Incorporating Equity into Healthcare Decision Making Around New Technologies

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Abstract

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Innovations in cancer care, such as the development of new pharmaceutical treatments, are widely recognized for their potential to extend lives and enhance quality of life. However, concerns persist regarding the equitable distribution of these innovations and their potential to exacerbate existing disparities in health outcomes. Moreover, the advent of cutting-edge clinical risk prediction tools presents a significant dilemma: while promising in guiding cancer treatment decisions, there is a pressing concern that these technologies could embed discriminatory biases and perpetuate racial disparities in health outcomes. Specifically, the inclusion of race as a predictive factor in these algorithms raises alarms about the potential for differential treatment across racial groups, further entrenching inequities within the healthcare systems.

This study aimed to generate evidence to support the incorporation of equity considerations into healthcare decision processes surrounding these innovative developments. Aim 1 utilized a

quasi-experimental approach to evaluate the impact of cancer innovations on both population-level survival and health disparities across income levels. Our findings revealed improved survival rates in lung cancer and melanoma, juxtaposed with exacerbated disparities across income levels, suggesting a plausible causal link between new innovations and health disparities. Aim 2 employed a microsimulation model to examine the long-term health disparity implications of omitting race from a colon cancer survival prediction tool. The model projected that omitting race from this tool for adjuvant chemotherapy recommendations could worsen survival for Black patients and widen the disparity gap. These findings underscore the importance of integrating equity considerations into the fabric of policies governing the evaluation, adoption, and diffusion of innovative healthcare solutions to mitigate their disparity impacts.

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Above all, I want to thank my family, particularly my husband Ellwood, and my children Felice and Thalia, for being my constant source of inspiration and for indulging me with the opportunity to pursue this 5-year passion project.

Chapter 1. INTRODUCTION

Innovations in cancer care, such as new drugs and technologies, have increased longevity and improved quality of life for many people in the US. However, as more evidence emerges regarding socioeconomic disparities in cancer health outcomes and as cancer treatment costs continue to rise, concerns have arisen that these innovations do not benefit everyone equally, contributing to social disparities in health outcomes.[1-12] Historically underserved patients have been shown to have disproportionately higher prevalence and severity of cancer but are less likely to receive novel, guideline-concordant, or timely treatment.[1-4] People of color and low income families are more likely to be uninsured or underinsured and to experience cancer-related financial difficulties, creating another barrier to accessing care.[8-10,13] Despite the growing concerns, there is a **lack of causal evidence on the extent to which the adoption of new expensive cancer drugs systematically affects health disparities. This information is crucial to motivating and informing policy interventions to incorporate equity into drug adoption and diffusion processes in the US.**

Similarly, state-of-the art automated prognostic clinical algorithms are increasingly available to facilitate cancer treatment decisions,[14-18] promising to minimize provider bias in prescribing and improve cancer treatment decision-making. However, there are growing concerns that these algorithms may institutionalize discriminatory logics that perpetuate racial health disparities.[19] Recent studies have raised concerns that the inclusion of race as a predictor in clinical decision tools can lead to differential treatments across racial groups. Many clinicians, policy makers, and institutions have called for revisions of existing tools to remove the adjustment for race (i.e., use a "race-neutral" approach).[20,21] Our recent work and others have demonstrated that not considering race/ethnicity could result in inaccurate predictions that may

differentially harm racial/ethnic minority groups.[21-24] To date, **little is known about the downstream health disparity impacts of including or excluding race/ethnicity in risk models designed for clinical decision-making in cancer care. Understanding the downstream impacts of these tools will provide much-needed insights on their appropriate use to avoid exacerbating racial and ethnic disparities in health outcomes.** Nevertheless, similar to cancer drug adoption, **there is a lack of routine assessment of the disparity impacts of these algorithms before they are adopted into clinical practice, underscoring the need for a comprehensive evaluation framework.[25]**

The goal of this research was to reduce systemic disparities resulting from new technologies by providing robust evidence to facilitate the incorporation of health and financial equity into policies and guidelines. This was achieved through two specific aims.

In Aim 1, we investigated whether the approval of new oncologic treatments systematically contributed to mortality disparities by neighborhood-level income among patients with advanced non-small cell lung cancer and melanoma. We employed a difference-in-difference-in-differences analytic approach to assess this impact.

In Aim 2, we used an existing colon cancer survival calculator designed to guide adjuvant treatment decisions as a case study. We constructed a microsimulation model to compare the downstream racial disparity implications of using the "race-sensitive" version vs. "race-neutral" version of this algorithm to guide cancer treatment decisions.

Chapter 2. INNOVATIONS AT THE EXPENSE OF HEALTH EQUITY? THE EFFECT OF ADVANCES IN CANCER TREATMENT ON DISPARITIES IN MORTALITY BY NEIGHBORHOOD-LEVEL INCOME

2.1 ABSTRACT

Background: In the last decade, advanced lung cancer and melanoma have witnessed a surge in FDA-approved treatment innovations. Yet, the impact of these advancements on population-level survival and survival disparities remains unclear.

Methods: We analyzed data from the Surveillance, Epidemiology, and End Results registry, including 357,095 adults diagnosed with advanced melanoma, non-small cell lung cancer (NSCLC), bladder cancer, uterine cancer, head and neck cancer, and liver cancer between 2007 and 2016. The primary outcome was 2-year survival post-diagnosis. We evaluated changes in this outcome with treatment advancement and quantified survival disparities as the differences in these changes between high- and low-income counties. Using a difference-in-difference-in-differences approach, we compared outcomes in NSCLC and melanoma with cancers lacking similar advancements.

Results: Between 2007 and 2016, cancer treatment approvals resulted in an adjusted survival increase of 3.7 percentage points (95%CI, 2.7, 4.6) for NSCLC and 16.8 percentage points (95%CI 14.5, 19.2) for melanoma. The approval of EGFR TKIs and anti-PD-1 immunotherapies for NSCLC increased survival disparities between high- and low-income counties by 2.4 percentage points (95%CI, 0.07, 4.7). The approval of PD-1 inhibitors and BRAF/MEK

inhibitors for melanoma resulted in an increase in survival disparity by 6.1 percentage points (95%CI, 0.1, 12.1).

Conclusions: While FDA approvals have significantly improved survival in NSCLC and melanoma, they have also exacerbated survival disparities. These findings indicate a possible causal link between new innovations and health disparities, emphasizing the need to integrate equity considerations into policies surrounding drug pricing, coverage, and diffusion to mitigate disparity impacts.

2.2 INTRODUCTION

Over the past two decades (2001-2020), advancements in cancer prevention, screening, treatment, and survivorship care are believed to have contributed to a 27% decline in cancer mortality rates.[26] Despite this progress, significant disparities persist in cancer outcomes based on race and ethnicity, socioeconomic status (SES), and geographic location. Specifically, individuals of lower SES and those residing in rural areas are less likely to receive effective cancer treatments and more likely to experience poorer survival rates after diagnosis.[5-7] Moreover, low income individuals often lack health insurance coverage,[10,27,28] limiting their access to high-quality cancer therapies.[7,29]

There are growing concerns that pharmaceutical companies are incentivized to prioritize the development of new and sophisticated cancer therapies that may not be accessible or affordable for all patients.[30] Some are worried that the rapid introduction of expensive cancer pharmaceutical innovations may exacerbate existing disparities in cancer outcomes. However, causal evidence that links the introduction of new therapies to health disparities remains scarce, likely due to complex historical, structural, and multilevel factors influencing disparities over time.[31-34] Challenges such as high drug prices and the complexity of the US healthcare system complicate the assessment of new drug impacts on disparities. Recognizing the need for equity, there are calls to integrate "pharmacoequity" into public policies to ensure fair access to quality medications.[35] There is also a growing desire to incorporate equity considerations into value assessment frameworks and guidelines for new treatments. To advance these goals, evidence is crucial on how pharmaceutical innovations affect health disparities across socioeconomic groups.

The goal of this study is to fill this research gap by moving the health inequity discussion beyond merely describing the presence of socioeconomic disparities in cancer outcomes to understanding the underlying pathways contributing to such disparities in the US. Specifically, we examined whether new oncologic treatment approval has systematically contributed to the disparities in mortality by neighborhood-level income. Demonstrating a causal link between the approval of new oncologic innovations and socioeconomic disparities in health could provide an impetus for formally incorporating equity into policies and guidelines around the approval, pricing, adoption, and diffusion of new therapies and to address systemic inequities.

2.3 METHODS

Data source and study population

This retrospective quasi-experimental study utilized data from the Surveillance Epidemiology and End Results (SEER) 22 cancer registries, covering approximately 42% of the US population.[36] The registries contain patient demographics, cancer status, and death information. The study population consisted of adults aged 18 and above diagnosed with advanced stage non-small cell lung cancer (NSCLC), melanoma, uterine cancer, head and neck cancer, liver cancer, and bladder cancer between January 1, 2007, to December 31st, 2016. (Table S1.1) Last date of follow up was December 31st, 2020. Patients diagnosed by death certificate or autopsy were excluded, as were cases with missing mortality or county-level median income information (Figure S1.1).

Study Periods and Groups

Our "intervention" cancer groups are NSCLC and melanoma. These cancers were chosen as study candidates because they have seen a significant increase in the pace of innovation in pharmaceutic treatments over our study period (2007 to 2016), evidenced by Food and Drug Administration (FDA) approvals (Table S1.2, Table S1.3). For NSCLC, we separated the study period into three treatment breakthrough phases: the "Pre-innovation era" (2007-2009), "Innovation era 1" (2010-2012) following the approval of epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) for first-line maintenance, and "Innovation era 2" (2013-2016) following the approval of EGFR-TKI for first-line treatment and anti-PDL1 immunotherapy for second line. For melanoma, the study period was also divided into three phases: "Pre-innovation era" (2007-2010), "Innovation era 1" (2011-2013) following the approvals of immune checkpoint inhibitor (anti-CTLA-4 antibody ipilimumab) and targeted therapy for first-line treatment, and "Innovation era 2" (2014-2016) following the approvals of anti-PD-1immunotherapies nivolumab and pembrolizumab. Patients diagnosed in the year immediately before each era were censored to account for any washout period effects. Uterine, head and neck, bladder, and liver cancers, without new treatment approvals during the study period, served as controls.

Outcome Measures

Our main outcomes included 2-year overall survival (binary: yes/no) and disparities in 2-year overall survival by county-level median household income, categorized into income tertiles: <$60,000 a year, $60,000 - $74,999, and $75,000 or more annually. Survival disparity was measured as the absolute difference between the most advantaged (highest income) and least advantaged (lowest income) groups.

Analysis

For each intervention cancer group, we compared the effects of new cancer therapy approvals on survival by income levels using a difference-in-difference-in-differences analytic approach. We estimated a linear probability regression model for 2-year survival, with 2-way and 3-way interactions among cancer intervention group (vs. controls), income level, and post-drug approval period. Linear probability regression was preferred over logistic regression due to its unbiased estimation properties in the presence of fixed effects.[37] The model adjusted for age (grouped as 20-45, 46-65, 66-85, and >85), sex (female, male), marital status, first primary cancer, SEER registry region, and location of residence (metropolitan or non-metropolitan areas). We also included a fixed effect for each year to control for any potential shocks or policy changes that could have affected cancer survival, e.g., the Affordable Care Act's major coverage expansions that became effective in 2014. Finally, we included a fixed effect for each cancer type to account for differences in baseline level of survival in each cancer type.

We assessed parallel trends in 2-year overall survival between controls and intervention groups in the "pre-innovation era" using linear probability regression models. We estimated interaction terms between year indicators and cancer intervention group (vs. controls), controlling for all covariates that were included in the main analysis. This test was repeated within income subgroups.

We used recycled predictions to generate adjusted estimates of the effect of drug approvals. Bootstrap replications (1000x) were used to generate the 95% confidence intervals.

We performed four sets of sensitivity analyses: (1) without a washout period; (2) using 1-year survival as the outcome, (3) using 3-year survival as the outcome, and (4) stratifying by age (<65 vs. ≥65).

2.4 RESULTS

The final sample consisted of 357,095 patients, including 275,546 with NSCLC, 12,195 with Melanoma, and 69,354 in the control group. The mean age was 68 (standard deviation 12), with 44% female, 9% Hispanic, 12.5% non-Hispanic Black, 0.5% American Indian or Alaska Native, 6% Asian or Pacific Islander, and 72% non-Hispanic White. Table 1 shows the patient characteristics by cancer groups. Compared to controls, NSCLC patients were older and more likely non-Hispanic White. Melanoma patients had a higher proportion of female and non-Hispanic White, compared to controls.

Table 1: Patient Characteristics of Cancer Patients in the Intervention Cancer Groups vs. the Control Cancer Group

	NSCLC (N=275,546)	Melanoma (N=12,195)	Controls[a] (N=69,354)	Overall (N=357,095)
Age				
Mean (SD)	68.4 (11.2)	64.6 (14.8)	64.6 (12.6)	67.6 (11.7)
Median [Min, Max]	69.0 [18.0, 90.0]	65.0 [18.0, 90.0]	64.0 [18.0, 90.0]	68.0 [18.0, 90.0]
Age Category				
18-45	6168 (2.2%)	1287 (10.6%)	3988 (5.8%)	11443 (3.2%)
46-65	101384 (36.8%)	4839 (39.7%)	33570 (48.4%)	139793 (39.1%)
66-85	156291 (56.7%)	5393 (44.2%)	29048 (41.9%)	190732 (53.4%)
>85	11703 (4.2%)	676 (5.5%)	2748 (4.0%)	15127 (4.2%)
Sex				
Female	123372 (44.8%)	3862 (31.7%)	29837 (43.0%)	157071 (44.0%)
Male	152174 (55.2%)	8333 (68.3%)	39517 (57.0%)	200024 (56.0%)
Race and Ethnicity				
Hispanic (All Races)	21215 (7.7%)	761 (6.2%)	10127 (14.6%)	32103 (9.0%)
Non-Hispanic American Indian/Alaska Native	1121 (0.4%)	29 (0.2%)	457 (0.7%)	1607 (0.5%)
Non-Hispanic Asian or Pacific Islander	17449 (6.3%)	139 (1.1%)	5324 (7.7%)	22912 (6.4%)
Non-Hispanic Black	33796 (12.3%)	206 (1.7%)	10716 (15.5%)	44718 (12.5%)
Non-Hispanic Unknown Race	182 (0.1%)	24 (0.2%)	98 (0.1%)	304 (0.1%)
Non-Hispanic White	201783 (73.2%)	11036 (90.5%)	42632 (61.5%)	255451 (71.5%)
First Primary Cancer	223095 (81.0%)	9124 (74.8%)	58589 (84.5%)	290808 (81.4%)

Married (including common law) or had unmarried or domestic partner	119029 (43.2%)	5529 (45.3%)	26701 (38.5%)	151259 (42.4%)
Nonmetropolitan County[b]	40297 (14.6%)	1713 (14.0%)	8626 (12.4%)	50636 (14.2%)
County-level median household income				
$60K-75K	93845 (34.1%)	4307 (35.3%)	24413 (35.2%)	122565 (34.3%)
$75K	82603 (30.0%)	3997 (32.8%)	20612 (29.7%)	107212 (30.0%)
<$60K	99098 (36.0%)	3891 (31.9%)	24329 (35.1%)	127318 (35.7%)
Year of Diagnosis				
2007	27205 (9.9%)	921 (7.6%)	5883 (8.5%)	34009 (9.5%)
2008	27451 (10.0%)	934 (7.7%)	6134 (8.8%)	34519 (9.7%)
2009	27306 (9.9%)	941 (7.7%)	6190 (8.9%)	34437 (9.6%)
2010	27453 (10.0%)	1162 (9.5%)	6567 (9.5%)	35182 (9.9%)
2011	27660 (10.0%)	1177 (9.7%)	6783 (9.8%)	35620 (10.0%)
2012	28039 (10.2%)	1317 (10.8%)	7118 (10.3%)	36474 (10.2%)
2013	28004 (10.2%)	1381 (11.3%)	7456 (10.8%)	36841 (10.3%)
2014	28116 (10.2%)	1554 (12.7%)	7713 (11.1%)	37383 (10.5%)
2015	27818 (10.1%)	1460 (12.0%)	8041 (11.6%)	37319 (10.5%)
2016	26494 (9.6%)	1348 (11.1%)	7469 (10.8%)	35311 (9.9%)

NSLCL, Non-small cell lung cancer; SD, Standard deviation
[a]Controls consisted of patients diagnosed with head and neck, uterine, bladder, or liver cancers
[b]Nonmetropolitan counties include those adjuvant and not adjuvant to a metropolitan area

Trends in 2-year survival

Two-year survival trends remained stable over time for control cancers (Figure S1.2). Using parallel trend tests, we found no evidence of divergent trends in survival outcomes and income-specific survival outcomes pre-innovation between the intervention and the control groups (Figure S1.3, S1.4, Table S1.4).

FDA approvals in lung cancer were associated with a significant increase in 2-year survival of 1.2 percentage points (95%CI 0.1, 2.3) in the first innovation era, and 2.4 percentage points (95%CI 1.5, 3.4) in the second, totaling 3.7 percentage points (95%CI 2.7 to 4.6) in both periods (Figure 1, Table 2). For melanoma, FDA approvals were associated with an increased survival

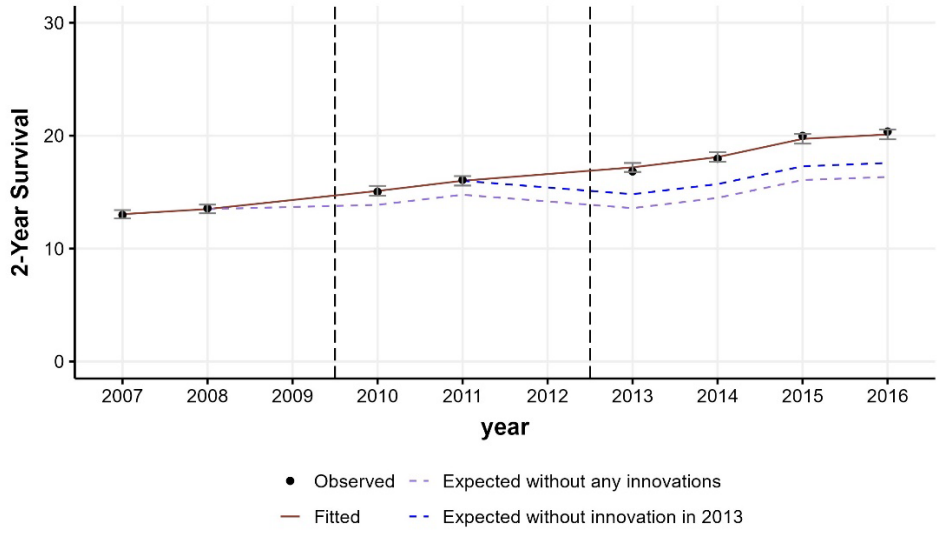
of 10.3 percentage points (95%CI: 7.6, 12.8) in the first era, and 6.7 percentage points (95%CI: 4.3,9.3) in the second, totaling 16.8 percentage points (95%CI: 14.5, 19.2) across both periods.

FDA approvals in lung cancer showed no significant change in income-based survival disparity in the first innovation era (-0.05 percentage point, 95%CI -2.9, 2.8) and an increase in disparity of 2.4 percentage points (95%CI 0.07, 4.7) in the second era (Figure 2, Table 3), totaling 2.4 percentage points (95%CI 0.06, 4.7) over both eras. In Melanoma, FDA approvals were associated with no change in survival disparity in the first era (-2.2 percentage points; 95%CI: -8.9, 4.2) but a 6.1 (95%CI: 0.1, 12.1) increase in the second era. The total change across both eras was not significant (3.9 percentage points, 95%CI -1.3, 9.2).

Figure 1: Adjusted 2-year survival over time and expected survival in the absence of the innovations

Vertical dashed lines indicate the time when an innovation was approved by the Food and Drug Administration. The 95%CIs were obtained using 1000 bootstrap samples.

a) <u>Lung Cancer</u>



b) Melanoma

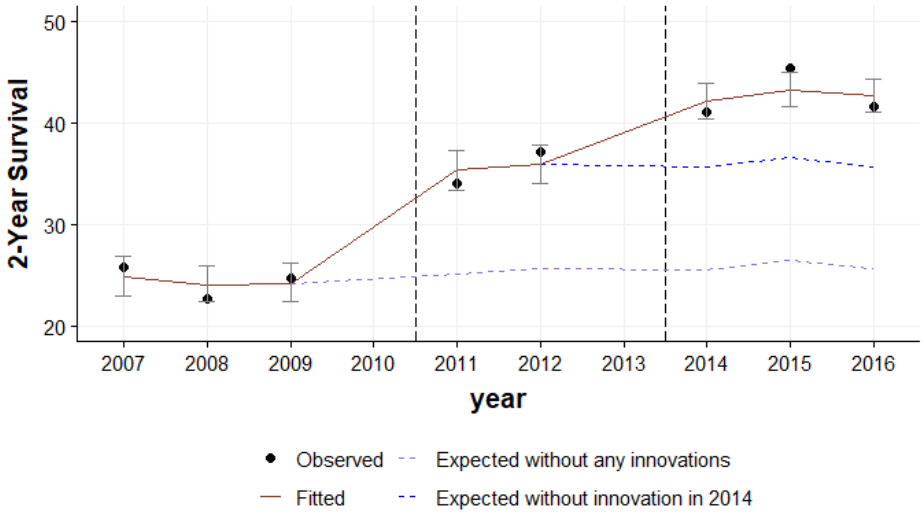


Table 2: Estimated effects of cancer innovations on 2-year survival among patients with NSCLC and melanoma

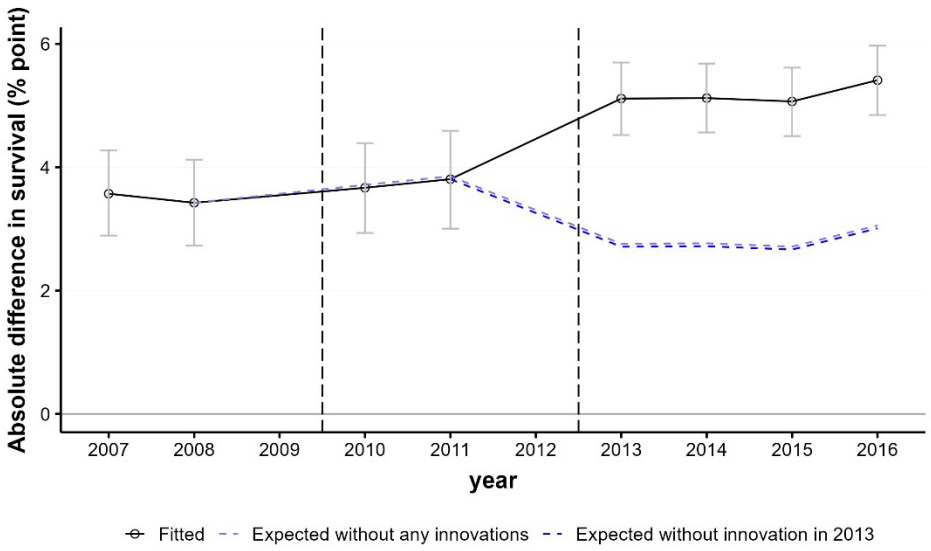
	2-Year Survival, % (95%CI)		Estimated Change in survival in each era, % point (95%CI)	Estimated Total Change in Survival, % point (95%CI)
	With Innovation[a]	Without Innovation during that Period[b]		
NSCLC				
Pre-innovation (2007-2009)	13.3 (13.0 to 13.6)			
Innovation era 1 (2010-2012)	15.6 (15.2 to 15.9)	14.3 (13.3 to 15.4)	1.2 (0.1 to 2.3)	
Innovation era 2 (2013-2016)	18.8 (18.5 to 19.0)	16.3 (15.3 to 17.2)	2.4 (1.5 to 3.4)	3.7 (2.7 to 4.6)
Melanoma				
Pre-innovation (2007-2010)	24.4 (22.8 to 26.2)			
Innovation era 1 (2011-2013)	35.7 (33.9 to 37.5)	25.5 (23.6 to 27.5)	10.3 (7.6 to 12.8)	
Innovation era 2 (2014-2016)	42.7 (41.2 to 44.2)	36.0 (34.0 to 38.1)	6.7 (4.3 to 9.3)	16.8 (14.5 to 19.2)

CI, confidence interval, obtained through 1000 bootstraps.
[a]Values are the model adjusted estimates of 2-year survival in the innovation era in the presence of innovation in that period.
[b]Values are the model adjusted estimates of 2-year survival in the innovation era in the absence of innovation in that period.

Figure 2: Observed disparity in 2-year survival across county-level income level over time, measured in absolute difference, and the expected disparity in the absence of the innovations

Vertical dashed lines indicate the time when an innovation was approved by the Food and Drug Administration. The 95%CIs were obtained using 1000 bootstrap samples.

a) Lung Cancer



b) Melanoma

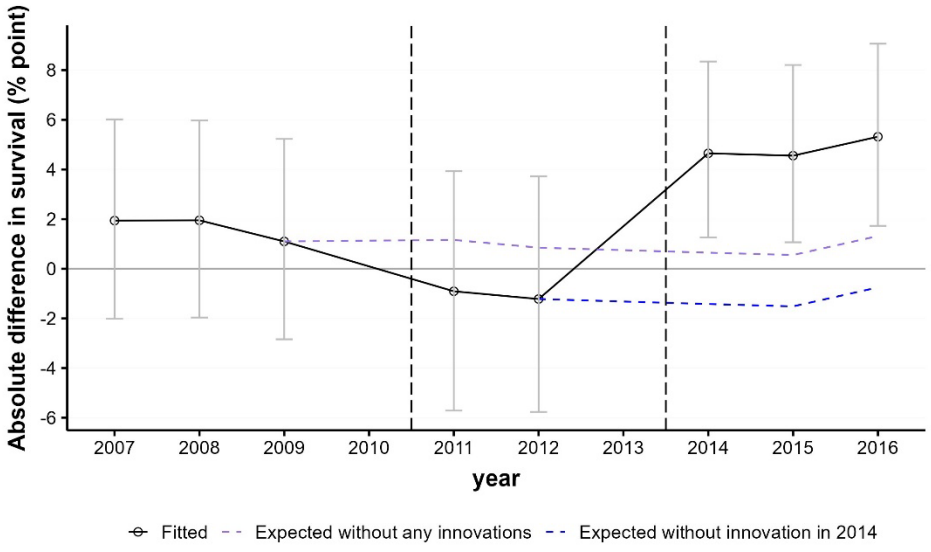


Table 3: Estimated effects of innovations on disparities in 2-year survival by county-level income among patients with NSCLC and melanoma

	Disparity[a], % point (95%CI)		Estimated Change in Disparity with each Innovation, % point (95%CI)	Estimated Total Change in Disparity, % point (95%CI)
	With Innovation[b]	Without Innovation during that Period[c]		
NSCLC				
Pre-innovation (2007-2009)	3.5 (2.8 to 4.2)			
Innovation era 1 (2010-2012)	3.7 (3.0 to 4.5)	3.8 (1.0 to 6.5)	-0.05 (-2.9 to 2.8)	
Innovation era 2 (2013-2016)	5.3 (4.8 to 5.8)	2.9 (0.6 to 5.1)	2.4 (0.07 to 4.7)	2.4 (0.06 to 4.7)
Melanoma				
Pre-innovation (2007-2010)	1.7 (-2.1 to 5.5)			
Innovation era 1 (2011-2013)	-1.1 (-5.8 to 3.9)	1.2 (-3.4 to 5.7)	-2.2 (-8.9 to 4.2)	
Innovation era 2 (2014-2016)	4.8 (1.5 to 8.5)	-1.3 (-6.5 to 4.0)	6.1 (0.1 to 12.1)	3.9 (-1.3 to 9.2)

CI, confidence interval, obtained using 1000 bootstrap samples.
[a]Disparity in 2-year survival is calculated by subtracting 2-year survival in the lowest income from the highest income group.
[b]Values are the model adjusted estimates of disparity in the post-innovation period in the presence of innovation in that period.
[c]Values are the model adjusted estimates of disparity in the post-innovation period in the absence of innovation in that period.

All sensitivity analyses of our primary outcome produced estimates within the 95% confidence intervals of the base-case result (Figure S1.5). The increase in disparity in the second innovation era appeared more pronounced among patients under 65 compared to those 65 or older, but the confidence intervals overlapped.

2.5 DISCUSSION

To our knowledge, this is the first study that uses a causal framework to examine the impact of cancer treatment approvals on cancer survival disparity across income groups. We found that cancer therapy approvals between 2008 and 2016 were associated with significant improvements

in survival among patients diagnosed with advanced lung cancer and melanoma. However, some treatment approvals also contributed to increased inequality in cancer survival across income groups, suggesting that new treatment introductions may be an important source of health disparity.

Over the last decade, the rapid introduction of many cancer innovations has revolutionized treatment for patients with advanced cancers. Our findings generally agree with other research showing that pharmaceutical innovations have contributed to improvements in population-level cancer survival.[38-43] Our study benefited from employing a triple difference-in-difference-in-differences design, incorporating control groups. This design enables us to account for external shocks or policy changes that may have influenced cancer survival rates over time and better isolate the effects of the pharmaceutical innovations amidst other factors.

Our study found evidence that some innovations did not benefit all groups equally, consistent with previous research showing disparities in innovation uptake across different demographics.[44,45] Our study extended these findings by demonstrating a link to the disparity in health outcomes, showing that patients in low-income neighborhoods experienced lesser survival improvements from some cancer innovations, further exacerbating health disparities.

We found that the introduction of the anti-PD-1 immunotherapies and combination BRAF/MEK inhibitors widened the disparity gap in melanoma survival. Several mechanisms could have contributed to these disparities, including differential innovation uptake, treatment benefits, and treatment adherence. Studies have shown a notable increase in PD-1 inhibitor uptake post-2014 approvals,[46] but uptake was slower among Medicaid patients, non-academic centers, and counties with higher proportion of racial and ethnic minorities.[47-49] These differential uptakes likely contributed to the observed survival disparities. Future studies should delve into these

mechanisms to identify potential solutions for addressing survival disparities associated with new innovations.

In comparison, the FDA approvals of Ipilimumab and targeted therapies for melanoma around 2011 did not significantly impact survival disparities across income groups. This may be attributed to Ipilimumab's high toxicity profile and slow uptake, along with limited adoption of targeted therapies.[46] Notably, there was a gradual increase in Ipilimumab use pre-2011 FDA approval (9% pre-approval and 19% post-approval),[44] with consistent income-based disparity in its receipt both before and after approval.[50] These factors may have hampered our ability to detect a significant change in survival disparity post-Ipilimumab and targeted therapy approvals.

For NSCLC, the approval of targeted therapy EGFR TKI as first line treatment and subsequent introduction of anti-PD-1 immunotherapy significantly increased survival disparities. This rise may be partially attributed to differential uptake of PD-1 inhibitors and EGFR TKIs across groups. While PD-1 inhibitor use surged as second-line treatment since 2013,[51] disparities persisted, with racial and ethnic minorities, low-income individuals, Medicaid beneficiaries, and those in high-poverty areas less likely to receive them.[44,52,53] Targeted therapy utilization remained relatively low (10-20% of first-line therapy recipients) and stable over time, with similar disparities noted. [54] Even among EGFR mutation-positive patients treated with EGFR TKIs, Black patients exhibited worse survival, possibly due to disparate downstream care.[55] Interestingly, we did not detect an increase in survival disparity following the 2010 approval of EGFR TKI as maintenance therapy across income levels, possibly due to its prior approval for advanced NSCLC patients with relapse in 2004.

It is worth noting that some of the innovations examined, e.g., EGFR TKI and anti-PD-1 immunotherapies, were only eligible to patients with specific mutations (Table S1.3).

Consequently, their impacts on population-level survival disparities may have been attenuated. Our ability to detect significant survival improvement and disparities at a population-level underscores their impact. Exploratory analysis revealed that patients under 65, more likely to have commercial insurance than Medicare, may experience a somewhat higher, albeit statistically insignificant, impact on survival disparities from new innovations. Future studies should further examine the role of insurance in mitigating health disparity impacts of innovations.

Our findings have important implications for policymakers and health systems striving to improve population health while reducing health inequalities. They emphasize the necessity of community collaboration to implement strategies to mitigate the disproportionate impact of effective medical innovations. These strategies may include enhancing affordability of cancer interventions through better insurance designs, such as expanding Medicaid eligibility, or eliminating cost-sharing for cancer patients receiving high-value care. They may also include broad dissemination of information related to the new innovations to low-income neighborhoods and community hospitals and streamlining medical treatments to reduce patient effort.[56] It is also essential to incorporate health disparity consequences into drug approval and coverage decisions and value assessments, which could motivate the prioritization of innovations that reduce health inequities, encourage investments in innovations that have a greater benefit for the underserved populations, and systematically minimize disparity impacts. Clinic-level interactions could also address potential treatment barriers and financial concerns with patients.

Our study results align with the fundamental cause theory, which suggests that effective medical innovations are instrumental to increasing social inequalities in health. This is because people of higher SES, and as an extension, people residing in high SES neighborhoods, are better

positioned to benefit from these innovations due to better access to resources (knowledge, power, prestige, money, social connections).[32,57,58] More advantaged neighborhoods also have better healthcare facilities with technological resources, specialists, and board-certified physicians.[58,59] The persistent relationship between SES and health disparities implies that efforts to reduce the health disparity impacts of new innovations cannot be focused on addressing the mechanisms that link low-income neighborhoods to health outcomes alone. Instead, they need to address structural and environmental inequalities through policies that aim at removing barriers to treatment (e.g., improve public transportation, increase Medicaid acceptance, and mandate paid sick leave), reducing economic stress (e.g. financial assistance and basic income programs), and improving the structural environment (e.g. air quality, housing, safety, nutrition, physical activity, education).

Our study has several limitations. First, we focused on pharmaceutical innovations in two cancer types, potentially limiting generalizability to other innovations and tumor types; however, our approach could easily be applied to other cancer types to address similar questions. Second, we did not account for advances in surgery, diagnostics, radiotherapy, and medical devices, though these likely did not coincide with drug approvals. Previous research has demonstrated that the rate of non-pharmaceutical innovation is not positively correlated with drug innovations in the US,[60] suggesting that it is unlikely that we overestimated the impact of pharmaceutical innovation by not accounting for other medical innovations. Third, the difference-in-difference-in-differences analysis relies on the assumption that there are no systematic differences in the disparity trends other than the effect of innovations between the treatment and control cancer groups. Although we tested the validity of the parallel trend assumption, other factors like changes in smoking or comorbidities may have differentially contributed to the increase in

survival disparity in our treatment groups. Fourth, our analysis ended in 2016, possibly underestimating the impact of the 2015 approvals of the anti-PD-1 immunotherapies and combination therapies for first line treatments for patients with melanoma. Future studies should aim at understanding the impact of these therapies beyond our study timeframe. Fifth, we only assessed survival up to three years due to dataset limitations. It is possible that disparities in survival may differ with a longer follow-up timeframe, although we observed consistent patterns of survival disparity at one, two and three years. Future study should consider extending the survival analysis window, while also mindful to the potential disruptive effects of the COVID-19 pandemic in 2020. Finally, multiple innovations approved in some time periods make it challenging to attribute disparity increase to a single innovation. However, this scenario mirrors real-world complexities, where multiple innovations often coexist. Therefore, evaluations of innovations' disparity impacts should consider existing and potentially competing innovations for a comprehensive understanding.

2.6 CONCLUSIONS

Our quasi-experimental study showed that the introduction of effective cancer innovations increased population-level health among patients with advanced lung cancer and melanoma, but also widened the survival gap across county-level income groups. These findings highlighted the tenacious relationship between socioeconomic status, medical innovations, and health, and have important implications for policy makers and health systems who want to pursue the dual goals of advancing population health through innovations and achieving health equity.

Chapter 3. THE HEALTH DISPARITY IMPACT OF OMITTING RACE AND ETHNICITY FROM A COLON CANCER RISK PREDICTION TOOL: A MICROSIMULATION STUDY

3.1 ABSTRACT

Importance: Policy decision-makers and the medical community are increasingly seeking clinical risk prediction tools that are race-neutral (do not include race as a decision factor). However, the omission of race and ethnicity from these tools has sometimes led to inaccurate risk predictions for minoritized racial groups. Yet, the implications for health disparity remain uncertain.

Objective: To evaluate the long-term impact of omitting race from a colon cancer decision tool for adjuvant chemotherapy recommendations on health outcomes, healthcare costs, and health disparities.

Design: A microsimulation study

Setting: Large integrated health system in Southern California

Participants: We simulated the disease progression of 4839 adults with stage II and III colon cancer who underwent surgical resection. The model was populated with electronic health records (EHR) data and inputs from literature. We included an extra health state to address racial bias in cancer recurrence ascertainment within the EHR.

Main Outcomes and Measures: Projected 30-year quality-adjusted life-years (QALYs), health care costs, and the distribution of QALYs among racial groups under three adjuvant chemotherapy treatment scenarios: 1) current practice, 2) guided by a colon cancer decision tool that included race, 3) guided by the same tool with race omitted.

Results: The simulation estimated that using a colon cancer decision tool to guide adjuvant treatment decisions, compared to current practice, could improve average per-patient health by 0.048 QALYs, increase costs by $3221, and reduce overall health inequality across racial and ethnic groups by 0.20 QALYs. Omitting race from the decision tool had minimal effect on overall health gain or costs but resulted in 13% fewer Black patients receiving adjuvant treatment, a decrease of 0.07 QALYs for Black patients, and contributed to a 0.13 QALY widening of the health disparity gap.

Conclusion and Relevance: Omitting race from a clinical decision tool that guides colon cancer chemotherapy could harm disadvantaged groups and worsen health disparities. Our study showed how a microsimulation framework can assess these impacts while addressing data biases. These findings are crucial for health policy decision-makers and clinicians who seek decision tools that prioritize both race-neutrality and the mitigation of health disparities.

3.2 INTRODUCTION

State-of-the art automated prognostic clinical algorithms are increasingly available to facilitate medical treatment decisions,[14-18] potentially reducing clinician bias and improving treatment decision-making. However, concerns are rising that these algorithms may institutionalize discriminatory logics that perpetuate racial health disparities.[19] Recent studies have raised concerns that including race, a social construct, as a predictor in clinical decision tools can lead to racial profiling and differential treatments across racial groups. Many clinicians, policy makers, and institutions have called for revisions of existing clinical decision tools to remove the adjustment for race (i.e., use a "race-neutral" approach).[20-22]

However, some studies caution against completely disregarding race and ethnicity, as doing so may result in inaccurate predictions and treatment assignments that may differentially harm racial and ethnic minority groups.[21-24] For example, simply removing race from a urinary tract infection risk calculator was shown to lead to unnecessary catheterization among Black children, increasing discomfort, potential adverse events, and healthcare costs.[61,62] Similarly, eliminating race from a lung cancer decision tool reduced the likelihood of African American patients being offered potentially curative lung cancer surgery.[63] In colorectal cancer, we also demonstrated that omitting race in a cancer recurrence prediction tool resulted in less accurate predictions for racial and ethnic minority patients.[24]

So far, the literature predominantly examines how omitting race in clinical decision tools may affect prediction accuracy and treatment assignments among patient subgroups. However, its impact on patients' quality of life, survival, and disparities remains unclear.[25] This study aims to address this gap by assessing the clinical consequences of omitting race from clinical decision tools. Specifically, we used an existing colon cancer survival calculator for adjuvant

chemotherapy decisions as a case study.[64] This calculator includes race as a predictor, akin to others criticized for propagating "race-based medicine".[21] Using data from a large integrated health system, we adopted a decision-analytic approach to estimate the impact of omitting the race variable in the colon cancer survival tool on overall health outcomes and healthcare costs, and the distribution of health across racial and ethnic groups. Results from this research will contribute to the debate on "race-neutral" vs. "race-sensitive" algorithm and offer a framework for evaluating health disparity implications of clinical algorithms in other settings. They will offer crucial information for health policy decision-makers, clinicians, and researchers who seek clinical decision tools that prioritize both race-neutrality and the mitigation of health disparities.

3.3 METHODS

Data Source and Study Population

This study used de-identified linked cancer registry and electronic health record data from an integrated health system, Kaiser Permanente Southern California (KPSC), covering over 4.7 million members across 15 hospitals in Southern California. This insured population is socioeconomically diverse and reflects that of the Southern California census population. The dataset includes demographic information, diagnoses, procedures, medications, and mortality data.

The study cohort comprised adult patients diagnosed with stage II to III colon cancer between 2008 and 2021 who underwent resection (n= 4839), with follow-up until July 31st, 2023. Exclusion criteria are detailed in Figure S2.1. Race and ethnicity was obtained from membership or utilization data, preferred language, and birth certificates,[65] with categories including Asian, Hawaiian, or Pacific Islander (API); Black or African American (Black); Hispanic; non-Hispanic

White (NHW); and multiracial or other. There was no unknown or missing race and ethnicity. Due to small sample size, the multiracial or other subgroup was excluded from the analyses.

A waiver of informed consent was granted by the University of Washington institutional review board (#2270). This study adheres to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2022) guidelines (Table S2.3).[66]

Treatment Decision Scenarios Under Comparison

We generated two sets of mortality risk scores for our study cohort. The "race-sensitive" scores were estimated by applying an existing colon cancer survival calculator from the MD Anderson Cancer Center,[64,67] which incorporates age, sex, tumor stage, tumor grade, and race (White, Black, vs. Other) to estimate 5-year mortality risk. The "race-neutral" risk scores were computed by applying the same risk calculator with the race variable turned "off ", i.e., the coefficient for race was set to zero for all patients, consistent with practices adopted by some institutions and groups to exclude race from existing risk calculators.[68,69]

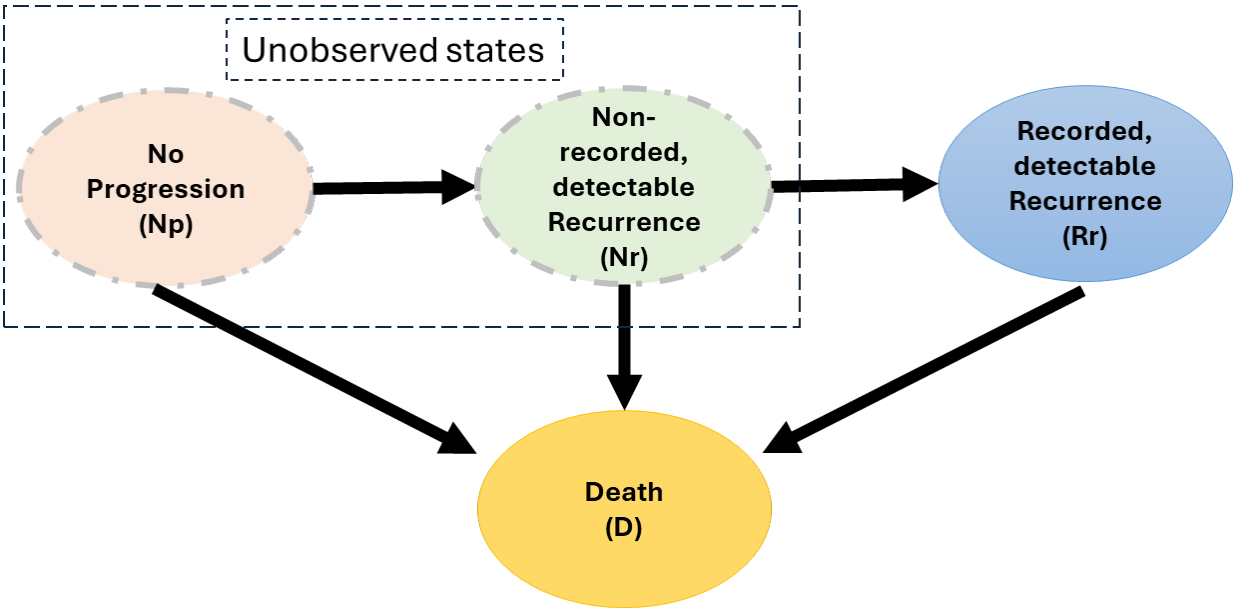
Three adjuvant treatment decision scenarios were compared: current practice (reflecting how adjuvant chemotherapy was being used in actual practice), "race-sensitive" risk scores, and "race-neutral" risk scores. Adjuvant treatment decisions for the two risk-score-based scenarios were operationalized under a threshold objective where treatments were given to patients with risk scores above a certain risk threshold. The primary analysis employed a 15% risk of death threshold, which was deemed clinically relevant in this setting by our clinical expert. Sensitivity analysis explored thresholds of 10%, 25%, and 35%.

Simulation Model

We developed, validated, and calibrated a cohort microsimulation model to estimate the heterogeneous natural histories of colon cancer patients post-surgery. This model aims to compare the effects of the three treatment decision scenarios on costs and health outcomes (measured in quality-adjusted life years (QALY)), and the distribution of health across racial and ethnic groups.

The model consists of four clinical states: No Progression (Np), Non-recorded recurrence (Nr), Recorded Recurrence (Rr), and Death. (Figure 3) Each patient from our cohort enters the model via the Np state and may progress through various events with or without adjuvant treatment, including cancer recurrence. If their cancer recurs, they will enter the Nr state, and can then subsequently enter the Rr state when their recurrence becomes recorded in the data. In each of the health states, the patient faces a risk of dying.

Figure 3: Model Schematic for Natural History of Colon Cancer Progression



In our dataset, recorded recurrence was identified based on healthcare utilization patterns associated with metastatic disease, which has been validated in previous studies (Appendix S2.1).[70,71] However, patients who experience cancer recurrence without receiving healthcare services, such as surgery, may not be accurately captured in the electronic health records. Additionally, delays in accessing healthcare services for recurrence may lead to a distorted perception of the duration to recurrence. Our previous work has shown disparities in capturing recurrence events using healthcare utilization across racial groups.[72] To address this data bias, we introduced a hidden unobserved state, the Nr state. This state captures recurrence events that may not have been promptly or comprehensively captured by utilization patterns in the electronic health records due to delays or absence of healthcare interventions following recurrence. This is important because ignoring the racial bias inherent in the data could introduce bias in the evaluation.

This discrete-time microsimulation model had annual cycles over a 30-year time horizon to capture long-term effects.

Model Inputs

Transitions across health states

We estimated patient-specific transition rates from the Rr state to death by fitting a parametric survival model to the observed data from patients who experienced a recorded recurrence. Additionally, we performed a detailed review of clinical notes for a random sample of 342 patients to identify the true occurrences and timings of recurrences. In this subset, we estimated the time from the true recurrence to the recorded recurrence by fitting a parametric survival

model, allowing us to derive patient-specific transition rates from Nr to Rr. For each model, we examined three parametric survival distributions – exponential, Weibull, and Gompert – and selected the most appropriate distribution based on the lowest Akaike information criterion (AIC) and visual inspection of model fit.[73]

We assumed that patients in the Nr state do not receive treatment for their recurrence and hence have similar mortality as those in the Rr state without treatment. Rates of death from Np were specific to age, sex, and race and ethnicity and were estimated using the US life table and the California to US mortality rate ratios (with deaths related to colorectal cancer removed).[74] (Appendix S2.2)

Transition rates from Np to Nr were not directly observed in our data. To estimate these rates, we utilized a Bayesian calibration approach with Incremental Mixture Importance Sampling.[75,76] This method allowed us to adjust the model to align with clinically relevant outcomes: overall survival, recorded recurrence, and death before a recorded recurrence, as estimated by Kaplan-Meier analyses from our cohort data.

All transition rates were estimated quarterly and then converted to annual probabilities using matrix exponential.[77] Details of the estimation and calibration of the transition parameters can be found in Appendix S2.2.

Treatment effect

We did not estimate the treatment effect of adjuvant chemotherapy directly in the observed data due to confounding by indication. Instead, we separately estimated non-recorded recurrence rates among treated and untreated patients and calculated rates for each patient under alternate treatment scenarios (i.e. under adjuvant treatment for those who did not receive it, and under no

adjuvant treatment for those who did receive it) using the hazard ratio estimates from published literature. (Appendix S2.3)

Costs and Health

Costs were estimated from the health system's perspective. All costs, estimated in 2023 US dollars, were obtained from literature, including adjuvant treatment (assumed to be 12 cycles of FOLFOX) costs, treatment-related toxicity costs, administrative costs, and healthcare costs across care phases. Health, assessed via QALYs, captures patients' length of life and health-related quality of life. All health utility estimates were sourced from literature (Table 4). We used a commonly used 3% annual discount rate to adjust future costs and QALYs to present value.

Table 4: Model Parameters

Parameter	Estimate	95%CI	Source
Clinical parameters			
Effectiveness of adjuvant chemotherapy on disease-free survival as a hazard ratio, compared to no adjuvant chemotherapy	0.47	0.19-0.76	Estimated using median disease-free survival estimates from Zha et al[78] (see Appendix S2.3)
Rate of Recorded recurrence (Years 0 to 4)	Specific to adjuvant treatment status and patient characteristics		Based on exponential survival model (see Appendix S2.2)
Rate of Recorded recurrence (Year 5 to 10)	Specific to adjuvant treatment status		Based on exponential survival model (see Appendix S2.2)
Rate of Non-recorded Recurrence	Specific to adjuvant treatment status and patient characteristics	Posterior 95% credible interval	Applied multiplier to rate of recorded recurrence and calibrated to overall survival, recurrence, and death before recurrence data (see Appendix S2.2)

Rate of transitioning from Non-recorded Recurrence to Recorded recurrence	Specific to patient characteristics		Based on exponential survival model in chart review subset (see Appendix S2.2)
Background mortality (California non-colorectal cancer related deaths)	Age-, race-, and sex-specific		Estimated using US life tables and California to US Mortality Ratios (see Appendix S2.2)
Rate of transitioning from Recorded Recurrence to Death	Specific to patient characteristics		Based on Gompertz survival model (see Appendix S2.2)
Rate of transitioning from Recorded Recurrence to Death	Specific to patient characteristics		Estimated using Rate of transitioning from Recorded recurrence to death / hazard ratio of antitumor therapy (see Appendix S2.2)
After recurrence: Hazard Ratio of death with antitumor therapy, compared to supportive care alone	0.52	0.34-0.70	Estimated using median survival estimates from Hamers et al. and Biller et al.[79,80] (see Appendix S2.3)
Cost Parameters (2023 US$)			
Cost of treatment			
Adjuvant FOLFOX chemotherapy per cycle (12 cycles over 6 months)	1554	1241 - 1864	Alarid-Escudero et al.[81]
Administrative costs per cycle	351	281 – 422	Goldstein et al[82]
Adjuvant Treatment toxicity cost			
Grade 3-4 neutropenia	212	189-250	
Febrile neutropenia	5654	3016-13309	Ayvaci et al.[83]
Grade 3-4 diarrhea	188	156-220	
Proportion experiencing toxicity			
Grade 3-4 neutropenia	41.1%		André et al.[84]
Febrile neutropenia	1.8%		
Grade 3-4 diarrhea	10.8%		
Cancer Care without recurrence (annual)	53778	52579 - 55360	Yabroff et al.[85]
Initial (first 12 months)			
Continuing (annual)	4094	2699 - 4317	
Cancer care with recurrence (annual)	10927	9701-12155	Alarid-Escudero et al.[81]
Addition Costs at End of Life, by cause of death (last 12 months)			
Death from colon cancer	59443	57464-61423	Alarid-Escudero et al.[81]
Death from other cause	12847	10727-14967	Alarid-Escudero et al.[81]
Utility parameters			
First 6 months			
Without adjuvant chemotherapy	0.84	0.82-0.87	Ramsey et al.[86], Robles-Zurita et al.[87]
With adjuvant chemotherapy			
Well	0.81	0.79-0.85	Robles-Zurita et al.[87]
Minor toxicity	0.73	0.6-0.84	Best et al.[88]
Major toxicity	0.59	0.49-0.68	

Percentage with minor toxicity	41.1		André et al.[84]
Percentage with major toxicity	50.9		
6-17 months (among those who received adjuvant chemo)			
Percentage of minor toxicity	39.7		André et al.[84]
Percentage of major toxicity	1.3		
18 -60 months (among those who received adjuvant chemo)			
Percentage of minor toxicity	23.2		André et al.[84]
Percentage of major toxicity	0.5		
Months 6-60 No toxicity	0.85	0.82-0.87	Robles-Zurita et al.[87]
Months 60+	0.90	0.84–0.93	Robles-Zurita et al.[87]
Recurrence	0.45	0.24-0.67	van den Brink et al.[89], Ness et al.,[90] Attard et al.[91]

FOLFOX, fluorouracil combined with oxaliplatin

Model Outcomes

The primary simulated outcomes of interest were overall mean discounted QALYs and discounted costs, as well as the distribution of the discounted QALYs across racial and ethnic groups: API, Black, Hispanic, and NHW.

We assessed changes in QALY distribution across the treatment scenarios using two measures: Absolute Difference (QALYs of most advantaged group minus QALYs of least advantaged group) and Relative Gap (Absolute Difference divided by QALYs in least advantaged group). We defined the most and least advantaged groups based on population-level expected life expectancies at birth in the US (2019): API (86 years), Hispanic (82 years), NHW (79 years), and Black (75 years).[92] The most and least advantaged groups are the API and Black, respectively. Interventions widening the health gap between these two groups are considered to increase health disparity.

Model Analysis

For the risk-based scenarios ("race-sensitive" or "race-neutral" risk scores), individuals in the colon cancer cohort were assigned to adjuvant chemotherapy based on their risk scores and treatment risk threshold, while actual chemotherapy status was used for the "current practice" scenario. We then simulated the outcomes using the microsimulation model for each individual according to their assigned treatment statuses. To account for stochastic uncertainty, simulations were repeated 100 times to reach convergence (see Appendix S2.4). Estimates were derived from the mean of these runs.

To address uncertainty in model inputs, we performed probabilistic sensitivity analyses by sampling 500 sets of input parameters from their respective distributions and simulating outcomes.

Sensitivity analyses examined how the results varied across different risk threshold cutoffs and pre-specified subgroups: stage II cancer, stage III cancer, and patients under age 80 at diagnosis.

Analyses were performed using R version 4.1.2 (R Project for Statistical Computing).

3.4 RESULTS

Our cohort consisted of 4839 colon cancer patients (mean (SD) age 66.2(13.6) , 2481 (51.3%) female). Among these patients, 529(11%) identified as API, 644(13%) Black, 1294(27%) Hispanic, and 2372(49%) NHW. Patient characteristics are shown in Table S2.1.

Overall differences among treatment decision scenarios

Under current practice, 50.3% of the colon cancer patients received adjuvant chemotherapy, with estimated mean discounted QALYs of 8.67, and mean discounted cost of $127,066 over 30 years. (Table 5)

Table 5: Overall Quality-Adjusted Life Years, Costs, and health disparity impacts

Inequality Metric	Current Practice	"Race-sensitive" Risk Score[a]	"Race-neutral" Risk Score[a]	Incremental		
				"Race-sensitive" Risk Score[a] - current practice	"Race-neutral" Risk Score[a] - current practice	"Race-neutral" Risk Score - "Race-sensitive" Risk Score[a]
Overall						
Proportion receiving treatment	50.3%	68.2%	68.0%	+17.9%	+17.7%	-0.2%
Mean Costs	$127,066	$130,287	$130,227	+$3,221	+$3,160	-$60
Mean QALY	8.67	8.72	8.72	+0.048	+0.049	0.0010
Health Disparity						
Absolute Difference[b] (QALY)	1.55	1.35	1.48	-0.20	-0.06	+0.13
Relative Gap[c] (%)	19.0%	16.3%	18.1%	-2.7%	-1.0%	+1.7%

QALY, Quality-adjusted Life Years

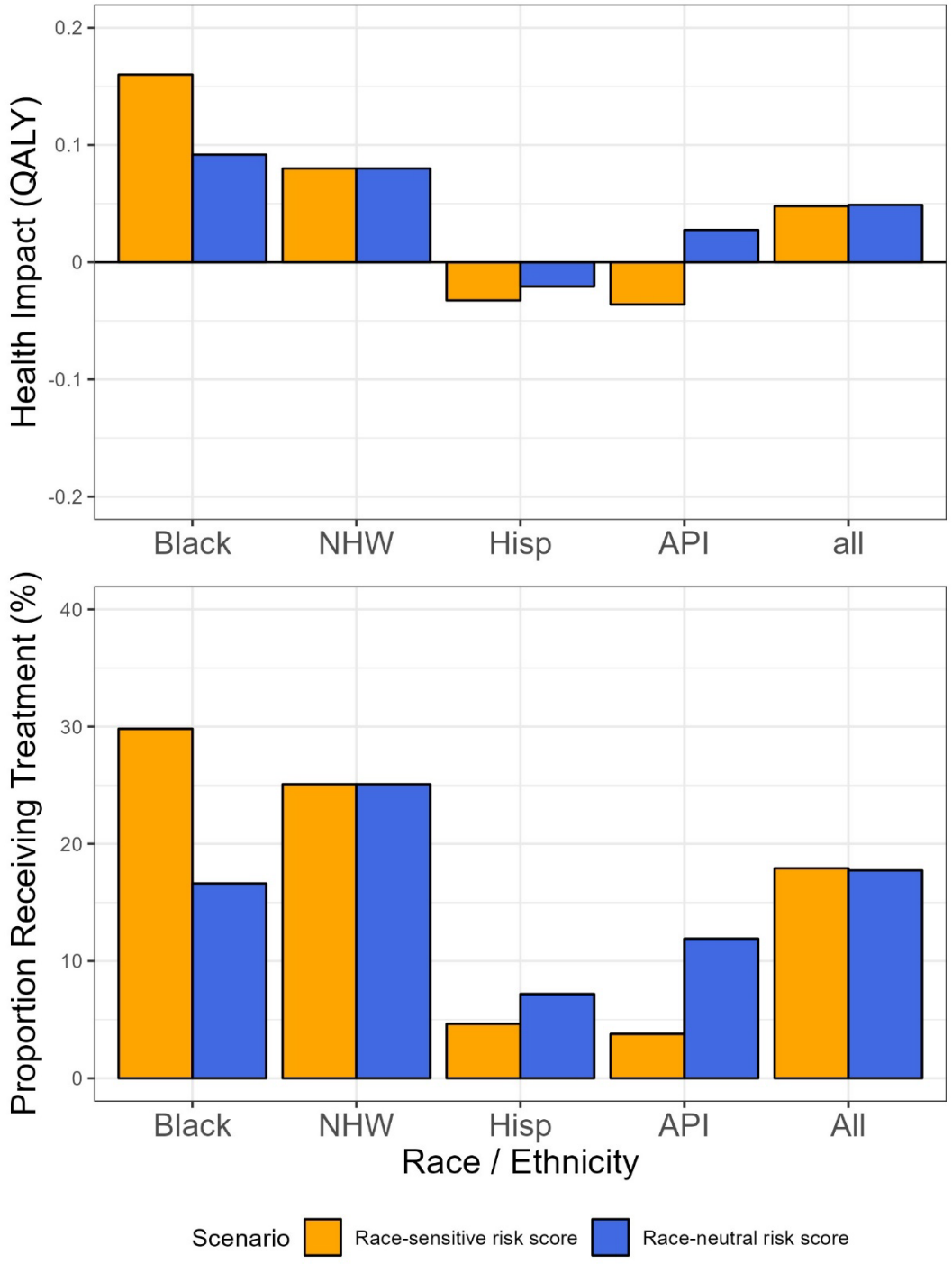
[a] Applying a 15% risk threshold cutoff

[b]Absolute Difference is determined by subtracting the QALYs of least advantaged group (Asian, Hawaiian, or Pacific Islander) from those of the most advantaged group (Black or African American). A positive value signifies a health disparity.

[c]Relative Gap is determined by dividing the absolute difference by the QALYs in least advantaged group (Black or African American). A positive percentage indicates the presence of a health disparity.

In the "race-sensitive" risk score-based treatment decision scenario (15% risk threshold), 18% more patients would receive adjuvant treatment compared to current practice, with a per-patient cost increase of $3221 and QALY gain of 0.048. The "race-neutral" risk score-based treatment decision scenario (at the same threshold) produced similar overall costs and QALYs. (Table 5)

Figure 4: Impact of making adjuvant treatment decisions based on "race-sensitive" risk scores and "race-neutral" risk scores, on health and the proportion of patients receiving treatment, compared to current practice, by racial and ethnic groups



Black, Black or African American; NHW, non-Hispanic White; API, Asian, Hawaiian, or Pacific Islander; QALY, Quality-adjusted Life Years

Impact on Health Distribution

Adopting the "race-sensitive" risk score-based treatment decision strategy, compared to current practice, showed a gradient effect on health across racial groups (Figure 4, Table S2.2), with Black patients gaining the most QALYs (0.16), followed by NHW (0.08), while Hispanic and API patients experienced QALY losses (-0.03 and -0.04, respectively).

Adopting a "race-neutral" risk score-based treatment decision strategy resulted in a more moderate gradient effect on health compared to the "race-sensitive" scenario. In the "race-neutral" approach, the health gain for Black patients was decreased by 0.07 QALYs, while NHW patients saw no change because the risk model coefficient for this group was already zero. Moreover, health gains for the Hispanic and API patients were higher under the "race-neutral" scenario, indicating a less equitable distribution of benefits across groups.

Impact on the Proportion Receiving Treatment

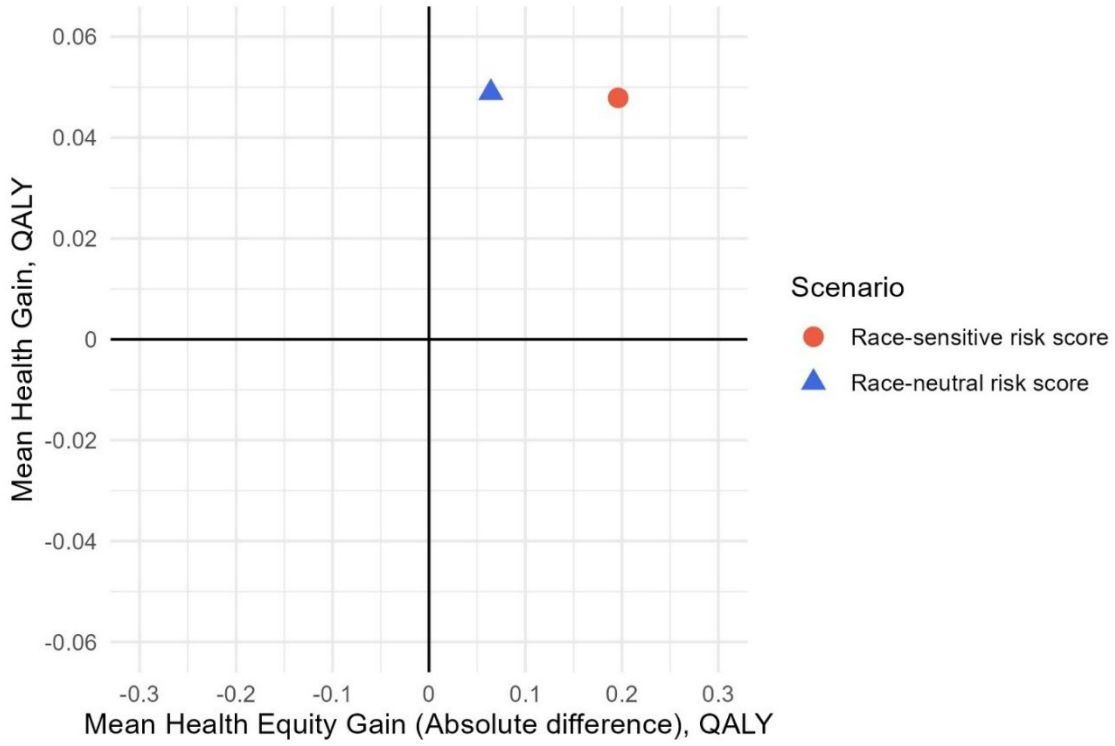
Under current practice, more Hispanic and API patients are receiving adjuvant chemotherapy compared to Black and NHW patients (Table S2.2). In the "race-sensitive" scenario, the proportion of patients receiving chemotherapy increased for all groups, with the increase among Black patients the highest at 30%, followed by NHW at 25% (Figure 4, Table S2.2).

Omitting race in the risk score ("race-neutral" scenario) resulted in 13% fewer Black patients receiving treatment, while 2.6% and 8.1% more Hispanic and API patients received treatment, respectively.

Combining overall health gain and health equity gain

Figure 5 illustrates the overall mean health gain vs. health equity gain for each risk-based strategy compared to current practice. The "race-sensitive" strategy increased overall health (higher overall QALYs), and reduced health inequality across racial and ethnic groups by 0.20 QALYs on the absolute scale (2.7% on the relative scale) (Table 5). In contrast, the "race-neutral" risk score strategy yielded a similar increase in overall health but a smaller reduction in health inequality (0.06 QALYs on the absolute scale, 1.0% on the relative scale). Omitting race from the risk score resulted in an increase of health inequality by 0.13 QALYs on the absolute scale and 1.7% on the relative scale compared to the "race-sensitive" strategy (Figure 3, Table 2).

Figure 5: Equity Impact Plane. Overall Mean Health Gain vs. Health Equity Gain for the "race-neutral" and "race-sensitive" risk score-based treatment scenarios, compared to current practice.



QALY, Quality-adjusted Life Years; Health equity gain is the reduction of health inequality, defined as the difference in QALYs between the most advantaged group (Asian or Pacific Islanders) and the least advantaged group (Black or African American).

Robustness Check

The finding that omitting race from the risk score would widen the health disparity gap remained consistently robust across different risk thresholds (Figures S2.2 and S2.3). This result also held true within pre-specified patient subgroups, including those diagnosed under 80 years old and those with stage II or stage III disease.

Probabilistic sensitivity analysis indicated that the "race-neutral" risk score increased health inequality 94.0% of the 500 iterations (Figure S2.4), compared to the "race-sensitive" risk score.

3.5 DISCUSSION

To our knowledge, this is the first study to quantify the health disparity impacts of omitting race from clinical prediction decision tools. Our microsimulation showed that using prediction tools to guide colon cancer adjuvant treatment decisions could improve overall population health and narrow the distribution of health across racial and ethnic groups by distributing more health gain towards the more disadvantaged groups. We showed that omitting race as a risk factor in the prediction tool had minimal effect on overall health gain or costs but redistributed health in a way that disproportionately harmed already disadvantaged groups in our healthcare system. Specifically, we found that omitting race from the decision tool resulted in fewer Black patients receiving adjuvant treatment, worse health outcomes for Black patients, and widened the health disparity gap.

Our study contributes to the ongoing debate around the use of race and ethnicity variables in clinical risk prediction tools by quantifying their potential impacts on health distribution across racial and ethnic groups. However, it is important to acknowledge that incorporating race, a

social construct, into these tools can generate harm beyond the health outcomes measured in this study. Racial profiling, patient distrust, and the perpetuation of the false notion that race is a biological variable are potential consequences of race-based medicine that can cause persistent harm to minoritized racial and ethnic groups. Policy makers, clinicians, and institutions hoping to transition from race-sensitive tools without causing systemic harm towards marginalized populations need to better understand the multiple sources of harm and consider these trade-offs carefully. It is imperative to incorporate the patients' and the public's preferences in these conversations.

Simulations, such as the ones in this study, are crucial for evaluating the downstream health disparity impacts of clinical risk prediction algorithms prior to deployment to ensure that the tools do not exacerbate health disparities. However, these simulations often hinge on the quality of the data used to generate the input parameters and could introduce bias when data quality varies across subgroups, particularly in capturing important health states like recurrence.[72] Relying on biased data for simulation could add another layer of racial bias to the simulation results. We demonstrated the feasibility of accounting for such data bias by incorporating a non-recorded recurrence state in our model. Future study should explore additional methods to mitigate data bias when simulating subgroup specific outcomes.

This study has several limitations. First, the cohort consisted of insured individuals from a Southern California health maintenance organization, limiting generalizability. Second, simulation models inherently require multiple assumptions, such as perfect risk calculator uptake and acceptance of the assigned treatment, which may not align with real-world scenarios and could differ by subgroups, potentially affecting the impact of the risk calculators on outcomes. We also assumed homogeneity in adjuvant treatment type, adherence, and benefit. Data on

treatment heterogeneity is currently lacking. Future studies should consider individual treatment effects. Third, our "race-neutral" scenario represents a situation where the race coefficient is turned "off". While this offers valuable insights and aligns with the strategies adopted by some institutions and groups to make tools "race-neutral",[68,69] it may not reflect outcomes achieved through completely refitting the risk prediction tool without race. Fourth, our health disparity measures only compared extreme groups, overlooking those in the middle. Future studies could employ more comprehensive equity measures and consider societal equity preferences. Finally, while we accounted for biases in recurrence outcomes, similar considerations may be needed for other model inputs. Future studies should explore how measurement errors in these factors could affect results.

3.6 CONCLUSIONS

Omitting race and ethnicity in a colon cancer risk prediction model may substantially increase health outcome disparity across racial and ethnic groups. These findings have implications for clinical decision making in practice, as well as policies that could mitigate harm from clinical decision tools.

Chapter 4. IMPLICATIONS AND POTENTIAL IMPACT OF FINDINGS

The treatment paradigm for patients with advanced cancer has changed dramatically in the last decade. Our study showed that cancer innovations have contributed to significant improvements in population-level cancer survival. However, these innovations may also have led to the escalation of survival disparities between areas of different income levels. Our results highlight the importance of concurrently assessing the health benefits and health disparities of new innovations. They also emphasize the necessity of integrating equity considerations into policies surrounding drug approval, pricing, insurance coverage, and diffusion alongside innovations to ensure that advancements in healthcare promote population health without widening the health disparity gap.

Our study also contributes to the ongoing debate around the use of race and ethnicity variables in clinical risk prediction tools by quantifying the potential impacts of such decisions on the distribution of health across racial and ethnic groups. We demonstrated the feasibility of using a microsimulation framework to evaluate these impacts, taking into account the bias in the data that is often used to parameterize such models. Our findings have implications for health policy decision-makers, clinicians, and researchers who seek clinical decision tools that prioritize both race-neutrality and the mitigation of health disparities.

Taken together, this research has the potential to reduce health and financial disparities by transforming the way we adopt, cover, and use oncologic drugs.

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SUPPLEMENTARY MATERIALS

APPENDIX FOR CHAPTER 2

Chapter 2 Appendix Table of Contents

Figure S1.1: Inclusion and Exclusion Criteria

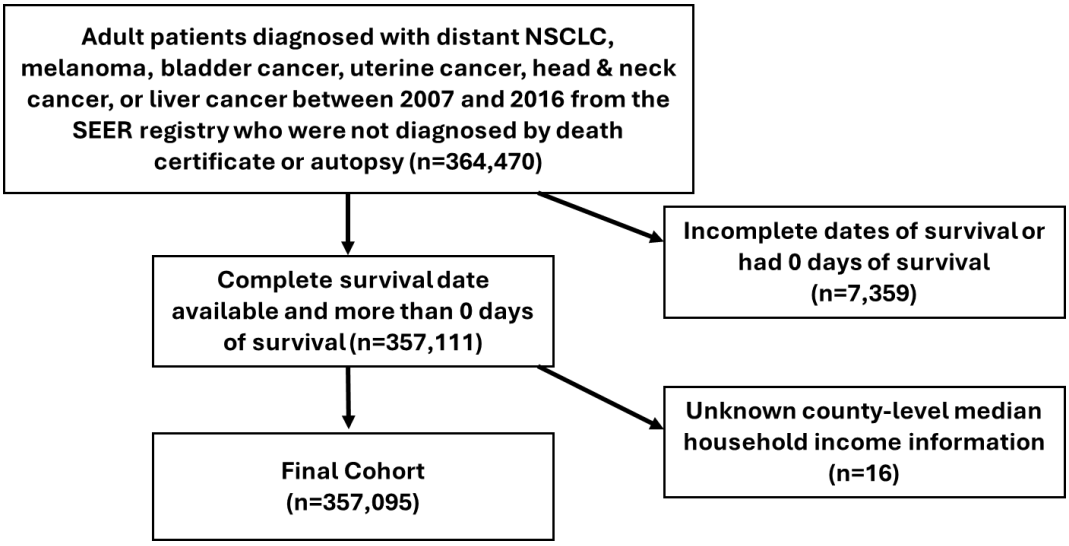


Figure S1.2: Unadjusted 2-year survival over time in the control cancer groups.

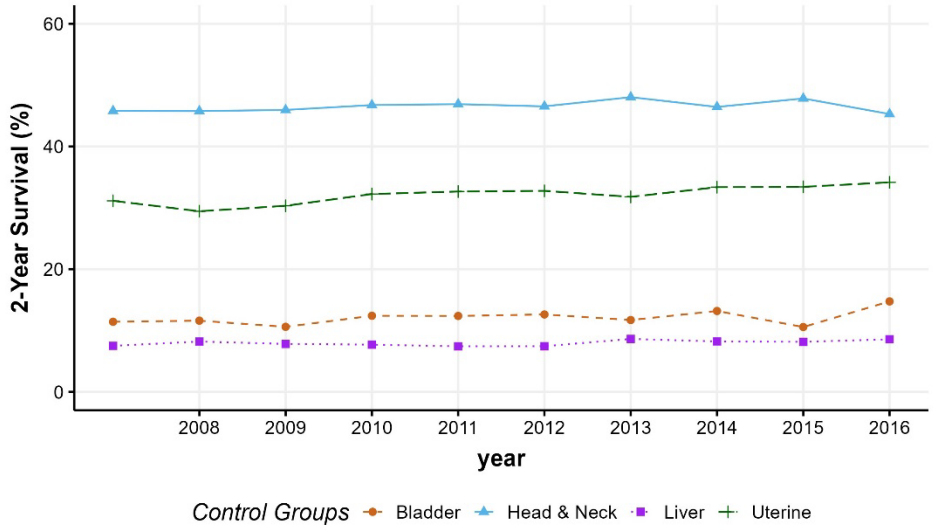
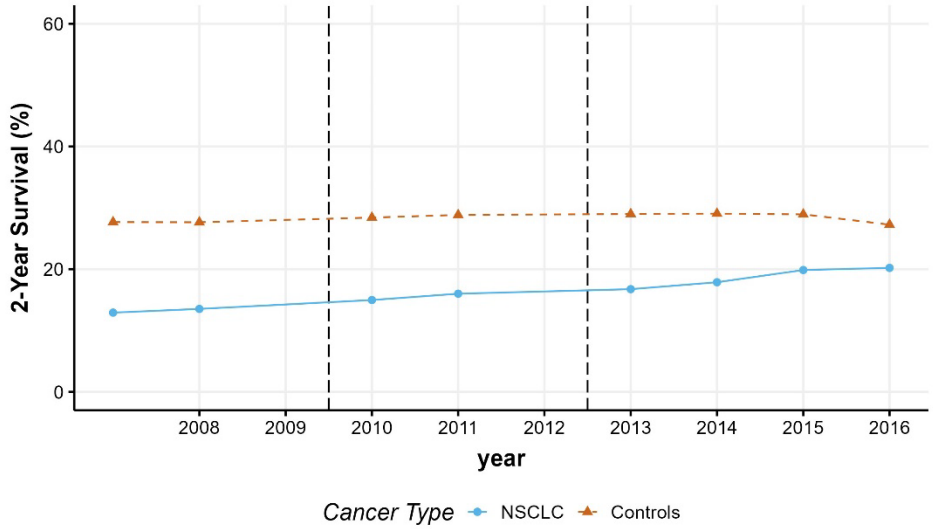


Figure S1.3: Unadjusted 2-year survival over time in the intervention and control cancers.

Vertical dashed lines indicate the time when innovations were approved by the Food and Drug Administration. Data from the year prior to innovations were excluded to allow for a washout period during which some patients may have benefited from the new innovations that were introduced the year after

a) Lung Cancer vs. Controls



b) Melanoma vs. Controls

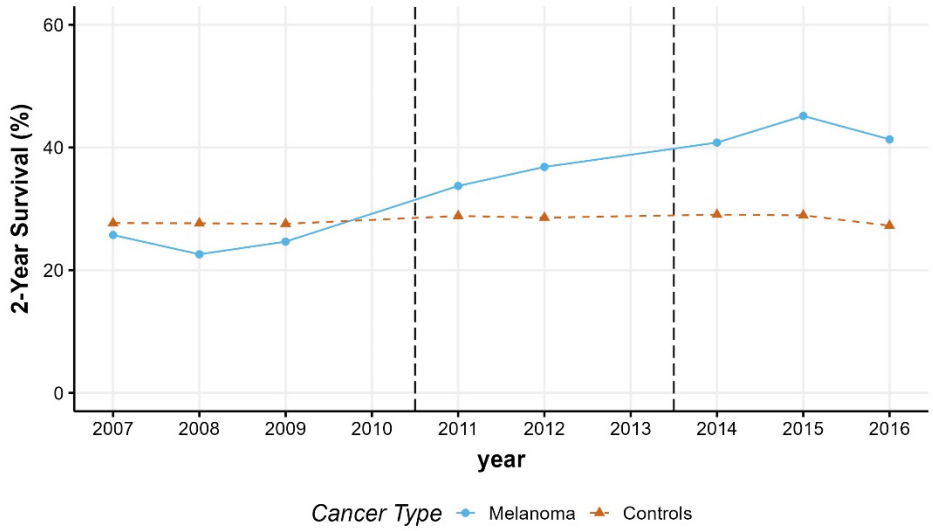
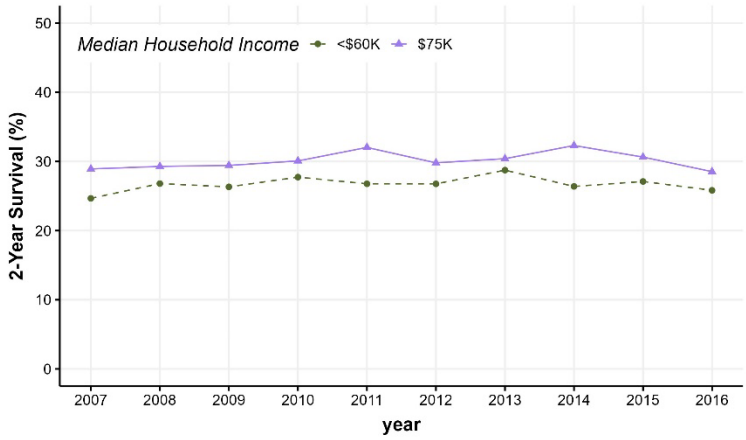
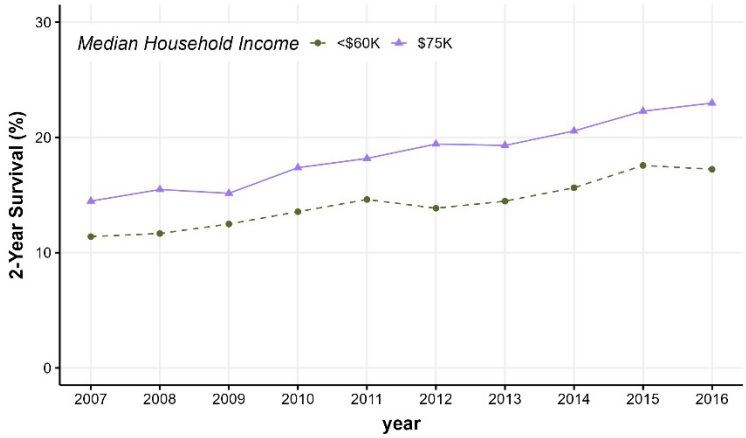


Figure S1.4: Unadjusted 2-year survival over time by county-level income.

a) Controls



b) NSCLC



c) Melanoma

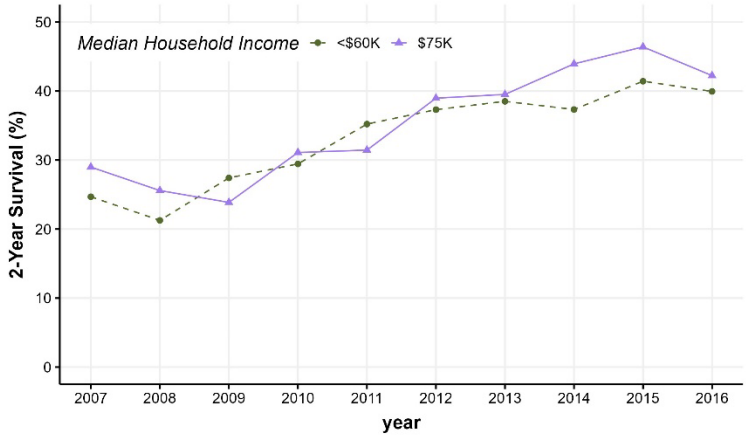
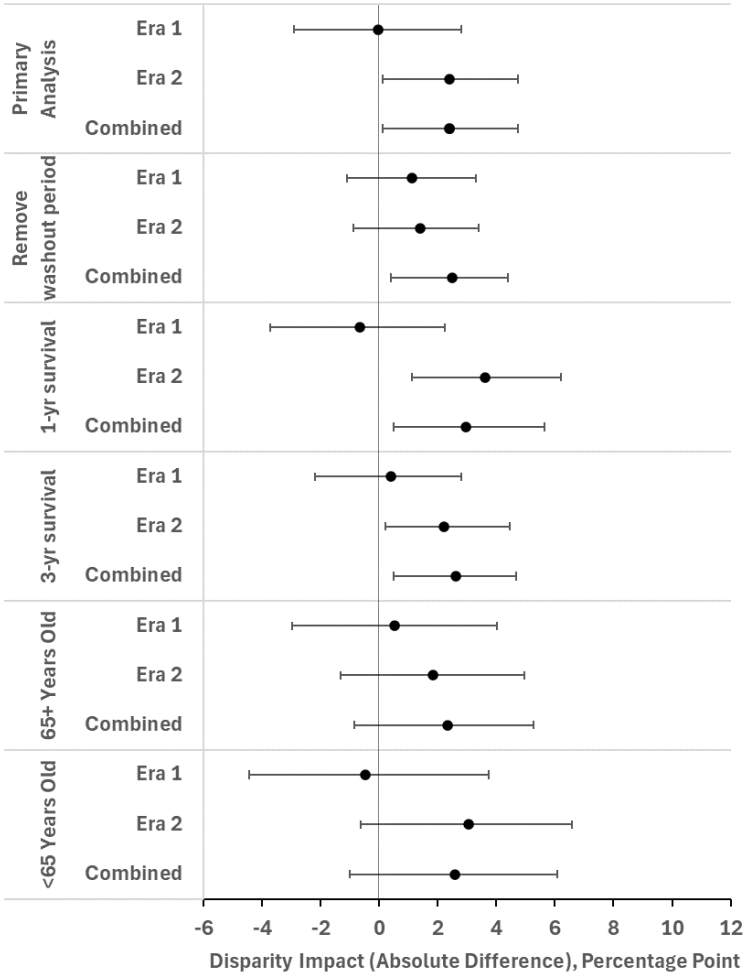


Figure S1.5 Sensitivity Analysis

a) NSCLC



b) Melanoma

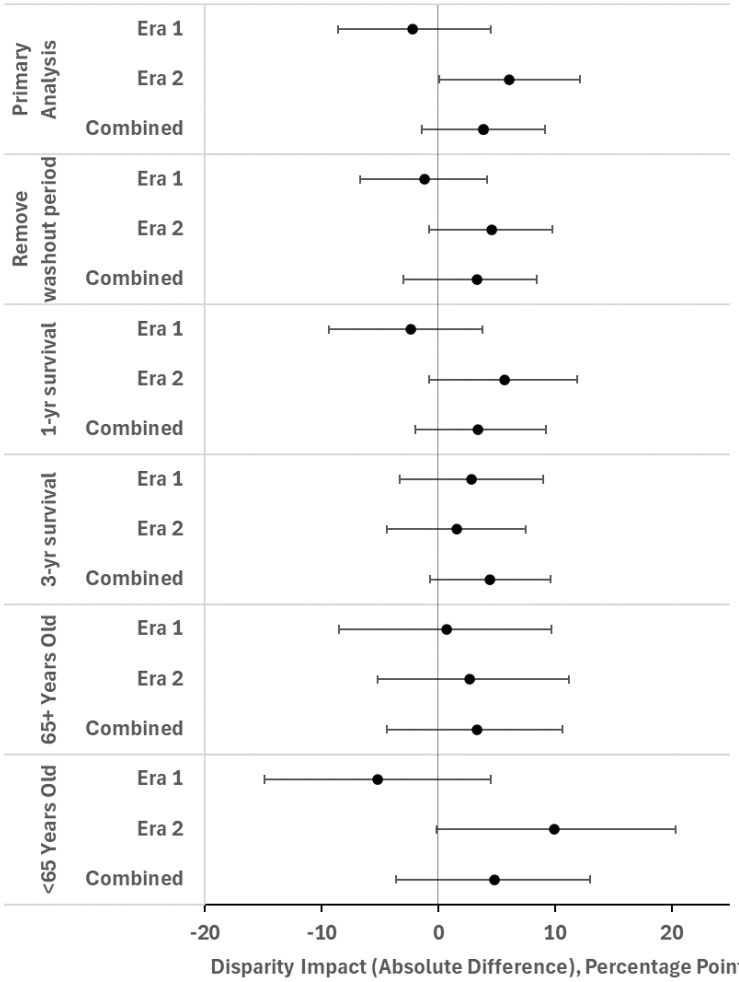

Primary Analysis
Era 1
Era 2
Combined
Remove washout period
Era 1
Era 2
Combined
1-yr survival
Era 1
Era 2
Combined
3-yr survival
Era 1
Era 2
Combined
65+ Years Old
Era 1
Era 2
Combined
<65 Years Old
Era 1
Era 2
Combined
-20
-10
0
10
20
Disparity Impact (Absolute Difference), Percentage Point

Table S1.1: Identification of Distant Cancer in the SEER Registry

Cancer Type	Code
NSCLC	ICD-O-3: 8003-8004, 8012-8015, 8021-8022, 8030-8035, 8046, 8050-8052, 8070-8076, 8078, 8082-8084, 8090, 8094, 8120, 8123, 8140-8141, 8143-8145, 8147, 8190, 8200-8201, 8211, 8240-8241, 8243-8246, 8249- 8255, 8260, 8290, 8310, 8320, 8323, 8333, 8401, 8430, 8440, 8470-8471, 8480-8481, 8490, 8503, 8507, 8525, 8550, 8560, 8562, 8570-8572, 8574-8576 AND Primary Site: C34.0-C34.3, C34.8, C34.9
Melanoma	ICD-O-3: 8720-8780, 8790 Primary Site: C44.0- C44.9
Bladder	Site code ICD-O-3: Urinary Bladder
Uterine	Primary site C54.0-C54.3, C54.8, C54.9, C55.9, C58.9
Head and Neck	Site code ICD-O-3: Lip, Tongue, Floor of Mouth, Gum and Other Mouth, Nasopharynx, Hypopharynx, Other Oral Cavity and Pharynx, Larynx
Liver	Primary site: C22.0 Liver

Table S1.2: Key Innovations in Advanced NSCLC between 2008 and 2015

Approval Year	Agents approved by FDA	Eligible Population
2010	**April:** Erlotinib – First-line maintenance	Patients with Non-squamous NSCLC (~70% of NSCLC patients) and epidermal growth factor receptor (EGFR) positive (~24% of patients)[1]
2013	**May:** Erlotinib—First-line treatment	All NSCLC patients; EGFR positive
	July: Afatinib – First-line treatment	Patients with Non-squamous NSCLC and EGFR positive
2015	**March/September:** Nivolumab –Second-line treatment	Programmed death-ligand 1 (PD-L1)-positive (~61% of patients)[2]
	October: Pembrolizumab – Second-line treatment	Programmed death-ligand 1 (PD-L1)-positive (~61% of patients)[2]
	November: Osimertinib – Second-line treatment	EGFR T790M mutation (~71% of EGFR positive patients)[3]

NSCLC, Non-small cell lung cancer

We excluded all targeted therapies with eligible populations <5%. The post-approval eras are: "Innovation era 1"— the era after the approval of EGFR tyrosine kinase inhibitor (TKI) for first line maintenance (2010-2012) and "Innovation era 2" – the era after the approval of EGFR TKI for first-line treatment and the introduction of 2nd line anti-PD-1 immunotherapy (2013-2016)

Table S1.3: Key Innovations in Advanced Melanoma between 2008 and 2015

Approval Year	Agents approved by FDA	Eligible Population
2011	**March:** Ipilimumab – First-line treatment	All patients
	August: Vemurafenib – First-line treatment	Patients with BRAF V600E mutation (~50% of patients have BRAF mutations, and over 90% of those are V600E mutations)[4]
2013	**May:** Trametinib and Dabrafenib – First-line treatment	Patients with BRAF V600E or V600K mutation (~50% of patients have BRAF mutations; over 90% of those are V600E mutations and 5% V600K)[4]
2014	**January:** Trametinib + Dabrafenib combination (BRAF/MEK inhibitor combination)– First-line treatment	Patients with BRAF V600E or V600K mutation (~50% of patients have BRAF mutations; over 90% of those are V600E mutations and 5% V600K)[4]
	September: Pembrolizumab – Second-line treatment	All patients
	December: Nivolumab – Second-line treatment	All patients
2015	**October:** Nivolumab + ipilimumab combination – First-line treatment	~50% patients without BRAF mutations[4]
	December: Pembrolizumab + ipilimumab combination – First-line treatment	All patients
	December: Pembrolizumab – First-line treatment	All patients
2016	**January: Nivolumab + ipilimumab Combination – First-line treatment**	All patients

The post-approval eras are : "Innovation era 1" – the era after the first approval of immune checkpoint inhibitor (anti-CTLA-4 antibody ipilimumab) and targeted therapy for first-line treatment (2011-2013) and "Innovation era 2" –the era combination BRAF/MEK inhibitors and anti-PD-1 immunotherapies (Pembrolizumab and Nivolumab) were introduced (2014-2016)

Table S1.4: Pre-innovation period parallel trend testing

Parallel trends in 2-year overall survival between controls and intervention groups were assessed in the "pre-innovation era" using linear probability regression models. We estimated interaction terms between year indicators and cancer intervention group (vs. controls), controlling for all covariates that were included in the main analysis. This test was repeated within income subgroups.

Model	**Pre-innovation period Interaction term**	**Coefficient (95%CI)**	**P-value**
NSCLC **All**	Intervention*year_2008	0.008 (-0.01 to 0.02)	0.27
NSCLC **Lowest income (<$60K)**	Intervention*year_2008	-0.015 (-0.04 to 0.01)	0.21
NSCLC **Highest income ($75K+)**	Intervention*year_2008	0.015 (-0.01 to 0.04)	0.25
Melanoma **All**	Intervention*year_2008 Intervention*year_2009	-0.03 (-0.07 to 0.01) 0.02 (-0.02 to 0.06)	0.20 0.28
Melanoma **Lowest income (<$60K)**	Intervention*year_2008 Intervention*year_2009	-0.05 (-0.12 to 0.02) -0.06 (-0.001 to 0.13)	0.17 0.07
Melanoma **Highest income ($75K+)**	Intervention*year_2008 Intervention*year_2009	-0.03 (-0.1 to 0.04) -0.009 (-0.08 to 0.06)	0.37 0.79

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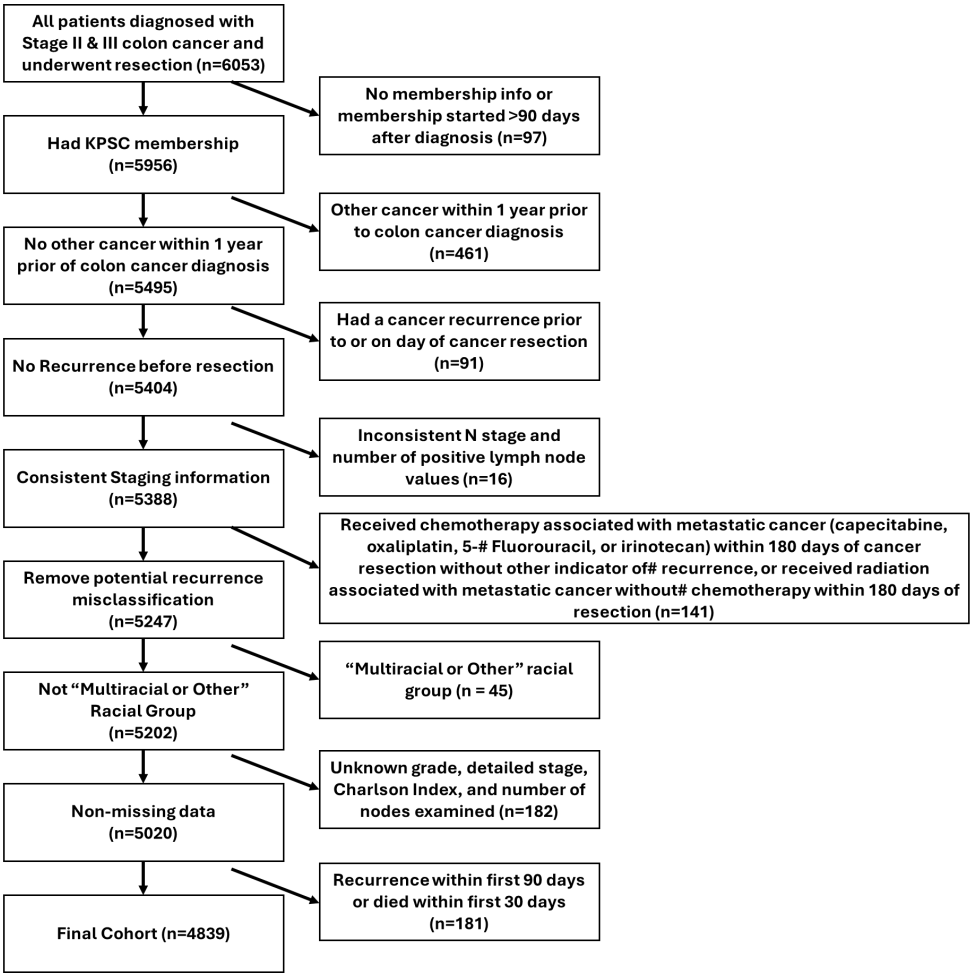
2. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. Apr 09 2016;387(10027):1540-1550. doi:10.1016/S0140-6736(15)01281-7
3. Pereira I, Gaspar C, Pina M, Azevedo I, Rodrigues A. Real-World T790M Mutation Frequency and Impact of Rebiopsy in Patients With EGFR-Mutated Advanced Non-Small Cell Lung Cancer. *Cureus*. Dec 17 2020;12(12):e12128. doi:10.7759/cureus.12128
4. Ascierto PA, Kirkwood JM, Grob JJ, et al. The role of BRAF V600 mutation in melanoma. *J Transl Med*. Jul 09 2012;10:85. doi:10.1186/1479-5876-10-85

APPENDIX FOR CHAPTER 3

Chapter 3 Appendix Table of Contents

Figure S2.1: Inclusion and Exclusion Criteria



Note: We excluded patients with recurrence within the first 90 days after resection because their resection may be incomplete, and they would not be eligible for adjuvant treatment. Deaths within 30 days of resection are likely due to surgical complications or comorbidities and are also excluded.

Appendix S2.1 Approach to ascertaining colon cancer recurrence from electronic health records.

Recorded recurrence was identified in our dataset using diagnosis codes and health care utilization patterns associated with metastatic disease deemed valid in previous studies.[1,2]

Patients were considered to have a colon cancer recurrence if they had any of the following:

1) A prescription for any of the adjuvant colon cancer drugs (fluorouracil, oxaliplatin, capecitabine) more than 90 days after the end of adjuvant therapy;

2) A prescription for any of the metastatic CRC drugs (irinotecan, cetixumab, panitumumab, bevacizumab, aflibercept, ziv-aflibercept, regorafenib, trifluridine, ramcirumab, nivolumab, pembrolizumab) anytime;

3) A prescription for any anti-cancer therapy associated with a metastatic ICD diagnosis code (ICD9: 197, 198, ICD10: C78, C79) anytime;

4) Received radiation therapy more than 90 days after the end of adjuvant therapy;

5) A primary colon cancer surgery procedure ≥ 225 days (7.5months) after KPSC Cancer Registry surgery date;

6) A metastatic surgery procedure;

7) Any imaging performed associated with a metastatic diagnosis, defined by having any imaging impression text in the exam summary from the radiologist that mentioned potential recurrence or evidence of metastatic disease and at least one occurrence of a metastatic cancer diagnosis code (ICD9: 197, 198, ICD10: C78, C79) within 30 days of the imaging date in the patients' history or encounter records; or

8) A hospice referral with a metastatic ICD diagnosis code.

Appendix S2.2 Estimation and calibration of the transition parameters

1. Transition Rate from the recorded recurrence (Rr) state to Death

Patient-specific transition rates from the Rr state to death were estimated by fitting a parametric survival model on the observed data among the subset of patients who developed a recorded recurrence. We examined three parametric survival distributions: exponential, Weibull, and Gompertz, and the Gompertz distribution was selected as the most appropriate distribution based on the lowest Akaike information criterion (AIC) and visual inspection of model fit.[3] The covariates included in the model are age, sex, detailed stage (IIA, IIB, IIIA, IIIB, IIIC), race and ethnicity, Charlson Index, tumor grade, tumor sidedness, smoking status, marital status, primary insurance (commercial, Medicare, other), number of nodes examined and positive node ratio, perineural invasion, bowel perforation or obstruction, distance from home to closest medical center providing oncology care (in miles), and the neighborhood deprivation index from the American Community Survey.

2. Transition Rate from the non-recorded recurrence (Nr) state to the recorded recurrence (Rr) state

We performed a detailed chart review in a sample of 324 patients to obtain the occurrences and timing of true recurrences. Among these patients, 150 experienced a recurrence. Among the patients who had a recurrence, 51 were NHW, 43 were Hispanic, 47 were Black/Africa Americans, and 9 were API. We then fitted a parametric survival model in this data subset to estimate the time from the true (chart review) recurrence to the recurrence recorded in the electronic health record. This is the patient-specific transition rates from Nr to Rr. We examined three parametric survival distributions: exponential, Weibull, and Gompertz, and the

exponential distribution was selected as the most appropriate distribution based on the lowest Akaike information criterion (AIC) and visual inspection of model fit.[3] The covariates included in the model are age, sex, stage (II vs. III), race and ethnicity, Charlson Index (>2 or ≤2), and census level median household income (<=$60,000 vs. >$60,000).

3. Transition Rate from the Non-recorded recurrence (Nr) state to Death

We assumed that each patient's rate of dying in each cycle from the Nr state was similar to their rate of dying with a recorded recurrence but without treatment for the metastatic disease. We assumed that patients in the Nr state would not receive any antitumor therapy for their metastatic disease (otherwise their recurrence would have been recorded). To estimate this transition, we first estimated the rate of dying with a recorded recurrence from the fitted parametric survival model (see above) at quarter 1 for each patient. We then divided this rate by the Hazard Ratio of death with antitumor therapy for metastatic disease (Table 1) to obtain the rate of dying without treatment. We assumed the rate of dying from non-recorded recurrence would remain at this rate over time since patients would not be treated for recurrence.

4. Transition Rate from the Non-progression (Np) state to Death

Rates of death from Np were specific to age, sex, and race and ethnicity. To estimate this transition rate at each cycle, we first estimated the US mortality rate (age, sex, and race and ethnicity-specific) for each patient using the US life table from 2019.[4] We then multiplied that by the California to US race-specific mortality rate ratios to obtain the California-specific rates. The mortality rate ratio was calculated by dividing the total deaths in California by the total deaths in the US in 2019 in each racial/ethnic group. These estimates were obtained via the KFF

website based on data from the Centers for Disease Control and Prevention.[5] Finally, we multiplied the product by the non-colorectal cancer rate ratio in California, calculated as follows:

$$Non-colorectal\ cancer\ rate\ ratio = \frac{1 - \frac{California\ colorectal\ cancer\ mortality}{California\ mortality}}{1 - colorectal\ cancer\ prevalence\ in\ California}$$

The race and ethnicity-specific California colorectal cancer mortality and California mortality were both 2016-2020 estimates. The prevalences of colorectal cancer were race and ethnicity specific 5-year prevalence as of January 1st, 2020. These estimates were obtained from the US Cancer Statistics Data Visualization Tool.[6]

5. **Transition Rate from the Non-progression (Np) state to the Non-recorded recurrence (Nr) state**

Transition rates from Np to Nr could not be directly estimated from our data because Np and Nr were unobserved. Instead, we estimated the patient-specific transition rates from Np to Nr with and without adjuvant treatment by calibrating the model to match a set of clinically relevant target outcomes. To reduce the number of parameters that would need to be calibrated, we assumed that the transition rates from Np to Nr are equivalent to the rates of recorded recurrence observed in the dataset, scaled by an overall multiplier m as well as patient characteristics-specific multipliers:

$$\begin{aligned}&\text{Rate of Transition from Np to Nr}\\&= \mathrm{m} \times \mathrm{m}_{\mathrm{female}} \times \mathrm{m}_{\mathrm{stage3}} \times \mathrm{m}_{\mathrm{age50}} \times \mathrm{m}_{\mathrm{age5060}} \times \mathrm{m}_{\mathrm{age7080}} \times\\&\quad \mathrm{m}_{\mathrm{age80}} \times \mathrm{m}_{\mathrm{Black}} \times \mathrm{m}_{\mathrm{Hisp}} \times \mathrm{m}_{\mathrm{API}} \times \mathrm{m}_{\mathrm{Charlson}} \times \mathrm{m}_{\mathrm{Income}} \times \text{rate of Rr}\end{aligned}$$

For each of the covariates that was included in the estimation of the transition from Nr to Rr, we included a multiplier to adjust for their transition from Np to Nr. This resulted in a total of 12 unknown multipliers that needed to be estimated via calibration.

Calibration to estimate the unknown parameters

We used a calibration process to estimate the values of the 12 unknown multipliers that would allow us to estimate the transition rates from Np to Nr. We first defined a clinically plausible range for each of our unknown parameters and selected a set of 65 observable outcomes observed from our data to serve as calibration targets. They were Kaplan-Meier estimates of the overall disease-free survival (yearly, from year 1 to 10), disease-free survival among NHW patients (yearly, from year 1 to 10), disease-free survival among Black patients (yearly, from year 1 to 10), disease-free survival among Hispanic patients (yearly, from year 1 to 10), disease-free survival among API (yearly, from year 1 to 10), overall survival (yearly, from year 1 to 10), and the proportion of patients experiencing death without a recurrence (yearly, from year 1 to 5).

We then applied a Bayesian calibration approach using the incremental mixture importance sampling (IMIS) algorithm to identify the set of parameter values that maximized the fit between model outcomes and these calibration targets.[8,9] The prior distributions for the unknown parameters were specified as uniform distributions, with prespecified ranges shown in table below. We assumed that the calibration targets were normally distributed and computed an aggregated likelihood measure by adding the log-likelihoods across all targets.

We sampled 1000 input sets from the posterior distribution and obtained the 95% credible intervals for the parameters for the probability sensitivity analysis. The best-fitting parameter set with the highest posterior probability (i.e., the maximum-a-posteriori) was used as the base case of our deterministic analysis (see table below).

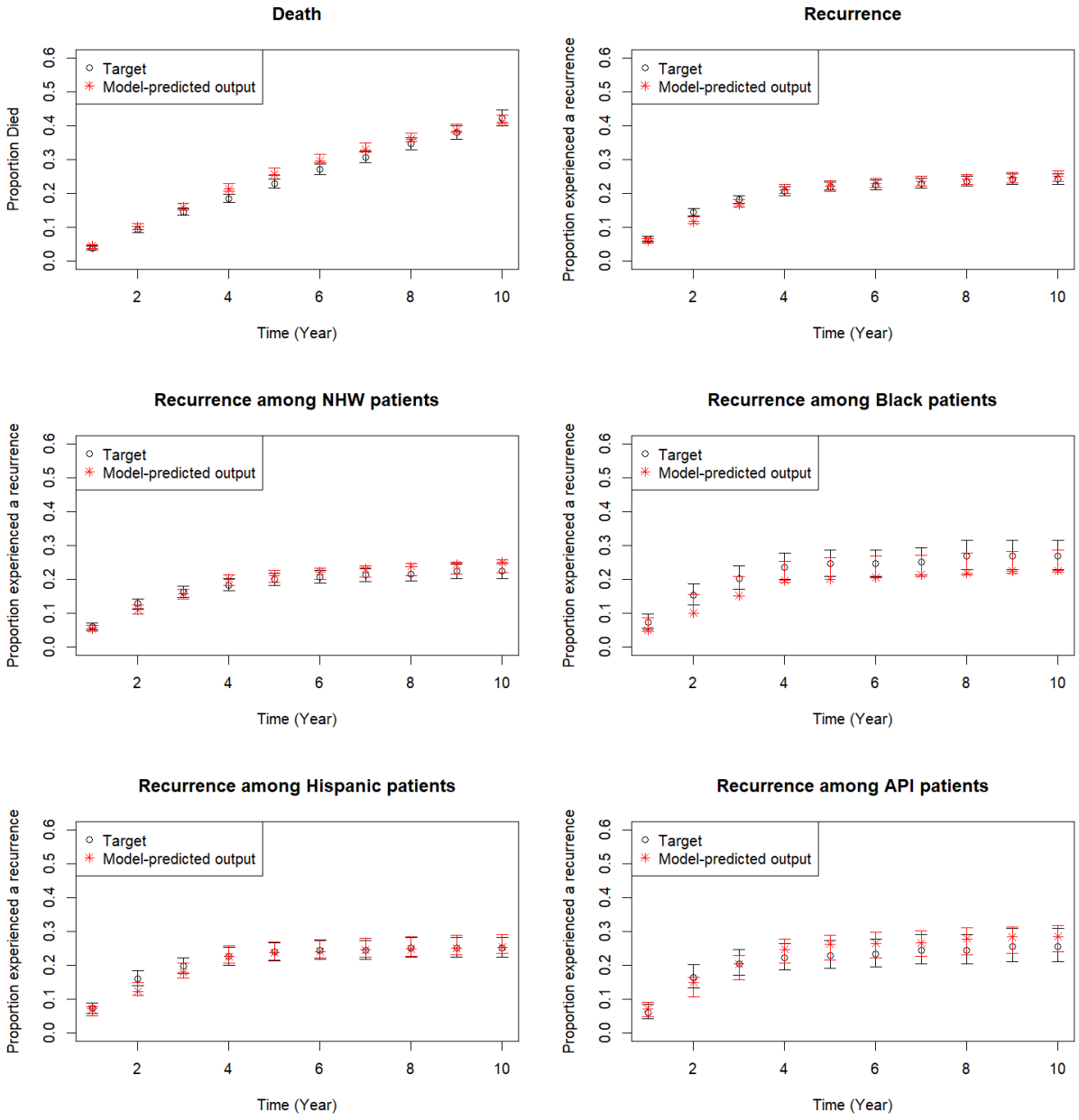
List of calibrated parameters, their prespecified prior ranges, posterior mean and distribution, and best-fitting values

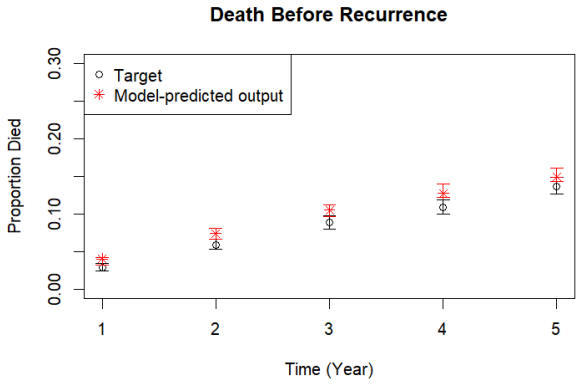
Parameter	Description	Prior Ranges	Posterior Mean	Best-fitting value	95% credible intervals
m	Overall Multiplier	0.9-1.5	0.94	0.94	0.93 to 0.96
m_female	Multiplier for female	0.5-1.2	0.64	0.65	0.59 to 0.65
m_stage3	Multiplier for patients with stage 3 cancer	1.0-2.0	1.07	1.08	1.01 to 1.08
m_age50	Multiplier for patients <50 years old	0.9-2.0	1.35	1.35	1.29 to 1.41
m_age5060	Multiplier for patients 50-59 years old	0.5-2.0	0.83	0.87	0.62 to 0.87
m_age7080	Multiplier for patients 70-79 years old	0.9-2.0	1.30	1.30	1.28 to 1.33
m_age80	Multiplier for patients ≥80 years old	1.8-5.0	2.43	2.45	2.31 to 2.45
m_Black	Multiplier for Black patients	0.9-2.0	1.03	1.02	1.02 to 1.16
m_Hisp	Multiplier for Hispanic patients	0.9-2.0	1.00	1.00	0.97 to 1.06
m_API	Multiplier for API patients	0.9-2.0	0.99	1.00	0.93 to 1
m_Charlson	Multiplier for patients with Charlson score ≥2	0.7-1.5	0.95	0.96	0.9 to 0.96
m_income	Multiplier for census level median household income >$60,000	1.0-2.0	1.66	1.64	1.64 to 1.81

Model Validation

We examined how well the final calibrated model fit the observed targets by visually inspecting the predicted outputs vs. the 65 calibration targets. (see figures below). We drew 1000 calibrated parameter sets from their joint posterior distribution, and then propagated the uncertainty of the calibrated parameters by generating the model-predicted outcomes for each of the parameter sets. We quantified the uncertainty around the model-predicted output as 95% posterior predicted intervals.

eAppendix2_figure1. Comparing model-predicted outputs and observed overall deaths, recorded recurrence, recorded recurrence by race and ethnicity, and deaths before recorded recurrence, from years 1 to 10.





Rate of Rr

To estimate the rates of Rr, we fitted three parametric survival models to the cohort data for time to recorded recurrence since resection. The first model was fitted with data from the first 4 years after primary resection among patients who received adjuvant treatment. The second was fitted with data from the first 4 years after primary resection among patients who did not receive adjuvant treatment. The third was fitted with data from year 5 onwards among all patients. The 5-year time cut off for model fitting was chosen because previous studies have shown that 95% of the cancer recurrences happen within the first 4 years after resection.[7] After this time, rates of recurrence are relatively low. We modeled the rates of recurrence separately for those who received adjuvant treatment and those who did not within the first 4 years. From the 5th year onwards, we assumed that the rates of recurrence would no longer differ by adjuvant treatment receipt status.

For each parametric survival model, we examined three distributions: exponential, Weibull, and Gompertz. The exponential distribution was selected for all three models as the most appropriate distribution based on the lowest Akaike information criterion (AIC) and visual inspection of model fit.[3] The covariates included in the models were age, sex, detailed stage (IIA, IIB, IIIA,

IIIB, IIIC), race and ethnicity, Charlson Index, tumor grade, tumor sidedness, smoking status, marital status, primary insurance (commercial, Medicare, other), number of nodes examined and positive node ratio, perineural invasion, bowel perforation or obstruction, distance from home to closest medical center providing oncology care (in miles), neighborhood deprivation index from the American Community Survey.

Converting transition rates into probabilities

All transition rates were estimated quarterly and then converted to annual probabilities using matrix exponential. We used the *expm* function in R to compute the matrix exponential. Specifying the transitions as rates allows patients to make more than one transition within a single cycle, which more closely reflects actual disease progression.[10] It also avoids bias in the discretization of continuous time in state transition models, leads to a model with fewer parameters, and reduces computational burden by allowing longer cycle lengths.[10] We compared the outcome estimates using a quarterly cycle vs. an annual cycle and found similar results. We therefore opted to use an annual cycle length to reduce computational burden.

Appendix S2.3 Estimation of treatment effects

Hazard ratio (HR) estimates for adjuvant therapy

We assumed that patients who received adjuvant therapy received 12 cycles (6-month course) of fluoropyrimidine with oxaliplatin (FOLFOX), which reflects the NCCN guidelines for stage II and III colon cancer patients at high risk of recurrence. We did not estimate the treatment effect of FOLFOX on cancer recurrence directly from our data due to confounding by indication in the real-world data. Instead, we used published estimates to minimize bias from confounding. Specifically, we used disease-free survival estimates from a model-based meta-analysis published in 2022 that extracted data from 20 studies (42 trial arms in total).[11] This meta-analysis reported median disease-free survival rates of 86.3 months (95%CI 67.6, 110.6) and 40.8 months (95% CI: 23.7, 69.6) months in the adjuvant chemotherapy group and the surgery-only group, respectively. Using this information, we estimated a HR of recurrence of 0.47 (40.8/86.3) with adjuvant chemotherapy, with a 95%CI of 0.19-0.76.

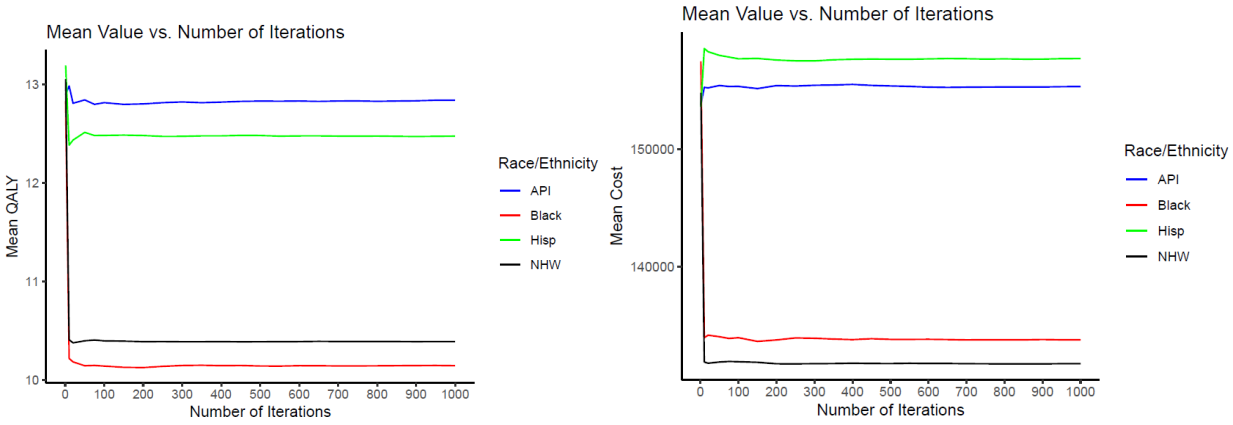
HR estimates for the treatment of metastatic disease

We used published median survival estimates to calculate the treatment effects of antitumor therapy for metastatic disease. Specifically, we obtained the median survival estimates of patients receiving any antitumor therapy vs. usual care from published studies.[12,13] The reported estimates of the median disease-free survival rates were 17.3 months (95%CI 16.5, 18.5) for the treated group and 6 to 12 months for the group with supportive care only (we used the reported range as 95% CI and assumed a median of 9 months). Using this information, we estimated a HR of death of 0.52 (95%CI 0.34-0.70) with any antitumor therapy.

Appendix S2.4 Convergence test to determine number of simulations

To determine how many simulations are sufficient to account for the 1st order stochastic uncertainty in the microsimulation model, we evaluated the convergence of the main outcome estimators (mean QALYs and Costs) with increasing number of simulations. We considered a change in outcome of <0.5% as "convergence". The goal of this converge test was to identify a simulation count above which the percent change in outcomes was lower than this threshold. We observed that when the simulation iteration count exceeds 50, the changes in both outcomes for all racial and ethnic groups were <0.5%. The final simulation iteration count to account for stochastic uncertainty in our study was selected to be 100.

eAppendix4_figure 1. Values of mean QALY and costs by racial and ethnic group by number of simulations.



eAppendix4_figure 2. Changes of mean QALY and costs by racial and ethnic group by number of simulations.

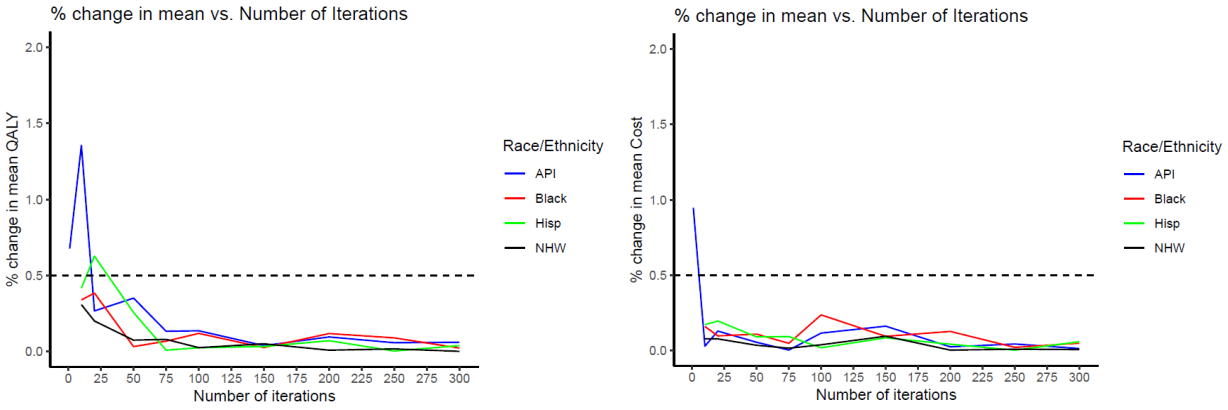


Table S2.1 Patient Characteristics

	Black (N=644)	NHW (N=2372)	Hispanic (N=1294)	API (N=529)	Overall (N=4839)
Age at diagnosis					
Mean (SD)	65.9 (12.7)	69.2 (12.8)	61.7 (14.3)	64.2 (13.1)	66.2 (13.6)
Median [Min, Max]	66.0 [27.0, 90.0]	71.0 [25.0, 90.0]	62.0 [18.0, 90.0]	65.0 [25.0, 90.0]	67.0 [18.0, 90.0]
Age Categories					
<50	60 (9.3%)	166 (7.0%)	270 (20.9%)	70 (13.2%)	566 (11.7%)
50-59	149 (23.1%)	381 (16.1%)	314 (24.3%)	121 (22.9%)	965 (19.9%)
60-69	171 (26.6%)	573 (24.2%)	296 (22.9%)	148 (28.0%)	1188 (24.6%)
70-79	163 (25.3%)	690 (29.1%)	253 (19.6%)	122 (23.1%)	1228 (25.4%)
80+	101 (15.7%)	562 (23.7%)	161 (12.4%)	68 (12.9%)	892 (18.4%)
Female	364 (56.5%)	1203 (50.7%)	649 (50.2%)	265 (50.1%)	2481 (51.3%)
Stage					
2A	291 (45.2%)	1140 (48.1%)	581 (44.9%)	226 (42.7%)	2238 (46.2%)
2B	20 (3.1%)	100 (4.2%)	43 (3.3%)	17 (3.2%)	180 (3.7%)
3A	45 (7.0%)	159 (6.7%)	94 (7.3%)	43 (8.1%)	341 (7.0%)
3B	210 (32.6%)	738 (31.1%)	441 (34.1%)	174 (32.9%)	1563 (32.3%)
3C	78 (12.1%)	235 (9.9%)	135 (10.4%)	69 (13.0%)	517 (10.7%)
Tumor Grade					
Well-differentiated	39 (6.1%)	208 (8.8%)	101 (7.8%)	34 (6.4%)	382 (7.9%)
Moderately differentiated	513 (79.7%)	1605 (67.7%)	967 (74.7%)	396 (74.9%)	3481 (71.9%)
Poorly differentiated	89 (13.8%)	531 (22.4%)	220 (17.0%)	96 (18.1%)	936 (19.3%)
Undifferentiated	3 (0.5%)	28 (1.2%)	6 (0.5%)	3 (0.6%)	40 (0.8%)
Tumor Sidedness					
Left Colon	176 (27.3%)	721 (30.4%)	464 (35.9%)	244 (46.1%)	1605 (33.2%)
Right Colon	422 (65.5%)	1501 (63.3%)	761 (58.8%)	256 (48.4%)	2940 (60.8%)
Unspecified	46 (7.1%)	150 (6.3%)	69 (5.3%)	29 (5.5%)	294 (6.1%)
Bowel Perforation or Obstruction	355 (55.1%)	1358 (57.3%)	910 (70.3%)	340 (64.3%)	2963 (61.2%)
Primary Insurance					
Commercial	313 (48.6%)	798 (33.6%)	677 (52.3%)	260 (49.1%)	2048 (42.3%)
Medicare	302 (46.9%)	1430 (60.3%)	513 (39.6%)	231 (43.7%)	2476 (51.2%)

Other	29 (4.5%)	144 (6.1%)	104 (8.0%)	38 (7.2%)	315 (6.5%)
Married, common law, registered domestic partner					
No	332 (51.6%)	1025 (43.2%)	445 (34.4%)	172 (32.5%)	1974 (40.8%)
Yes	303 (47.0%)	1300 (54.8%)	825 (63.8%)	355 (67.1%)	2783 (57.5%)
Missing	9 (1.4%)	47 (2.0%)	24 (1.9%)	2 (0.4%)	82 (1.7%)
Charlson Comorbidity Index Score within 12 months prior to diagnosis					
≤1	391 (60.7%)	1473 (62.1%)	871 (67.3%)	371 (70.1%)	3106 (64.2%)
>1	253 (39.3%)	899 (37.9%)	423 (32.7%)	158 (29.9%)	1733 (35.8%)
Smoking Status					
Never/ Passive/ Quit	577 (89.6%)	2156 (90.9%)	1208 (93.4%)	480 (90.7%)	4421 (91.4%)
Current	60 (9.3%)	201 (8.5%)	76 (5.9%)	40 (7.6%)	377 (7.8%)
Missing/unknown	7 (1.1%)	15 (0.6%)	10 (0.8%)	9 (1.7%)	41 (0.8%)
Census area level: % with college education or higher					
<40%	168 (26.1%)	174 (7.3%)	404 (31.2%)	44 (8.3%)	790 (16.3%)
40-60%	201 (31.2%)	613 (25.8%)	448 (34.6%)	157 (29.7%)	1419 (29.3%)
60-80%	175 (27.2%)	967 (40.8%)	296 (22.9%)	200 (37.8%)	1638 (33.9%)
>80%	74 (11.5%)	532 (22.4%)	79 (6.1%)	111 (21.0%)	796 (16.4%)
Missing	26 (4.0%)	86 (3.6%)	67 (5.2%)	17 (3.2%)	196 (4.1%)
Census area level: Median household income >$60,000	341 (53.0%)	1783 (75.2%)	685 (52.9%)	404 (76.4%)	3213 (66.4%)

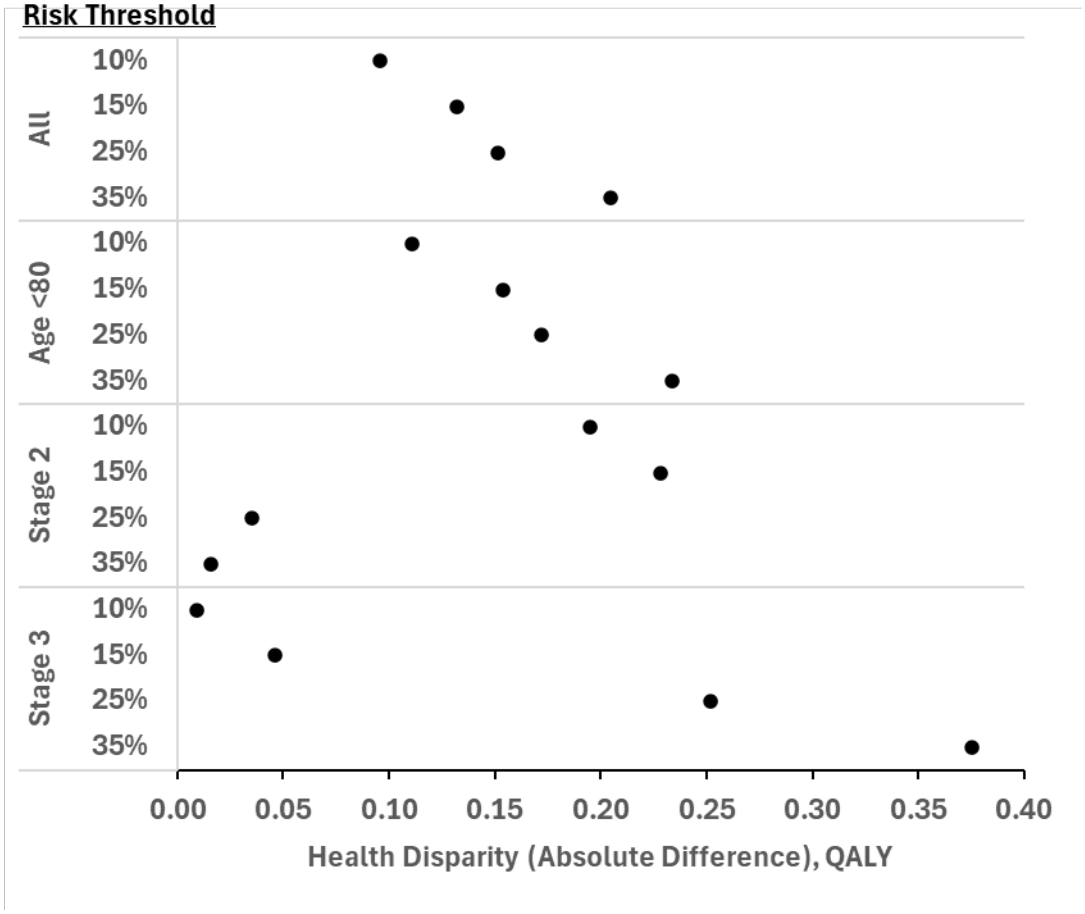
Black, Black or African American; NHW, non-Hispanic White; API, Asian, Hawaiian, or Pacific Islander; SD, standard deviation

Table S2.2 Treatment Receipt and Health, by Subgroup

				Incremental		
	Current Practice	"Race-sensitive" Risk Score[a]	"Race-neutral" Risk Score[a]	"Race-sensitive" Risk Score[a] vs. current practice	"Race-neutral" Risk Score[a] vs. current practice	"Race-neutral" Risk Score vs. "Race-sensitive" Risk Score[a]
			Proportion Receiving Adjuvant Chemotherapy			
Weighted Average	50.3%	68.2%	68.0%	17.9%	17.7%	-0.2%
Black	49.1%	78.9%	65.7%	29.8%	16.6%	-13.2%
NHW	46.3%	71.4%	71.4%	25.1%	25.1%	0%
Hispanic	56.3%	60.9%	63.4%	4.6%	7.2%	2.6%
API	54.6%	58.4%	66.5%	3.8%	11.9%	8.1%
			Quality-adjusted Life Years			
Weighted Average	8.67	8.72	8.72	0.048	0.049	0.001
Black	8.13	8.29	8.22	0.16	0.090	-0.07
NHW	7.99	8.07	8.07	0.080	0.080	0
Hispanic	9.78	9.74	9.76	-0.033	-0.021	0.012
API	9.68	9.64	9.71	-0.036	0.028	0.064

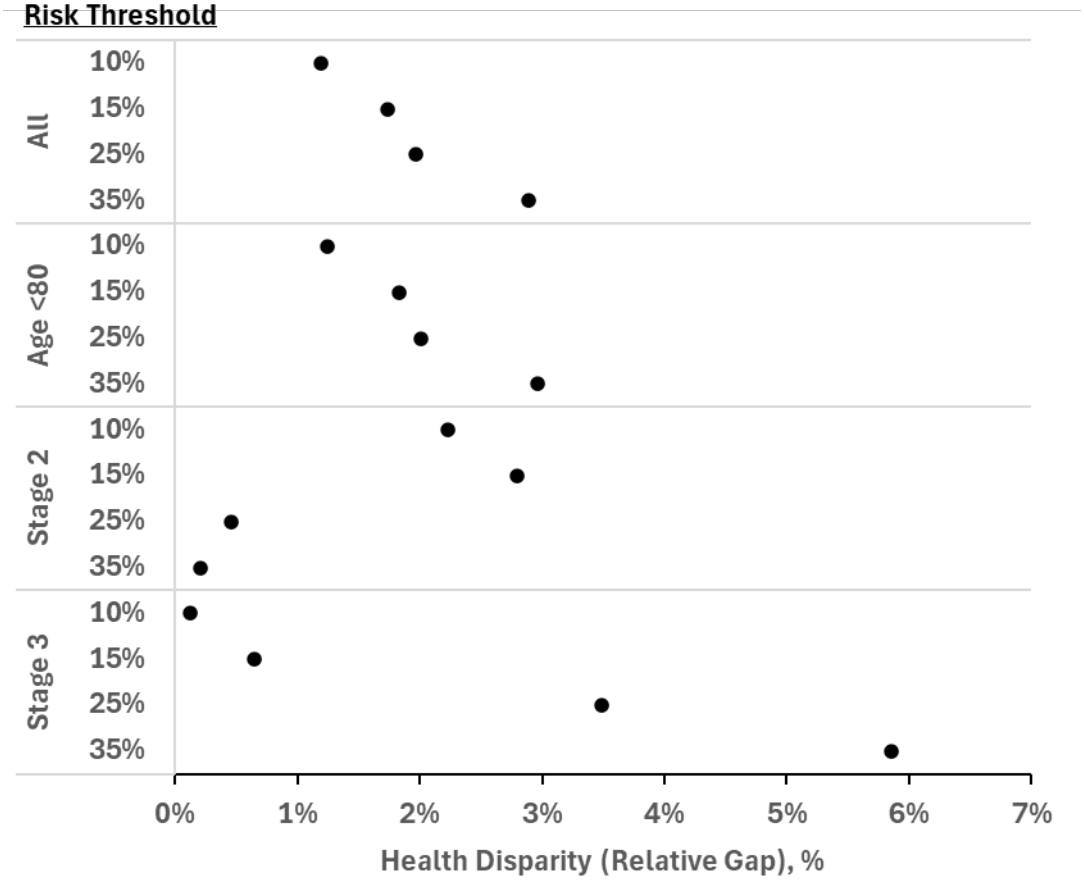
Black, Black or African American; NHW, non-Hispanic White; API, Asian, Hawaiian, or Pacific Islander
[a]Applying a 15% risk threshold cutoff

Figure S2.2. The health disparity impact (in absolute terms) of using a "race-neutral" risk score for treatment decisions compared to a "race-sensitive" risk score by subgroup and at varying risk thresholds.



Note: Only 6% and 1.5% of stage II patients have risks above 25% and 35% risk thresholds, respectively. As a result, very few stage II patients would receive adjuvant treatment at these thresholds and the impact of including or omitting race in the risk score is minimal. Similarly, more than 99% of stage III patients have risks above 10%, meaning that almost all patients would receive treatment at this threshold. The impact of including or omitting race for treatment decisions at this threshold for stage 3 patients is minimal.

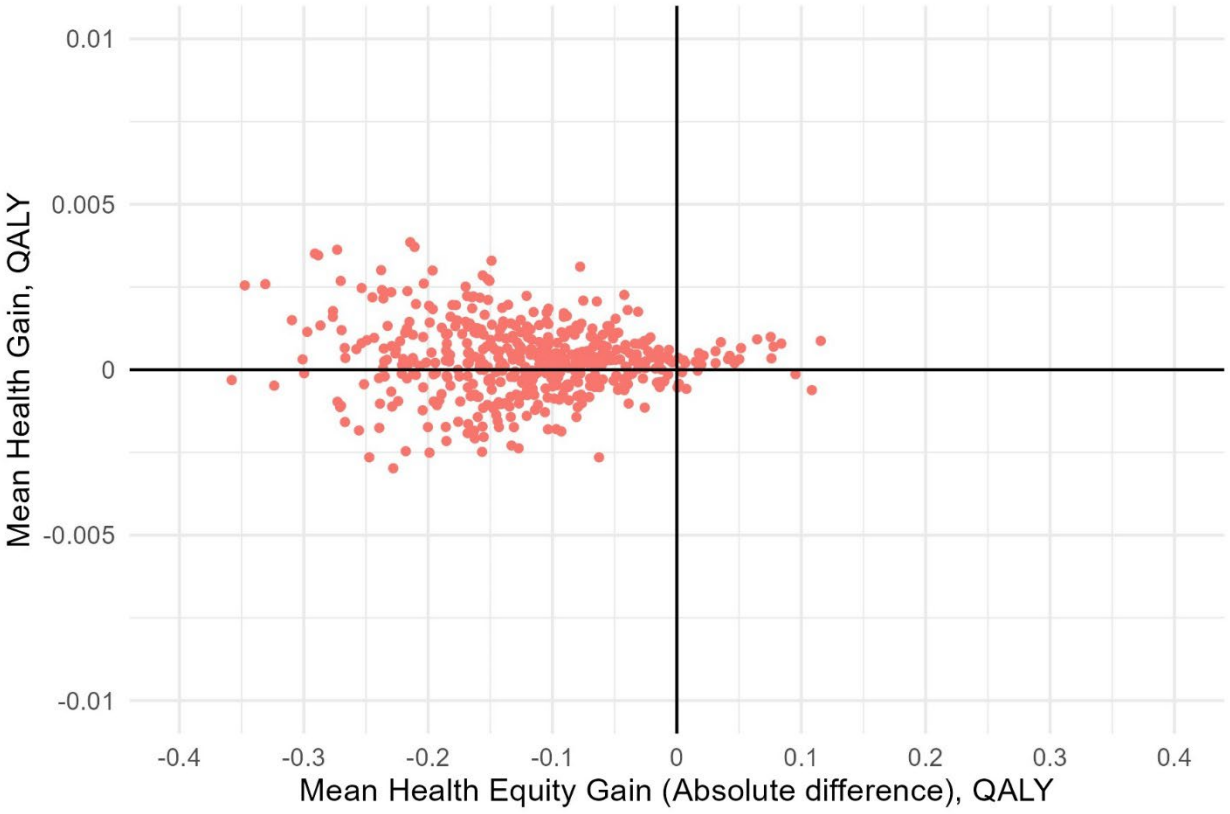
Figure S2.3. The health disparity impact (in relative terms) of using a "race-neutral" risk score for treatment decisions compared to a "race-sensitive" risk score by subgroup and at varying risk thresholds.



Note: Only 6% and 1.5% of stage II patients have risks above 25% and 35% risk thresholds, respectively. As a result, very few stage II patients would receive adjuvant treatment at these thresholds and the impact of including or omitting race in the risk score is minimal. Similarly, more than 99% of stage III patients have risks above 10%, meaning that almost all patients would receive treatment at this threshold. The impact of including or omitting race for treatment decisions at this threshold for stage 3 patients is minimal.

Figure S2.4. Probabilistic sensitivity analysis results shown on an equity impact plane. Overall Mean Health Gain vs. Health Equity Gain for the "race-neutral" risk score-based treatment scenarios, compared to the "race-sensitive" risk score-based treatment scenario.

Each dot represents an iteration from the probabilistic sensitivity analysis. The "race-neutral" risk score reduced health equality (increased health inequality) 94.0% of the 500 iterations. It had minimal effect of mean health gain (health gain was >0 for 64.2% of the 500 iterations).



Appendix S2.5. Health Economics Analysis Plan

This analysis plan provides a detailed description of the pre-planned analyses for this study.

Goal and Overall Design. The goal of this specific aim is to understand the impact of considering race in clinical risk calculators to guide treatment decisions on health outcomes, costs, and racial health disparities, using an existing calculator for colon cancer survival as an example. We will use microsimulation models to assess the disparity impacts of three adjuvant chemotherapy treatment scenarios: 1) based on the existing "race-sensitive" risk calculator, 2) based on a "race-neutral" version of this same calculator (with race turned "off"), and 3) based on current practice.

Data Sources. We will use de-identified linked cancer registry and electronic health record data from an integrated health system, Kaiser Permanente Southern California (KPSC). The linked dataset contains information related to demographics, diagnoses, procedures, drugs, and death.

Study Sample. The study sample will consist of adult patients diagnosed with stage II to III colon cancer between 2008 and 2021 who underwent resection. Last day of follow-up will be July 31st, 2023. We will exclude those diagnosed with appendix cancer, had other primary cancer within 1 year prior to colon cancer diagnosis, had no membership information, died, experienced cancer recurrence prior to resection, or had unknown tumor grade or incompatible nodal stage information.

Candidate Survival Prediction Model. We will use the MD Anderson Cancer Center (MDACC) survival prediction calculator[56] as the candidate model, which included race as a predictor. This calculator was previously validated by Lemini et al. using multi-site data from 2012 and 2013, with an area under the receiver operating characteristic curve (AUC) of 0.644.[81]

Risk Scores.

"Race-sensitive" and "race-neutral" risk scores. We will generate a set of "race-sensitive" colon cancer risk scores for our study cohort by applying the MDACC survival calculator as-is (since race is a predictor in the model), and a set of "race-neutral" risk scores by applying the calculator with the race variable turned off ", i.e., the coefficient for race will be zero for all patients.

Statistical Analysis.

Treatment Scenarios: We will compare the long-term outcome disparity impacts of assigning adjuvant chemotherapy across three different adjuvant treatment scenarios: 1) based on "race-sensitive" risk scores, 2) based on "race-neutral" risk scores, and 3) current practice. We will assume perfect adherence for treatment scenarios 1 and 2. Treatment decisions for the first two scenarios will be operationalized under a threshold objective where treatment will be given to patients above a certain risk threshold. We will use a 15% risk of death threshold for the primary analysis and will investigate other thresholds in a sensitivity analysis: 10%, 25%, 35% and 45%, a range our clinical expert deemed clinically relevant in this setting.

Microsimulation model: We will use a microsimulation model to simulate the sequence of possible events each patient in our cohort may experience after colon cancer resection. We will simulate separately possible events with and without adjuvant treatment. The model will consist of four clinical states: No Progression, Non-recorded recurrence (Nr), Recorded Recurrence (Rr), and Death. The Nr state (a hidden unobserved state) was added to capture recurrence events that may not have been recorded in the EHR because patients did not receive healthcare services for their recurrences. This is an important state to consider as the Nr rates may differ across racial groups. The discrete-time simulation model will have monthly cycles over a 30-year time

horizon, a timeframe our clinical expert considered clinically relevant for colon cancer outcomes. The simulated outcomes of interests are QALYs, and total costs. We will apply a 3% annual discount rate for all costs and QALYs. Adjuvant and metastatic treatment effects, health utilities, and costs and their ranges associated with adjuvant chemotherapy treatment will be obtained from the literature.

Estimating Model Transition Probabilities*:* Patient-specific transition rates will be estimated from the KPSC data whenever possible by fitting parametric survival curves to the data. For the unobserved transitions (e.g. from Np to Nr), we will obtain the transition rates using calibration.

We will not estimate the treatment effect of adjuvant chemotherapy directly in the observed data due to confounding by indication. Instead, we will estimate recurrence rates separately among patients who received adjuvant treatment and those who did not, and then calculated the rates of recurrence for each patient under alternate treatment scenarios (i.e. under adjuvant treatment for those who did not receive it, and under no adjuvant treatment for those who did receive it) using the hazard ratio estimates for adjuvant treatment from published literature. To transform rates to probabilities, we will derive the transition probability matrix using matrix transformation to minimize bias.

Incremental Health Disparity

We will assess changes in QALY distribution across the treatment scenarios using the Absolute Difference and Relative Gap.

Uncertainty Analysis

We will simulate the outcomes from the original population 100 times and take the average of the outcomes. This process allows us to estimate the 1st order stochastic uncertainty in the

realization of individual event and outcome. To determine the impact of uncertainty of model inputs on results, we will probabilistic sensitivity analyses by sampling 500 sets of input parameters from their respective distributions and simulating outcomes.

Sensitivity Analysis

We will examine how the health disparity results vary across different risk threshold cutoffs and in these subgroups: patients diagnosed with stage II cancer, stage III cancer, and those under age 80 at diagnosis.

Table S2.3. CHEERS 2022 Checklist

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Title
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Abstract
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Introduction
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	Appendix
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Results
Setting and location	6	Provide relevant contextual information that may influence findings.	Methods
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Methods
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Methods
Time horizon	9	State the time horizon for the study and why appropriate.	Methods
Discount rate	10	Report the discount rate(s) and reason chosen.	Methods
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Methods
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Methods
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Methods
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Methods
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Methods
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Methods
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Methods and Appendix
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Methods
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Methods
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Methods

Topic	No.	Item	Location where item is reported
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	N/A
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Results and Table
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Results and Table
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Results
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Not reported
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Discussion
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	End of manuscript
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	End of manuscript

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