

# Modeling the Population Outcomes of Cost-Related Nonadherence: Model Report

Prepared for:  
Sean Dickson  
Director, Health Policy  
West Health Policy Center

September 21, 2020

**Table of Contents**

1.1 Executive Summary ..... 3

    1.1.1 Introduction ..... 3

    1.1.2 Methods ..... 3

    1.1.3 Results ..... 3

    1.1.4 Conclusion ..... 3

1.2 Introduction ..... 4

1.3 Methods ..... 4

    1.3.1 Model Structure ..... 4

        1.3.1.1 Population ..... 5

        1.3.1.2 Perspective ..... 6

        1.3.1.3 Time Horizon ..... 6

        1.3.1.4 Counterfactual Scenarios ..... 6

    1.3.2 Model Inputs and Data Sources ..... 6

        1.3.2.1 Population ..... 7

        1.3.2.2 Baseline Resource Use ..... 9

        1.3.2.3 Price Elasticities and Offset Effects ..... 9

        1.3.2.4 Policy Intervention ..... 11

    1.3.3 Summary of Key Assumptions ..... 12

1.4 Results ..... 13

1.5 Discussion ..... 14

    1.5.1 Limitations ..... 15

1.6 Conclusion ..... 15

1.7 References ..... 17

## **1.1 Executive Summary**

### *1.1.1 Introduction*

Prior works have estimated that medication nonadherence alone costs the United States (US) \$100 billion per year (Osterberg 2005); however, medication nonadherence may stem from a variety of causes. Due to rising out-of-pocket costs for medications covered by Medicare Part D, medication affordability is a documented influencer of medication adherence and an important concern among Medicare Part D beneficiaries with chronic conditions. Although the frequency of cost-related nonadherence and its risk factors have been previously examined, the aggregate economic impacts of morbidity and mortality to the Medicare program have not been previously isolated and explored.

### *1.1.2 Methods*

A Microsoft Excel-based population model was developed from the Medicare perspective to estimate the changes in adherence, mortality, and costs that would result from eliminating cost-related nonadherence among Medicare beneficiaries. Specifically, the analysis considers non-Low-Income Subsidy (LIS) Medicare beneficiaries with at least 1 to 2 chronic conditions or non-LIS Medicare beneficiaries with 1 of 5 chronic conditions selected for their representativeness in price elasticity and offset effects (atrial fibrillation [AF], chronic kidney disease [CKD], chronic obstructive pulmonary disease [COPD], diabetes mellitus [DM], and ischemic heart disease [IHD]). The target population incurs baseline pharmacy costs, medical costs, and risk of disease-related mortality at a baseline level of adherence and cost-sharing over 10 years beginning in 2021. These outcomes may be reduced when reductions in cost-sharing increase medication adherence according to the price elasticity of demand, spurring associated reductions in medical costs and disease-related mortality. Results are presented in 2020 US dollars for each year of the analysis and as 10-year totals for the changes in number of deaths and costs.

### *1.1.3 Results*

In the base-case analysis, the elimination of out-of-pocket costs in the outpatient pharmacy setting improves adherence by a relative change of 4.5% to 17.0% across each setting (14.6%, AF; 13.0%, CKD; 10.0%, COPD; 4.5%, DM; 17.0%, IHD; 12.3%, Medicare), which can lead to an improvement in the beneficiaries' overall health condition. Consequently, a decrease in the risk of disease-related death is observed across all scenarios, culminating in approximately 1.1 million deaths avoided over 10 years for all non-LIS Medicare patients with at least 1 to 2 chronic conditions. Similarly, the improved health condition is also predicted to reduce medical spending by \$177.4 billion over the same period. Moreover, the improvement in adherence, the shift of out-of-pocket pharmacy costs to the Medicare budget, and the increased number of living beneficiaries have contributed to an estimated increase of \$375.7 billion in pharmacy spending over 10 years.

### *1.1.4 Conclusion*

By eliminating cost-related nonadherence among beneficiaries with at least 1 to 2 chronic conditions, Medicare would save \$177.4 billion in avoidable medical costs and reduce total deaths by about 1.1 million over 10 years. Because out-of-pocket costs would shift to Medicare, prescription drug consumption would increase with increases in adherence and the number of living beneficiaries. Consequently, total pharmacy costs are estimated to rise by \$375.7 billion over 10 years.

## 1.2 Introduction

Medication adherence refers to how well patients follow the instructions given by their healthcare providers for taking a medication regimen. Medication nonadherence, or the extent to which a patient does not follow the medication regimen prescribed by their healthcare provider, occurs more often in conditions that are chronic or asymptomatic vs acute or symptomatic (Osterberg 2005). Medication nonadherence may stem from a variety of root causes, including perceived need for medications, perceived concerns about medications, and medication affordability (McHorney 2009, Osterberg 2005). Regardless of cause, medication adherence has significant consequences, such as uncontrolled signs and symptoms of disease, excess healthcare resource use, and reduced quality of life (Viswanathan 2012).

In 1996, Johnson and Bootman published a conceptual model of drug-related morbidity and mortality to estimate the costs of negative outcomes associated with outpatient drug therapy from a United States (US) third-party payer perspective. The analysis focused on 8 previously identified outpatient drug therapy problems: untreated indication, improper drug selection, subtherapeutic dosage, failure to receive drugs, overdosage, adverse drug reactions, drug interactions, and drug use without indication. Their decision tree model, which estimated the probabilities of negative outcomes based on a telephone survey of ambulatory clinical pharmacists, estimated that ambulatory drug-related morbidity and mortality cost US third-party payers \$76.6 billion annually. Over the next 20 years, Johnston and Bootman's 1996 estimate would be updated 3 times with new costs (Ernst and Grizzle 2001, NEHI 2008, Watanabe 2018). The 2008 estimate by the New England Healthcare Institute (NEHI) garnered particular attention, estimating that nonadherence combined with suboptimal prescribing, drug administration, and diagnosis could cost the US nearly \$300 billion per year; separately, the report cited prior works estimating that nonadherence alone costs the US \$100 billion per year (NEHI 2008).

Due to rising out-of-pocket costs for medications covered by Part D, medication affordability is an important concern among Medicare beneficiaries with chronic conditions. When high out-of-pocket costs cause patients to limit their medication consumption by rationing medication, skipping doses, or discontinuing therapy, patients may no longer adhere to the regimen prescribed by their doctor. Although the frequency of this subtype of nonadherence, termed "cost-related nonadherence," and its risk factors have been explored previously, the economic effects related to its morbidity and mortality have not been isolated in the aforementioned analyses. However, ongoing discussions and subsequent decisions about healthcare reform and changes to the Medicare Part D benefit design would be ill-informed without appropriately examining the effects of any changes in out-of-pocket costs for Medicare beneficiaries.

The Gary and Mary West Health Policy Center cost-related nonadherence model was developed to isolate and estimate the impact that high out-of-pocket costs have on (1) medication adherence and mortality among Medicare beneficiaries, and (2) pharmacy and medical spending for the Medicare program. The analysis includes not only all non-Low-Income Subsidy (LIS) Medicare beneficiaries with 1 to 2 chronic conditions, but also those with 1 of 5 prevalent chronic diseases selected to represent heterogeneous archetypes of price elasticity and offset effects: atrial fibrillation (AF), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), and ischemic heart disease (IHD). Secondly, the model structure is designed to accommodate the basic policy features of H.R. 3, the Elijah E. Cummings Lower Drug Costs Now Act, in order to estimate its clinical and economic consequences.

## 1.3 Methods

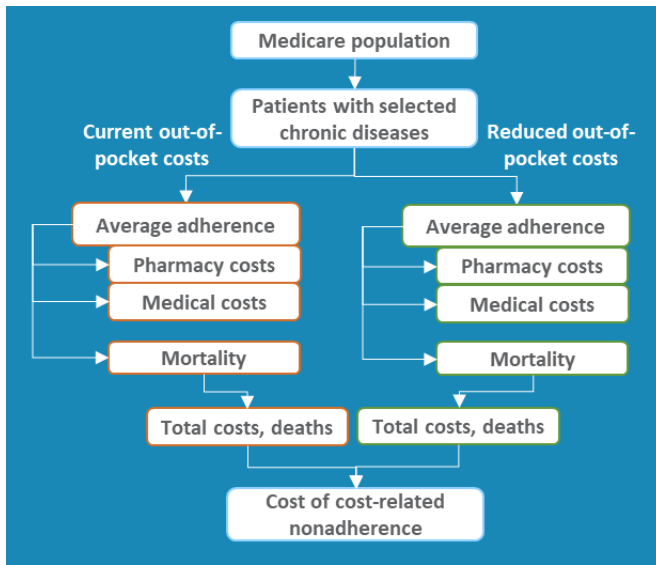
### 1.3.1 *Model Structure*

A Microsoft Excel-based population model was developed to estimate the changes in adherence, mortality, and costs when cost-related nonadherence is eliminated among non-LIS Medicare beneficiaries with at least 1 to 2 chronic conditions or those with 1 of 5 chronic conditions. As described in Section 1.3.1.1.1, the 5 chronic conditions were selected for their representativeness in price elasticity and offset effects.

The population model was developed from the perspective of Medicare, with an outlook of 10 years beginning in 2021. For the projected number of beneficiaries in each of year of the modeled horizon, the model incorporates estimates of baseline prevalence, incidence, all-cause mortality, and disease-related mortality to estimate the target

population in each of the 6 modeled scenarios. The target population incurs pharmacy and medical costs at their baseline level of adherence and cost-sharing; these medical costs may be reduced when reductions in cost-sharing increase medication adherence according to the price elasticity of demand, spurring an associated reduction in disease-related mortality. Results are presented in 2020 US dollars for each year of the analysis and as 10-year totals for the changes in number of deaths and costs (pharmacy costs, medical costs, and total costs) by comparing outcomes in the counterfactual scenario (where cost-related nonadherence does not exist) to outcomes in the base-case scenario (where high out-of-pocket costs cause cost-related nonadherence). A diagram illustrating the structure of the model is depicted in **Figure 1**.

**Figure 1. Model Structure**



### 1.3.1.1 Population

The target population includes Medicare beneficiaries who are ineligible for the Medicare Part D LIS. The number of non-LIS Medicare beneficiaries, comprising new and prevalent enrollees, is referenced individually in each year of the base-case analysis. In other words, the model does not calculate a population trace following 1 beginning cohort of patients.

Treatment adherence may have different magnitudes of impact on mortality, depending on the nature of the chronic condition. For example, patients with rheumatoid arthritis have very similar mortality rates compared to the general population, (Lacaille 2017) making it very unlikely that any improvement in adherence would improve the overall survival of these patients. As a result, improving cost-related nonadherence will only impact a subset of those non-LIS Medicare beneficiaries with  $\geq 1$  chronic condition. To that end, the target population of the overall Medicare analysis includes non-LIS Medicare beneficiaries with at least 1 to 2 chronic conditions, based on the median of the percentage of Medicare enrollees  $\geq 65$  years old with  $\geq 1$  chronic condition and the percentage of those with  $\geq 2$  chronic conditions. The target population for the each of the chronic disease analyses is calculated based on the prevalence of disease applied to the overall estimated non-LIS Medicare enrollment.

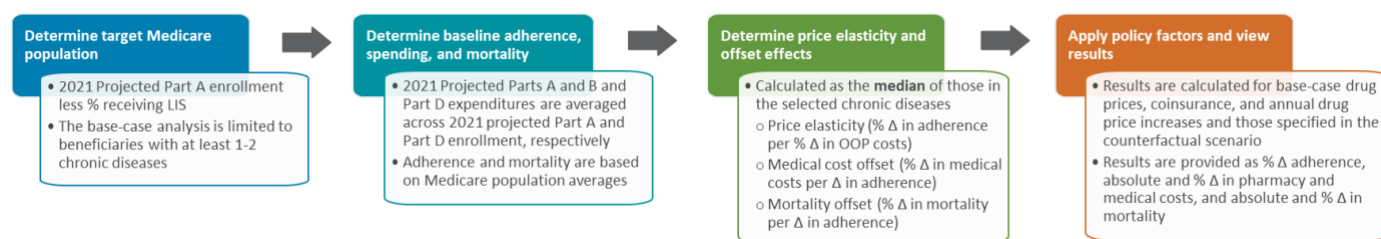
#### 1.3.1.1.1 Method of Extrapolation to the Medicare Program: Selection of Chronic Diseases

Chronic diseases were purposefully selected to represent possible combinations (high and low) of price elasticity and offset effects. To ensure that the median price elasticity and offset effect from those observed in the selected chronic diseases can be generalized to the overall Medicare population, the process of identifying potential chronic diseases to include in the analysis considered the most prevalent conditions among Medicare beneficiaries according to the Medicare Chronic Conditions Warehouse (CMS 2019). Compared to other selected chronic diseases, both CKD and AF have relatively low price elasticity and low cost offset effect. To improve the accuracy of extrapolation, CKD was excluded when extrapolating to the overall Medicare population so as not to cause a double counting with AF.

Prior to incorporating data for price elasticity of demand, we estimated relative price elasticity of demand by comparing the percentage of patients reporting cost-related nonadherence in each chronic disease to the percentage of patients categorized as adherent. Similarly, we estimated the medical cost offset effect and the mortality offset effect by performing a literature search to tabulate the baseline medical costs and mortality, as well as changes observed in adherent vs nonadherent patients. Subsequently, we benchmarked the magnitude of the expected price elasticity of demand, cost offset effect, and mortality offset effect relative to the other conditions and selected 5 conditions—AF, CKD, COPD, DM, and IHD—to represent the range of combinations of price elasticity of demand and offset effects. As described in Section 1.3.2.1, the prevalence of each of these conditions ranges from 9.5% to 28.8% of Medicare beneficiaries. Therefore, it is likely that the model represents the majority of Medicare beneficiaries.

**Figure 2** outlines the method for extrapolating the data to patients with chronic conditions in the overall Medicare program. From the data for each chronic condition, we calculated the median value for price elasticity of demand, cost offset effect, and mortality offset effect. These values were then applied to the input data for the target population, baseline adherence, baseline costs, and baseline mortality (determined separately). For example, the target population of the overall Medicare analysis is based on the number of Medicare beneficiaries who would not qualify for the Part D LIS and who have at least 1 to 2 chronic diseases. This target population is not derived from the 5 chronic disease analyses.

**Figure 2. Method for Extrapolation of Results to the Medicare Program**



Key: LIS – Low-Income Subsidy; OOP – out-of-pocket.

### 1.3.1.2 Perspective

The model assumes the perspective of the US Medicare program. Quality of life and indirect societal costs such as patient and caregiver productivity losses are not captured within the model. Only on-budget expenditures, including pharmacy and medical costs, are captured, alongside the annual number of deaths as a measure of mortality.

### 1.3.1.3 Time Horizon

A 10-year outlook of the effects related to cost-related medication nonadherence is considered.

### 1.3.1.4 Counterfactual Scenarios

Two counterfactual scenarios are studied with the model:

- By default, the analysis models the impact of eliminating patient cost-sharing (including copayments, coinsurances, deductibles, and catastrophic spending) in the counterfactual scenario.
- Additionally, the model is capable of incorporating other changes based on the policy levers outlined in H.R. 3, the Elijah E. Cummings Lower Drug Costs Now Act. A percentage change in drug list price (applied to the first year of the analysis) may be modeled, and a change in the average rate of annual drug list price increases may be included. These factors are held constant between the base-case and counterfactual scenarios when modeling the outcomes associated with cost-related nonadherence.

## 1.3.2 Model Inputs and Data Sources

The model is populated with base-case values determined from government- and literature-based estimates.

### 1.3.2.1 Population

The underlying population for the analysis is made up of non-LIS Medicare beneficiaries. The population in each year through 2029 is derived from the May 2018 baseline forecast from the Congressional Budget Office (CBO), which provides the average monthly enrollment in Medicare Part A. The corresponding population in 2030 is determined by applying the compound annual growth rate observed from 2021 through 2029 to the population forecasted by the CBO in 2029 (CBO 2018).

A portion of Medicare beneficiaries is eligible for the Part D LIS, which provides reduced premiums and cost-sharing. It is assumed that these enrollees would not experience a reduction in cost-sharing and would follow their medication regimens similarly in the base-case and counterfactual scenarios. Therefore, these enrollees are excluded by applying an estimate of the proportion of all Medicare Part A beneficiaries who would qualify for the LIS in Medicare Part D if enrolled (29%) in order to arrive at the baseline populations illustrated in **Table 1** (Cubanski 2019).

**Table 1. Number of Medicare Non-LIS Beneficiaries, 2021–2030**

Year	Value (Range for Sensitivity Analyses)	Standard Error	Distribution	Source
2021	45,440,000 (40,896,000–49,984,000)	2,318,367	Normal	CBO 2019, Cubanski 2019
2022	46,150,000 (41,535,000–50,765,000)	2,354,592	Normal	CBO 2019, Cubanski 2019
2023	47,570,000 (42,813,000–52,327,000)	2,427,041	Normal	CBO 2019, Cubanski 2019
2024	48,990,000 (44,091,000–53,889,000)	2,499,490	Normal	CBO 2019, Cubanski 2019
2025	50,410,000 (45,369,000–55,451,000)	2,571,939	Normal	CBO 2019, Cubanski 2019
2026	51,120,000 (46,008,000–56,232,000)	2,608,163	Normal	CBO 2019, Cubanski 2019
2027	52,540,000 (47,286,000–57,794,000)	2,680,612	Normal	CBO 2019, Cubanski 2019
2028	53,960,000 (48,564,000–59,356,000)	2,753,061	Normal	CBO 2019, Cubanski 2019
2029	54,670,000 (49,203,000–60,137,000)	2,789,286	Normal	CBO 2019, Cubanski 2019
2030	55,948,432 (50,353,589–61,543,275)	2,854,512	Normal	CBO 2019, Cubanski 2019, assumption

Key: CBO – Congressional Budget Office; LIS – Low-Income Subsidy.

The analysis of the impact of cost-related nonadherence is conducted for Medicare beneficiaries with at least 1 to 2 chronic conditions, calculated as the average of the percentage of Medicare enrollees aged at least 65 years with  $\geq 1$  chronic condition and those with  $\geq 2$  chronic conditions. Separately, the analysis is conducted for 5 groups of patients with certain chronic diseases. The target population for each of these 6 analyses is determined individually for each year of the analysis.

For each of the 5 chronic diseases, the target population in the first year of the analysis (2021) is determined by applying the baseline prevalence of disease to the underlying population (all non-LIS Medicare beneficiaries). Thereafter, these prevalent patients are at risk of dying from the chronic disease (disease-related mortality risk) or from other causes (all-cause mortality risk less disease-related mortality risk). Patients who do not die continue to the next year of the analysis, where they are joined by incident patients. The incident patient population is determined by multiplying the number of at-risk beneficiaries (all non-LIS Medicare beneficiaries less the prevalent patient population) by the annual incidence. For Medicare, in each year of the analysis, the underlying population is multiplied by 75.56%, based on averaging the percentages of patients with  $\geq 1$  (68.87%) and  $\geq 2$  chronic conditions (82.24%), respectively.

In the counterfactual scenario, improvements in medication adherence may result in a reduced risk of disease-related mortality. When this occurs, the number of deaths in each year of the analysis is less than the number of deaths in the corresponding year of the analysis under the base-case scenario. To avoid overestimating the impact of cost-related nonadherence, any lives saved are added to the target population in the subsequent year of each analysis.

The epidemiological parameters used to determine the target population size for each analysis are provided in **Table 2**.

**Table 2. Target Population Parameters**

Parameter	Value (Range for Sensitivity Analyses)	Standard Error	Distribution	Source
<b>AF</b>				
<i>Baseline prevalence</i>	9.50% (8.55%, 10.45%)	0.48%	Beta	CMS 2019
<i>Annual incidence</i>	2.79% (2.51, 3.07%)	0.14%	Beta	Piccini 2012
<i>Annual AF-related mortality<sup>a</sup></i>	3.30% (2.97%, 3.63%)	0.17%	Beta	CDC 2020
<i>Annual all-cause mortality</i>	16.70% (15.03%, 18.37%)	0.85%	Beta	Piccini 2012
<b>CKD</b>				
<i>Baseline prevalence</i>	14.50% (13.05%, 15.95%)	0.74%	Beta	USRDS 2019
<i>Annual incidence</i>	4.40% (3.96%, 4.84%)	0.22%	Beta	NKUDIC 2012
<i>Annual CKD-related mortality<sup>b</sup></i>	1.23% (1.11%, 1.35%)	0.06%	Beta	CDC 2020
<i>Annual all-cause mortality</i>	11.54% (10.39%, 12.69%)	0.59%	Beta	USRDS 2018
<b>COPD</b>				
<i>Baseline prevalence</i>	11.60% (10.44%, 12.76%)	0.59%	Beta	CMS 2019
<i>Annual incidence</i>	4.40% (3.96%, 4.84%)	0.09%	Beta	McBurnie 2018
<i>Annual COPD-related mortality<sup>c</sup></i>	4.25% (3.83%, 4.68%)	0.22%	Beta	CDC 2020
<i>Annual all-cause mortality</i>	7.00% (6.30%, 7.70%)	0.36%	Beta	Gershon 2010
<b>DM</b>				
<i>Baseline prevalence</i>	27.40% (24.66%, 30.14%)	1.40%	Beta	CMS 2019
<i>Annual incidence</i>	3.00% (2.70%, 3.30%)	0.15%	Beta	Andes 2019
<i>Annual DM-related mortality<sup>d</sup></i>	1.46% (1.31%, 1.61%)	0.08%	Beta	CDC 2020
<i>Annual all-cause mortality</i>	6.88% (6.19%, 7.57%)	0.35%	Beta	Carnethon 2010
<b>IHD</b>				
<i>Baseline prevalence</i>	28.80% (25.92%, 31.68%)	1.47%	Beta	CMS 2019
<i>Annual incidence</i>	0.99% (0.90%, 1.08%)	0.05%	Beta	Kent 2015
<i>Annual IHD-related mortality<sup>e</sup></i>	2.90% (2.61%, 3.19%)	0.15%	Beta	CDC 2020
<i>Annual all-cause mortality</i>	6.88% (6.19%, 7.57%)	0.35%	Beta	Menzin 2008
<b>Medicare</b>				
<i>% with ≥1 chronic disease</i>	75.56% (68.87%, 82.24%)	3.41%	Beta	CMS 2019
<i>Annual mortality</i>	4.45% (4.45%, 4.47%)	0.01%	Beta	Krumholz 2015

<sup>a</sup> ICD-10 codes: I48 (atrial fibrillation and flutter).

<sup>b</sup> ICD-10 codes: N18.0 (end-stage renal disease); N18.1 (chronic kidney disease, stage 1); N18.2 (chronic kidney disease, stage 2); N18.3 (chronic kidney disease, stage 3); N18.4 (chronic kidney disease, stage 4); N18.5 (chronic kidney disease, stage 5); N18.8 (other chronic renal failure); N18.9 (chronic renal failure, unspecified).

<sup>c</sup> ICD-10 codes: J40 (bronchitis, not specified as acute or chronic); J41.0 (simple chronic bronchitis); J41.1 (mucopurulent chronic bronchitis); J41.8 (mixed simple and mucopurulent chronic bronchitis); J42 (unspecified chronic bronchitis); J43.0 (MacLeod syndrome); J43.1 (panlobular emphysema); J43.2 (centrilobular emphysema); J43.8 (other emphysema); J43.9 (emphysema, unspecified); J44.0 (chronic obstructive pulmonary disease with acute lower respiratory infection); J44.1 (chronic obstructive pulmonary disease with acute exacerbation, unspecified); J44.8 (other specified chronic obstructive pulmonary disease); J44.9 (chronic obstructive pulmonary disease, unspecified).

<sup>d</sup> ICD-10 codes: E10–E14 (diabetes mellitus).

<sup>e</sup> ICD-10 codes: I20–I25 (ischemic heart diseases).

Key: AF – atrial fibrillation; CDC – Centers for Disease Control and Prevention; CKD – chronic kidney disease; CMS – Centers for Medicare & Medicaid Services; COPD – chronic obstructive pulmonary disease; DM – diabetes mellitus; ICD-10 – International Classification of Diseases, 10th Revision; IHD – ischemic heart disease; NKUDIC – National Kidney and Urologic Diseases Information Clearinghouse; USRDS – United States Renal Data System.



### 1.3.2.2 Baseline Resource Use

Disease-related pharmacy and medical costs are considered in each of the 5 chronic disease-specific analyses of cost-related nonadherence. Because of the conservative assumption that improvements in adherence to medications used in each chronic disease improve only disease-specific (vs all-cause) spending and mortality, only disease-specific spending was considered in the analysis. However, all-cause spending per patient in the Medicare program was considered, since global changes in adherence were considered in that scenario. Pharmacy spending represents total projected mandatory Part D outlays in 2021 averaged across projected non-LIS Part D beneficiaries. Meanwhile, medical spending represents total projected mandatory outlays across Parts A and B averaged across the projected average monthly enrollment in Part A in 2021 (CBO 2019).

Baseline adherence and cost values are provided in **Table 3**.

**Table 3. Baseline Adherence Values and Costs**

Parameter	Value (Range for Sensitivity Analyses)	Standard Error	Distribution	Source
<b>AF</b>				
<i>Adherence</i>	73.00% (71.87%, 74.13%)	0.58%	Beta	Zhou 2015
<i>AF-related pharmacy costs</i>	\$3,533 (\$3,454, \$3,612)	\$40	Gamma	Datar 2019
<i>AF-related medical costs</i>	\$14,800 (\$13,888, \$15,712)	\$465	Gamma	Datar 2019
<b>CKD</b>				
<i>Adherence</i>	57.30% (56.75%, 57.85%)	0.58%	Beta	Park 2014
<i>CKD-related pharmacy costs</i>	\$2,957 (\$2,661, \$3,253)	\$151	Gamma	Honeycutt 2013
<i>CKD-related medical costs</i>	\$4,651 (\$4,186, \$5,116)	\$237	Gamma	Honeycutt 2013
<b>COPD</b>				
<i>Adherence</i>	55.00% (49.50%, 60.50%)	2.81%	Beta	Nishi 2018
<i>COPD-related pharmacy costs</i>	\$716 (\$682, \$750)	\$17	Gamma	Dalal 2011
<i>COPD-related medical costs</i>	\$2,029 (\$1,723, \$2,335)	\$156	Gamma	Dalal 2011
<b>DM</b>				
<i>Adherence</i>	75.97% (75.82%, 76.12%)	0.08%	Beta	Boye 2016
<i>DM-related pharmacy costs</i>	\$1,360 (\$1,350, \$1,370)	\$5	Gamma	Boye 2016
<i>DM-related medical costs</i>	\$3,902 (\$3,838, \$3,966)	\$33	Gamma	Boye 2016
<b>IHD</b>				
<i>Adherence</i>	79.00% (71.10%, 86.90%)	4.03%	Beta	Erickson 2014
<i>IHD-related pharmacy costs</i>	\$2,359 (\$2,321, \$2,397)	\$19	Gamma	Menzin 2008
<i>IHD-related medical costs</i>	\$13,113 (\$12,509, \$13,717)	\$308	Gamma	Menzin 2008
<b>Medicare</b>				
<i>Adherence</i>	85.31% (76.78%, 93.84%)	4.35%	Beta	Lester 2016
<i>Pharmacy costs</i>	\$2,640 (\$2,376, \$2,904)	\$135	Gamma	CBO 2019
<i>Medical costs</i>	\$12,094 (\$10,885, \$13,303)	\$617	Gamma	CBO 2019

Key: AF – atrial fibrillation; CBO – Congressional Budget Office; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; DM – diabetes mellitus; IHD – ischemic heart disease.

### 1.3.2.3 Price Elasticities and Offset Effects

The existence of cost-related nonadherence implies that adherence to medications would increase if out-of-pocket costs were lower. To model the change in adherence that would result from lower costs to patients, the price

elasticity of demand was estimated for each of the 5 chronic disease states. The price elasticity of demand is calculated from the literature as the percentage change in adherence for every 1 percentage point change in out-of-pocket spending. For this analysis, price elasticities were derived from a retrospective study that used data from Medicare Part D beneficiaries to estimate the price elasticity of demand with respect to coinsurance as patients entered the coverage gap, where out-of-pocket costs increase (Einav 2018). To translate drug class-specific elasticities to therapeutic area-specific elasticities, an average of the price elasticities for representative drug classes was determined.

Cost offsets were derived from the literature as the percentage change in medical costs per 1% absolute increase in adherence. Similarly, mortality offsets were determined based on prior research as the percentage change in mortality per 1% absolute increase in adherence; however, in the model, adherence to medication within a disease state only carries the potential of lowering disease-related (vs all-cause) mortality. As provided in **Table 4**, values for cost and mortality offset effects are less than 0, indicating that medical costs and the risk of dying from disease-related causes decrease with each 1% improvement in adherence (eg, an increase of 0.01 in an adherence measure like the proportion of days covered would produce some corresponding, relative decrease in medical costs and disease-related mortality). For Medicare, the price elasticity of demand, medical cost offset effect, and mortality offset effect were determined by taking the median of the respective values in 4 chronic disease states (AF, COPD, DM and IHD). Price elasticity and offset effect values are provided in **Table 4**.

**Table 4. Price Elasticities and Offset Effects**

Parameter	Value (Range for Sensitivity Analyses)	Standard Error	Distribution	Source
<b>AF</b>				
<i>Price elasticity<sup>a</sup></i>	-0.146% (-0.131%, -0.161%)	0.007%	Normal	Einav 2018
<i>Cost offset effect</i>	-0.228% (-0.205%, -0.251%)	0.012%	Normal	Deshpande 2018
<i>Mortality offset effect</i>	-0.7% (-0.29%, -1.07%)	0.199%	Normal	Borne 2017
<b>CKD</b>				
<i>Price elasticity<sup>b</sup></i>	-0.130% (-0.117%, -0.143%)	0.007%	Normal	Einav 2018
<i>Cost offset effect</i>	-0.114% (-0.103%, -0.125%)	0.006%	Normal	Lee 2011
<i>Mortality offset effect</i>	-0.8% (-0.40%, -1.30%)	0.230%	Normal	Molnar 2016
<b>COPD</b>				
<i>Price elasticity<sup>c</sup></i>	-0.100% (-0.090%, -0.110%)	0.005%	Normal	Einav 2018
<i>Cost offset effect</i>	-0.430% (-0.387%, -0.473%)	0.0022%	Normal	Toy 2011
<i>Mortality offset effect</i>	-0.6% (-0.54%, -0.65%)	0.028%	Normal	Vestbo 2009
<b>DM</b>				
<i>Price elasticity<sup>d</sup></i>	-0.045% (-0.041%, -0.050%)	0.002%	Normal	Einav 2018
<i>Cost offset effect</i>	-0.180% (-0.162%, -0.198%)	0.009%	Normal	Boye 2016
<i>Mortality offset effect</i>	-1.0% (-0.68%, -1.28%)	0.153%	Normal	Ho 2006
<b>IHD</b>				
<i>Price elasticity<sup>e</sup></i>	-0.170% (-0.153%, -0.187%)	0.009%	Normal	Einav 2018
<i>Cost offset effect</i>	-0.550% (-0.495%, -0.605%)	0.028%	Normal	Bansilal 2016
<i>Mortality offset effect</i>	-0.6% (-0.50%, -0.70%)	0.051%	Normal	Shalev 2009
<b>Medicare<sup>f</sup></b>				
<i>Price elasticity</i>	-0.123% (-0.111%, -0.135%)	0.006%	Normal	Assumption
<i>Cost offset effect</i>	-0.329% (-0.296%, -0.362%)	0.017%	Normal	Assumption
<i>Mortality offset effect</i>	-0.7% (-0.72%, -0.59%)	0.033%	Normal	Assumption

<sup>a</sup> Average for calcium-channel blocking agents (-0.10%), class III antiarrhythmics (-0.06%), class 1c antiarrhythmics (-0.08%), coumarin derivatives (-0.35%), and beta-adrenergic-blocking agents (-0.14%).

<sup>b</sup> Average for loop diuretics (-0.24%), replacement preparations (-0.10%), and vitamin D (-0.05%).

<sup>c</sup> Average for selective beta-2-adrenergic agents (-0.07%), adrenals (-0.05%), and antimuscarinics (-0.18%).

<sup>d</sup> Average for biguanides (-0.07%) and insulins (-0.02%). Sulfonylureas (0.00%), thiazolidinediones (0.05%), and dipeptidyl peptidase-4 inhibitors (0.10%) were excluded as positive values were due to sampling error (as reported by the authors).

<sup>e</sup> Average for HMG-CoA reductase inhibitors (-0.23%), beta-adrenergic-blocking agents (-0.14%), angiotensin II receptor antagonists (-0.39%), nitrates and nitrites (-0.04%), and direct vasodilators (-0.05%). Platelet-aggregation inhibitors (0.02%) were excluded as positive values were due to sampling error (as reported by the authors).

<sup>f</sup> Values for Medicare represent the median of 4 chronic disease states (AF, COPD, DM and IHD).

Key: AF – atrial fibrillation; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; DM – diabetes mellitus; IHD – ischemic heart disease.

### 1.3.2.4 Policy Intervention

The model base-case represents the status quo, and values for medical service price inflation, Medicare Part D cost-sharing, annual drug list price increases are based on recent retrospective data and CBO forecasts. For example, the cost-sharing percentage was determined based on total copayment, coinsurance, deductible, and catastrophic spending per patient in 2017, which was then divided by the sum of this value and per-patient non-LIS Medicare outlays. Rebate as % of list price was included to adjust for discounts and rebates from the list price.

In the counterfactual scenario, 2 of these factors (cost-sharing and annual drug list price increase) may be modified from the base-case, and a third factor (change in baseline drug list price) provides the ability to model an immediate change in pharmacy costs. In the base-case analysis, with the objective to quantify the economic and clinical impacts of cost-related nonadherence to the Medicare program, the percentage change in cost-sharing is set to  $-100\%$ , while other factors remain constant as described in **Table 5**.

**Table 5. Policy Parameters**

Parameter	Value (Range for Sensitivity Analyses)	Standard Error	Distribution	Source
Base-case scenario				
<i>Inflation of medical services</i>	3.8% (3.4%, 4.2%)	0.20%	Normal	BLS 2020
<i>Cost-sharing</i>	12.1% (9.1%, 11.1%)	0.52%	Beta	CBO 2019, Cubanski 2019
<i>Annual drug list price increases</i>	5.7% (5.1%, 6.3%)	0.3%	Normal	IQVIA 2019
<i>Rebate in 2021 as % of list price</i>	46%			IQVIA 2019
Counterfactual scenario				
<i>% change in cost-sharing</i>	$-100.0\%$ ( $-100.0\%$ , $-100.0\%$ )	0.0%	Beta	Assumption
<i>% change in drug list price</i>	0.0% (0.0%, 0.0%)	0.0%	Normal	Assumption
<i>% change in annual drug list price increases</i>	0.0% (0.0%, 0.0%)	0.0%	Normal	Assumption
<i>Rebate in 2021 as % of list price</i>	46%			Assumption

Key: BLS – Bureau of Labor Statistics; CBO – Congressional Budget Office.

### 1.3.3 Summary of Key Assumptions

Economic models are simplified representations of a complex reality. As such, this model is subject to some assumptions, which are further detailed in the list below.

- Medicare enrollment is based the estimated average monthly enrollment in Medicare Part A through 2029. Estimates in 2030 are derived by applying the compound annual growth rate underlying the estimates for 2021 through 2029.
- By default, the population considered in the Medicare scenario is limited to an average of the percentage of patients with  $\geq 1$  chronic condition and the percentage of patients with  $\geq 2$  chronic conditions.
- The incidence rates of the 5 targeted chronic disease states are not influenced by improved adherence and are thus constant throughout the modeled time horizon.
- Incidence and disease-related mortality do not change over time except as influenced by changes in out-of-pocket costs to patients in the counterfactual scenario. All-cause mortality is constant throughout the time horizon in the base-case and counterfactual scenarios.
- All deaths occur at the end of a given year and, within this model, are reported in the following year.
- Pharmacy costs represent only disease-related outpatient pharmacy costs, which are affected by changes in adherence according to the price elasticity of demand for outpatient prescription drugs in each chronic disease state.
- Pharmacy costs in the Medicare scenario represent projected mandatory non-LIS Part D outlays, adjusted upward to include patient cost-sharing; medical costs in the same scenario represent projected mandatory Part A and B outlays. To arrive at the average cost per patient, these amounts are averaged across projected non-LIS Part D enrollment and all Part A enrollment, respectively. This calculation assumes that spending is the same for all Medicare beneficiaries (including those without at least 1 to 2 chronic conditions) and is thus likely an underestimation of pharmacy and medical spending at baseline.
- Medical costs grow at the rate of inflation determined by the consumer price index for medical care services. The rates at which pharmacy costs grow in the base-case and counterfactual scenarios are

provided separately. By default, the base-case value is based on the growth of list drug prices observed during 2018.

- It is assumed that a proportion of pharmacy costs are paid by patients as out-of-pocket costs. Cost-sharing is not included as a reduction to medical expenses incurred by Medicare.
- Policy levers that influence out-of-pocket costs to patients include changes in drug list prices, changes in cost-sharing, and limits on annual price increases for drugs.
- Price elasticity values are based on averages of reported price elasticities of demand across various drug classes within each therapeutic area. Price elasticities greater than 0 are excluded from the average calculated price elasticity because of sampling error reported by the authors (Einav 2018).
- The median price elasticity of demand and offset effects derived from the selected therapeutic areas (AF, COPD, DM, and IHD) represent the price elasticity of demand of offset effects in the overall Medicare population.
- Adherence may not exceed 100% in the base-case and counterfactual scenarios and only affects disease-related mortality and costs.

## 1.4 Results

In the base-case analysis, using population forecasts provided by the CBO, an elimination of out-of-pocket costs in the outpatient pharmacy setting improves adherence by a relative change of 4.5% to 17.0% across each of the 6 analyses (14.6%, AF; 13.0%, CKD; 10.0%, COPD; 4.5%, DM; 17.0%, IHD; 12.3%, Medicare). Accordingly, a decrease in the risk of disease-related death is observed across all scenarios; as more patients survive each year of the analysis in the counterfactual scenario (compared to the base-case scenario), the number of Medicare beneficiaries increases. Coupled with improvements in adherence, an increase in the number of living beneficiaries and the shift of out-of-pocket pharmacy costs to the Medicare budget produce an increase in pharmacy spending from Medicare's perspective in each setting. Increases in pharmacy costs are partially offset by reductions in medical costs, which are most dramatic in the first years of the analysis. This is explained by the annual accumulation of beneficiaries in the counterfactual scenario, corresponding to a reduction in disease-related mortality. The results of each scenario are illustrated in **Table 6**, with a detailed accounting of costs over time in **Table 7**.

**Table 6. Results for Incremental Changes in Costs (in Billions, \$) and Deaths (in Thousands)**

Year	AF		CKD		COPD		DM		IHD		Medicare	
	Costs <sup>a</sup>	Deaths <sup>b</sup>	Costs <sup>a</sup>	Deaths <sup>b</sup>	Costs <sup>a</sup>	Deaths <sup>b</sup>	Costs <sup>a</sup>	Deaths <sup>b</sup>	Costs <sup>a</sup>	Deaths <sup>b</sup>	Costs <sup>a</sup>	Deaths <sup>b</sup>
2021	\$1.5	-10.6	\$3.5	-4.8	\$0.4	-7.4	\$2.2	-6.2	-\$6.1	-30.6	\$11.6	-104.2
2022	\$2.0	-11.3	\$4.3	-5.5	\$0.5	-7.3	\$2.4	-6.2	-\$5.4	-28.2	\$14.2	-101.5
2023	\$2.6	-11.9	\$5.1	-6.0	\$0.6	-7.2	\$2.6	-6.2	-\$4.8	-26.1	\$15.5	-104.9
2024	\$3.1	-12.5	\$5.9	-6.6	\$0.7	-7.1	\$2.8	-6.2	-\$4.2	-24.3	\$17.0	-108.0
2025	\$3.7	-13.0	\$6.8	-7.0	\$0.8	-7.0	\$3.1	-6.2	-\$3.6	-22.6	\$18.7	-111.1
2026	\$4.3	-13.3	\$7.7	-7.4	\$0.9	-6.9	\$3.3	-6.2	-\$3.1	-21.1	\$20.2	-112.6
2027	\$4.9	-13.7	\$8.7	-7.8	\$1.0	-6.8	\$3.6	-6.3	-\$2.5	-19.7	\$22.1	-115.8
2028	\$5.5	-14.1	\$9.7	-8.1	\$1.2	-6.7	\$3.9	-6.3	-\$2.0	-18.6	\$24.2	-118.9
2029	\$6.2	-14.4	\$10.7	-8.4	\$1.3	-6.5	\$4.2	-6.4	-\$1.5	-17.5	\$26.2	-120.4
2030	\$6.8	-14.7	\$11.8	-8.7	\$1.5	-6.4	\$4.6	-6.5	-\$1.1	-16.6	\$28.5	-123.3
Total <sup>c</sup>	\$40.5	-129.6	\$74.2	-70.4	\$8.9	-69.3	\$32.6	-62.7	-\$34.3	-225.2	\$198.4	-1,120.7

Key: AF – atrial fibrillation; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; DM – diabetes mellitus; IHD – ischemic heart disease; US – United States.

<sup>a</sup> Costs are expressed in billions of US dollars.

<sup>b</sup> Deaths are expressed in thousands.

<sup>c</sup> Values may not sum due to rounding.

**Table 7. Detailed Cost Results for Incremental Changes in Medical and Pharmacy Costs (in Billions, \$)**

Year	AF <sup>a</sup>		CKD <sup>a</sup>		COPD <sup>a</sup>		DM <sup>a</sup>		IHD <sup>a</sup>		Medicare <sup>a</sup>	
	Med.	Rx.	Med.	Rx.	Med.	Rx.	Med.	Rx.	Med.	Rx.	Med.	Rx.
2021	-\$1.6	\$3.0	-\$0.3	\$3.7	-\$0.3	\$0.7	-\$0.3	\$2.5	-\$12.7	\$6.6	-\$14.3	\$26.0
2022	-\$1.6	\$3.6	-\$0.3	\$4.5	-\$0.3	\$0.7	-\$0.3	\$2.6	-\$12.1	\$6.7	-\$13.8	\$28.0
2023	-\$1.6	\$4.1	-\$0.3	\$5.4	-\$0.2	\$0.8	-\$0.3	\$2.8	-\$11.6	\$6.8	-\$14.9	\$30.4
2024	-\$1.6	\$4.7	-\$0.3	\$6.2	-\$0.2	\$0.9	-\$0.2	\$3.1	-\$11.1	\$6.9	-\$15.9	\$32.9
2025	-\$1.6	\$5.3	-\$0.3	\$7.1	-\$0.2	\$1.0	-\$0.2	\$3.3	-\$10.7	\$7.1	-\$17.0	\$35.7
2026	-\$1.6	\$5.8	-\$0.3	\$8.0	-\$0.2	\$1.2	-\$0.2	\$3.5	-\$10.3	\$7.3	-\$17.9	\$38.1
2027	-\$1.6	\$6.5	-\$0.3	\$8.9	-\$0.2	\$1.3	-\$0.2	\$3.8	-\$10.0	\$7.5	-\$19.1	\$41.2
2028	-\$1.6	\$7.1	-\$0.3	\$9.9	-\$0.2	\$1.4	-\$0.2	\$4.1	-\$9.7	\$7.7	-\$20.3	\$44.6
2029	-\$1.6	\$7.7	-\$0.2	\$10.9	-\$0.2	\$1.5	-\$0.2	\$4.4	-\$9.5	\$7.9	-\$21.4	\$47.6
2030	-\$1.6	\$8.4	-\$0.2	\$12.0	-\$0.2	\$1.7	-\$0.2	\$4.8	-\$9.3	\$8.2	-\$22.7	\$51.3
Total <sup>b</sup>	-\$15.7	\$56.3	-\$2.6	\$76.8	-\$2.4	\$11.2	-\$2.3	\$34.9	-\$107.0	\$72.6	-\$177.4	\$375.7

<sup>a</sup> Costs are expressed in billions of US dollars.

<sup>b</sup> Values may not sum due to rounding.

Key: AF – atrial fibrillation; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; DM – diabetes mellitus; IHD – ischemic heart disease; Med. – medical; Rx. – pharmacy; US – United States.

## 1.5 Discussion

The results of this analysis indicate that cost-related nonadherence can increase Medicare spending on medical services by \$177.4 billion over 10 years. This increased medical spending does not, however, stop mortality from cost-related nonadherence – an additional 1.1 million Medicare beneficiaries die from this cost-related nonadherence over 10 years.

Our analysis is comparable to recent estimates of the implications of nonadherence reported in the published literature. In analyses of the cost of all medication-related problems in the US, NEHI and Watanabe estimated that drug-related morbidity and mortality cost \$300 billion to \$528.4 billion annually (NEHI 2008; Watanabe 2018). Data on nonadherence-related problems suggest a cost of \$100 billion annually (NEHI 2008). However, these analyses were undertaken from the perspective of the entire US. Our analysis, which produced an estimate of approximately \$20 billion annually, is limited to the Medicare perspective. Further, our analysis only estimates the impact of 1 subset of nonadherence: cost-related nonadherence. Nonadherence may occur for a variety of other factors, including forgetfulness, efficacy concerns, or safety concerns (Osterberg 2005).

The results of this model indicate that cost-related nonadherence accounts for roughly about 20% of all costs related to nonadherence (\$20 billion as a percentage of \$100 billion). Considering data on the percentage of patients who report cost-related nonadherence in each of the included disease states, this seems to be a conservative approximation. Approximately 11.4% of patients report cost-related nonadherence in stroke prevention (Levine 2013), 31% in CKD (Frankenfield 2011), 31% in COPD (Castaldi 2010), 16% in DM (Williams 2013), and 12.6% in IHD (Khera 2019). Considering that the percentage of patients characterized as adherent to their medications ranges from 30% to 60% in each of these diseases (Rolnick 2013, Bansilal 2016; Park 2014; Deshpande 2018), it is apparent that cost-related nonadherence is a significant contributor to suboptimal pharmacotherapy.

In addition to approximating the impacts of cost-related nonadherence, the model may be adapted to represent H.R. 3, the Elijah E. Cummings Lower Drug Costs Now Act. In a suggested scenario calibrated to approximate CBO's analysis of H.R. 3, a -30.0% change in cost-sharing and -80% change in drug list prices set to increase by 4.0% per year yield a 7-year estimate similar to that from the CBO. Without mortality offsets, the analysis estimates savings of \$483.6 billion from Medicare's perspective over 7 years; with mortality offsets, the estimated savings decrease to approximately \$475.9 billion. Additionally, with mortality offsets, the calibrated H.R. 3

scenario analysis predicts 656,967 fewer deaths over 7 years (an average of 93,852 lives saved annually) due to the effects of improved adherence on disease-related mortality. The monetary savings are comparable to CBO's estimate of the budgetary effects of Title I, II, and III of H.R. 3 (-\$475.9 billion) when calculated as the impact of each component in the first 7 years after implementation.

These parameter approximations for the percentage changes in cost-sharing, drug list prices, and annual drug list price increases, which were derived by calibrating the results of the present analysis with the results of the CBO analysis, are associated with some limitations. In the analysis by the CBO, drug price reductions are phased in via negotiations from 2023 through 2025, a portion of cost-sharing is shifted from patients to Medicare in 2022, and inflation rebates (retroactive to prices in 2016) occur beginning in 2021 (CBO 2019). However, in the analysis with this model, all components of H.R. 3 take effect at year 1 (2021). Thus, direct comparisons of 7-year results (2021–2027) or 10-year results (2021–2029) are difficult without calculating the effects directly after implementation of each component in the CBO analysis. Additionally, the present analysis implements at year 1 the combined effects of price referencing and negotiation as well as the retroactive effect of inflation rebates on drug list prices. Thus, the percentage change in drug list prices estimated to replicate the results of H.R. 3 should be interpreted with caution. A portion of the estimated -80% change in drug list prices may be explained by these retroactive inflation rebates, which require rebates corresponding to excess annual drug list price increases (up to 7% [IQVIA 2019]) relative to the annual growth in US consumer price index for all urban consumers (approximately 2% [BLS 2020]) from 2016 through 2020. Finally, to our knowledge, the CBO does not incorporate the impact of improved adherence on reducing the risk of disease-related death.

### 1.5.1 Limitations

Because models are a simplification of a more complicated, real-life set of circumstances, our analysis is subject to some important limitations.

First, the analysis only estimates the changes in out-of-pocket costs, drug list prices, and drug list price increases over 10 years. Caution should be taken if extrapolating cost estimations beyond the horizon demonstrated in this model. As the analysis moves further in time, more uncertainty in the estimates should be anticipated, as changes in economic circumstances, healthcare innovation, and policy are likely.

Secondly, consistent with the primary objective to quantify the cost of cost-related nonadherence, the model does not incorporate the effects that any factors besides out-of-pocket costs may have on medication adherence. Medication-taking behaviors are known to be influenced by many factors, including the patient's perceived need for the medication and the patient's concern for side effects.

Next, our analysis extrapolates the price elasticity of demand, cost offset effect, and mortality offset effect from 5 chronic diseases. Although these chronic diseases were selected specifically for their predicted representativeness in prevalence, price elasticity of demand, and offset effects, the results may differ if data from other diseases were to better reflect the overall behavior of all Medicare beneficiaries with chronic conditions.

Finally, the parameters included in our analysis are subject to uncertainty. Data on baseline costs, baseline adherence, price elasticities of demand, cost offsets, and mortality offsets are largely derived from retrospective studies. These studies are subject to commonly referenced limitations due to non-interventional designs and potential for confounding and effect modification. In particular, it was noted that some disease states were associated with a cost offset and mortality offset on either side of the respective medians. We suggest that improvements in adherence may improve morbidity (and thus medical costs) in symptomatic conditions, while similar improvements in adherence may disproportionately benefit mortality in more silent, asymptomatic conditions. To better identify and understand the effects of parameter uncertainty in these input data and values for other parameters, we conducted robust one-way and probabilistic sensitivity analyses, which gave results consistent with the deterministic output of the model.

## 1.6 Conclusion

By eliminating cost-related nonadherence among beneficiaries with at least 1 to 2 chronic conditions, Medicare would save \$177.4 billion in avoidable medical costs and reduce total deaths by about 1.1 million over 10 years. Because out-of-pocket costs would shift to Medicare, prescription drug consumption would increase with

increases in adherence and the number of living beneficiaries. Consequently, total pharmacy costs are estimated to rise by \$375.7 billion over 10 years.



## 1.7 References

- Andes LJ, Li Y, Srinivasan M, Benoit SR, Gregg E, Rolka DB. Diabetes prevalence and incidence among Medicare beneficiaries - United States, 2001-2015. *MMWR Morb Mortal Wkly Rep*. 2019;68(43):961-966.
- Bansilal S, Castellano JM, Garrido E, et al. Assessing the impact of medication adherence on long-term cardiovascular outcomes. *J Am Coll Cardiol*. 2016 Aug 23;68(8):789-801.
- Borne RT, O'Donnell C, Turakhia MP, et al. Adherence and outcomes to direct oral anticoagulants among patients with atrial fibrillation: findings from the Veterans Health Administration. *BMC Cardiovasc Disord*. 2017;17(1):236.
- Boye KS, Curtis SE, Lage MJ, Garcia-Perez LE. Associations between adherence and outcomes among older, type 2 diabetes patients: evidence from a Medicare Supplemental database. *Patient Prefer Adherence*. 2016;10:1573-1581.
- Bureau of Labor Statistics. CPI – all urban consumers. All items in U.S. city average. <https://data.bls.gov/timeseries/CUUS0000SA0>. Accessed March 27, 2020.
- Bureau of Labor Statistics. CPI – all urban consumers. U.S. medical care services in U.S. city average. <https://data.bls.gov/timeseries/CUUR0000SAM2>. Accessed March 27, 2020.
- Carnethon MR, Biggs ML, Barzilay J, et al. Diabetes and coronary heart disease as risk factors for mortality in older adults. *Am J Med*. 2010;123(6):556.e1-556.e5569.
- Castaldi PJ, Rogers WH, Safran DG, Wilson IB. Inhaler costs and medication nonadherence among seniors with chronic pulmonary disease. *Chest*. 2010;138(3):614-620.
- Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple cause of death 1999-2018 on CDC WONDER Online Database, released in 2020. Data are from the multiple cause of death files, 1999-2018, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. <http://wonder.cdc.gov/mcd-icd10.html>. Accessed April 26, 2020.
- Centers for Medicare & Medicaid Services. Medicare Chronic Conditions Dashboard: region level. <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/CCDashboard>. Published April 5, 2019. Page last modified April 5, 2019. Accessed March 26, 2020.
- Congressional Budget Office. Medicare—CBO's May 2019 baseline. [https://www.cbo.gov/system/files/2019-05/51302-2019-05-medicare\\_0.pdf](https://www.cbo.gov/system/files/2019-05/51302-2019-05-medicare_0.pdf). Published May 2, 2019. Accessed February 11, 2020.
- Congressional Budget Office. Re: Budgetary effects of H.R. 3, the Elijah E. Cummings Lower Drug Costs Now Act. [https://www.cbo.gov/system/files/2019-12/hr3\\_complete.pdf](https://www.cbo.gov/system/files/2019-12/hr3_complete.pdf). Published December 10, 2019. Accessed March 27, 2020.
- Cubanski J, Neuman T, Damico D. How many Medicare Part D enrollees had high out-of-pocket drug costs in 2017? Kaiser Family Foundation. <https://www.kff.org/medicare/issue-brief/how-many-medicare-part-d-enrollees-had-high-out-of-pocket-drug-costs-in-2017/>. Published June 21, 2019. Access March 24, 2020.
- Dalal AA, Shah M, Lunacsek O, Hanania NA. Clinical and economic burden of patients diagnosed with COPD with comorbid cardiovascular disease. *Respir Med*. 2011 Oct;105(10):1516-1522.
- Datar M, Crivera C, Rozjabek H, et al. Comparison of real-world outcomes in patients with nonvalvular atrial fibrillation treated with direct oral anticoagulant agents or warfarin. *Am J Health Syst Pharm*. 2019 Feb 9;76(5):275-285.
- Deshpande CG, Kogut S, Willey C. Real-world health care costs based on medication adherence and risk of stroke and bleeding in patients treated with novel anticoagulant therapy. *J Manag Care Spec Pharm*. 2018;24(5):430-439.
- Einav L, Finkelstein A, Polyakova M. Private provision of social insurance: drug-specific price elasticities and cost sharing in Medicare Part D. *Am Econ J Econ Policy*. 2018;10(3):122-153.

- Erickson SC, Leslie RS, Qiu W, Patel BV. Adherence trends for 3 chronic disease medication classes among differently insured populations. *Am J Pharm Benefits*. 2014;6(1):32-37.
- Ernst FR, Grizzle AJ. Drug-related morbidity and mortality: updating the cost-of-illness model. *J Am Pharm Assoc (Wash)*. 2001 Mar-Apr;41(2):192-199.
- Frankenfield DL, Howell BL, Wei II, Anderson KK. Cost-related nonadherence to prescribed medication therapy among Medicare Part D beneficiaries with end-stage renal disease. *Am J Health Syst Pharm*. 2011 Jul 15;68(14):1339-1348.
- Gershon AS, Wang C, Wilton AS, Raut R, To T. Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in Ontario, Canada, 1996 to 2007: a population-based study. *Arch Intern Med*. 2010 Mar 22;170(6):560-5. Erratum in: *Arch Intern Med*. 2010 Jun 28;170(12):1023.
- Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med*. 2006 Sep 25;166(17):1836-1841.
- Honeycutt AA, Segel JE, Zhuo X, Hoerger TJ, Imai K, Williams D. Medical costs of CKD in the Medicare population. *J Am Soc Nephrol*. 2013;24(9):1478-1483.
- IQVIA Institute. Medicine use and spending the U.S. <https://www.iqvia.com/insights/the-iqvia-institute/reports/medicine-use-and-spending-in-the-us-a-review-of-2018-and-outlook-to-2023>. Published May 9, 2019. Accessed April 1, 2020.
- Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. *Arch Intern Med*. 1995 Oct 9;155(18):1949-1956.
- Kent ST, Safford MM, Zhao H, et al. Optimal use of available claims to identify a Medicare population free of coronary heart disease. *Am J Epidemiol*. 2015;182(9):808-819.
- Khera R, Valero-Elizondo J, Das SR, et al. Cost-related medication nonadherence in adults with atherosclerotic cardiovascular disease in the United States, 2013 to 2017. *Circulation*. 2019 Dec 17;140(25):2067-2075.
- Krumholz HM, Nuti SV, Downing NS, Normand SL, Wang Y. Mortality, hospitalizations, and expenditures for the Medicare population aged 65 years or older, 1999-2013 [published correction appears in JAMA. 2015 Aug 25;314(8):837]. *JAMA*. 2015;314(4):355-365.
- Lacaille D, Avina-Zubieta JA, Sayre EC, Abrahamowicz M. Improvement in 5-year mortality in incident rheumatoid arthritis compared with the general population—closing the mortality gap. *Ann Rheum Dis*. 2017;76:1057-1063.
- Lee A, Song X, Khan I, et al. Association of cinacalcet adherence and costs in patients on dialysis. *J Med Econ*. 2011;14(6):798-804.
- Lester CA, Look KA, Chui MA. Is the currently used prescription adjudication date a good proxy for calculating medication refill adherence? *J Manag Care Spec Pharm*. 2016 Nov;22(11):1311-1317.
- Levine DA, Morgenstern LB, Langa KM, et al. Recent trends in cost-related medication nonadherence among stroke survivors in the United States. *Ann Neurol*. 2013;73(2):180-188.
- McBurnie M, Mularski RA, Gillespie S, et al. COPD diagnosis incidence rates and utilization in Medicare and commercially insured patients. *Am J Respir Crit Care Med*. 2018;197:A2516.
- McHorney CA. The adherence estimator: a brief, proximal screener for patient propensity to adhere to prescription medications for chronic disease. *Curr Med Res Opin*. 2009 Jan;25(1):215-238.
- Menzin J, Wygant G, Hauch O, Jackel J, Friedman M. One-year costs of ischemic heart disease among patients with acute coronary syndromes: findings from a multi-employer claims database. *Curr Med Res Opin*. 2008 Feb;24(2):461-468.
- Molnar MZ, Gosmanova EO, Sumida K, et al. Predialysis cardiovascular disease medication adherence and mortality after transition to dialysis. *Am J Kidney Dis*. 2016;68(4):609-618.

- National Kidney and Urologic Disease Information Clearinghouse. Kidney disease statistics for the United States (NIH Publication No. 12-3895). [https://www.niddk.nih.gov/-/media/Files/Kidney-Disease/KU\\_Diseases\\_Stats\\_508.pdf](https://www.niddk.nih.gov/-/media/Files/Kidney-Disease/KU_Diseases_Stats_508.pdf). Published June 2012. Accessed March 26, 2020.
- New England Healthcare Institute. Thinking outside the pillbox: a system-wide approach to improving patient medication adherence for chronic disease: a NEHI research brief. August 2009. [https://www.nehi.net/writable/publication\\_files/file/pa\\_issue\\_brief\\_final.pdf](https://www.nehi.net/writable/publication_files/file/pa_issue_brief_final.pdf). Accessed February 11, 2020.
- Nishi SPE, Maslonka M, Zhang W, Kuo YF, Sharma G. Pattern and adherence to maintenance medication use in Medicare beneficiaries with chronic obstructive pulmonary disease: 2008-2013. *Chronic Obstr Pulm Dis*. 2018;5(1):16-26.
- Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005 Aug 4;353(5):487-497.
- Park H, Rascati KL, Lawson KA, et al. Adherence and persistence to prescribed medication therapy among Medicare Part D beneficiaries on dialysis: comparisons of benefit type and benefit phase. *J Manag Care Spec Pharm*. 2014 Aug;20(8):862-876.
- Piccini JP, Hammill BG, Sinner MF, et al. Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circ Cardiovasc Qual Outcomes*. 2012;5(1):85-93.
- Rolnick SJ, Pawloski PA, Hedblom BD, Asche SE, Bruzek RJ. Patient characteristics associated with medication adherence. *Clin Med Res*. 2013;11(2):54-65.
- Shalev V, Chodick G, Silber H, Kokia E, Jan J, Heymann AD. Continuation of statin treatment and all-cause mortality: a population-based cohort study. *Arch Intern Med*. 2009 Feb 9;169(3):260-268.
- Toy EL, Beaulieu NU, McHale JM, et al. Treatment of COPD: relationships between daily dosing frequency, adherence, resource use, and costs. *Respir Med*. 2011 Mar;105(3):435-441.
- United States Renal Data System. 2018 USRDS Annual Data Report: epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD; 2018. <https://www.usrds.org/2018/view/Default.aspx>. Accessed March 26, 2020.
- United States Renal Data System. 2019 USRDS Annual Data Report: epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD; 2019. <https://www.usrds.org/2019/view/Default.aspx>. Accessed March 26, 2020.
- Vestbo J, Anderson JA, Calverley PM, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD. *Thorax*. 2009 Nov;64(11):939-943.
- Viswanathan M, Golin CE, Jones CD, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Ann Intern Med*. 2012 Dec 4;157(11):785-795.
- Watanabe JH, McInnis T, Hirsch JD. Cost of prescription drug-related morbidity and mortality. *Ann Pharmacother*. 2018 Sep;52(9):829-837.
- Williams J, Steers WN, Ettner SL, Mangione CM, Duru OK. Cost-related nonadherence by medication type among Medicare Part D beneficiaries with diabetes. *Med Care*. 2013;51(2):193-198.
- Zhou M, Chang HY, Segal JB, Alexander GC, Singh S. Adherence to a novel oral anticoagulant among patients with atrial fibrillation. *J Manag Care Spec Pharm*. 2015 Nov;21(11):1054-1062.