Original Article

Association between immigrant status and advanced cancer patients' location and quality of death

Ana I. Tergas, MD, MPH [iD] [1,2,3]; Holly G. Prigerson, PhD[3,4]; Megan J. Shen, PhD [iD] [3,4]; Andreea I. Dinicu, MD, MPH [iD] [5];
Alfred I. Neugut, MD, PhD [iD] [5,6,7,8]; Jason D. Wright, MD[6,7,8]; Dawn L. Hershman, MD, MS [iD] [5,6,7,8]; and
Paul K. Maciejewski, PhD[3,4,9]

BACKGROUND: Cancer patients often prefer to die at home, a location associated with better quality of death (QoD). Several studies demonstrate disparities in end-of-life care among immigrant populations in the United States. This study aimed to evaluate how immigrant status affects location and quality of death among patients with advanced cancer in the United States. **METHODS:** Data were derived from Coping with Cancer, a federally funded multi-site prospective study of advanced cancer patients and caregivers. The sample of patients who died during the study period was weighted (N_w = 308) to reduce statistically significant differences between immigrant (N_w = 49) and nonimmigrant (N_w = 259) study participants. Primary outcomes were location of death, death at preferred location, and poor QoD. **RESULTS:** Analyses adjusted for covariates indicated that patients who were immigrants were more likely to die in a hospital than home (adjusted odds ratio [AOR], 3.33; 95% confidence interval [CI], 1.65–6.71) and less likely to die where they preferred (AOR, 0.42; 95% CI, 0.20–0.90). Furthermore, immigrants were more likely to have poor QoD (AOR, 5.47; 95% CI, 2.70–11.08). **CONCLUSIONS:** Immigrants, as compared to nonimmigrants, are more likely to die in hospital settings, less likely to die at their preferred location, and more likely to have poor QoD. *Cancer* 2022;128:3352-3359. © 2022 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

LAY SUMMARY:
• Cancer patients typically prefer to die in their own homes, which is associated with improved quality of death.
• However, disparities in end-of-life care among immigrant populations in the United States remain significant.
• Our study found that immigrants are less likely to die in their preferred locations and more likely to die in hospital settings, resulting in poorer quality of death.

KEYWORDS: caregivers, end of life care, health care disparities, immigration, neoplasms.

INTRODUCTION

In 2018, the United States (US) was home to 44.8 million immigrants.[1] Immigrants face significant obstacles to receipt of optimal medical care, including language barriers, poverty, lack of insurance, and access to health care resources.[2–4] These factors contribute to inequities among these communities. Immigrants are especially vulnerable when it comes to disparities in end-of-life (EoL) care and those with advanced cancer are twice as likely as nonimmigrants to receive aggressive end of life care.[2–7]

Discrepancies in preferences and outcomes are associated with worse EoL care and poor quality of death (QoD).[8–10] Moreover, caregivers of patients who die in hospitals are at higher risk of mental illness.[10,11] Most patients prefer dying in a noninstitutional setting,[12,13] yet many die in an institutional setting. A randomized controlled trial outlining patient preference in EoL care found congruence in preferred location of death with actual place of death to be 37.5% for those who prefer home death versus 62.5% for those who prefer hospital death.[8] Recently, there has been an increase in cancer deaths occurring at home or in hospice settings.[13,14] Nevertheless, inconsistencies between preferred and actual location of death contribute to half of all cancer patients dying in hospitals.[13,15–18] Lack of health care resources, low income, and non-White race are correlated with higher rates of hospital deaths.[19–21] Low income is associated with more aggressive EoL care, as measured by increased rates of hospitalization in the last month of life.[21]

Decreasing intensive care unit (ICU) admissions is vital to addressing disparities in EoL care and minimizing Medicaid costs.[2,22–24] Likewise, understanding EoL care disparities for immigrants is necessary to provide values-consistent EoL

care.[5] Although some studies outline EoL care disparities among immigrants, knowledge about location and quality of death among immigrants with terminal diseases is limited. This study aims to evaluate how immigrant status affects location of death and caregiver reported QoD among patients with advanced cancer in the United States.

MATERIALS AND METHODS
Sample
The sample ($N = 302$) is the same as that of a prior investigation of the impact of immigrant status on aggressive end-of-life care[2] and represents a subset of patients who participated in Coping with Cancer (CwC), a federally funded (CA106370), prospective, multi-institutional cohort study of advanced cancer patients and their caregivers and who died within the study observation period.

CwC participants were recruited between September 2002 and February 2008 from Yale Cancer Center (New Haven, Connecticut), Veterans Affairs (Virginia) Connecticut Healthcare System Comprehensive Cancer Clinics (West Haven, Connecticut), Parkland Hospital (Dallas, Texas), Simmons Comprehensive Cancer Center (Dallas, Texas), Dana-Farber Cancer Institute (Boston, Massachusetts), and New Hampshire Oncology-Hematology (Hookset, New Hampshire). Eligibility criteria included diagnosis of advanced cancer (distant metastases; disease refractory to one or more lines of cytotoxic chemotherapy), a physician-estimated life-expectancy of 6 months or less, adequate stamina to complete a baseline interview, and English or Spanish proficiency. Staff members administered interviews in English or Spanish depending on participant preference. Overall, 611 (92.4%) and 50 (7.6%) patient-participant interviews were conducted in English and Spanish, respectively. We excluded patients who met criteria for serious cognitive impairment as measured by a Short Portable Mental Status Questionnaire score of 6 or greater.[25] Participants received $25 per interview. Review boards of participating institutions approved study procedures; participants provided written informed consent.

Of 939 eligible patients, 661 (70.4%) participated. Reasons for nonparticipation included: "not interested" ($n = 106$), "caregiver refuses" ($n = 32$), and "too upset" ($n = 21$). Participants were more likely than nonparticipants to be Hispanic (78 of 661, 11.8% vs. 17 of 252, 6.7%; $p = .025$) but otherwise did not differ in socio-demographic characteristics. Most participants (384 of 661, 58.1%) died during the study observation period. Patients who died were more likely to be younger,

non-White, unmarried, uninsured, and less educated at study entry (all $p < .05$) than patients who survived the study observation period (277 of 661, 41.9%).

Among the 384 patients who died, 38 (9.9%) were excluded due to missing sociodemographic or post-mortem outcomes data; 39 (10.2%) were excluded because they expressed no preference for the goals of EoL care used to define values-inconsistent aggressive EoL care; and five (1.3%) were excluded because there were too few in the examined group to draw reliable conclusions about differences by race (i.e., three Asians and two Native Americans). Overall, 82 patients (21.4%; 12 immigrants, 64 nonimmigrants, and six missing data on immigrant status) were excluded from the sample for these reasons. Patients excluded from the sample did not differ from those included in the sample with respect to immigrant status, age, sex, race/ ethnicity (within the White, Black, and Latino categories), years of education, and marital status. Patients excluded from the sample due to lack of a preference for goals of EoL care did not differ from those excluded due to missing data alone with respect to these same sociodemographic characteristics. Our final subset of participants consisted of 302 terminally ill cancer patients who died within the study observation period.

Measures
Socio-demographic characteristics
During a baseline interview conducted by trained research staff, patients reported immigrant status, age, sex, race/ ethnicity, education, health insurance status, and marital status. Patients' sites of recruitment were coded to indicate geographic region (Northeast vs. Southwest) and academic medical setting (yes/no [Y/N]).

Preference for EoL care
We asked patients if they preferred: (1) a course of treatment that focused on extending life as much as possible, even if it meant more pain and discomfort, or (2) a plan of care that focused on relieving pain and discomfort as much as possible, even if that meant not living as long. Responses were coded as preferring "life-extending EoL care" or "symptom-directed, comfort EoL care."

Medical care near death
Within 3 weeks of death, the formal or informal caregiver (typically a family member or a friend of the patient) most involved in the patient's informal care during the last week of life provided information in a post-mortem interview (Appendix S1). We obtained additional information on health care received in the last

week of life from the patient's medical chart. Building on prior reports,[26,27] we operationalized patient's receipt of aggressive medical care near death as use of mechanical ventilation, cardiopulmonary resuscitation, feeding tubes, or antibiotics in the last week of life (yes/no). In support of this indicator's construct validity, aggressive care near death was positively associated with patient death in an intensive care unit ($r = 0.38$, $p < .001$) and negatively associated with home hospice utilization near the end of life ($r = -0.34$, $p < .001$).

Patients who indicated a preference for symptom-directed, comfort care in their baseline interview but who received aggressive medical care (as defined above) in the last week of life were coded as receiving, as opposed to not receiving, values-inconsistent aggressive medical care near death (Y/N).

Location of death

We obtained the location of a patient's death either from his/her medical chart or caregiver. During the post-mortem interview, we asked "Do you think that (PLACE OF DEATH) was where (PATIENT) would have most wanted to die?" (Y/N) to assess whether the patient died in the preferred setting.

QoD

In the post-mortem interview, we asked: "Just prior to the death of the patient (e.g., his/her last week; when last seen), how would you rate his/her level of…" "psychological distress?" (0 = none; 10 = extremely upset); "physical distress?" (0 = none; 10 = extremely distressed); "overall QOL in the last week of life/death?" (0 = worst possible; 10 = best possible). Consistent with prior studies,[28,29] ratings for these items were averaged (after reverse coding the psychological and physical distress items) such that greater composite scores represent better QoD on a scale of 0 (worst possible) to 10 (best possible). These QoD items are internally consistent (Cronbach's $\alpha = 0.76$) and represent a single, unidimensional QoD construct.[29] To facilitate analysis and interpretation (e.g., in the use of logistic regression and reporting of an odds ratio between immigrant status and QoD), this continuous QoD measure was dichotomized such that the lower quartile (QoD ≤4; $n = 72$ [24.0%]), as opposed to the upper three qualities (QoD >4; $n = 228$ [76.0%]), was designated poor QoD. Mean (SD) QoD scores in the poor and not poor QoD groups were 2.5 (1.2) and 7.5 (1.6), respectively. The overall distribution of the QoD score within the study sample is presented in the accompanying Appendix S2.

Statistical analysis

As in our prior report,[2] to isolate effects of immigrant status on study outcomes, we employed propensity score weights and covariate adjustment to minimize sociodemographic differences and control for potential effects of those differences between immigrant and nonimmigrant advanced cancer patient groups. Propensity score weighting is a method of matching samples to facilitate causal inference for between-group effects.[30] As in our prior report,[2] we employed stabilized inverse probability propensity weights[31] to match immigrant and nonimmigrant groups with respect to age category, gender, race/ethnicity, education level, health insurance status, marital status, recruitment site geographic region, and academic setting. An analysis of covariate imbalance between immigrant and nonimmigrant groups in the stabilized inverse probability propensity weighted sample, in accordance with standard practices[32–34] and documented in our prior report,[2] supported adjusting for patient sex and education level in analyses of study outcomes in the stabilized inverse probability propensity weighted (hereafter "weighted") sample ($N_w = 308$).

Using the weighted sample, we estimated rates of locations of death, death at preferred location, and poor QoD for immigrant and nonimmigrant groups. Logistic regression models estimated adjusted odds ratios for associations between immigrant status and location of death, death at preferred location, and poor QoD. We adjusted estimates for location of death for patient sex and education level and estimates for preferred location of death and poor QoD (i.e., outcomes relying on post-mortem survey respondents' judgments) for patient sex and education level and post-mortem survey respondent (i.e., caregiver). We examined the possibility that receipt of values-inconsistent aggressive EoL care mediates an inverse association between immigrant status and death at preferred location using logistic regression models within Baron and Kenny's[35] framework for evaluating mediation. We also examined the possibility that immigrant status modifies an association between preference for life-extending, as opposed to symptom-directed, comfort, EoL care and poor QoD using a multiple logistic regression model for poor QoD that included main and interactive effects of immigrant status and preference for life-extending EoL care.

We conducted analyses using SAS statistical software, version 9.4 (Cary, North Carolina). We based statistical inferences on two-sided tests with $p < .05$ taken to be statistically significant.

TABLE 1. Sociodemographic comparison between immigrant and nonimmigrant advanced cancer patient groups (weighted sample; N_w = 308)

| | Full sample | | Immigrant | | Nonimmigrant | | Comparison | | |
| | N_w = 308 | | N_w = 49 | | N_w = 259 | | | | |
Characteristic	n_w	%	n_w	%	n_w	%	χ^2	df	p
Age, y							0.00	1	1.000
<65	205	66.5	32	66.6	172	66.5			
≥65	103	33.5	16	33.4	87	33.5			
Sex							3.32	1	.068
Male	160	51.9	19	39.9	140	54.1			
Female	148	48.1	29	60.1	119	45.9			
Race and ethnicity							0.29	2	.865
White	208	67.7	35	71.0	174	67.0			
Black	55	18.0	8	16.2	47	18.3			
Latino	44	14.3	6	12.8	38	14.6			
Education							2.15	1	.142
Up to 12 y	168	54.7	31	64.3	137	52.9			
Beyond 12 y	139	45.3	17	35.7	122	47.1			
Insurance status							0.88	1	.349
Insured	198	64.4	34	70.3	164	63.3			
Not insured	110	35.6	14	29.7	95	36.7			
Marital status							1.34	1	.248
Married	165	53.7	22	46.1	143	55.1			
Not married	142	46.3	26	53.9	116	44.9			
Region							1.17	1	.278
Northeast (CT, NH, MA)	154	50.2	21	43.0	133	51.5			
Southwest (TX)	153	49.8	28	57.0	126	48.5			
Academic medical center							0.64	1	.425
Yes	116	37.6	21	42.7	95	36.7			
No	192	62.4	28	57.3	164	63.3			

Abbreviations: CT, Connecticut; MA, Massachusetts; NH, New Hampshire; TX, Texas.

RESULTS

The weighted sample was 33.5% older (65+ years of age) adults; 48.1% female; 67.7%, 18.0%, and 14.3%, White, Black, and Latino, respectively; 45.3% educated beyond high school; 35.6% uninsured; 53.7% married; 50.2% from the Northeast; and 37.6% recruited at an academic medical center (Table 1). There were no significant sociodemographic differences between the immigrant and nonimmigrant patient groups. Those excluded from the study due to missing data were less likely to be insured than those not excluded (49.3% vs. 62.6%, $p < .05$).

In the weighted sample, adjusting for patient sex and education level, immigrants were more likely than nonimmigrants to die in a hospital (AOR, 3.33; 95% CI, 1.65–6.71) or nursing home (AOR, 3.22; 95% CI, 1.09–9.51) as opposed to at home (Table 2). Adjusting for patient sex, education level, and post-mortem survey respondent (i.e., caregiver), immigrant as opposed to nonimmigrant advanced cancer patients were less likely to die in a preferred location (AOR, 0.42; 95% CI, 0.20–0.90) and more likely to have poor QoD (AOR, 5.47; 95% CI, 2.70–11.08).

In the weighted sample adjusting for covariates, immigrant patients were more likely to receive values-inconsistent aggressive EoL care (AOR, 3.42; 95% CI, 1.64–7.14) and less likely to die at preferred location (AOR, 0.42; 95% CI, 0.20–0.90; model A) than nonimmigrant patients (Table 3). However, in a model including immigrant status and receipt of values-inconsistent aggressive EoL care (model B), only values-inconsistent aggressive EoL care (AOR, 0.13; 95% CI, 0.07–0.26) and not immigrant status was associated with death at preferred location.

In a multiple logistic regression analysis of patients' poor QoD in the weighted sample adjusting for covariates, we found a significant interaction between the effects of immigrant status and preference for life-extending EoL care on poor QoD (interaction AOR, 0.16; $p = .022$). Table 4 displays the differential effects of immigrant status and preference for life-extending EoL care on poor QoD associated with this interaction. Among patients who preferred symptom-directed, comfort EoL care, immigrants were nearly 10 times more likely than nonimmigrants to have had poor QoD (AOR, 9.53; $p < .001$). Among nonimmigrant patients, those who preferred life-extending as opposed to symptom-directed, comfort EoL care were almost three times more likely to have had poor QoD (AOR, 2.89; $p = .002$).

TABLE 2. Associations between immigrant status and study outcomes of interest (weighted sample; $N_w = 308$)

	Immigrant		Nonimmigrant		Immigrant versus nonimmigrant		
	$N_w = 49$		$N_w = 259$				
Outcome	n_w	%	n_w	%	AOR	95% CI	p
Location of death							
ICU	0	0.4	19	7.5	0.10	0.00–7.48	.291
Hospital (non ICU)	21	43.5	47	18.1	3.33	1.65–6.71	.000
Nursing home	7	13.8	12	4.8	3.22	1.09–9.51	.034
Inpatient hospice	0	0.8	37	14.3	0.08	0.00–1.90	.119
Home	20	41.4	143	55.3	Ref.		
Death at preferred location							
Yes	21	57.6	183	72.2	0.42	0.20–0.90	.026
No	16	42.4	71	27.8	Ref.		
Poor QoD							
Yes	31	62.9	58	22.7	5.47	2.70–11.08	.000
No	18	37.1	199	77.3	Ref.		

Note: Missing data: preferred location (9), poor QoD (2). All AOR adjusted for patient sex and level of education. AOR for death at preferred location and poor QoD also adjusted for post-mortem survey respondent (i.e., formal or informal caregiver).
Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; QoD, quality of death.

TABLE 3. Values-inconsistent aggressive EoL care as a mediator of the effect of immigrant status on death at preferred location (weighted sample; $N_w = 291$)

	Values-inconsistent aggressive EoL care, Y/N			Death at preferred location, Y/N (model A)			Death at preferred location, Y/N (model B)		
Predictor	AOR	95% CI	p	AOR	95% CI	p	AOR	95% CI	p
Immigrant, Y/N	3.42	1.64–7.14	.000	0.42	0.20–0.90	.026	0.63	0.27–1.45	.275
Values-inconsistent aggressive EoL care, Y/N							0.13	0.07–0.26	.000

Note: All AOR adjusted for patient sex and level of education; AORs for death at preferred location also adjusted for post-mortem survey respondent (i.e., formal or informal caregiver).
Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; EoL, end-of-life; N, no; Y, yes.

TABLE 4. Differential effects of immigrant status and preference for life-extending EoL care on poor QoD (weighted sample; $N_w = 306$)

		Poor QoD (Y/N)		
Effect of	Within group	AOR	95% CI	p
Immigrant (Y/N)	Preferring life-extending EoL care	1.57	0.43–5.73	.498
	Preferring comfort EoL care	9.53	4.05–22.40	.000
Preferring life-extending EoL care (Y/N)	Immigrant	0.48	0.12–1.93	.298
	Nonimmigrant	2.89	1.50–5.59	.002

Note: All AOR adjusted for patient sex, level of education, and post-mortem survey respondent (i.e., formal or informal caregiver).
Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; EoL, end-of-life; N, no; QoD, quality of death; Y, yes.

DISCUSSION

We found that immigrant status among patients with advanced cancer is associated with dying in an institutional setting, dying in an unpreferred setting, and having a poor perceived QoD. Our findings contribute to our prior work demonstrating that immigrant status among patients with advanced cancer was associated with more aggressive, and more values-inconsistent EoL care.[2] In this study, values-inconsistent aggressive EoL care mediated the effect of immigrant status on death at the patient's preferred location.[35] That is, immigrants were less likely to die at a preferred location not directly because they were immigrants but because of the values-inconsistent aggressive EoL care they received because they were immigrants.

In our study, immigrants were more likely to die in hospitals and nursing homes. Hospice enrollment is associated with higher rates of at home vs in-hospital death.[9] Rates of hospice use among Hispanic/Latino, which

account for over 50% of foreign-born US residents, and non-Hispanic White cancer patient populations are nearly identical.[36] However, Hispanic/Latino patients are still more likely to die in hospitals, indicating a target for improvement of EoL care.[37] In-hospital death has been associated with lack of caregiver support and lack of home-based care.[26,38] These barriers may be important for immigrants who do not have caregivers or are unable to access these health services due to low health literacy, lack of support system, or insufficient resources.

Previous studies have outlined the increased likelihood of receiving values-inconsistent EoL care among immigrants.[2,6] Our study extends these findings by suggesting that immigrants may not die where they prefer because they receive values-inconsistent aggressive EoL care. Thus, values-inconsistent aggressive EoL care is at odds not only with immigrant patients' goals for EoL care but also with where immigrant patients wish to die. Our study found that a higher proportion of immigrants die in hospital settings, even after adjusting for sociodemographic factors. This is likely associated with systemic inequities leading to poorer EoL care outcomes for marginalized communities.[21,42,43] Such factors include low income, uninsured or publicly insured status, and inadequate palliative care or hospice services.[42] For immigrants, cultural and communication barriers are additional obstacles in receiving values-consistent EoL care. Improving access to EoL care for immigrant populations by focusing on provider cultural competency, improved health literacy, and access to health care facilities will likely decrease the risk of receiving values-inconsistent care and of dying in an institutional setting.

Immigrants in our study were less likely to die in a preferred location, which may be related to an increased need for goals of care (GoC) discussions and culturally competent EoL care among this population. GoC discussions are imperative in eliciting EoL care preferences from patients. Although providers are willing to engage in GoC discussions, various factors are perceived as barriers, including non-English speaking patients, family difficulty accepting poor prognosis, medical mistrust, and different cultural approaches to GoC conversations.[39] Additionally, language barriers, level of family involvement, and generational group of the patient have been reported to increase complexity in coordinating EoL care and may contribute to disparities in EoL and QoD.[40] One study showed that cultural values, including hesitation about prognosis and a family-centered system, significantly influenced EoL care decisions in some Hispanic/Latino patients.[41] These findings highlight the importance of culturally competent

medical training to ensure that providers are equipped with tools to engage in effective GoC discussions with immigrant patients.

Among patients who preferred symptom-directed, comfort EoL care, we found that immigrants were 10 times more likely than nonimmigrants to have poor perceived QoD. Thus, immigrant patients' desires for symptom-directed, comfort EoL care does not translate to better QoD the way nonimmigrant patients' desires for symptom-directed, comfort EoL care does. Patients who can avoid hospitalizations at EoL are regarded as having higher QoD,[44] due in part to the challenge of transitioning from active treatment to full comfort measures in the hospital. Increased use of acute care at EoL is associated with late initiation of palliative care. Contrarily, earlier initiation of palliative care may be important in elucidating goals of care and likelihood of nonhospital death.[45] Early referral to palliative care, given the scarcity of board-certified palliative care specialists,[46] may prevent terminally ill patients from needing hospitalization and increase the likelihood of at-home death, improving QoD.[47] These findings provide evidence that expanding immigrants' early access to palliative care and appropriately timed hospice referrals is imperative for improving QoD.

One major study strength includes the assessment of actual versus preferred location of death, as assessed by post-mortem caregiver surveys, and perceived QoD in a large cohort of immigrant and nonimmigrant advanced cancer patients. Additionally, the propensity score matching analysis factors for sociodemographic factors like insurance status and education. Nevertheless, we recognize certain limitations. First, we relied on self-reported immigration status, which may have led to inaccurate representation in our analysis. Second, we could not discern between documented and undocumented immigrants, who are at even higher risk for receiving value inconsistent EoL care.[4,24,48] Third, the propensity score resulted in an immigrant study population of primarily European descent. Fourth, the study population came from primarily academic medical centers, which are more likely to be in urban settings and have a wider range of treatments offered. Additional limitations include small sample size and reduced generalizability given language requirement, as well as combined data on race and ethnicity within the CwC database. Furthermore, retrospective determination of preferred location of death based on post-mortem interview may lead to additional bias.

We can conclude that immigrant status is associated with values-inconsistent EoL care, leading to higher likelihood of dying in an unpreferred setting and decreasing

perceived QoD. Immigrants are more likely to encounter lack of accessible and affordable health care and language and cultural barriers, which may contribute to disparities in EoL care. Providing bilingual and bicultural EoL care, engaging in GoC discussions, and referring earlier to palliative care are critical in improving immigrant EoL care and QoD. Additional research, focused specifically on immigrant populations, examining potential causes of observed poorer immigrant QoD, including unmet social needs such as financial and transportation barriers, as well as the role of documentation status, is warranted. Additionally, the impact of the coronavirus disease 2019 pandemic on QoD could further enhance our understanding of these disparities.

AUTHOR CONTRIBUTIONS
Ana I. Tergas: Conceptualization, funding acquisition, methodology, supervision, writing–original draft, and writing–review and editing. **Holly G. Prigerson:** Conceptualization, funding acquisition, methodology, writing–original draft, and writing–review and editing. **Megan Johnson Shen:** Conceptualization, funding acquisition, methodology, writing–original draft, and writing–review and editing. **Andreea I. Dinicu:** Writing–original draft and writing–review and editing. **Alfred I. Neugut:** Conceptualization, methodology, and writing–review and editing. **Jason D. Wright:** Conceptualization, methodology, and writing–review and editing. **Dawn L. Hershman:** Conceptualization, methodology, and writing–review and editing. **Paul K. Maciejewski:** Conceptualization, funding acquisition, methodology, supervision, and writing–review and editing.

CONFLICTS OF INTEREST
Alfred I. Neugut has consulted for Otsuka, GlaxoSmithKline, Eisai, United Biosource Corp and Hospira; has grant support from Otsuk; and he is on the medical advisory board of EHE International. Ana I. Tergas has consulted for Auro Vaccines and Immunomics. Jason Wright reports grant support from Merck and is an independent contractor for Wolters Klewer Health. The other authors made no disclosures.

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