Background: Treatment for metastatic breast cancer (MBC) that is not concordant with the NCCN Guidelines for Breast Cancer has been associated with higher healthcare utilization and payer costs. However, a significant knowledge gap exists regarding the impact of guideline-discordant care on patient cost responsibility. This study examined this question among patients with MBC in the year postdiagnosis.

Methods: This retrospective cohort study used data from the SEER-Medicare linked database from 2000 through 2013. Guideline discordance, defined by year-specific NCCN Guidelines, was assessed for first-line antineoplastic treatment and grouped into discrete categories. Patient cost responsibility (deductibles, coinsurance, copayments) in women with MBC were summed for all medical care received in the year postdiagnosis. The difference in patient cost responsibility by guideline discordance status was estimated using linear mixed-effect models.

Results: Of 3,709 patients with MBC surviving at least 1 year postdiagnosis, 17.6% (n=651) received guideline-discordant treatment. Median cost responsibility in the year postdiagnosis for patients receiving guideline-discordant treatment was $7,421 (interquartile range [IQR], $4,359–$12,983) versus $5,171 (IQR, $3,006–$8,483) for those receiving guideline-concordant care. In adjusted models, guideline-discordant treatment was significantly associated with $1,841 higher monthly Medicare spending compared with those who received guideline-concordant care.

Conclusions: Deviations from current treatment guidelines may have implications on patient healthcare cost responsibility. Additional research is needed to fully understand the mechanisms underlying how guideline deviation leads to greater costs for patients with MBC.
patients are responsible, and thus potentially increase financial toxicity in older patients with MBC. No prior work has differentiated the patient cost responsibility between those receiving guideline-discordant versus -concordant treatments. Therefore, we sought to determine the patient-level impact of NCCN Guideline–discordant treatment on patient cost responsibility in the year after index diagnosis for Medicare beneficiaries with MBC.

**Patients and Methods**

**Study Design and Sample**

This retrospective cohort study used data from 2000 through 2013 in the SEER-Medicare linked database to examine the association between guideline discordance and patient cost responsibility in women with MBC. Women with de novo (metastatic at diagnosis) MBC diagnosed in 2007 through 2013 or with stage I–III breast cancer diagnosed in 2000 through 2013 with subsequent secondary distant metastases in 2007 through 2013 who survived 1 year after index diagnosis were included in this study (Figure 1). Metastatic disease was identified based on ICD-9 claims on 2 separate dates for secondary cancer (197.XX–198.XX), excluding breast (198.81, 198.82, 198.2) and lymph nodes (196.XX). The index diagnosis date was defined as the de novo MBC diagnosis or the first claim date with ICD-9 codes for secondary cancer in patients with a primary early-stage breast cancer. Exclusion criteria included no anticancer treatment (chemotherapy, hormone therapy, targeted therapy), other nonbreast primary cancers, unknown hormone receptor status, or incomplete Medicare coverage (Parts A, B, D) in the year after index diagnosis. This study was approved by the University of Alabama at Birmingham Institutional Review Board. No informed consent was required because the analysis used deidentified data from the SEER-Medicare database.

**Outcome Measure**

The outcome of interest, patient cost responsibility, was defined as payment to providers for which Medicare beneficiaries were responsible through deductibles, co-insurance, and copayments, in the year after index diagnosis date. Overall and healthcare service–stratified costs to beneficiaries were summed from inpatient (Medicare Provider Analysis and Review), outpatient (Outpatient Standard Analytical Files), physician visit/carrier (National Claims History), durable medical equipment (DME), and Medicare Part D claims. Notably, data for Medicare Part B drug spending, which includes almost all infusion chemotherapy drugs and some oral chemotherapy drugs given at a doctor’s office, free-standing clinic, or hospital outpatient setting, was found in the outpatient, physician visit/carrier, and DME claim files.

**Guideline Discordance**

NCCN Guideline discordance was assessed using claims for initial antineoplastic treatment (hormonal medication, chemotherapy, or HER2-targeted therapy) after index diagnosis date. Details regarding the categorization of guideline discordance in this population were previously published. In brief, treatment regimens containing single drugs or combination therapy (same-day billing for ≥2 drugs) were identified using National Drug Codes, the Healthcare Common Procedure Coding System, and generic drug names from outpatient, physician visit/carrier, DME, or Medicare Part D claims. Regimens were matched to the version of NCCN Guidelines for Breast Cancer available at the exact treatment date. Regimens considered guideline-concordant changed over time, because the NCCN Guidelines are updated at least annually or as needed based on changes in clinical practice.
Guideline Discordance and Patient Cost in MBC

ORIgINAL RESEARCH

evidence for existing drugs or new drug approvals. However, minor changes were observed during the time frame of our study. Guideline discordance was defined as regimens received but not listed in the published NCCN Guidelines at time of treatment. Patients with unknown HER2 status were considered concordant if they received a HER2-positive or -negative regimen. Treatment regimens categorized as guideline-discordant were subsequently reviewed and grouped into discrete categories based on the reason for discordance, including (1) therapy mismatched with hormone receptor (HR) or HER2 status, (2) HER2-targeted therapy without chemotherapy, (3) nonapproved bevacizumab use, (4) adjuvant regimens received in the metastatic setting, and (5) miscellaneous reasons for guideline discordance, which included nonapproved agents or regimens usually received in cancers other than MBC, trastuzumab in nonapproved combinations, and approved agents or regimens received in nonapproved years.4,5

Covariates
Patient demographic and clinical characteristics were compared and used for model adjustment, including age at index diagnosis, race (white, black, other) type of MBC (de novo vs treated, secondary metastatic disease), HR status (positive vs negative vs unknown estrogen receptor [ER]/progesterone receptor status), HER2 status (positive vs negative vs unknown), NCI comorbidity index score, Medicare/Medicaid dual-eligibility status (never eligible vs eligible), and census tract education level (percentage of patients with less than high school education vs high school education or greater). NCI comorbidity index scores were based on claims for comorbid conditions in the year before the index diagnosis date and classified based on the Klabunde modification for comorbidities.13–16

Statistical Analysis
Patient characteristics were described using medians and interquartile ranges (IQRs) for continuous variables and frequencies (percentages) for categorical variables. Effect sizes were calculated using Cohen’s $d$ or Cramer’s $V$. To account for patient-level correlation, we estimated beta coefficients ($\beta$) and 95% confidence intervals evaluating the difference between patient cost responsibility by receipt of guideline-discordant treatment using linear mixed-effect models. Overall and healthcare service-stratified models were adjusted for patient demographic and clinical characteristics, including index diagnosis year, age at index diagnosis, race, MBC type, HR status, HER2 status, NCI comorbidity index score, Medicare/Medicaid dual-eligibility status, and census track education level. Sensitivity analyses were conducted for overall discordance and by category of guideline discordance using generalized linear models with a gamma distribution and log-link. Analyses were performed using SAS 9.4 (SAS Institute, Inc).

Results
Of 3,709 patients with MBC (median age, 69 years [IQR, 64–77]), 17.6% ($n=651$) received treatment discordant with NCCN Guidelines for Breast Cancer. Demographic and clinical characteristics for the study sample are shown in Table 1. Compared with patients receiving guideline-concordant care, those receiving discordant treatment were younger and were more often Medicare/Medicaid dual-eligible, HR-negative, and HER2-positive. Median patient cost responsibility in the year after index diagnosis was significantly higher for guideline-discordant versus -concordant care ($\$7,421$ [IQR $\$4,359–$12,983]$ vs $\$5,171$ [IQR $\$3,006–$8,483]$; $P<.001$).

After adjustments for patient demographic and clinical characteristics, guideline-discordant care was associated with significantly higher patient cost responsibility in the first year following index diagnosis ($\beta=\$1,841; 95% CI, $\$1,280–$2,401$) compared with guideline-concordant treatment. In addition, significant healthcare service-stratified patient cost responsibility differences were found for outpatient ($\beta=\$1,288; 95% CI, $\$800–$1,776$), physician visit/carrier ($\beta=\$326; 95% CI, $\$204–$449$), and Medicare Part D costs ($\beta=\$95; 95% CI, $\$1–$189$) between discordant and concordant treatment (Figure 2).

Figure 3 presents results from the adjusted models evaluating the association of patient cost responsibility with categories of guideline-discordant treatments. Patients receiving nonapproved bevacizumab ($n=58/651$; 9%) had the highest cost responsibility when compared with those receiving guideline-concordant treatment ($\beta=\$3,330; 95% CI, $\$1,711–$4,948$). Patients receiving HER2-targeted therapy without chemotherapy ($n=247/651$; 38%) also had significantly higher costs than those receiving discordant treatment ($\beta=\$2,078; 95% CI, $\$1,252–$2,904$), whereas those receiving therapy mismatched with their HR or HER2 status ($n=46/651$; 7%) had significantly lower costs than those receiving discordant treatment ($\beta=\$3,912; 95% CI, $\$5,796 to $\$2,027$). Costs for patients receiving adjuvant regimens in the metastatic setting ($n=73/651$; 11%) did not significantly differ from costs for those receiving guideline-concordant treatments ($\beta=\$1,196; 95% CI, $\$260 to $\$2,651$). Sensitivity analyses using generalized linear models showed similar results by overall and category of guideline discordance.

Discussion
This is the first study to show that receipt of guideline-discordant treatment is associated with significantly higher patient-specific cost responsibility for patients with MBC. This significant cost increase was seen for
both overall and healthcare service–stratified care costs, including outpatient, physician visit/carrier, and Medicare Part D costs. This study adds to previously published studies about guideline discordance focused on costs to payers, with most finding higher payer costs associated with treatment that is discordant with NCCN Guidelines. For example, when considering costs from a societal perspective, a study reported that an estimated $2.5 billion was spent in 2010 for 10 common chemotherapies that were used in discordance with NCCN Guidelines. The category with the highest patient cost responsibility—nonapproved bevacizumab—was associated with both an increased patient cost responsibility of almost $12,000 in the first year after diagnosis and a 40% increased hazard of mortality (hazard ratio, 1.40; 95% CI, 1.13–1.74). This category did not include patients who received paclitaxel with bevacizumab, because this combination was included in the NCCN Guidelines during our study period based on its accelerated approval for use in MBC in 2008. Ultimately, bevacizumab was found to pose life-threatening adverse effects with minimal benefit to patients with MBC, and its indication was removed in late 2010.

Table 1. Patient Characteristics (N=3,709)

<table>
<thead>
<tr>
<th>Guideline-Discordant</th>
<th>Guideline-Concordant</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Total, N</td>
<td>651</td>
<td>3,058</td>
</tr>
<tr>
<td>Median age at index diagnosis (IQR), y</td>
<td>66 (58–73)</td>
<td>70 (65–77)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>White</td>
<td>487 (74.8)</td>
<td>2,392 (78.2)</td>
</tr>
<tr>
<td>Black</td>
<td>99 (15.2)</td>
<td>390 (12.8)</td>
</tr>
<tr>
<td>Other</td>
<td>65 (10.0)</td>
<td>276 (9.0)</td>
</tr>
<tr>
<td>MBC type</td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>De novo</td>
<td>136 (20.9)</td>
<td>578 (18.9)</td>
</tr>
<tr>
<td>Secondary metastatic disease</td>
<td>515 (79.1)</td>
<td>2,480 (81.1)</td>
</tr>
<tr>
<td>Hormone receptor status a</td>
<td></td>
<td>.29</td>
</tr>
<tr>
<td>Positive</td>
<td>374 (57.5)</td>
<td>2,461 (80.5)</td>
</tr>
<tr>
<td>Negative</td>
<td>225 (34.6)</td>
<td>270 (8.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>52 (8.0)</td>
<td>327 (10.7)</td>
</tr>
<tr>
<td>HER2 status</td>
<td></td>
<td>.18</td>
</tr>
<tr>
<td>Positive</td>
<td>64 (9.8)</td>
<td>51 (1.7)</td>
</tr>
<tr>
<td>Negative</td>
<td>38 (5.8)</td>
<td>338 (11.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>549 (84.3)</td>
<td>2,669 (87.3)</td>
</tr>
<tr>
<td>NCI comorbidity index score, median (IQR)</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>Medicare/Medicaid dual-eligibility status</td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>Never dual-eligible</td>
<td>362 (55.6)</td>
<td>1,869 (61.1)</td>
</tr>
<tr>
<td>Dual-eligible</td>
<td>289 (44.4)</td>
<td>1,189 (38.9)</td>
</tr>
<tr>
<td>Census tract education level b, median (IQR)</td>
<td>82 (70–90)</td>
<td>83 (71–91)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; MBC, metastatic breast cancer.

aEstrogen/Progesterone receptor.
bPercentage of patients with high school education or greater.

Previous research has found differences in mortality by category of guideline discordance, despite a lack of difference when comparing concordance versus discordance of overall treatment. Our study adds that the category of guideline discordance also influences patient cost responsibility. Importantly, the category with the highest patient cost responsibility—nonapproved bevacizumab—was associated with both an increased patient cost responsibility of almost $12,000 in the first year after diagnosis and a 40% increased hazard of mortality (hazard ratio, 1.40; 95% CI, 1.13–1.74). However, this category did not include patients who received paclitaxel with bevacizumab, because this combination was included in the NCCN Guidelines during our study period based on its accelerated approval for use in MBC in 2008. Ultimately, bevacizumab was found to pose life-threatening adverse effects with minimal benefit to patients with MBC, and its indication was removed in late 2010.

Although the FDA does not consider cost-effectiveness during drug approval, one study found a cost to payers of $745,000 per quality-adjusted life-year in patients with MBC receiving combination bevacizumab/paclitaxel.
compared with paclitaxel alone. Our study shows that this extreme cost is not only restricted to payers but also passed down to patients. This effect may be exacerbated in the future as payers implement clinical pathway programs, potentially resulting in claim denial due to receipt of guideline-discordant treatment. This example represents a cautionary tale for physicians who add novel agents without proven benefit to treatment regimens, potentially incurring substantial patient costs, and also highlights the fact that guidelines may change over time. In formulating novel drugs or treatment guidelines, an emphasis on more patient-centered outcomes, such as decreased financial burden, prolonged overall survival, and quality of life, can be as valuable to patients as progression-free survival.

The lower cost responsibility seen for patients receiving therapy mismatched with HR/HER2 status was predominantly due to the use of oral hormone therapy in older patients with HR-negative MBC. We suspect that some physicians may have elected to prescribe hormone

![Figure 2](image-url)

**Figure 2.** Model-adjusted patient cost responsibility overall and stratified by healthcare services in the year after index MBC diagnosis (guideline-discordant, n=651; guideline-concordant, n=3,058). Models were adjusted for index diagnosis year, age at index diagnosis, race, MBC type, hormone receptor status, HER2 status, NCI comorbidity index score, Medicare/Medicaid dual-eligibility status, and census track education level.

Abbreviations: DME, durable medical equipment; MBC, metastatic breast cancer.

*Significant difference from guideline-concordant status (P<.05).

![Figure 3](image-url)

**Figure 3.** Model-adjusted overall patient cost responsibility by type of NCCN Guideline discordance in the year after index MBC diagnosis. Models were adjusted for index diagnosis year, age at index diagnosis, race, MBC type, hormone receptor status, HER2 status, NCI comorbidity index score, Medicare/Medicaid dual-eligibility status, and census track education level.

Abbreviations: HR, hormone receptor; MBC, metastatic breast cancer.

*Significant difference from guideline-concordant status (P<.05).
therapy for patients with HR-negative MBC deemed ineligible for chemotherapy. Although often well-tolerated, hormone therapy has adverse effects, such as hot flashes, weight gain, insomnia, and joint aches, with one study reporting that 46% of patients with ER-positive breast cancer took medication to control symptoms. Ultimately, no treatment may be a better choice than a guideline-discordant treatment associated with mild but persistent and bothersome adverse effects.

Conversely, higher cost responsibility was seen for patients receiving HER2-targeted therapy without chemotherapy. We believe this is due to HER2-targeted therapies being more expensive than hormonal therapies, and suspect that patients who may not otherwise tolerate chemotherapy are given HER2-targeted therapies without chemotherapy due to increased disease severity, adverse treatment adverse effects, or decreased functional status. These issues may result in increased patient spending on more frequent clinic visits, supportive medications to reduce treatment adverse effects, or supplies to address decreased functional status, such as walkers. More research is needed to determine how to effectively manage older patients with MBC experiencing treatment-related adverse effects, especially because a clinical benefit has been suggested for guideline-discordant single-agent trastuzumab as first-line monotherapy.

Little guidance exists on the optimal treatment strategy for older adults with MBC. Randomized clinical trials, which largely guide MBC treatment evidence, often exclude patients with advanced age due to eligibility criteria with restrictions on comorbidities and functional status. In studies of older adults with early-stage breast cancer, undertreatment with adjuvant capecitabine alone doubled the risk of death compared with standard chemotherapy, and overtreatment with lumpectomy plus tamoxifen and radiation therapy has shown no benefit compared with lumpectomy plus adjuvant therapy with tamoxifen alone. In our study of patients with MBC, with 74% of the patient sample aged ≥ 65 years and 31% aged ≥ 75 years, deviations from the NCCN Guidelines were noted in terms of both overtreatment, such as adjuvant regimens given in the metastatic setting, and undertreatment, such as HER2-targeted therapy given without chemotherapy, both of which resulted in higher patient costs compared with receipt of guideline-concordant care. These higher costs could be particularly impactful for older adults, who could incur the increased burden of out-of-pocket healthcare costs even with supplemental insurance, because most encounter a large decrease in annual income after retirement. Therefore, incorporating a geriatric assessment and considering patient preferences surrounding therapy costs are recommended to optimize treatment decision-making in older adults based on functional status, comorbidity, medication use, nutritional status, social status, cognition, and psychological concerns rather than chronologic age alone.

These findings underscore the potential for treating oncologists to influence patient cost responsibility based on treatment choice. Evidence has suggested that few oncologists are comfortable discussing costs with their patients, although most individuals with cancer are interested in discussion about out-of-pocket costs. This type of cost information is difficult to consider and often challenging to relay to patients due to continual changes in insurance coverage, drug costs, and healthcare policy. Despite this concern, oncologists believe that patient financial burden is an issue to be addressed. In a national survey of medical oncologists, 84% responded that patient costs would influence treatment recommendations. Kelly et al found that 83% of oncologists at an academic institution wished cost information was included in the NCCN Guidelines, potentially creating greater ease in patient-physician cost conversations. Although NCCN Evidence Blocks provide an estimate of the total treatment cost as a measure of value, a direct calculation of patient out-of-pocket costs is not included. Tools such as the ASCO Value Framework could be useful to guide both oncologists and patients with MBC in treatment decision-making when paired with NCCN Guidelines, because the Framework considers patient copay in its net health benefit calculation of a particular cancer treatment regimen. Thus, our work is critical, as we show that deviation from guidelines may influence patient healthcare expenses and that oncologists can play an important role in addressing patient financial burden.

Our results should be considered in the context of several limitations. Claims analysis is limited by the inability to identify who paid for patient-specific costs. Although we could not measure exact out-of-pocket costs for included patients, the cost estimates represent the direct medical costs for those without supplemental insurance and show the mirroring of patient and payer costs. Furthermore, the estimates herein likely underestimate the true patient out-of-pocket costs of cancer-related care, which could include indirect costs such as transportation, lodging, cosmetic or therapeutic items, mental health services, caregiving/childcare, and lost wages due to absence from work. Due to the set inclusion criteria, results may not be generalizable to patients with MBC who survive <1 year from diagnosis. Likewise, patient cost responsibility was not considered outside of 1 year postdiagnosis. We also did not consider the effect of catastrophic coverage on patient cost responsibility. Unmeasured confounders influencing patient costs may still exist because of the inability to capture variables using SEER-Medicare data, such as illness severity, functional status, or frailty. Claims for secondary malignancy also
vary in completeness and accuracy. Finally, a completely causal relationship between guideline discordance and patient cost responsibility cannot be established based on the current data or study design.

Conclusions

Our results showed that patient cost responsibility was nearly $2,000 higher for the approximately 18% of patients with MBC receiving NCCN Guideline–discordant versus –concordant care. These findings have important implications for training clinicians in terms of the importance of guideline-concordant care and the potential impact on patient cost responsibility. Our work can inform efforts to improve patient–clinician communication about the value of guideline-based care and the potential implications of financial burden associated with cancer treatments. As the costs of cancer care continue to increase and physicians shift to more value-based healthcare delivery systems, ongoing research should build on these findings to develop effective solutions targeting standardized treatments to avoid potentially unnecessary financial toxicity.

Acknowledgments

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the NCI; the Office of Research, Development, and Information, Centers for Medicare & Medicaid Services; Information Management Services, Inc.; and the SEER program tumor registries in the creation of the SEER-Medicare database.

Submitted January 8, 2019; accepted for publication April 30, 2019.

Previous presentation: This work was presented as an oral presentation at the Society for Medical Decision Making 40th Annual North American Meeting; October 13–17, 2018; Montreal, Quebec, Canada.

Author contributions: Study concept/design: Williams, Rocque. Provision of study material or patients: Rocque. Data collection/assembling: Williams, Azuero. Data analysis and interpretation: Williams, Azuero, Kenzik, Rocque. Manuscript writing: All authors. Final approval of manuscript: All authors.

Disclosures: Dr. Rocque has disclosed that she has received grant/research support from CareVive, Genentech, and Pfizer, and consulting fees/honoraria from Pfizer and Roche. All remaining authors have not received any financial consideration from any person or organization to support the preparation, analysis, results, or discussion of this article.

Correspondence: Courtney P. Williams, MPH, Division of Hematology and Oncology, University of Alabama at Birmingham, WTI 240, 1720 2nd Avenue South, Birmingham, AL 35294. Email: courtneyphillips@uabmc.edu

References