In recent years, the collection of treatment modalities for patients with advanced-stage NSCLC has evolved at a considerable rate. EGFR tyrosine kinase inhibitors and immune checkpoint inhibitors, such as programmed death-ligand 1 inhibitors, have profoundly transformed therapy and redefined what is possible for patients with stages III to IV NSCLC.\(^1,2\) In turn, guideline recommendations have been dynamic in adapting to this ever-changing treatment landscape. Together, these advances have been accompanied by an unprecedented shift in optimism among treatment providers; a recent survey by Rigney et al.\(^3\) found that 67% of oncologists reported adequate treatment options for patients with advanced-stage NSCLC, compared with only 36% just 10 years prior.

Despite these expanding treatment options and professional enthusiasm, actual treatment rates reveal the chasm between recommendations and reality. Analyses from the National Cancer Database (NCDB) revealed that the proportion of patients diagnosed with having advanced-stage NSCLC between 1998 and 2012 receiving no treatment actually increased over time.\(^4\) Furthermore, patients with advanced-stage NSCLC tend to undergo guideline-concordant treatment less frequently than patients with other cancers.\(^4\)–\(^10\) Using the Surveillance, Epidemiology, and End Results (SEER) database, Fang et al.\(^6\) found that 41% of non-Hispanic white and black patients diagnosed with having stage III NSCLC from 2006 to 2011 received guideline-concordant chemotherapy. For stage IV NSCLC, approximately 50% of patients in the NCDB between 1998 and 2012 received guideline-recommended treatment.\(^4\) By comparison, 60% of patients diagnosed with having stage III breast cancer between 2006 and 2011 and 77% of patients diagnosed with having stage IV breast cancer between 2010 and 2011 in the SEER database received guideline-concordant treatment.\(^5\)–\(^7\) Rates of guideline-concordant treatment for advanced-stage prostate cancer have also been comparatively promising, with 94% of non-Hispanic white or black patients diagnosed with having stage III prostate cancer from 2006 to 2011 receiving guideline-concordant curative therapy in radiation or prostatectomy.\(^6\) Among patients diagnosed with having stage IV prostate cancer, 80% in the SEER database from 2004 to 2014 received guideline-concordant androgen deprivation therapy.\(^8\) Studying stage III colorectal cancer, Monson et al.\(^9\) reported that 76% of patients in the NCDB between 2006 and 2011 received guideline-concordant neoadjuvant chemoradiotherapy. For stage IV colorectal cancer, 64% of patients in the SEER database in 2014 received
guideline-concordant chemotherapy with or without primary tumor resection. Together, these findings lead to a sobering realization that the promise of advanced NSCLC therapy is not optimally reaching patients treated in the real world and highlight the need to interrogate and address the causes of these discrepancies.

In this commentary, we argue that the wide-ranging impact of stigma (perceptions and internalizations of devalued status) in the context of lung cancer may be an important causal and exacerbating factor of this incomplete treatment penetrance and discuss the need for further confirmatory studies and appropriate interventions; however, we present this argument with the acknowledgment that clinical decision-making for advanced-stage lung cancer is exceptionally complex and that factors such as poor performance status may preclude delivery of guideline-recommended treatments for many patients. Widespread recognition of tobacco use as a significant risk factor for lung cancer remains among the most important efforts in medicine and public health, and dedicating greater attention to smoking cessation in the clinical setting may serve to improve lung cancer outcomes. Simultaneously, the accompanying emergence of smoking status and history as a source of stigma and its potential consequent influence on patient and provider-level behavior require further exploration. A well-established literature has detailed the impact of stigma as a disproportionate and formidable barrier to achieving the promise of lung cancer treatment through mechanisms related to psychosocial patient impact, patient-provider communication, and societal attitudes or behavior. Moreover, survey-based studies in Europe indicated that lung cancer is associated with higher levels of stigmatization compared with other cancers. In Germany, Ernst et al. identified higher levels of “isolation” and “internalized shame” dimensions of stigmatization using the Social Impact Scale among patients with lung cancer relative to patients with breast, prostate, or colon cancer. In the United Kingdom, Marlow et al. surveyed 1205 nonpatient participants to investigate stigma in lung, cervical, breast, skin, and colorectal cancers. The authors concluded that lung cancer was associated with higher stigma scores on all subscales of the Cancer Stigma Scale when compared with breast and cervical cancers; higher stigma on the “awkwardness,” “severity,” and “financial discrimination” subscales when compared with skin cancer; and higher stigma on all subscales except “awkwardness” when compared with colorectal cancer. The shared finding of greater stigma in lung cancer is particularly compelling given that the two studies differed both geographically and in the use of patient versus nonpatient participants.

Less evidence has directly tied stigma to adverse treatment decisions, but there are signals suggesting this connection, potentially driven through patient decisions, provider bias and nihilism, and policy-relevant factors. For example, a significant stigma-related theme identified through qualitative research centers on patients’ feelings of unworthiness for medical care and hesitancy in discussing treatment options and medical concerns. Furthermore, providers may be explicitly or implicitly biased and nihilistic toward patients with advanced-stage lung cancer, potentially limiting guideline-concordant treatment recommendations and referrals. In sum, the effects of stigma on multiple influencers of care, including patients, medical providers, and policy, may be robust contributors to NSCLC treatment discrepancies.

We recognize that stigma is not the only potential driver of NSCLC treatment inequities, although it may have multiplicative effects with other factors. Presentations of advanced-stage NSCLC are often complex, reflecting racial and socioeconomic status diagnostic disparities, along with significant comorbid conditions that may limit access to and suitability of guideline-concordant treatment. For example, across most advanced-stage cancers, patients of older age or black race are less likely to receive guideline-concordant treatment; these groups are disproportionately represented among advanced-stage NSCLC cases. Patients with advanced-stage cancers often present with a higher degree of clinical complexity, which is reflected in the increased latitude of corresponding guidelines compared with that of early stage cancers. In a similar vein, it is possible that the patient population with advanced-stage NSCLC possesses greater clinical heterogeneity and consequently warrants more frequent deviation from guideline-concordant care relative to other advanced-stage cancers. Standardized treatment recommendations may not always be appropriate for the full spectrum of clinical presentations within a specific cancer stage, and this may be especially true for advanced-stage lung cancer. Standard cytotoxic therapies for lung cancer may also be misperceived as more difficult to tolerate compared with treatments for other advanced-stage cancers, leaving patients and providers reluctant to pursue guideline-recommended care. Nevertheless, comparatively greater tolerability of endocrine treatment modalities for cancers associated with higher rates of guideline-concordant treatment may indeed underlie this observed disparity with respect to lung cancer. It is critical to acknowledge that some patients with advanced-stage NSCLC do not receive guideline-concordant care owing to their providers’ more nuanced interpretation of medical literature rather than lack of awareness or disregard for guideline recommendations. Particularly for administrative database studies, insufficient clinical information makes the
distinction between judicious treatment decisions and inappropriate cancer care particularly difficult if not impossible to parse.

Nevertheless, the observation that patients with advanced-stage NSCLC simultaneously face higher levels of stigma and are less likely to receive guideline-concordant care compared with patients with other cancers warrants greater attention in the medical community. Indeed, stigma is unlikely the sole driver of disproportionately low levels of guideline-concordant care, but stigma may contribute to and exacerbate already existing drivers. Further research is needed to fully delineate these relationships and identify appropriate targets for intervention. Promising studies of patient- and provider-level interventions to reduce stigma may also serve to ameliorate the stark treatment disparities in advanced-stage NSCLC. Patient-focused interventions may provide lung cancer education, increase awareness of stigma’s consequences, optimize communication strategies, and encourage patients to proactively seek information about treatment options from their providers and public health advocates. Potential opportunities for providers include educational initiatives to promote evidence-based referral and treatment practices. Empathic communication skills training for providers has been found to increase patient satisfaction with oncology care provider communication, which may facilitate more informed and mutually agreeable treatment decisions. These efforts are significant, but opportunities remain for more robust study of interventions that facilitate optimal treatment decisions by addressing stigma mechanisms. Nevertheless, it is also critical to acknowledge that the circumstances surrounding non–guideline-concordant treatment can be unclear, as large cancer registries do not capture the full compendium of clinically relevant variables, such as pulmonary function and performance status. In addition, lung cancer-related stigma may differ in the United States compared with other countries owing to variations in factors, such as health care access and equity or perceptions of the medical field. Therefore, certain themes presented in this article may have limited relevance outside of the United States.

Just as tobacco use was importantly identified as a prominent public health issue and major oncologic risk factor, the unintended but resultant stigma must be recognized as a significant modifiable factor that limits the promise of lung cancer care. Future research should seek to utilize survey-based methods and data sets that offer greater detail with respect to critical clinical variables (e.g., pulmonary function testing) in a prospective approach to better identify cases of non–guideline-concordant care and quantitatively characterize the relationship between stigma among providers and patients and the receipt of non–guideline-concordant treatment for advanced-stage NSCLC, ideally in the context of multivariate analysis. Subsequent studies could evaluate the efficacy of stigma-reducing initiatives and identify discrete domains for improvement. Improved awareness and communication practices are imperative to reduce lung cancer stigma and its continued adverse effects on the treatment and psychosocial burden of patients with advanced-stage NSCLC.

CRediT Authorship Contribution Statement

Terrance Peng: Methodology, Project administration, Writing - original draft, Writing - review & editing.

Heidi A. Hamann: Conceptualization, Methodology, Writing - original draft, Writing - review & editing.

Elizabeth A. David: Conceptualization, Methodology, Project administration, Supervision, Writing - original draft, Writing - review and editing.

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References

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: non-small cell lung cancer. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed April 2, 2021.

2. Planchard D. Adjuvant osimertinib in EGFR-mutated non-small-cell lung cancer. N Engl J Med. 2020;383:1780-1782.

3. Rigney M, Rapsomaniki E, Carter-Harris L, King JC. A 10-year cross-sectional analysis of public, oncologist, and patient attitudes about lung cancer and associated stigma. J Thorac Oncol. 2021;16:151-155.

4. David EA, Daly ME, Li CS, et al. Increasing rates of no treatment in advanced-stage non-small cell lung cancer patients: a propensity-matched analysis. J Thorac Oncol. 2017;12:437-445.

5. Fang P, He W, Gomez DR, et al. Influence of age on guideline-concordant cancer care for elderly patients in the United States. Int J Radiat Oncol Biol Phys. 2017;98:748-757.

6. Fang P, He W, Gomez D, et al. Racial disparities in guideline-concordant cancer care and mortality in the United States. Adv Radiat Oncol. 2018;3:221-229.

7. Poorvu PD, Vaz-Luis I, Freedman RA, et al. Variation in guideline-concordant care for elderly patients with metastatic breast cancer in the United States. Breast Cancer Res Treat. 2018;168:727-737.

8. Beebe-Dimmer JL, Ruterbusch JJ, Cooney KA, et al. Racial differences in patterns of treatment among men diagnosed with de novo advanced prostate cancer: a SEER-Medicare investigation. Cancer Med. 2019;8:3325-3335.
9. Monson JR, Probst CP, Wexner SD, et al. Failure of evidence-based cancer care in the United States: the association between rectal cancer treatment, cancer center volume, and geography. *Ann Surg.* 2014;260:625–632.

10. Gao X, Kahl AR, Goffredo P, et al. Treatment of stage IV colon cancer in the United States: a patterns-of-care analysis. *J Natl Compr Canc Netw.* 2020;18:689-699.

11. Ernst J, Mehnert A, Dietz A, Hornemann B, Esser P. Perceived stigmatization and its impact on quality of life - results from a large register-based study including breast, colon, prostate and lung cancer patients. *BMC Cancer.* 2017;17:741.

12. Marlow LA, Waller J, Wardle J. Does lung cancer attract greater stigma than other cancer types? *Lung Cancer.* 2015;88:104-107.

13. Hamann HA, Ver Hoeve ES, Carter-Harris L, Studts JL, Ostroff JS. Multilevel opportunities to address lung cancer stigma across the cancer control continuum. *J Thorac Oncol.* 2018;13:1062-1075.

14. Hamann HA, Williamson TJ, Studts JL, Ostroff JS. Lung cancer stigma then and now: continued challenges amid a landscape of progress. *J Thorac Oncol.* 2021;16:17-20.

15. Banerjee SC, Haque N, Schofield EA, et al. Oncology care provider training in empathic communication skills to reduce lung cancer stigma. *Chest.* 2021;159:2040-2049.