Original Article

Cost-Effectiveness of Full Coverage of Aromatase Inhibitors for Medicare Beneficiaries With Early Breast Cancer

Kouta Ito, MD, MS[1]; Elena Elkin, PhD[2]; Victoria Blinder, MD, MSc[3,4]; Nancy Keating, MD, MPH[5,6]; and Niteesh Choudhry, MD, PhD[1]

BACKGROUND: Rates of nonadherence to aromatase inhibitors (AIs) among Medicare beneficiaries with hormone receptor-positive early breast cancer are high. Out-of-pocket drug costs appear to be an important contributor to this and may be addressed by eliminating copayments and other forms of patient cost sharing. The authors estimated the incremental cost-effectiveness of providing Medicare beneficiaries with full prescription coverage for AIs compared with usual prescription coverage under the Medicare Part D program. **METHODS:** A Markov state-transition model was developed to simulate AI use and disease progression in a hypothetical cohort of postmenopausal Medicare beneficiaries with hormone receptor-positive early breast cancer. The analysis was conducted from the societal perspective and considered a lifetime horizon. The main outcome was an incremental cost-effectiveness ratio, which was measured as the cost per quality-adjusted life-year (QALY) gained. **RESULTS:** For patients receiving usual prescription coverage, average quality-adjusted survival was 11.35 QALYs, and lifetime costs were $83,002. For patients receiving full prescription coverage, average quality-adjusted survival was 11.38 QALYs, and lifetime costs were $82,728. Compared with usual prescription coverage, full prescription coverage would result in greater quality-adjusted survival (0.03 QALYs) and less resource use ($275) per beneficiary. From the perspective of Medicare, full prescription coverage was cost-effective (incremental cost-effectiveness ratio, $15,128 per QALY gained) but not cost saving. **CONCLUSIONS:** Providing full prescription coverage for AIs to Medicare beneficiaries with hormone receptor-positive early breast cancer would both improve health outcomes and save money from the societal perspective. ***Cancer*** **2013;119:2494-502.** © *2013 American Cancer Society.*

KEYWORDS: breast neoplasms; aromatase inhibitors; medication adherence; Medicare.

INTRODUCTION

Clinical practice guidelines recommend a 5-year course of aromatase inhibitors (AIs), administered as initial monotherapy or after tamoxifen, for postmenopausal women with hormone receptor-positive early breast cancer.[1,2] Despite their proven benefits over tamoxifen,[3] adherence to AIs remains suboptimal, and only a half of all patients complete the recommended 5-year course of therapy.[4-6] Failure to complete the recommended AI treatment is associated with an increased risk of death.[7] Although efforts to promote medication adherence have received substantial attention,[8-10] there are limited data regarding the efficacy of such interventions for patients with breast cancer.[11]

Currently, the cost of a 1-month supply of AIs can vary from $15 for generic anastrozole to $500 for brand-name letrozole, compared with $15 for generic tamoxifen.[12] Although Medicare provides coverage for AIs, patient copayments for these agents can be $30 or more per month.[13] Medication adherence reportedly was significantly lower among AI users who experienced higher out-of-pocket costs ($\geq$$15 per month).[6,14,15] Out-of-pocket costs may be even higher once patients enter the "doughnut hole" in the Medicare Part D program, and reaching this coverage gap is associated with substantial reductions in adherence to AIs.[15] Recent evidence suggests that reducing or removing patient cost sharing for essential drugs is a potential cost-effective strategy for enhancing medication adherence and improving health outcomes in patients with various chronic health conditions.[16-18] We sought to evaluate the long-term health and economic impact of providing full prescription coverage of AIs for Medicare beneficiaries with hormone receptor-positive early breast cancer.

Corresponding author: Kouta Ito, MD, MS, 11 Hills Beach Road, Biddeford, ME 04107; Fax: (207) 602-5891; kito@une.edu

The corresponding author is currently affiliated with the Department of Primary Care, University of New England College of Osteopathic Medicine.
[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [2]Center for Health Policy and Outcomes, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York; [3]Health Outcomes Research Group, Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York; [4]Breast Cancer Medicine Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York; [5]Division of General Internal Medicine and Primary Care, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [6]Department of Health Care Policy, Harvard Medical School, Boston, Massachusetts.

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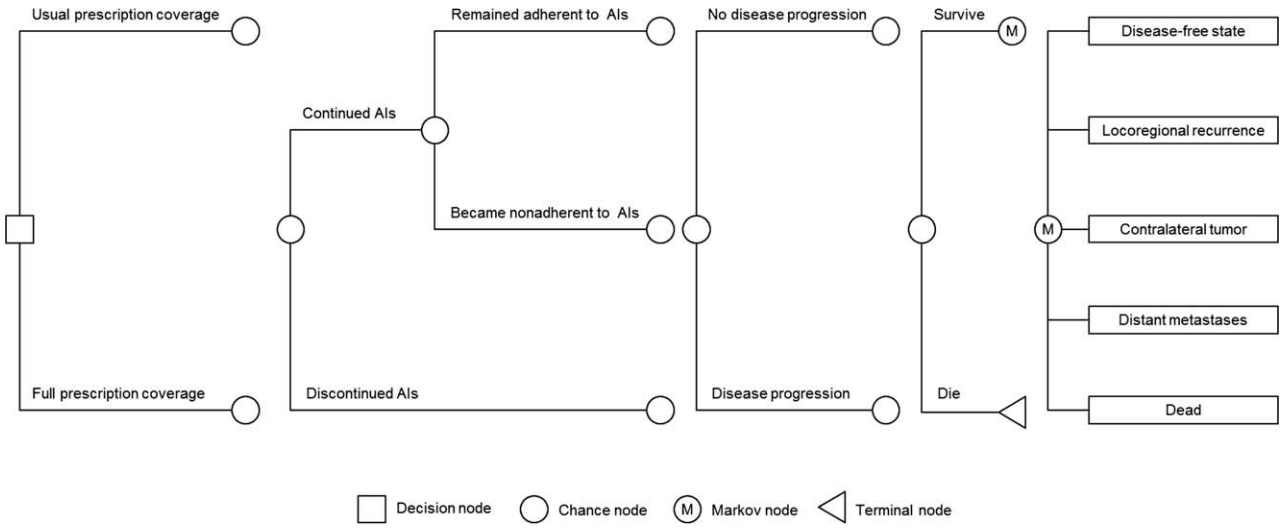

Figure 1. The Markov model structure is illustrated. At the decision node, patients were assigned to usual or full prescription coverage. Patients entered the model in the disease-free state. Depending on the type of prescription coverage, patients could discontinue aromatase inhibitors (AIs), continue but become nonadherent to AIs, or continue and remain adherent to AIs over the initial 5-year treatment period (see definitions in the text). Every year, patients were at risk for locoregional recurrence, contralateral tumor, or distant metastases. Throughout the patients' lifetime, all patients were at risk for death from causes unrelated to breast cancer.

MATERIALS AND METHODS

Model

We developed a Markov state-transition model simulating the use of AIs and the progression of breast cancer based on a previously published model (Fig. 1).[19] Over the initial 5-year treatment period, patients could discontinue AIs (defined as having a 180-day gap during which no prescription was filled in a given year), continue but become nonadherent to AIs (defined as having a medication possession rate $<80\%$), or continue and remain adherent to AIs (defined as having a medication possession rate $\geq 80\%$).[5] In the base case, we assumed that 30% of patients who stopped taking AIs switched to tamoxifen and completed the 5-year course of adjuvant hormone therapy.[6,20,21] Transition probabilities between health states were determined as a function of the use of adjuvant hormone therapy. The model used 1-year cycles, and the cohort was followed over its lifetime. All analyses were performed using TreeAge Pro Healthcare 2011 software (TreeAge Software Inc., Williamstown, Mass).

Population

The model simulated the prognosis of a hypothetical cohort of postmenopausal Medicare beneficiaries aged 65 years with hormone receptor-positive, stage I or II breast cancer beginning a 5-year course of adjuvant AIs after primary therapy (mastectomy or breast-conserving surgery with or without radiation).[3,22] The cohort's age was varied in sensitivity analyses.

Interventions

We compared the impact of full prescription coverage for AIs with the usual prescription coverage provided by the Medicare Part D program. Under usual prescription coverage, it was assumed that Medicare covered 67% of the drug cost of AIs (ie, \$40 per month), and patients received AIs by paying 33% of the drug cost (ie, \$20 per month).[12,13,23] Under full prescription coverage, it was assumed that Medicare paid for 100% of drug costs for those patients who were adherent to therapy.

Parameters

The model parameters are summarized in Table 1 and are described in greater detail in below.

Use of adjuvant hormone therapy

We simulated the temporal pattern of AI use based on an analysis of pharmacy claims in a health maintenance organization in California.[5] We modeled a linear decrease in both continuation and adherence rates between years 1 and 5. Because the impact of full prescription coverage on medication adherence among patients with breast cancer has not been tested, we applied the improvement in adherence to statins observed in the Post-Myocardial

TABLE 1. Model Parameters

Parameter	Value	Range	Distribution	Reference(s)
Age at initiation of AIs, y	65	65-80	Not assigned	DeSantis 2011[22]
HR of breast cancer recurrence in AI users compared with tamoxifen users	0.82	0.74-0.92	Log-normal	Regan 2011[25]
Proportion of patients who discontinued AIs in first year, %	14	50%-200% of the base-case value	Triangular	Hershman 2010[5]
Proportion of patients who discontinued AIs in years 2-5, % per y	6.5	50%-200% of the base-case value	Triangular	Hershman 2010[5]
Proportion of patients who became nonadherent to AIs in first year, %	22	50%-200% of the base-case value	Triangular	Hershman 2010[5]
Proportion of patients who became nonadherent to AIs in years 2-5, % per y	2	50%-200% of the base-case value	Triangular	Hershman 2010[5]
Absolute increase in adherence to AIs as a result of full prescription coverage, %	6.2	3.9-8.5	Beta	Choudrhy 2011[17]
Adherence to tamoxifen after the cessation of AIs, %	30	50%-200% of the base-case value	Beta	Sedju & Devine 2011,[6] Partridge 2003,[20] Owusu 2008[21]
Utility of breast cancer-related health states		50%-200% of the base-case utility loss	Gamma	Peasgood 2010[29]
Disease-free state	0.922			
Locoregional recurrence	0.789			
Contralateral tumor	0.789			
Distant metastases	0.424			
Utility of adjuvant hormone therapy	0.991	50%-200% of the base-case utility loss	Gamma	Peasgood 2010[29]
Direct medical cost of breast cancer-related health states, $ per y		50%-200% of the base-case costs	Gamma	Delea 2007,[24] Lamerato 2006[30]
Disease-free state	3186			
Locoregional recurrence	32,233			
Contralateral tumor	25,281			
Distant metastases				
First year	58,997			
Subsequent years	29,502			
Breast cancer death	6203			
Cost of informal caregiving for patients with disease recurrence, $ per event	2177	50%-200% of the base-case cost	Gamma	Hayman 2001[31]
Drug cost of AIs, $ per mo		50%-200% of the base-case costs	Gamma	GoodRx 2013,[12] Q1Medicare 2012,[13] Walters Kluwer Pharmacy Solutions 2013[23]
Total	60			
Out-of-pocket	20			
Drug cost of tamoxifen, $ per mo		50%-200% of the base-case costs	Gamma	
Total	15			GoodRx 2013,[12] Q1Medicare 2012,[13] Walters Kluwer Pharmacy Solutions 2013[23]
Out-of-pocket	5			
Discount rate, % per y	3	0-6	Not assigned	Gold 1996[33]

Abbreviations: AI, aromatase inhibitor; HR. hazard ratio.

Infarction Free Rx Event and Economic Evaluation (MI FREEE) trial[17] and varied this assumption widely in sensitivity analyses.

Clinical events

Incidence rates of breast cancer recurrence were taken from the previous cost-effectiveness analysis and the 8-year follow-up analysis of the Breast International Group (BIG) 1-98 trial.[24,25] Patients treated with 5 years of AIs continue to derive a carry-over benefit, with a lower risk of cancer recurrence, for an additional 5 years after the completion of therapy.[24-26] Because there are no data on whether such a carry-over benefit exists for patients who did not complete the full 5-year course of AIs, we conservatively assumed that the length of treatment offset period was equal to the duration of treatment, during which the benefit of AIs declined linearly over time to zero. Incidence rates of breast cancer recurrence in patients who received no adjuvant hormone therapy were estimated by dividing rates of recurrence for patients who received 5 years of tamoxifen by the proportional recurrence reductions of tamoxifen from a meta-analysis by the Early

TABLE 2. Base-Case Results

Strategy	Cost, $			Total QALYs	Incremental		ICER, $/QALY
	Drug	Healthcare	Total		Cost, $	QALYs	
Usual prescription coverage	2284	80,719	83,003	11.35	Reference		
Full prescription coverage	2442	80,286	82,728	11.38	−275	0.03	−8011

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Breast Cancer Trialists' Collaborative Group.[27] Background mortality rates were based on 2006 US life tables published by the National Center for Health Statistics.[28]

Quality of life

We assigned a utility to each health state that reflected the preference for, or desirability of, that health state. Utilities for breast cancer-related health states and adjuvant hormone therapy were taken from a published metaregression of standard gamble scores collected from community samples.[29]

Costs

Direct medical costs of breast cancer-related health states were based on health insurance claims in a large Midwestern health care system.[24,30] The societal cost of informal caregiving for patients who received treatment for cancer recurrence was obtained from a nationally representative survey.[31] We calculated a weighted average price of AIs using an online pharmacy database[12] and the current US market share (ie, 58% for generic anastrozole, 29% for generic letrozole, 9% for generic exemestane, 2% for brand-name letrozole, 1% for brand-name anastrozole, and 1% for brand-name exemestane).[23] In sensitivity analyses, we evaluated an alternate assumption that the drug cost of AIs fell to that of the least expensive AIs (ie, $15 per month for generic anastrozole). Because of the substantial variation in the benefits offered by Medicare Part D plans, we calculated a mean patient copayment for each AI using an online Medicare plan finding tool.[13] All costs were inflated to 2011 dollars using the Consumer Price Index for Medical Care for All Urban Consumers.[32]

Base-Case Analysis

In the base-case analysis, using the societal perspective, we assumed that drug costs were entirely covered by society (ie, patients and/or Medicare) for both usual and full prescription coverage, and providing full prescription coverage increased total drug spending only as a result of improved adherence. We calculated the incremental cost-effectiveness ratio (ICER) of a target strategy as its additional cost divided by its additional health benefit compared with the competing strategy. Health benefits were measured in quality-adjusted life years (QALYs) gained. We assumed a discount rate of 3% per year for both health benefits and costs.[33]

Sensitivity Analyses

To assess the robustness of our findings, we performed extensive deterministic sensitivity analyses. We obtained ranges tested from 95% confidence intervals when available; otherwise, we used from 50% to 200% of the base-case estimates. In a secondary analysis, we examined the perspective of Medicare. We also conducted a probabilistic sensitivity analysis in which the model was run using a value for each parameter down randomly from the distribution assigned to that parameter.[34] We ran 10,000 iterations to generate a cost-effectiveness acceptability curve demonstrating the probability that full prescription coverage is cost-effective at various willingness-to-pay thresholds compared with usual prescription coverage.

Model Validation

In the simulated cohort (mean age, 61 years), the 8-year disease-free and overall survival rates were 72% and 82%, respectively. These estimates calibrated well with observed data from the BIG 1-98 trial.[25]

RESULTS

Base-Case Analysis

For patients receiving usual prescription coverage, average quality-adjusted survival was 11.35 QALYs, and lifetime costs were $83,002 (Table 2). For patients receiving full prescription coverage, average quality-adjusted survival was 11.38 QALYs, and lifetime costs were $82,728. Compared with usual prescription coverage, full prescription coverage improved quality-adjusted survival by 0.03 QALYs per beneficiary and reduced costs by about $275 per beneficiary. Because it yielded greater health benefits at a lower cost, full prescription coverage dominated the strategy of usual prescription coverage. Savings from full

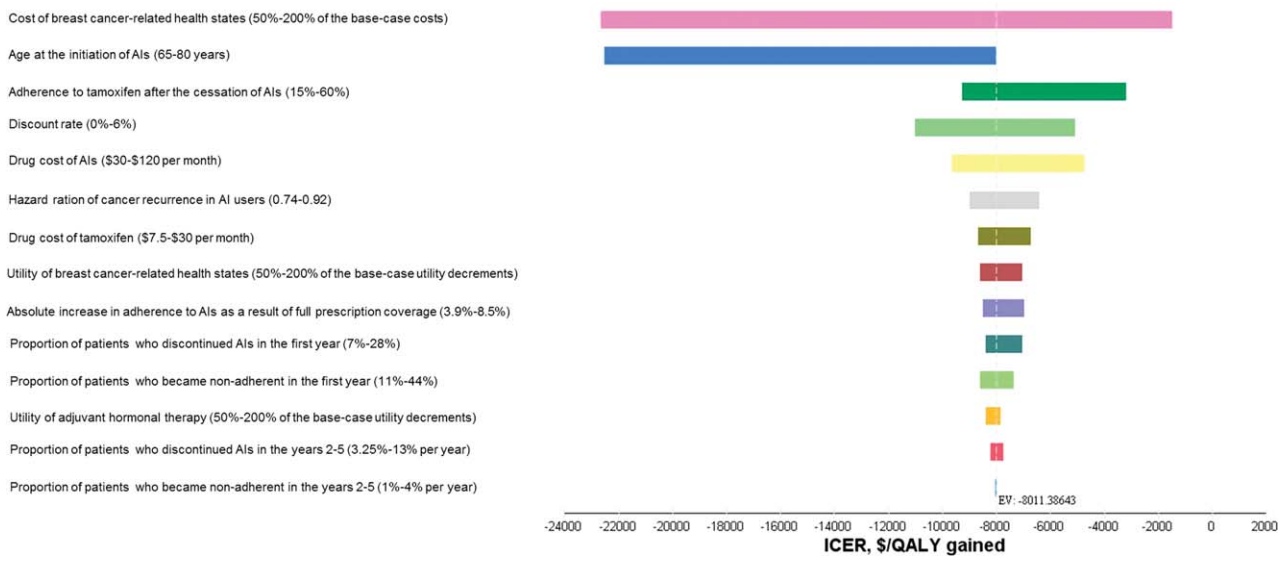

Figure 2. This is a Tornado diagram summarizing deterministic sensitivity analyses. Each bar represents the incremental cost-effectiveness ratios (ICERs) of full prescription coverage from the societal perspective for different assumptions concerning the parameter listed. The vertical dashed line indicates the estimated value (EV) of the ICER when all parameters are set at their base-case values. AI indicates aromatase inhibitors; $/QALY indicates US dollars per quality-adjusted life-years.

TABLE 3. Results From the Perspective of Medicare

	Cost, $				Incremental		
Strategy	Drug	Healthcare	Total	Total QALYs	Cost, $	QALYs	ICER, $/QALY
Usual prescription coverage	1523	78,395	79,918	11.35		Reference	
Full prescription coverage	2442	77,994	80,436	11.38	518	0.03	15,128

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

prescription coverage resulted entirely from cancer recurrence avoided and were somewhat offset by the higher prescription drug cost of AIs.

Sensitivity Analyses

At a conventional cost-effectiveness threshold of $100,000 per QALY gained, our findings were robust to all model parameters (Fig. 2). Full prescription coverage would remain preferred as long as the absolute increase in adherence from full prescription coverage was at least 0.1%. Full prescription coverage would remain cost saving (ie, would save both lives and money) compared with usual prescription coverage if the absolute increase in adherence from full prescription coverage was greater than 1.2%. Assuming a lower drug cost of AIs (ie, $15 per month for generic anastrozole), cost saving from full prescription coverage increased to $359 per beneficiary.

Repeating our analysis from the payer's perspective, the Medicare program incurred a larger increase in the prescription drug cost of AIs under full prescription coverage than that incurred under the base-case assumption of societal perspective. In contrast, full prescription coverage resulted in smaller incremental savings in nondrug health care costs from the perspective of Medicare, because the cost of informal caregiving is not incurred by Medicare. Overall, full prescription coverage cost Medicare an additional $518 per beneficiary. By using the perspective of Medicare, the ICER for full prescription coverage was $15,128 per QALY gained (Table 3). At a conventional cost-effectiveness threshold of $100,000 per QALY gained, full prescription coverage would remain preferred as long as the absolute increase in adherence from full prescription coverage was at least 1.4%. Full prescription coverage would become cost saving compared with usual prescription coverage if the absolute increase in adherence

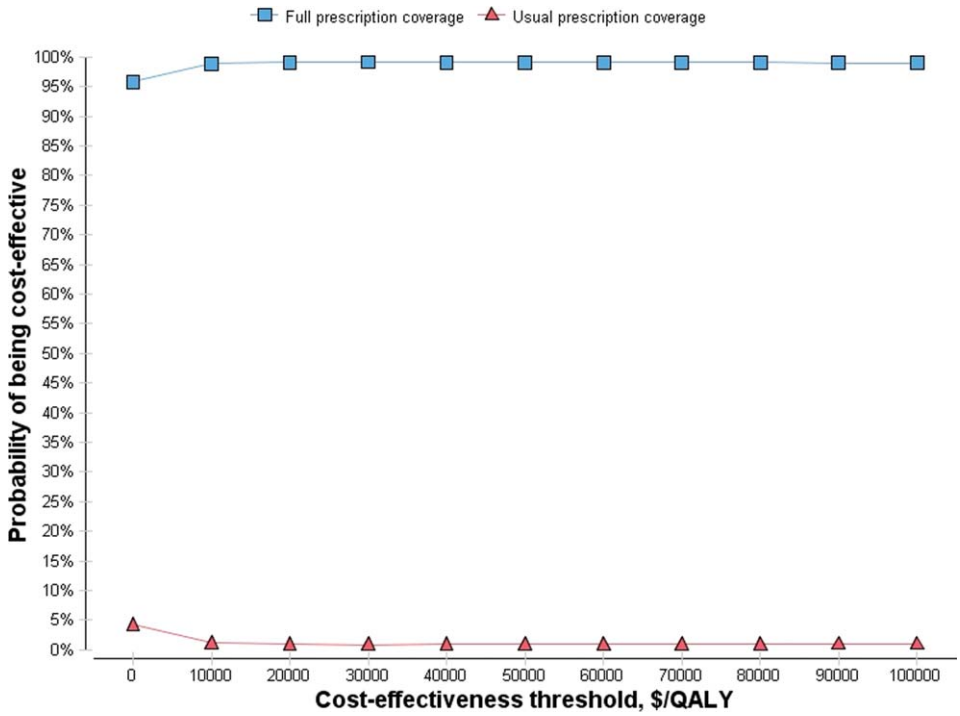

Figure 3. This is a cost-effectiveness acceptability curve for usual and full prescription coverage from the societal perspective. $/QALY indicates US dollars per quality-adjusted life-years.

from full prescription coverage was greater than 17%. Assuming a lower drug price of AIs (ie, $15 per month for generic anastrozole), full prescription coverage reduced the Medicare costs by $117 per beneficiary.

The results of the probabilistic sensitivity analysis are displayed in the cost-effectiveness acceptability curve. From the societal perspective, full prescription coverage was cost saving from the societal perspective in 96% of simulations, and its ICER was less than $100,000 per QALY gained in 99% of simulations (Fig. 3). From the Medicare perspective, full prescription coverage was cost saving in 0.04% of simulations, and its ICER was less than $100,000 per QALY gained in 98% of simulations (Fig. 4).

DISCUSSION

Our cost-effectiveness analysis suggests that, compared with the current Medicare Part D drug benefit, eliminating patient cost sharing for AIs for hormone receptor-positive early breast cancer would both improve health outcomes and save money from the societal perspective. We observed that the incremental cost of full prescription coverage for AIs could be offset entirely by the cost reductions from additional cancer recurrences that are averted. Average cost reductions of approximately $275 per beneficiary would save society almost $17 million for the approximately 60,000 Medicare beneficiaries who receive treatment for hormone receptor-positive early breast cancer every year.[22,35] Our results were robust to most of the model assumptions. In particular, full prescription coverage would continue to be reasonably cost-effective even if the increase in adherence was substantially smaller than our base-case estimate.

Cost sharing is a ubiquitous feature of the US health care system.[36-38] And, as the burden of cost sharing continues to grow, patients may increasingly avoid essential medical interventions.[36,39,40] Studies of patients with a variety of chronic health conditions have indicated that a 10% increase in patient cost sharing is associated with a reduction of 1% to 6% in spending on prescription drugs and an increase in the use of other resources, such as emergency departments and inpatient services.[36,41] One-third of patients with breast cancer report difficulty paying for medical bills, and almost half report skipping treatment or not filling prescriptions because of the cost.[42,43] For example, in a recent analysis of the Surveillance, Epidemiology, and End Results-Medicare database evaluating beneficiaries with hormone receptor-positive breast cancer, those who had copayments greater than $15 per month were >4 times more likely to abandon AIs than those who had copayments of less than $4.99 per

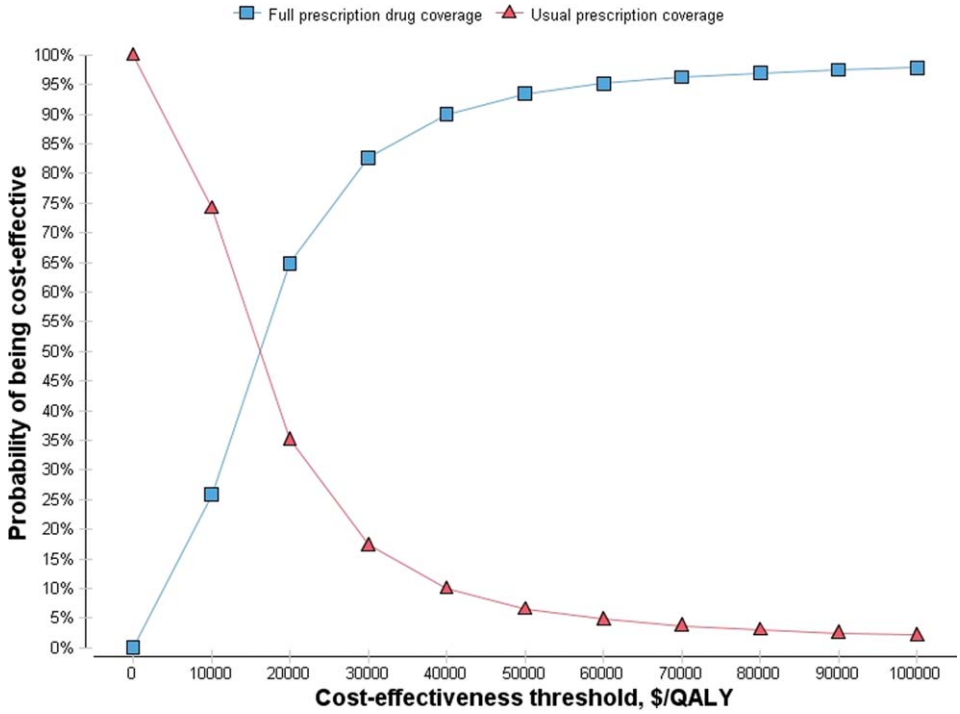

Figure 4. This is a cost-effectiveness acceptability curve for usual and full prescription coverage from the Medicare perspective. $/QALY indicates US dollars per quality-adjusted life-years.

month.[15] Furthermore, 3.4 million (14%) Medicare Part D beneficiaries reach the coverage gap each year.[44] A lack of financial assistance to help pay for drugs after reaching the coverage gap has been associated with a doubling in discontinuing essential drugs, including AIs.[15,45]

One logical response to these observations is to base cost sharing on value, rather than acquisition costs. This framework, widely known as value-based insurance design (VBID), is an approach to encourage the use of potentially life-saving, high-value services (ie, those that provide important health benefits relative to costs) by reducing or removing copayments.[46-48] For example, in a recent randomized controlled trial of commercially insured patients who were discharged from hospital after myocardial infarction, the elimination of patient cost sharing for evidence-based therapies not only increased medication adherence but also reduced the rates of major vascular events without increasing overall health spending.[17] Although VBID is encouraged by the Patient Protection and Affordable Care Act and has been implemented increasingly in the management of chronic health conditions, such as cardiovascular diseases, diabetes mellitus, and asthma,[16,18,49] the concept of VBID is relatively novel in cancer care.[50] Our findings support a reconsideration of how Medicare structures its benefits, especially for drugs with proven efficacy that are underused because of cost constraints.[51-54] In fact, in a sensitivity analysis conducted from the perspective of the Medicare program, we observed that full prescription coverage for AIs, although not cost saving, had a modest ICER and would be considered cost-effective relative to many interventions currently covered by Medicare.[55] While concerns mount over increasing Medicare budgets, our analysis suggests that lowering the drug cost of AIs to the level of the least expensive AI (ie, generic anastrozole) would make full prescription coverage cost saving also from the perspective of the Medicare program.

Our analysis is subject to several limitations. First, the estimated impact of eliminating patient cost sharing was not based on breast cancer-specific studies. Although our conclusion was robust to a range of assumptions about model parameters, prospective studies in patients with breast cancer are warranted. Second, we did not model predictors of nonadherence to AIs, such as larger tumor size, higher cytochrome P450 2D activity, history of mastectomy and radiation therapy, and follow-up by noncologists.[56] These predictors may have an independent impact on the prognosis of breast cancer. Third, we did not model the influence of toxicity profile of adjuvant hormone therapy on drug use.[57]

Breast cancer is a costly disease for patients, health care systems, and society. Thus, as the population ages and the number of Medicare beneficiaries increases relative to the rest of the population, so will the number of Medicare beneficiaries with hormone receptor-positive early breast cancer and the share of national health expenditures allocated to cancer recurrence after primary therapy. This cost-effectiveness analysis of a hypothetical cohort of Medicare beneficiaries suggests that, compared with the current Medicare Part D drug benefit, the elimination of patient cost sharing for adjuvant AIs for hormone receptor-positive early breast cancer would both improve health and save money from the societal perspective.

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The authors made no disclosures.

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