different treatments are administered to different patient populations and aid in improving access to high-quality care.

Materials and Methods

Data source

We created our retrospective cohort using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database (https://healthcaredelivery.cancer.gov/seermedicare/), which links records from the SEER cancer registries with Medicare claims data collected by the Center for Medicare and Medicaid Services (CMS). The National Cancer Institute's SEER program (http://seer.cancer.gov/) collects information on cancer incidence, survival, and patient demographics from the 17 SEER registries in the United States, comprising approximately 28% of the U.S. population. Medicare provides health insurance for approximately 97% of the United States population age 65 or older. Medicare coverage consists of several parts: Part A coverage is for hospital, skilled-nursing facility, hospice and home health care; Part B coverage is for physician and outpatient services; Part C refers to health maintenance organization (HMO) enrollment; and Part D coverage is for prescription drugs.

Study population

Within the SEER-Medicare data, we identified patients diagnosed at age 65 or older with stage IV, NSCLC as their only cancer between 2007, the first year for which Part D data records were available, and 2011, the last year with diagnosis data available at the time of this study. Data were available for claims made through the end of 2013. Stage IV lung cancers were identified as those with a Derived AJCC Stage Group (6th edition) of 70 through 74. Histology was captured through ICD-O-3 codes, with histological categories labeled according to the SEER Cancer Statistics Review (22). Among the categories, NSCLC included those with a category of large cell, squamous cell, adenocarcinoma, or "other non–small cell type" within the other type category.

Patients were excluded if they were not enrolled continuously in Medicare Parts A, B, and D from one year before diagnosis until death or end of the study period, or if they received Medicare benefits due to disability or end-stage renal disease. Patients were also excluded if they received benefits from an HMO during the study period, as HMOs do not submit detailed claims to Medicare.

Outcomes of interest

The two primary outcomes of interest were the receipt of a genetic test and treatment with erlotinib. In the years covered by our study, there was no CPT coding system for uniquely identifying a particular genetic test (23). Genetic tests were identified in claims data using a set of Current Procedural Terminology (CPT) codes known as "stacking codes," which corresponded to molecular pathology procedures performed in the genetic testing process (8, 24). Use of stacking codes in claims data is highly accurate in identifying genetic tests in patients with lung cancer (25). We identified a patient as having received a genetic test if their records reflected a claim, occurring after the date of lung cancer diagnosis, corresponding to the following stacking codes: 83912 in the Carrier claims file; 83890 to 83892, 83894, 83896, 83898, 83901 to 83904, 83907, 83909, 83914, and 83912 in the Outpatient claims file. The code 83912 refers to the interpretation and report of a genetic test, whereas the other codes capture specific molecular pathology procedures typically performed in the course of such a test (24). Treatment with erlotinib, which accounted for over 98% of lung cancer targeted therapy use in our patient cohort, was indicated for patients whose Part D event file records showed at least one prescription with a generic name of "Erlotinib HCL."

Explanatory variables

The primary socioeconomic variables of interest were income level and residence in a high-poverty location. Eligibility for or receipt of a low-income subsidy for Part D prescription drug costs was used as a proxy for low income level. The Part D enrollment file contains data on the monthly subsidy status of each Medicare beneficiary. A patient was marked as having low income if, for at least one month in the study period, they received or were deemed eligible for the low-income subsidy (i.e., had the value of the Denominator Cost Share Group variable equal to 01 through 08). Residence in a high-poverty location was indicated for those patients whose Census Tract Poverty Indicator variable in the Patient Entitlement and Diagnosis Summary File (PEDSF), which measures the percentage of census tract residents living in poverty, had a value of at least 10% poverty.

Other explanatory variables included several demographic and clinical patient factors. Urban residence was captured through the Urban/Rural variable in the PEDSF file, which classifies a patient's county of residence in terms of urban population size and adjacency to a metropolitan area according to a classification scheme created by the Department of Agriculture's Economic Research Service (https://www.ers.usda.gov/data-products/rural-urban-continuum-codes/). This study designed urban locations as those coded "Big Metro," "Metro," or "Urban," and less urban locations as those coded "Less Urban" or "Rural." Other patient factors included in the analysis were sex, race (white, Asian, black, Hispanic, and other/unknown, with the last category collapsed to avoid small cell sizes), histology (adenocarcinoma vs. other non–small cell), and age at diagnosis (below 75 vs. above). Comorbidity scores were calculated using the adaptation by Deyo and colleagues of the Charlson comorbidity index, collapsed into categories of 0/1/2/3+ (26–29). Trends in outcomes over time were measured with respect to diagnosis year, ranging from 2007 to 2011.

Statistical analysis

Descriptive statistics were calculated for the socioeconomic, clinical, and demographic variables. The associations between the explanatory and outcome variables were evaluated using Pearson's χ^2 tests for categorical variables and Student t tests for continuous variables.

We used multivariate logistic regression models to compute odds ratios (OR) and 95% confidence intervals (CI) for receiving a genetic test and for using erlotinib, adjusting for demographic, clinical, and SES characteristics. We took a sequential modeling approach, showing results for models adjusting for demographic variables only and adjusting for both clinical and demographic variables. For analysis of erlotinib treatment, we divided the study cohort with regard to whether the patient had received a genetic test or not, and then applied the regression model to each of these two population subsets. Interaction terms for diagnosis year and each one of the other explanatory variables were used to examine trends over time in the adjusted prevalence of genetic testing and of erlotinib treatment. For each model, a Hosmer and Lemeshow χ^2 test was performed to confirm goodness of fit.

This study was approved by the Institutional Review Board at Massachusetts General Hospital. All statistical analyses were conducted in SAS 9.4 (SAS Institute).

Results

Our study population consisted of 9,900 patients, of whom 1,040 (10.5%) had a genetic test and 1,327 (13.5%) received at least one erlotinib prescription. Univariate analysis (Table 1) showed that the percentage of patients having a genetic test increased with diagnosis year from 1.6% in diagnosis year 2007 to 22.4% in diagnosis year 2011, whereas the percentage using erlotinib decreased from 15.4% to 11.7% over the same time period (Table 2). Low-income patients were less likely than non–low-income patients to have a genetic test (7.8% vs. 12.7%) or to receive erlotinib treatment (12.4% vs. 14.1%). Patients residing in high-poverty areas were also less likely to have a genetic test (8.3% vs. 13.2%) or to receive erlotinib treatment (12.2% vs. 14.8%). Patients who were female, who have adenocarcinoma, or who reside in an urban area were more likely both to have a genetic test and to receive erlotinib treatment. Patients under age 75 at diagnosis were more likely to receive a genetic test and slightly less likely to be treated with erlotinib. Asians were most likely and blacks were least likely to receive either a genetic test or erlotinib. These patterns in erlotinib treatment occurred not only in the full patient cohort, but also within each subset based on testing status (Table 2).

After adjusting for demographic variables only, low-income status was significantly associated with a lower rate of genetic testing (OR, 0.73; 95% CI, 0.53–0.99; Table 3). Residence in a high-poverty area, however, was not significant. When adjusting for clinical and demographic factors, only adenocarcinoma histology (OR, 1.56; 95% CI, 1.18–2.07), diagnosis age under 75 (OR, 1.55; 95% CI, 1.19–2.01), and Charlson index of 3 or higher (OR, 0.53; 95% CI, 0.29–0.97) had a significant association with odds of genetic testing. Of the differences in genetic testing rates, only the difference based on having age under 75 at diagnosis was found to be changing over time; the difference narrowed with increasing diagnosis year (OR, 0.93; 95% CI, 0.88–1.00).

Table 1. Patient factors associated with genetic testing (univariate analysis)

	Had genetic test N (%)	No genetic test N (%)	P
SES Variables			
Income			<0.0001[a]
Low income	319 (7.8)	3,893 (92.4)	
Not low income	721 (12.7)	4,967 (87.3)	
High-poverty location			<0.0001[a]
High-poverty	439 (8.3)	4,870 (91.7)	
Not high-poverty	554 (13.2)	3,648 (86.8)	
Demographic and clinical characteristics			
Sex			<0.0001[a]
Female	590 (11.8)	4,432 (88.2)	
Male	450 (9.2)	4,428 (90.8)	
Race			<0.0001[a]
White	859 (10.8)	7,095 (89.2)	
Black	53 (5.3)	953 (94.7)	
Asian	74 (14.8)	425 (85.2)	
Hispanic	15 (7.7)	181 (92.3)	
Other or unknown	39 (15.9)	206 (84.1)	
Histology			<0.0001[a]
Adenocarcinoma	787 (15.3)	4,345 (84.7)	
Other non–small cell	253 (5.3)	4,515 (94.7)	
Age at diagnosis			0.0038[a]
Under 75	531 (11.5)	4,104 (88.5)	
75 or older	509 (9.7)	4,756 (90.3)	
Urban location			<0.0001[a]
Urban	908 (11.0)	7,345 (89.0)	
Not urban	86 (6.7)	1,208 (93.3)	
Diagnosis year			<0.0001[a]
2007	31 (1.6)	1,900 (98.4)	
2008	61 (3.2)	1,867 (96.8)	
2009	182 (9.1)	1,810 (90.9)	
2010	316 (15.5)	1,727 (84.5)	
2011	450 (22.4)	1,556 (77.6)	
Charlson index			<0.0001[a]
0	438 (14.4)	2,596 (85.6)	
1	283 (9.6)	2,671 (90.4)	
2	141 (8.7)	1,477 (91.3)	
3+	165 (8.0)	1,909 (92.0)	

[a]Significant at the 0.05 level.

Among untested patients, Asian race was significantly associated with higher rate of erlotinib treatment (OR, 2.45; 95% CI, 1.49–4.02) and black race with a lower rate (OR, 0.58; 95% CI, 0.35–0.97) as compared with non-Hispanic whites (Table 4). Female sex (OR, 1.45; 95% CI, 1.24–1.70) was also associated with erlotinib use. The difference in erlotinib treatment rate associated with female sex changed (narrowed) significantly as diagnosis year increased. Among patients who did receive a genetic test, low income status was associated with lower likelihood of erlotinib use (OR, 0.32; 95% CI, 0.13–0.79 for tested patients; Table 5), a difference that grew in magnitude with diagnosis year (OR, 1.26; 95% CI, 1.02–1.56). Results of multivariate analysis of erlotinib treatment based on the full study cohort (without partitioning by genetic testing status) are available in Supplementary Table S1.

Discussion

This retrospective study used SEER-Medicare data to examine whether disparities associated with socioeconomic, demographic, or clinical patient factors existed in genetic testing and erlotinib treatment among patients with late-stage NSCLC with Medicare diagnosed in 2007 through 2011, and whether

Table 2. Patient factors associated with erlotinib treatment (univariate analyses)

	Entire cohort		Had genetic test		No genetic test	
	Treated with erlotinib (*N*; %)	*P*	Treated with erlotinib (*N*; %)	*P*	Treated with erlotinib (*N*; %)	*P*
SES Variables						
Income		0.0131[a]		0.5622		0.1282
Low income	523 (12.4)		73 (22.9)		450 (11.6)	
Not low income	804 (14.1)		177 (24.6)		657 (12.6)	
High-poverty location		0.0002[a]		0.6300		0.0026[a]
High-poverty	646 (12.2)		102 (23.2)		544 (11.2)	
Not high-poverty	622 (14.8)		136 (24.6)		486 (13.3)	
Demographic and clinical characteristics						
Sex		<0.0001[a]		0.0178[a]		<0.0001[a]
Female	807 (16.1)		158 (26.8)		649 (14.6)	
Male	520 (10.7)		92 (20.4)		428 (9.7)	
Race		<0.0001[a]		0.0004[a]		<0.0001[a]
White	966 (12.1)		189 (22.0)		777 (11.0)	
Black[b]	88 (8.8)		<11 (<20.8)		>77 (>8.1)	
Asian	169 (33.9)		28 (37.8)		141 (33.2)	
Hispanic[b]	33 (16.8)		<11 (<73.3)		>22 (>12.2)	
Other or unknown	71 (29.0)		17 (43.6)		54 (26.2)	
Histology		<0.0001[a]		0.1359		<0.0001[a]
Adenocarcinoma	868 (16.9)		198 (25.2)		670 (15.4)	
Other non–small cell	459 (9.6)		52 (20.6)		407 (9.0)	
Age at diagnosis		0.1351		0.1615		0.1736
Under 75	596 (12.9)		118 (22.2)		478 (11.7)	
75 or older	731 (13.9)		132 (25.9)		599 (12.6)	
Urban location		<0.0001[a]		0.0051[a]		0.0061[a]
Urban	1143 (13.9)		228 (25.1)		915 (12.5)	
Not urban[b]	127 (9.8)		<11 (<12.8)		>116 (>9.6)	
Diagnosis year		0.0002[a]		<0.0001[a]		<0.0001[a]
2007	298 (15.4)		14 (45.2)		284 (15.0)	
2008	270 (14.0)		23 (37.7)		247 (13.2)	
2009	291 (14.6)		60 (33.0)		231 (12.8)	
2010	233 (11.4)		70 (22.5)		163 (9.4)	
2011	235 (11.7)		83 (18.4)		152 (9.8)	
Charlson index		0.0088[a]		0.0088[a]		<0.0001[a]
0	26 (15.8)		126 (28.8)		419 (16.1)	
1	32 (22.7)		66 (23.3)		332 (12.4)	
2	66 (23.3)		32 (22.7)		148 (10.0)	
3+	126 (28.8)		26 (15.7)		160 (8.4)	

[a]Significant at the 0.05 level.
[b]Data masked to comply with SEER-Medicare policy regarding cells <11.

any such disparities changed over time. Our results show that low-income status is associated with lower rates of genetic testing after accounting for demographic factors, and lower rates of erlotinib treatment among tested patients after adjusting for all factors. Race and sex were associated with erlotinib treatment for untested patients. In addition, adenocarcinoma histology was associated with genetic testing, as was younger age at diagnosis. Of all discrepancies found, only the ones due to age at diagnosis in genetic testing and female sex in erlotinib treatment among untested patients were found to be decreasing over the study time period, whereas income-based disparities in erlotinib treatment among tested patients were increasing.

Little is known about disparity trends in genetic testing or targeted therapy usage. (Racial disparity trends in receipt of surgery or chemotherapy as cancer treatment have been investigated and shown to be relatively stable over time; refs. 16, 30). Given that knowledge about the role of genetic testing and the proper indication for erlotinib in NSCLC was continually developing over our study time period, we sought to investigate whether increasing knowledge benefitted all patients equally.

Erlotinib was first approved by the Food and Drug Administration in 2004 for use in locally advanced or metastatic NSCLC. Although it was not until 2016 that erlotinib's FDA approval was limited to patients who have certain EGFR mutations, there is evidence that the rate of genetic testing among patients with lung cancer had been increasing before this (8, 23) as awareness grew of its potential benefits (as reflected by, e.g., a provisional clinical opinion from the American Society of Clinical Oncology, published in 2011, recommending a genetic test before first-line EGFR TKI treatment; ref. 10). Our results showing that later diagnosis years in the 2007 to 2011 time period correspond to higher genetic testing rates is in line with this trend. Increasing awareness of biomarkers' relevance to treatment choice may also explain our results showing erlotinib treatment not similarly increasing with time, given that only a minority of patients with NSCLC harbor an EGFR mutation (31).

Low-income patients in our study were identified through the proxy of eligibility for a low-income subsidy for Part D prescription costs. According to CMS, in 2018, a single beneficiary may qualify for the low-income subsidy with up to $18,210 in yearly income and up to $14,000 in resources, and a beneficiary may be deemed eligible automatically due to having full Medicaid

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Table 3. Patient factors associated with genetic testing (multivariate analysis)

	Model 1; Without clinical variables		Model 2; With clinical variables included	
	OR (CI)	*P*	OR (CI)	*P*
SES Variables				
Low income	0.73 (0.53–0.99)	0.0425[a]	0.78 (0.57–1.08)	0.1335
High-poverty location	0.84 (0.64–1.1)	0.2146	0.82 (0.62–1.08)	0.1553
Demographic and clinical characteristics				
Female	1.13 (0.88–1.46)	0.3408	1.14 (0.88–1.48)	0.3275
Black (vs. white)	1.20 (0.47–3.1)	0.7012	1.16 (0.43–3.14)	0.7639
Asian (vs. white)	0.96 (0.35–2.64)	0.9422	0.95 (0.34–2.62)	0.9161
Hispanic (vs. white)	1.77 (0.36–8.67)	0.4795	1.95 (0.4–9.43)	0.407
Other/unknown (vs. white)	0.53 (0.14–2.04)	0.3534	0.50 (0.13–1.96)	0.318
Urban location	1.59 (0.96–2.64)	0.0706	1.60 (0.96–2.66)	0.0725
Diagnosis year	2.17 (1.82–2.6)	<0.0001[a]	2.18 (1.81–2.63)	<0.0001[a]
Adenocarcinoma	—	—	1.56 (1.18–2.07)	0.0021[a]
Under 75 at diagnosis	—	—	1.55 (1.19–2.01)	0.001[a]
Charlson index 3+ (vs. 0)	—	—	0.53 (0.29–0.97)	0.0393[a]
Charlson index 2 (vs. 0)	—	—	1.41 (0.82–2.41)	0.214
Charlson index 1 (vs. 0)	—	—	0.81 (0.51–1.29)	0.3857
Diagnosis year interaction variables				
Low income	1.01 (0.94–1.09)	0.7793	1.01 (0.93–1.09)	0.8961
High-poverty location	1.00 (0.94–1.07)	0.8947	1.02 (0.95–1.09)	0.5733
Female	1.00 (0.95–1.07)	0.8785	0.99 (0.93–1.05)	0.713
Black (vs. white)	0.82 (0.65–1.04)	0.0989	0.83 (0.65–1.07)	0.1464
Asian (vs. white)	1.14 (0.9–1.46)	0.2786	1.14 (0.89–1.45)	0.3126
Hispanic (vs. white)	0.82 (0.55–1.23)	0.3386	0.81 (0.55–1.21)	0.2998
Other/unknown (vs. white)	1.31 (0.95–1.82)	0.0993	1.31 (0.95–1.82)	0.1038
Urban location	0.94 (0.83–1.05)	0.2852	0.94 (0.83–1.05)	0.2743
Adenocarcinoma	—	—	1.01 (0.94–1.08)	0.8285
Under 75 at diagnosis	—	—	0.93 (0.88–1)	0.0353[a]
Charlson index 3+ (vs. 0)	—	—	1.10 (0.96–1.27)	0.1648
Charlson index 2 (vs. 0)	—	—	0.90 (0.79–1.02)	0.0972
Charlson index 1 (vs. 0)	—	—	1.04 (0.93–1.16)	0.4995

[a]Significant at the 0.05 level.

Table 4. Patient factors associated with erlotinib treatment (multivariate analysis); patients who did not have genetic test

	Model 1; Without clinical variables		Model 2; With clinical variables included	
	OR (CI)	*P*	OR (CI)	*P*
SES Variables				
Low income	0.82 (0.69–0.97)	0.024[a]	0.86 (0.72–1.02)	0.0896
High-poverty location	1.05 (0.9–1.24)	0.5348	1.06 (0.9–1.25)	0.5066
Demographic and clinical characteristics				
Female	1.50 (1.29–1.75)	<0.0001[a]	1.45 (1.24–1.7)	<0.0001[a]
Black (vs. white)	0.52 (0.31–0.85)	0.0093[a]	0.58 (0.35–0.97)	0.0382[a]
Asian (vs. white)	2.34 (1.45–3.78)	0.0005[a]	2.45 (1.49–4.02)	0.0004[a]
Hispanic (vs. white)	0.83 (0.36–1.93)	0.6679	0.64 (0.26–1.58)	0.3304
Other/unknown (vs. white)	1.80 (0.97–3.35)	0.0636	1.85 (0.97–3.53)	0.0602
Urban location	1.01 (0.8–1.28)	0.943	1.02 (0.81–1.3)	0.8552
Diagnosis year	0.90 (0.8–1.01)	0.0758	0.89 (0.79–1.01)	0.0735
Adenocarcinoma	—	—	1.14 (0.98–1.33)	0.0989
Under 75 at diagnosis	—	—	0.91 (0.78–1.06)	0.2072
Charlson index 3+ (vs. 0)	—	—	0.79 (0.58–1.09)	0.1489
Charlson index 2 (vs. 0)	—	—	0.97 (0.7–1.34)	0.8541
Charlson index 1 (vs. 0)	—	—	1.05 (0.82–1.36)	0.6808
Diagnosis year interaction variables				
Low income	1.02 (0.92–1.02)	0.5302	1.03 (0.97–1.09)	0.4011
High-poverty location	0.97 (0.96–1.08)	0.2537	0.97 (0.92–1.03)	0.3238
Female	0.95 (0.91–1)	0.8955	0.95 (0.9–1)	0.0439[a]
Black (vs. white)	0.96 (0.81–1.13)	0.5901	0.94 (0.8–1.12)	0.4964
Asian (vs. white)	1.04 (0.9–1.22)	0.5723	1.02 (0.87–1.19)	0.835
Hispanic (vs. white)	1.04 (0.8–1.35)	0.7945	1.11 (0.84–1.46)	0.4608
Other/unknown (vs. white)	0.99 (0.8–1.21)	0.8963	0.96 (0.78–1.19)	0.7338
Urban location	1.01 (0.93–1.09)	0.8955	1.00 (0.92–1.08)	0.9808
Adenocarcinoma	—	—	1.05 (0.99–1.1)	0.09
Under 75 at diagnosis	—	—	1.05 (0.99–1.1)	0.0824
Charlson index 3+ (vs. 0)	—	—	0.99 (0.89–1.09)	0.7842
Charlson index 2 (vs. 0)	—	—	0.97 (0.87–1.07)	0.5177
Charlson index 1 (vs. 0)	—	—	1.00 (0.92–1.08)	0.9733

[a]Significant at the 0.05 level.

Table 5. Patient factors associated with erlotinib treatment (multivariate analysis); patients who had a genetic test

	Model 1; Without clinical variables		Model 2; With clinical variables included	
	OR (CI)	P	OR (CI)	P
SES Variables				
Low income	0.31 (0.14–0.72)	0.0064[a]	0.32 (0.13–0.79)	0.0131[a]
High-poverty location	1.16 (0.61–2.19)	0.6555	1.12 (0.58–2.17)	0.7304
Demographic and clinical characteristics				
Female	0.76 (0.42–1.38)	0.3696	0.68 (0.36–1.3)	0.2422
Black (vs. white)	1.72 (0.13–23.64)	0.684	2.14 (0.14–32.75)	0.5843
Asian (vs. white)	2.64 (0.27–25.97)	0.4048	2.64 (0.26–26.73)	0.4108
Hispanic (vs. white)	0.06 (0–7.91)	0.2529	0.03 (0–3.77)	0.1547
Other/unknown (vs. white)	4.04 (0.1–156.89)	0.454	6.45 (0.16–260.1)	0.3229
Urban location	2.13 (0.49–9.24)	0.3115	2.16 (0.48–9.71)	0.3159
Diagnosis year	0.93 (0.55–1.56)	0.7763	0.87 (0.5–1.51)	0.6181
Adenocarcinoma	—	—	1.26 (0.59–2.66)	0.5506
Under 75 at diagnosis	—	—	1.13 (0.6–2.12)	0.7003
Charlson index 3+ (vs. 0)	—	—	0.78 (0.16–3.93)	0.7659
Charlson index 2 (vs. 0)	—	—	3.40 (0.83–13.89)	0.0879
Charlson index 1 (vs. 0)	—	—	0.49 (0.15–1.59)	0.2347
Diagnosis year interaction variables				
Low income	1.26 (1.03–1.53)	0.0248[a]	1.26 (1.02–1.56)	0.034[a]
High-poverty location	0.98 (0.83–1.14)	0.771	0.99 (0.84–1.16)	0.8966
Female	1.14 (0.98–1.32)	0.0816	1.16 (0.99–1.35)	0.0745
Black (vs. white)	0.72 (0.37–1.4)	0.3303	0.72 (0.36–1.43)	0.3462
Asian (vs. white)	0.88 (0.52–1.51)	0.6526	0.87 (0.51–1.51)	0.6246
Hispanic (vs. white)	2.15 (0.65–7.07)	0.2074	2.42 (0.75–7.78)	0.1385
Other/unknown (vs. white)	0.85 (0.36–1.99)	0.7086	0.76 (0.32–1.79)	0.5247
Urban location	0.90 (0.64–1.27)	0.552	0.89 (0.63–1.27)	0.5349
Adenocarcinoma	—	—	0.97 (0.8–1.17)	0.753
Under 75 at diagnosis	—	—	0.93 (0.8–1.09)	0.3778
Charlson index 3+ (vs. 0)	—	—	0.96 (0.65–1.41)	0.8201
Charlson index 2 (vs. 0)	—	—	0.74 (0.52–1.06)	0.0966
Charlson index 1 (vs. 0)	—	—	1.23 (0.93–1.64)	0.1532

[a]Significant at the 0.05 level.

coverage, enrollment in the Medicare Savings Program, or receipt of Supplemental Security Income benefits (https://www.medicare.gov/your-medicare-costs/help-paying-costs/get-help-paying-costs.html/). We found that after adjusting for demographic variables, low-income status was associated with significantly lower rates of both genetic testing and erlotinib treatment, but the statistical significance of these associations was weakened after adjusting for three clinical factors (histology, age at diagnosis, and comorbidity index). This was particularly pronounced in the case of genetic testing: a Charlson comorbidity index of 3 or higher was the explanatory measure most negatively associated with testing. EGFR testing usually requires biopsy (32), a surgical procedure that may present risks for patients with more comorbidities, and there is a well-established relationship between lower socioeconomic status and higher comorbidity level (33, 34). Thus, although low socioeconomic status per se may not impede access to genetic testing, the higher comorbidity rate in low-SES populations appears to create a *de facto* socioeconomic disparity.

We found that low patient income was also associated with lower erlotinib treatment rates, particularly for patients with known mutation status, and that this disparity was widening over time for these patients. Erlotinib, like other targeted therapies, is known to be a high-cost medication (35), and its cost increased substantially over the study period (36). It is noteworthy that we found the low-income patients in our study paid much less out-of-pocket for erlotinib (as measured by the patient pay amount corresponding to each prescription in the Medicare Part D Prescription Drug Event file): $42 versus $1,247 per patient per month for eligible patients versus non-eligible. Therefore, it is not

clear that unaffordable out-of-pocket expense serves as the mechanism for reduced erlotinib treatment in our low-income cohort. More research is needed to elucidate this mechanism. It has been suggested that providers may "implicitly ration" treatment based on patient income level (15).

Previous work has shown that a high-poverty residence is associated with lower rates of genetic testing and erlotinib treatment (14), as well as of cancer treatment generally (37, 38). However, we found that after correcting for an individual's income level, a significant association with community-level poverty did not remain for either outcome. This is notable given that community poverty level has been used as a proxy for individual SES in a number of studies examining relationships between SES and cancer outcomes. In our data, the association between low-income status and high-poverty residence was found to be weak (Cramer's V = 0.2791), though highly significant (P < 0.0001).

Patients who are female, Asian, or have adenocarcinoma are known to have higher prevalence of EGFR mutation (39, 40). Previous studies have indicated increased genetic testing rates for female and Asian patients (8, 23), whereas our study does not; this may be because we have adjusted for adenocarcinoma histology in our genetic testing analysis, whereas the other studies did not. However, the lack of racial or sex-based discrepancies in genetic testing is a positive sign, suggesting that perceived relative likelihood of having an EGFR mutation based on these factors is not affecting genetic testing rates.

The erlotinib treatment patterns among untested patients, on the other hand, suggest the existence of race- and sex-based

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disparities. Although it is not known from our study what causes the association of black race with erlotinib treatment rates, one possibility is that this disparity reflects whatever underlying causes drive other disparities for black patients observed in the context of cancer treatments, including lower rates of chemotherapy and surgery for lung cancer (16, 30). Another mechanism that may be at play, particularly with respect to the associations with female sex and Asian race, is that these characteristics are taken into account when evaluating how likely the patient is to possess an EGFR mutation, and consequently to be eligible for erlotinib treatment. In the case of tested patients, presumably the decision to treat with erlotinib would be driven more directly by the patient's known actual EGFR mutation status. It is also possible that patients who do not receive a genetic test from their healthcare provider represent a subset who are also more likely to experience racial treatment disparities due to latent variables pertaining to quality of care for these patients.

Our finding that genetic testing rate is associated negatively with older age at diagnosis (as shown previously; refs. 8, 14, 23) may reflect a relationship that has been demonstrated between advanced age and lung cancer treatment more broadly. Patients of advanced age are generally more likely to refuse cancer treatment, due to, for example, comorbid conditions (41). The age disparity that remains even after correcting for comorbidity level, however, does raise the question of whether older patients have lower access to genetic testing not because they are sicker, but simply because they are older. Comorbidity-independent age-based disparity has already been documented in the more general context of active treatment for NSCLC (42–44), and our result implies that this disparity may also exist in targeted therapy treatment specifically. Further investigation is warranted to determine whether this disparity could be due to patient preferences or to inappropriate undertreatment. Nevertheless, the decreasing trend in the genetic testing disparity based on age may indicate that, over time, more older patients are at least considering the possibility of targeted therapy treatment.

Our study demonstrates that even as precision therapy has yielded increasingly effective treatments for patients with NSCLC, some disparities in treatment rates have persisted. During the study period, the field of targeted therapy was rapidly evolving, and this remains true for precision therapy in NSCLC even in the present day. For example, it has been established in recent years that a particular EGFR mutation, known as T790M, is associated with acquired resistance to standard EGFR TKIs, including erlotinib (45), and subsequently a newer EGFR TKI, osimertinib, has been shown to be more effective than erlotinib in patients with T790M (46). This discovery has raised new questions about optimal targeted therapy regimens. Cancer immunotherapy is also a very active field of research. PD-L1 expression testing, in particular, has much in common with EGFR testing in our study: It is currently recommended but not required for patients with NSCLC (12); PD-L1 expression predicts outcomes for immunotherapy patients, although only a minority of NSCLCs are associated with high PD-L1 expression (47); and patient factors are associated with high expression levels (47). As precision treatments

continue to be refined, healthcare providers must be aware that disparities can persist even as the field advances.

This study has several limitations. Given that this is a retrospective study, it was not possible to fully control for potential confounding variables. There are elements of socioeconomic status beyond income and residence—education level, for example—that we were not able to include in our analysis. Furthermore, due to the nature of genetic test coding during the study period, it was not possible to distinguish an EGFR test from a genetic test more generally, and the results of patients' genetic tests were not available. In addition, the SEER-Medicare database, which represents patients from 17 registries, may contain geographic bias and not be representative of the United States as a whole. Another limitation common to SEER-Medicare analyses is that the restriction to patients continuously enrolled over the study period and patients without HMOs, done to ensure a complete longitudinal analysis, may have excluded patients who were disenrolled from Medicare (for example, due to non-payment of premiums) and thus had an effect on the socio-demographic makeup of the study cohort.

In conclusion, our results demonstrate that discrepancies, including socioeconomic and racial gaps, have persisted in the complex and continually evolving field of precision medicine for lung cancer, and that renewed attention to narrowing disparities is needed so that all patients may benefit equally from paradigm-changing advances in cancer treatment.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The statements contained herein are solely those of the authors and do not represent or imply concurrence or endorsement by NCI.

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Disparities and Trends in Genetic Testing and Erlotinib Treatment among Metastatic Non–Small Cell Lung Cancer Patients

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