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John M. Varlotto
University of Massachusetts Medical School

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Population-based differences in the outcome and presentation of lung cancer patients based upon racial, histologic, and economic factors in all lung patients and those with metastatic disease

John Michael Varlotto1,2, Richard Voland3, Kerrie McKie2, John C. Flickinger4, Malcolm M. DeCamp5, Debra Maddox6, Paul Rava1,2, Thomas J. Fitzgerald1,2, Geoffrey Graeber2,7, Negar Rassaei8, Paulo Oliveira2,9, Suhail Ali10, Chandra Belani10, Jonathan Glanzman1,2, Heather A. Wakelee11, Manali Patel11, Jennifer Baima12, Jianying Zhang13 & William Walsh2,6

1Department of Radiation Oncology, University of Massachusetts Medical Center, Worcester, Massachusetts
2University of Massachusetts Medical School, Worcester, Massachusetts
3School of Nursing, University of Wisconsin, Madison, Wisconsin
4Department of Radiation Oncology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania
5Division of Thoracic Surgery, Feinberg School of Medicine, Northwestern University, Chicago, Illinois
6Department of Medical Oncology, University of Massachusetts Medical Center, Worcester, Massachusetts
7Division of Thoracic Surgery, University of Massachusetts Medical Center, Worcester, Massachusetts
8Department of Pathology, Penn State Hershey Medical Center, Hershey, Pennsylvania
9Division of Pulmonary, University of Massachusetts Medical Center, Allergy and Critical Care Medicine, Worcester, Massachusetts
10Penn State Hershey Cancer Institute, Hershey, Pennsylvania
11Division of Medical Oncology, Stanford University, Palo Alto, California
12Department of Orthopedics and Rehabilitation, University of Massachusetts Medical Center, Worcester, Massachusetts
13Department of Quantitative Sciences, University of Massachusetts Medical School, Worcester, Massachusetts

Keywords
Disparities, insurance, lung cancer, marriage, metastatic lung cancer, outcomes, race, socio-economic factors

Abstract
To investigate the interrelation between economic, marital, and known histopathologic/therapeutic prognostic factors in presentation and survival of patients with lung cancer in nine different ethnic groups. A retrospective review of the SEER database was conducted through the years 2007–2012. Population differences were assessed via chi-square testing. Multivariable analyses (MVA) were used to detect overall survival (OS) differences in the total population (TP, N = 153,027) and for those patients presenting with Stage IV (N = 70,968). Compared to Whites, Blacks were more likely to present with younger age, male sex, lower income, no insurance, single/widowed partnership, less squamous cell carcinomas, and advanced stage; and experience less definitive surgery, lower OS, and lung cancer-specific (LCSS) survival. White Hispanics presented with younger age, higher income, lower rates of insurance, single/widowed partnership status, advanced stage, more adenocarcinomas, and lower rates of definitive surgery, but no difference in OS and LCSS than Whites. In the TP and Stage IV populations, MVAs revealed that OS was better or equivalent to Whites for all other ethnic groups and was positively associated with insurance, marriage, and higher income. Blacks presented with more advanced disease and were more likely to succumb to lung cancer, but when adjusted for prognostic factors, they had a better OS in the TP compared to Whites. Disparities in income, marital status, and insurance rather than race affect OS of patients with lung cancer. Because of their presentation with advanced disease, Black and Hispanics are likely to have increased benefit from lung cancer screening.
Introduction

In the United States, lung cancer occurs in approximately 225,000 patients and is associated with over 160,000 deaths annually [1]. However, despite the prevalence of this malignancy, the influence and/or interrelation between economic and insurance factors as well as ethnicity have been poorly studied. One recent study did investigate racial/ethnic differences in lung cancer incidence and mortality in women, but found no differences in fully adjusted models [2]. Additionally, another report demonstrated lung cancer rates have dropped faster in Black women than the rates in Whites since the 1990s [3]. A National Cancer Database project [5] found income and race (White, Black, and Asian) were not related to survival, but patients with Medicaid or who were uninsured had worse outcomes [5].

The purpose of our analysis was to study whether marital status, household income, insurance type, and ethnicity play a role in the presentation and prognosis of all patients with NSCLC and those presenting with metastatic disease in the United States. We feel this investigation is unique because we investigate the racial groups in terms of their presenting economic, histopathologic, and marital status and assess whether racial differences account for differing prognoses.

Materials and Methods

Data source/cohopt selection

The “SEER-18” database was available since the year 2000 [6] and covers approximately 28% of the American population [6]. The years 2007–2012 were queried to identify patients with microscopically confirmed NSCLC as their first primary tumor.

Outcomes and presenting characteristics were examined for all patients (153,027) and patients with metastatic disease (70,968) for whom sufficient information was collected to assess the outcomes in relation to patient, economic, histopathologic, and insurance variables.

Outcome variables and other covariates

The main purpose of our analysis was to examine whether there were differences in presenting characteristics and outcome in nine different ethnic groups by examining marital status, household income, and insurance type in addition to established histopathologic (tumor location, size, differentiation, stage, and histology), treatment factors (radiation and definitive surgical procedure), and patients factors (age, gender, marital status, presenting year, and SEER registry site). The patients with lung cancer were split into nine different ethnic groups as follows: White non-Hispanic (White), Black, White Hispanic (Hispanic), American Indian/Alaskan native (AI/AN), Chinese, Japanese, South Asian (Asian Indian and Pakistani), other Asians (OA, Filipino, Thai, Vietnamese, Korean, Kampucheane, Laotian, and Hmong), and other races (OR, Chamorran, Fiji Islander, Guamanian, Hawaiian, Melanesian, Micronesia, New Guinean, Pacific Islander, Polynesian, Samoan, Tahitian, Tongan, unknown, and others) in both the TP and Stage IV populations. The number of Black Hispanic patients was scant in both the TP (1.0%) and the Stage IV groups (0.7%), thus precluding the possibility of considering a separate patient category, and thus, Black Hispanic patients are included in the Black category, similar to a past study [7]. Throughout this manuscript, the term population(s) will refer to total population of patients with lung cancer and those with Stage IV disease, while group(s) will refer to the nine different ethnicities.

At the time of our analysis, SEER did not contain information regarding whether systemic therapy was given, nor does SEER contain information regarding the systemic agents that were used. SEER does contain information including the following: year of diagnosis (1975–2014), sex, patient age (1–84 and 85+), SEER registry location, median household income, insurance, marital status, origin recode (Hispanic, non-Hispanic), race/ethnicity, tumor location, primary site, sequence number, grade, laterality, tumor size, tumor extension, number of nodes examined, number of nodes positive, TNM stages, Mets at diagnosis, type of surgery, cause of death, vital status, and survival months.

Statistical analysis

Chi-square and t-tests compared differences between the ethnic groups with respect to treatment and patient/tumor characteristics. Cox proportional hazards models (Therneau, Grambsch) [8] were used to calculate adjusted hazard ratios with their 95% confidence intervals and to show how treatment and other covariates were related to overall survival OS and LCSS. Medicare eligibility was controlled through use of two strata for age at diagnosis (≥65 years old vs. <65 years) because individual cases will change when they enroll in Medicare.

Results

Median follow-up time was calculated by the methods of Schenper and Smith in which death becomes a censored
follow-up time and was noted to be 35 and 31 months in the TP and Stage IV groups, respectively [9].

Complete demographic and histologic details of the TP (153,027) and Stage IV (70,968) populations can be seen in Table 1. Median age in the TP and Stage IV are 68.0 and 67.0, respectively. There was a male predominance to both populations (54.1%- TP, and 55.8%- Stage IV). The three largest ethnic groups in the TP and Stage IV population were White, Black, and Hispanic and were 74.4%, 12.3%, and 5.7%; and 72.3%, 13.2%, and 6.3%, respectively. A similar proportion of the Stage IV (31.7%) and TP (32.3%) patients presented with a low median family income (<$50,000). The majority were married with 51.6% and 51.2% in the TP and Stage IV, respectively. 82.3% and 80.1% of TP and Stage IV patients

Table 1. Demographic characteristics of both the TP and Stage IV patients.

|                      | All Patients (TP) | Stage IV patient |
|----------------------|-------------------|------------------|
|                      | N = 153,027       | N = 70,968       |
| Age—year, median     | 68.0              | 67.0             |
| Sex                  |                   |                  |
| Female               | 70,212 (45.9%)    | 31,353 (44.2%)   |
| Male                 | 82,815 (54.1%)    | 39,615 (55.8%)   |
| Race                 |                   |                  |
| White Hispanic       | 8579 (5.6%)       | 4441 (6.3%)      |
| White non-Hispanic   | 114,013 (74.5%)   | 51,296 (72.3%)   |
| Black                | 18,852 (12.3%)    | 9360 (13.2%)     |
| Chinese              | 2413 (1.6%)       | 1261 (1.8%)      |
| Japanese             | 1229 (0.8%)       | 567 (0.8%)       |
| South Asian          | 451 (0.3%)        | 238 (0.3%)       |
| Other Asians         | 4831 (3.2%)       | 2544 (3.6%)      |
| Other Races          | 1957 (1.3%)       | 943 (1.3%)       |
| American Indian/Alaskan | 702 (0.46%)   | 318 (0.45%)      |
| SEER registry        |                   |                  |
| Alaska Natives       | 199 (0.13%)       | 76 (0.11%)       |
| Atlanta              | 4629 (3.0%)       | 2226 (3.1%)      |
| California excl SF/SJMLA | 30,007 (19.6%) | 14,304 (20.2%)   |
| Connecticut          | 8088 (5.30%)      | 3639 (5.1%)      |
| Detroit              | 9852 (6.4%)       | 4632 (6.5%)      |
| Greater Georgia      | 14,260 (9.3%)     | 6380 (9.0%)      |
| Hawaii               | 2375 (1.6%)       | 1159 (1.6%)      |
| Iova                 | 6805 (4.4%)       | 3205 (4.5%)      |
| Kentucky             | 13,916 (9.1%)     | 5980 (8.4%)      |
| Los Angeles          | 11,437 (7.5%)     | 5789 (8.2%)      |
| Louisiana            | 10,783 (7.0%)     | 4767 (6.7%)      |
| New Jersey           | 17,451 (11.4%)    | 7796 (11.0%)     |
| New Mexico           | 2610 (1.7%)       | 1215 (1.7%)      |
| Rural Georgia        | 353 (0.23%)       | 140 (0.20%)      |
| San Francisco–Oakland | 7081 (4.6%)    | 3469 (4.9%)      |
| San Jose–Monterey    | 3203 (2.1%)       | 1635 (2.3%)      |
| Seattle              | 8271 (5.4%)       | 3726 (5.3%)      |
| Utah                 | 1707 (1.1%)       | 830 (1.2%)       |
| Income               |                   |                  |
| <$50,000             | 49,407 (32.3%)    | 22,524 (31.7%)   |
| $50,000–74,000       | 81,027 (52.9%)    | 37,933 (53.5%)   |
| ≥75,000              | 22,593 (14.8%)    | 10,511 (14.8%)   |
| Marital status       |                   |                  |
| Divorced             | 18,851 (12.3%)    | 8815 (12.4%)     |
| Married              | 78,957 (51.6%)    | 36,349 (51.2%)   |
| Separated            | 1785 (1.2%)       | 895 (1.3%)       |
| Single               | 21,126 (13.8%)    | 10,872 (15.3%)   |
| Unknown              | 6032 (3.9%)       | 2866 (4.0%)      |
| Domestic Partner     | 126 (0.082%)      | 60 (0.084%)      |
| Widowed              | 26,150 (17.1%)    | 11,111 (15.7%)   |
| Tumor stage          |                   |                  |
| Unknown              | 3174 (2.0%)       | 0                |
| I                    | 34,255 (22.3%)    | 0                |
| II                   | 7825 (5.1%)       | 0                |
| III                  | 39,979 (26.1%)    | 0                |
| IV                   | 70,968 (46.3%)    | 70,968 (100.0%)  |
| Insurance            |                   |                  |
| Insured              | 125,876 (82.3%)   | 56,859 (80.1%)   |
| Medicaid             | 20,741 (13.6%)    | 10,324 (14.5%)   |

(continues)
were insured. Adenocarcinoma was the predominant histology in both populations (52.6%, TP; and 55.5%, Stage IV).

Table S1 supplemental contains the unadjusted demographic, histologic, and treatment details in the TP and used Whites as the reference group. Blacks were presented with younger age, more males, lower median household income, more uninsured, higher stages, lower percentage of squamous cell carcinomas, lower rates of definitive surgery, and lower OS/LCSS. Hispanics were presented at a younger age, higher median household income, more uninsured, higher percentage of metastatic disease, higher percentage of adenocarcinomas, and lower rates of definitive surgery, but had a similar OS/LCSS. The Japanese were presented with a highest mean age (72.8), the only female predominance (51.2%), and the highest rates of insurance (96.4%), but there were a similar OS and LCSS compared to Whites. Whites were presented with the higher percentage of Stage I disease (23.4%) than all except for the South Asian and AI/AN. South Asians were presented with the highest percentage of metastatic disease at 52.8%. The Chinese were presented with the highest

Figure 1. (A) Unadjusted overall survival by ethnic group in the total population. (B) Multivariable-adjusted overall survival by ethnic group in the total population.
percentage of adenocarcinomas (69.4%), while AI/AN were presented with the highest percentage of squamous cell carcinomas (30.8%). Whites had significantly higher rates of definitive surgical procedures except for the Chinese, Japanese, and South Asians. As compared to the White population, OS and LCSS were significantly greater in the Chinese, South Asians, other Asians, and other racial groups. Blacks had a lower OS and LCSS. Unadjusted OS by ethnic group can be found in Figure 1A.

Multivariable analyses for OS and MVA-adjusted OS in the TP can be seen in Table 2 and Figure 1B. Advancing age (P < 0.0001, HR = 1.185) and male sex (P < 0.0001, HR = 1.245) were associated with worse OS. Whites had a lower OS than all races (HR = 0.705–0.977) except for AI/AN who had a similar OS (P = 0.4890, HR = 0.963). OS was lower for lower (P = 0.0097, HR = 1.024) and better for higher median household incomes (P < 0.0001, HR = 1.0001).
HR = 0.936). Insured patients had a better OS than the uninsured, those on Medicaid and those with unknown insurance (all \( P < 0.0001, HR = 1.195–1.277 \)). Married patients had a better OS than separated, single, widowed, and unknown (all \( P \leq 0.0004, HR = 1.062–1.166 \)). As compared to Stage I, Stages II-IV had a worse OS with increasing HRs with stage (all \( P < 0.0001, HR = 1.622–3.290 \)). The lower lobes and mainstem bronchi locations were associated with worse OS. All histologies had a worse OS (all \( P < 0.0001, HR = 1.113–1.536 \)) than adenocarcinomas. Compared to well-differentiated tumors, other tumor grades had worse OS (all \( P < 0.0001, HR = 1.372–1.731 \)). Patients who received radiation (\( P < 0.0001, HR = 0.759 \)) or definitive surgery (\( P < 0.0001, HR = 0.331 \)) had a better OS. OS by insurance, income, and marital status for TP can be seen in Figure 2A–C.

Multivariable analyses for OS for the Stage IV population can be seen in Table 3. Age (\( P < 0.0001, HR = 1.017 \)) and male sex (\( P < 0.0001, HR = 1.233 \)) were associated with worse OS. All races had better OS than Whites (HR = 0.709–0.898) except for AI/AN and Blacks who had a similar OS. OS decreased for lower incomes (\( P = 0.0484, HR = 1.025 \)) and increased for higher incomes (\( P < 0.001, HR = 0.934 \)). Insured patients had a better OS than uninsured and those with Medicaid and unknown insurance (all \( P < 0.0001, HR = 1.195–1.277 \)). Married patients or those with a domestic partner had better OS than those not living in a stable partner situation (divorced, \( P < 0.0001, HR = 1.154 \); widowed, \( P < 0.0001, HR = 1.149 \); separated, \( P = 0.0009, HR = 1.134 \); and unknown, \( P = 0.0023, HR = 1.069 \)). Involvement of mainstem bronchi and right lower lobe was deleterious for OS. All other histologies were associated with a worse OS compared to adenosquamous cell carcinoma or adenocarcinoma (all \( P < 0.0001, HR = 1.107–1.482 \)). All tumors differentiation compared to well-differentiated had significantly worse OS (all \( P < 0.0001, HRs = 1.258–1.702 \)). Palliative radiation significantly improved OS (\( P < 0.0001, HRs = 0.896 \)). Starting in the year 2010, OS started to significantly improve with progressively lower HRs each year.

**Discussion**

A major finding of our analysis is Blacks often present at a younger age, have worse prognostic characteristics, and a lower OS/LCSS than Whites. However, after multivariable adjustment, Blacks have a better OS in the TP and similar OS in the Stage IV patients as compared to Whites. Blacks present with many poor prognostic factors including the following: lower median household income, single/widowed partnership status, higher male predominance, more uninsured, higher stages, and lower rates of definitive surgery. However, Blacks did present at a younger age and have a lower percentage of squamous cell carcinomas, both of which are associated with a better prognosis. As insurance, presentation stage, and surgical eligibility can be altered, there is hope that outcomes for Blacks can be improved with better access to insurance and by increased CT screening [10]. In comparison with
Whites, Hispanics presented with a higher proportion of several risk factors associated with poor prognosis including more uninsured, a lower proportion of Stage I/II tumors, and lower rates of definitive surgery, but there was no detrimental effect on the unadjusted OS or LCSS in the TP. Furthermore, MVAs demonstrated OS was significantly better for Hispanics compared to Whites in both the TP and Stage IV populations. It should be noted that previous analysis demonstrated this preferential OS benefit associated with Hispanics may be limited to those who are foreign-born as compared to those born in the United States [11]. Because the East Asian populations are enriched for the EGFR mutation tumors [12], it is not surprising the Chinese, South Asian, other Asians, and Japanese had a better adjusted OS in the TP/Stage IV populations, although this analysis lacks details on the mutational status of tumors.

In both MVAs for OS in the TP and Stage IV populations, male sex, poorer tumor differentiation, higher tumor stage, and advanced age were shown to be poor prognostic features and have been well established [13, 14]. Furthermore, palliative radiation therapy was found to be important for OS in the Stage IV population.

### Table 3. Multivariate Analysis for OS in Stage IV population, N = 70,968.

| Variable                        | P-value | Hazard ratio |
|---------------------------------|---------|--------------|
| Age—year                        | <0.0001 | 1.017        |
| Sex                             |         |              |
| Female                          | –       | 1.0          |
| Male                            | <0.0001 | 1.233        |
| Race                            |         |              |
| White non-Hispanic              | –       | 1.0          |
| White Hispanic                  | <0.0001 | 0.924        |
| Black                           | 0.1704  | 0.982        |
| Chinese                         | <0.0001 | 0.709        |
| Japanese                        | 0.0281  | 0.898        |
| South Asian                     | <0.0001 | 0.729        |
| Other Asians                    | <0.0001 | 0.776        |
| Other Races                     | <0.0001 | 0.800        |
| American Indian/Alaskan Native  | 0.9669  | 0.997        |
| SEER Registry                   |         |              |
| Alaska Natives                  | 0.3708  | 1.136        |
| Atlanta                         | 0.6764  | 0.987        |
| California excl SF/SJM/LA       | 0.2900  | 1.022        |
| Connecticut                     | –       | 1.0          |
| Detroit                         | 0.7774  | 1.007        |
| Greater Georgia                 | 0.0971  | 1.042        |
| Hawaii                          | 0.0229  | 1.097        |
| Iowa                            | 0.0442  | 1.057        |
| Kentucky                        | 0.0487  | 1.052        |
| Los Angeles                     | 0.0346  | 0.950        |
| Louisiana                       | 0.0044  | 1.078        |
| New Jersey                      | 0.9390  | 0.998        |
| New Mexico                      | 0.9163  | 1.004        |
| Rural Georgia                   | 0.9052  | 1.011        |
| San Francisco–Oakland           | 0.5813  | 1.015        |
| San Jose–Monterey               | 0.4999  | 0.975        |
| Seattle                         | 0.9550  | 1.001        |
| Utah                            | 0.6367  | 1.020        |
| Income                          |         |              |
| <$50,000                        | 0.0484  | 1.025        |
| $50,000–74,000                  | <0.0001 | 1.0          |
| ≥$75,000                        | <0.0001 | 0.934        |
| Insurance                       |         |              |
| Insured                         | –       | 1.0          |
| Medicaid                        | <0.0001 | 1.195        |
| Uninsured                       | <0.0001 | 1.273        |
| Unknown                         | <0.0001 | 1.277        |
| Marital status                  |         |              |
| Married                         | –       | 1.0          |
| Divorced                        | <0.0001 | 1.154        |
| Separated                       | 0.0009  | 1.134        |
| Single                          | <0.0001 | 1.167        |
| Unknown                         | 0.0023  | 1.069        |
| Domestic Partner                | 0.1157  | 1.283        |
| Widowed                         | <0.0001 | 1.149        |
| Lateral location                |         |              |
| Right upper                     | –       | 1.0          |
| Bronchus, Left                  | <0.0001 | 1.210        |
| Bronchus, Right                 | <0.0001 | 1.330        |
| Bronchus, Unknown               | 0.0104  | 1.308        |
| Left Lower                      | 0.0607  | 1.029        |
| Left Upper                      | 0.5952  | 1.006        |

(continues)
Involvement of the mainstem bronchi and lower lobes was associated with worse OS. Although it can be hypothesized that the involvement of the mainstem bronchi can contribute to an increased mortality due to postobstructive pneumonia and/or hypoxia, the survival decrement noted with the lower lobe locations may be due to a greater involvement of normal lung volumes. Because of the known ability of radiation to alleviate symptoms in Stage IV lung cancer [15], we feel the OS benefit noted with radiation in this study may be due to its palliation of central-based obstructive masses.

Since 2010 (2009 in TP), a consistent improvement in OS was noted in both populations. Although our analysis is unable to identify reasons for this progressive improvement, we feel the reasons are multifactorial. We speculate better staging with frequent use of CT/PET scanning [16] is associated with better outcomes. However, the benefits in the Stage IV population may have also been due to the recognition of chemotherapeutic regimens based upon histology [17] and benefits of targeted therapeutic agents for EGFR mutations [18] and EML4-ALK translocations [19]. Unfortunately, SEER does not contain information regarding the mutations or systemic therapy.

In both patient populations, MVA demonstrated higher income was positively associated with OS. Lower socioeconomic status was previously shown to affect cancer mortality and to be associated with modifiable risk factors such as smoking, diet, BMI, and lower levels of physical activity [20]. Unfortunately, these modifiable risk factors are not contained within SEER-18, but information concerning insurance is available and is more strongly correlated with OS than income. Furthermore, cigarette smoking is noted to be more prevalent in lower socioeconomic groups [21] and could account for the lower OS associated with economic factors. The effects of not being insured have greater effect on OS not only in this population group, but in our companion article concerning surgical patients in these same ethnic groups. It is interesting to note patients with Medicaid have similar hazard ratios for adverse outcomes as compared to those without insurance. We hypothesize the poor outcomes noted in the Medicaid population may be due to the socioeconomic conditions of individuals who have this coverage or possibly due to provider differences. Similar poor outcomes of patients who are receiving Medicaid or who are uninsured have recently been reported in patients with testicular cancers, glioblastomas, and head and neck cancers [22–24]. Nevertheless, hopefully, Medicaid expansion will provide better health outcomes for patients with cancer and has already been associated with increases in medication adherence, preventive care, and healthcare quality [25]. In a database of 75 countries obtained from the World Bank and WHO (1990–2010), unemployment was associated with increased lung cancer mortality, but only in men [26]. The effects of unemployment on cancer mortality appeared to be mitigated by universal health coverage. Our results suggest the type of insurance can affect the prognosis of patients with short expected survivals, that is, Stage IV. Although higher lung cancer mortality was recently noted in the mid-South [27] and our analysis indicates there is worse OS in Kentucky and Louisiana in both patient populations, the effects of geography on poor prognosis in our study were not limited to those areas. Our results show married patients or those with a domestic partner have a significantly longer survival, even in metastatic disease. Although our results conflict with those of a past investigation [28] in patients with lung cancer, other investigators have noted unmarried patients with lung cancer had a greater incidence of depression, less social support, and a survival decrement [29].

SEER-18 lacks many variables including smoking, diet, BMI, levels of physical activity, type of chemotherapeutic agents, radiation doses/volumes, surgical complications, medical office visits, and patient comorbidities. Therefore, our analysis cannot account for these variables.

It should be noted that there are past studies that have shown that Blacks have uniformly worse outcomes than Whites [30–33], our study is more comprehensive in that we assess nine different ethnic groups and because we adjust for marital, economic, histopathologic, and insurance variables. Our comprehensive analysis allows for a unique finding that Blacks may have better (TP) or similar (Stage IV) outcomes as compared to the White population. Therefore, because the White Hispanic and Black populations present at more advanced stages and have better outcomes, we feel that increased lung cancer screening would be preferentially better in these patients. Such a clear pathway for survival improvement in the White population cannot be ascertained in our population. Unfortunately, SEER does not contain genomic information by race or otherwise. However, at present, genomic information in patients with lung cancer is not prevalent enough (5% or 10% frequency) in ethnic groups other than Whites in the Cancer Genome Atlas (TCGA) [34].

**Conclusion**

In summary, our analysis does demonstrate racial disparities do exist in the presentation of the Black and Hispanic populations with lung cancer. Both groups were presented with lower rates of insurance, higher stages, and lower rates of definitive surgery. Blacks had a lower OS/LCSS, but when adjusted for histopathologic, therapeutic, marital status, and economic factors, they had a better OS in the TP than Whites. Disparities in income, marital status,
Socioeconomic Factors Affect Outcomes more than Race

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and insurance rather than ethnicity affect OS of patients with lung cancer. Because of their more common presentation with advanced disease, the Black and Hispanic groups may benefit preferentially from screening. Our analyses support the expansion of lung cancer screening to people at higher risk of presenting with advanced stage secondary to limited access to health care due to lower income and lack of insurance, particularly in the Black and Hispanic groups. Specifically, affordable and quality healthcare needs to be provided to these at-risk populations possibly by education/health literacy and care navigators/coordinators. However, the outcome improvement in the White population may need attention in areas other than just screening.

Conflict of Interest
None declared.

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Supporting Information
Additional supporting information may be found in the online version of this article:
Table S1. Contains the demographic, histologic, and treatment details in the TP for the nine different ethnic groups.