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Costs and Use of Oral Anti-cancer Medications among Senior Medicare Part D Beneficiaries

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Costs and Use of Oral Anti-cancer Medications among Senior Medicare Part D Beneficiaries

A dissertation submitted in partial fulfillment of the requirements for
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by

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ALL	Acute Lymphoblastic Leukemia
AI	Aromatase Inhibitor
BAAS	Basel Assessment of Adherence Scale
CAP	Competitive Acquisition Program
CML	Chronic Myeloid Leukemia
CMS	Center for Medicare and Medicaid Services
CPD	Chronic Pulmonary Disease
CPI	Consumer Price Index
CPI-U-RS	Consumer Price Index Research Series
CPT	Current Procedural Terminology
CRN	Cost-Related Nonadherence
DE	Dual Eligible
ED	Emergency Department
EPV	Events per Variable
ESRD	End-Stage Renal Disease
EGFR	Epidermal Growth Factor Receptor
FPL	Federal Poverty Level
HHS	Department of Health and Human Services

HRQL	Health Related Quality of Life
ICD	International Classification of Diseases
ICL	Initial Coverage Limit
LIS	Low Income Subsidy
MA-PD	Medicare Advantage Prescription Drug Programs
MCBS	Medicare Current Beneficiary Survey
MEMS	Microelectronic Monitoring System
MEPS	Medical Expenditure Panel Survey
MMR	Major Molecular Response
MPR	Medication Possession Ratio
MSP	Medicare Savings Programs
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHIS	National Health Interview Survey
OOP	Out-of-Pocket
OR	Odds Ratio
OTC	Over-the-Counter
PDP	Prescription Drug Plan

QI	Qualifying Individuals
ResDAC	Research Data Assistance Center
RR	Relative Risk
SLMB	Specified Low-Income Medicare Beneficiaries
TKI	Tyrosine Kinase Inhibitors
TRIAD	Translating Research into Action for Diabetes
VIF	Variance Inflation Factor
ZCTA	Zip Code Tabulation Areas

ABSTRACT

COSTS AND USE OF ORAL ANTI-CANCER MEDICATIONS AMONG SENIOR MEDICARE PART D BENEFICIARIES

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Oral cancer drugs are branded and expensive medications that generally do not have generics available. The restrictions of the Medicare Part D program, including the coverage gap and high cost-sharing, and the high cost of oral chemotherapy may lead to patients' non-adherence to medication. Few studies have examined the cost and utilization of oral anti-cancer medications. This study will be the first to examine the costs associated with the use of oral anti-cancer medications and the impact of cost-sharing and type of prescription drug subsidy on medication discontinuation in the Medicare Part D elderly population.

Objectives: To determine the usage and costs of oral cancer treatment in elderly Medicare Part D beneficiaries and to examine the relationship between out of pocket costs and medication discontinuation or delay.

Methods: A cross-sectional study of the spending and usage of oral cancer drugs in the Medicare Part D population was conducted. A 5% random sample of 2008 Medicare beneficiaries was used. The study sample included all members of this group who: 1) were 65 years of age and older and 2) filled at least one prescription for imatinib,

erlotinib, anastrozole, letrozole, or thalidomide. We examined the average costs patients paid per day, the cost that the Part D plan paid per day, and the total cost that patients paid for the entire year for each drug. The demographic characteristics and type of prescription drug subsidy of Part D beneficiaries who used oral cancer drugs were reported in frequency counts and percentages. We also determined the percentage of enrollees who entered the Part D coverage gap, the time and duration that they fell into the coverage gap, the number of beneficiaries who discontinued treatment and the association between OOP costs and medication discontinuation or delay, controlling for polypharmacy, prescription coverage and socio-demographic factors.

Results: Prescription drug subsidy was categorized in four groups: 1) Dual Eligible (DE), 2) full Low Income Subsidy (LIS), 3) partial LIS, and 4) no subsidy. Mean out-of-pocket (OOP) costs per day were between $0.03 and $0.09 for DE beneficiaries, between $0.04 and $0.23 for full LIS beneficiaries, between $1.17 and $6.34 for partial LIS beneficiaries and between $2.93 and $36.84 for beneficiaries who did not receive a subsidy. On average, the beneficiaries who used oral cancer medications were between 75 and 76 years of age. Over half of oral cancer medication users were Caucasian and female. Over two-thirds of oral cancer medication users received no subsidies for their prescription coverage. About 99% of users of the more expensive drugs - imatinib, erlotinib and thalidomide - entered the coverage gap and the majority of these entered the coverage gap at the time of their first fill. In contrast, beneficiaries who filled the less expensive drugs - anastrozole and letrozole - entered the coverage gap later. Less than 7% entered the coverage gap at the time of the first fill of their prescriptions. Beneficiaries who used imatinib, erlotinib, or thalidomide spent approximately a month

in the coverage gap. Over the course of a year, the majority of their time was spent in the catastrophic phase. Approximately 33-60% of total oral cancer drug users discontinued their therapies. About 50% of these discontinued during the coverage gap for anastrozole and letrozole and about 80% discontinued during the catastrophic phase for imatinib, erloinib and thalidomide. OOP costs were associated with medication discontinuation for all five oral cancer drugs. The odds of discontinuation and delay increased 101%, 170%, and 264% for each $100 increase in OOP spending for imatinib, erlotinib and thalidomide users, respectively. The odds of discontinuation and delay increased 9%-10%, and 6-8% for every $10 increase in OOP spending for anastrozole and letrozole users, respectively.

Conclusions: About 33-60% of all users discontinued their therapies. Beneficiaries receiving subsidies had low OOP costs, averaging between $0.03 and $6.34 per day. Beneficiaries on the more expensive drugs and not having subsidies had high OOP costs, averaging between $15.66 and 36.84 per day. Higher OOP costs were associated with an increased likelihood of discontinuation or delay.

CHAPTER 1

INTRODUCTION

In 2011, cancer was the second leading cause of death in the United States. Out of 2,512,873 total deaths in the U.S., the number of deaths from cancer was 575,313.[1] In 2010, the direct costs for cancer treatment were $124.57 billion in the U.S. Expenditures are likely to increase as new medications, such as treatments that work against targeted cancer cells, and other more advanced therapies reach the market.[2]

A substantial and increasing number of cancer patients are now being treated with oral cancer therapy. The total US cancer drug market was estimated to be $35 billion in 2011 and the growth rate was estimated to be between 15 and 16 percent.[3] By comparison, in 2010, the oral cancer drug market was estimated to be between $5 billion and $7 billion with an annual growth rate between 20 and 30 percent.[4] It has also been estimated that more than twenty-five percent of the 400 antineoplastic drugs in the development pipelines are oral agents.[5] Currently, twenty-four oral cancer agents are in phase 3 clinical trials.[6]

Nonadherence with drug treatment is a major problem for patients with chronic diseases. For example, nonadherence rates were between 21%-35% for diabetes patients,[7-9] 21%-32% for post-myocardial infarction patients,[10,11] 13%-41% for epileptic patients,[12-15] and 50%-61% for hypertensive patients.[16-18] Nonadherence has been linked to both negative health outcomes and increased healthcare expenditures.[15,19-21] For example, nonadherence to chronic drug therapy has been associated with increases in relapse risk in acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), and schizophrenia,[22,23] increased emergency department (ED) visits in epilepsy,

hypertension, chronic heart disease, diabetes, and hypercholesterolemia,[14,15,24] increased hospitalizations in epilepsy, heart failure, myocardial infarction, and diabetes,[9,14,15,25,26] increased mortality in heart failure, myocardial infarction, and diabetes,[9,25,26] reduced responses to treatment in CML,[27,28] and lower event free survival in CML and heart failure.[29,30] Adherence is likely to be a major problem for patients on oral cancer drugs because of the high cost of oral chemotherapy. Most oral cancer drugs are branded and expensive medications that do not have generics available. Moreover, high cost of prescriptions is a major cause of nonadherence to medications.[31-33]

Older patients are both more likely to have cancer and to be at risk for adherence problems with oral cancer drugs.[34-38] The number of cancer survivors in the US increased from 9.8 million in 2001 to 13.7 million in 2012.[39,40] Over half of that population, (i.e. approximately 9.72 million) was elderly (aged 60 years old or older).[40] The National Cancer Institute (NCI) reported that the 2004-2008 incidence rates for cancer in individuals aged 65 years and older were 2,127.8 cases per 100,000 population compared with 223.8 cases per 100,000 population for those aged under 65 (age adjusted to 2000 US standard population).[41] The restrictions of the Part D drug program, including the coverage gap and high cost-sharing, and the high cost of oral chemotherapy result in high patient out-of-pocket (OOP) spending for cancer drugs.[42] For example, a beneficiary enrolled in Universal American's Community CCRx Basic plan filling lenalidomide (Revlimid®) paid $4,263 OOP for the first month of treatment in 2009. This included a $295 deductible and a 55 percent cost-sharing of the drug price $7,214. OOP spending of this magnitude would pose a substantial financial burden and could result in patients stopping their treatment.

In addition, most elderly Medicare beneficiaries are retirees and have limited incomes; half have incomes less than 200% of the Federal Poverty Level (FPL).[43,44] A recent study showed that Part D enrollees who did not have previous drug insurance coverage were more likely to have low income, with personal annual incomes of less than $25,000, compared with elderly who were not Part D enrollees.[45] As a result, high OOP spending could have a substantial impact on elderly patients' ability to obtain and adhere to drug therapy.

The Medicare Part D prescription drug benefit became effective on January 1, 2006. The purpose of this program was to improve prescription drug coverage and increase access to medications by offering affordable prescription drugs to Medicare beneficiaries. Medicare Part D prescription drug plans use cost-sharing strategies to contain unnecessary and costly use of brand-name prescription drugs. Enrollees are required to pay initial deductibles and cost-sharing for their medications. The Part D benefit is offered to consumers through private health plans. Two types of drug benefit plans are available to beneficiaries: standalone prescription drug plans (PDPs) and Medicare Advantage Prescription Drug (MA-PD) plans. Both PDPs and MA-PD plans offer prescription coverage, but MA-PD plans additionally offer medical coverage. The majority of Medicare beneficiaries have enrolled in PDPs since Part D was implemented. [46,47]

The Standard Part D benefit includes four benefit phases: deductible, pre-initial coverage limit (pre-ICL), ICL or coverage gap (also known as the doughnut hole), and catastrophic coverage. Beneficiaries are required to pay the full amount of their medication costs during the ICL or coverage gap. The standard initial deductible, ICL, OOP threshold, and catastrophic coverage levels vary each year based on drug prices.[48] Part D benefit plans may also offer alternative benefit designs, such as using formulary tiers, decreasing deductibles, and offering coverage during the coverage gap. Part D monthly premiums are determined by the plans;[2] additionally, they are based on beneficiaries' incomes. Enrollees whose gross annual incomes exceed set amounts are required to pay higher monthly premiums.[49]

In 2008, the standard benefit in PDPs included an initial $275 deductible. Beneficiaries paid 25% coinsurance for total medication costs between $276-2,510; beneficiaries were required to pay 100% of their medication costs after exceeding the initial coverage limit of $2,510; and they paid a 5% coinsurance after annual prescription costs exceeded $5,726.25 (catastrophic coverage). Before enrollees exited the coverage gap ($5,726.25), they had to pay total OOP drug costs of $4,050 (True OOP or OOP threshold).[5] The maximum OOP spending has increased every year from $3,600 in 2006 to $3,850 in 2007 and $4,050 in 2008.[48]

According to 2008 national Medicare Part D plan statistics, there were a total of 1,824 Part D plans, of which approximately 71% offered no coverage during the gap. The lowest monthly premium was available at $9.80 with no gap coverage and the highest was $107.50 offering coverage for preferred generics during the gap.[50] At that time, no Part D plans offered full coverage for all brands and generics in the coverage gap.[51]

Most plans use tiered cost-sharing; expensive drugs are frequently included on a specialty tier. Antineoplastics, immunologics, antivirals, and antibacterials account for more than half of specialty drugs. Since 2006, specialty tiers have been used increasingly by plans: in PDPs they increased from 63 to 76 percent and in MA-PDs from 67 to 90 percents from 2006 to 2008.[52]

Tier structures can differ among plans. Most PDP plans provide tiered formularies in which beneficiaries pay larger amounts for non-preferred drugs. In general, plans are required to provide at least two drugs in each therapeutic class. However, antineoplastic medications are one of six classes of drugs for which plans are required to cover "all" or "substantially all" medications in the class on their formularies.[47,53] The Center for Medicare and Medicaid Services (CMS) has set the maximum cost-sharing for specialty drugs at 25 percent, but plans are allowed the flexibility to charge a higher cost-sharing if it is combined with lower deductibles. Half of plans charge their members up to 33 percent coinsurance for specialty tier medication.[52]

The Medicare Benefit and Cancer Medications

Injectable oncolytic products and some oral chemotherapy are covered by Medicare Part B and provided in physician offices. Oral dosage forms are covered under Part B if they are available in injectable forms or as prodrugs. The eight oral cancer drugs that are currently available under Part B include capecitabine (Xeloda®), methotrexate, cyclophosphamide (Cytoxan®), temozolomide (Temodar®), busulfan (Myleran®), etoposide (VePesid®), melphalan (Alkeran®), topotecan hydrochloride (Hycamtin®). Otherwise, self-administered and oral cancer drugs are covered under Medicare Part D.[54] Oral cancer medications may also be covered by Part D if they have indications for conditions other than cancer in at least one of the three mandated compendia. These compendia include American Hospital Formulary Service Drug Information, US Pharmacopeia-Drug Information, and DRUGDEX Information System.[55] Part D drug plans cannot include the eight Part B covered oral cancer drugs (previously mentioned) on their formularies if the indications are solely for cancer treatment. However, if those drugs are used for other indications, they can be included under a prior authorization program.[53,56]

Medicare excluded reimbursement for self-administered cancer medications when it was implemented in 1965. In 1993, Congress authorized coverage for seven oral cancer drugs with injectable equivalents.[57] In 2005, Congress authorized and funded a demonstration project for coverage for oral and self-administered drugs. The demonstration project included thirteen cancer drugs in 50,000 eligible patients. Coverage of oral medications, including cancer drugs, was expanded to cover all Medicare enrollees in 2006.[58]

Typically, the differences between oral and injectable cancer agents are the following: 1) oral cancer drugs are covered under the pharmacy benefit but injectable agents are covered by the medical benefit; 2) oral agents are dispensed by a pharmacy whereas injectable products are administered in a physician's office;[59] and 3) oral cancer agents are more expensive than injectable medications. As a result, patients have higher cost-sharing for oral cancer drugs.[5,59] Also, Part B enrollees pay a lower cost-sharing percentage for their therapy than Part D beneficiaries. For example, Part B enrollees paid 20 percent cost-sharing in 2008,[2] but Part D patients paid, on average, a $250 deductible, 25% coinsurance during the pre-ICL phase, and the full amount of medication costs when they entered the coverage gap.[46] Medicare beneficiaries who enroll in Part D prescription drug plans also paid higher cost-sharing than those who have private insurance coverage.[60]

Oral Cancer Medications

Patients prefer using oral chemotherapy rather than parenteral drugs. The main reasons for the preference for oral therapy include convenience, avoidance of intravenous access issues, flexibility for timing and location of administration, and increased quality of life.[61-64] Particular concerns when prescribing oral agents are compliance and that physicians are unable to monitor side effects of oral cancer agents.[5,47,65,66] Patients have the full responsibility to manage their medications. As a result, patients may decide, without medical advice, to reduce the dose or stop taking oral agents. Moreover, higher cost-sharing for oral cancer drugs may increase non-compliance.[67,68]

In addition, the lack of availability of less expensive generics leads to higher costs for oral cancer drugs. More than 75 percent of Food and Drug Administration (FDA)-approved oral cancer drugs were brand name drugs.[69] High cost of oral cancer agents is a significant reason that patients delay or skip their treatment.[70] Consequently, providers must consider cost when prescribing an oral cancer agent.[71-73]

In prescribing oral cancer medication, health providers shift the majority of responsibility directly to patients to manage their regimens. Therefore, adequate patient education is required to ensure that patients receive oral chemotherapy safely and effectively.[18] Oral chemotherapy prescriptions can be filled in any pharmacies, including "community pharmacies, mail-order pharmacies, specialty pharmacies, hospital pharmacies, through the physician's office as part of Competitive Acquisition Program (CAP), or through an office based pharmacy."[5] A recent study reported a number of community pharmacists who were unfamiliar with oral chemotherapy.[74] As a result, patients who filled their prescriptions for oral chemotherapy at a community pharmacy

may have received inadequate information or misunderstood the instructions for taking the oral agent.[5]

Increases in the use of oral oncolytic drugs present challenges to patients.[5] The cost of oral agents averages approximately $43,000 per patient per year.[6] As a result, Medicare beneficiaries could enter the coverage gap quickly. However, some patients who have financial difficulty could apply for pharmaceutical assistance programs offered by the pharmaceutical companies.[2,6,75] Medicare enrollees with low income may be eligible for the low income subsidy (LIS) program, in which they pay lower cost-sharing for their prescriptions. For example, regular Part D patients paid a $275 deductible and 25% of prescription costs up to the coverage gap, then the full cost of their medication. LIS patients with full subsidies paid $2.25 (Generic) and $5.60 (Brand) copays if they had resources less than $6,120 or 15% coinsurance if their resources were between $6,120-$20,210. Full subsidy patients with resources below $6,120 were not required to pay copayments in the catastrophic coverage phase; otherwise they paid copayments of $2.25 (Generic) and $5.60 (Brand).[3] Resources are determined from assets that can be converted to cash within 20 days, including stocks, bonds, and bank accounts. However, home, car and life insurance policies are not included in the resource limit.[76]

The reasons that enrollees could stop filling prescriptions due to cost may come from lack of awareness of cost-sharing, low income, or financial burden. A recent study showed that a majority of beneficiaries were not aware of the coverage gap in their benefit plans or of the amount of copayments that they were required to pay. Only one-fifth of enrollees paying copayments could identify the amount of generic and brand name co-pays.[77] The awareness of the coverage gap was highest among enrollees who

reached the gap. Greater than one third of beneficiaries reported cost-related behaviors such as switching to generics or reducing adherence. Moreover, enrollees with higher annual drug costs had higher magnitudes of cost-related responses; more than half of beneficiaries (57%) with $3,500 and greater of annual drug costs reported cost related behaviors.[77]

Part D Oral Cancer Drugs in the Current Study

This study examined the top five oral cancer drugs of 2008 that were covered by Part D. In order by sales, they are: imatinib (Gleevec®), anastrozole (Arimidex®), letrozole (Femara®), erlotinib (Tarceva®), and thalidomide (Thalomid®).[78]

The non-steroidal aromatase inhibitors, anastrozole and letrozole, are used in early and advanced breast cancer in postmenopausal women. National Comprehensive Cancer Network (NCCN) guidelines recommend using the non-steroidal aromatase inhibitors as an adjuvant endocrine therapy for five years of treatment in postmenopausal women or in premenopausal women as sequential therapy following 2-3 years of tamoxifen. Because there is biological equivalence between these agents;[79] if patients are unable to tolerate the first aromatase inhibitor, they could switch to use the second medication.[80]

Imatinib and erlotinib are members of a class of drugs known as tyrosine kinase inhibitors (TKIs). Imatinib was first approved for use in chronic myeloid leukemia (CML) patients in 2001. Imatinib is a long-term treatment that depends on hematologic, cytogenetic, and molecular responses.[81] Patients with CML require daily treatment during the chronic phase of the disease. The initial treatment is 400 mg once daily for at least 3 months with follow-up evaluation required. If there are complete cytogenetic, hematologic and molecular responses, the same doses can be continued up to 12 months of treatment with follow-up evaluation every 3 months; however, the doses can be increased to 800 mg if there are minor cytogenetic responses.[81] Treatment with imatinib

is continued until disease progression or patient intolerance toxicities. Therefore, theoretically treatment with imatinib can continue for many years.

In patients who are resistant or intolerant to imatinib, the newer generation of TKI medications, including dasatinib and nilotinib has been approved as a second-line therapy for CML in 2006 and 2007, respectively.[82]

Erlotinib has been approved for second line monotherapy or maintenance treatment for advanced or metastatic non-small cell lung cancer (NSCLC) since 2004.[83] A dosage of 150 mg once daily is suggested for use in non-small cell lung cancer treatment. The NCCN guidelines recommend using erlotinib as a first line therapy only for patients with epidermal growth factor receptor (EGFR) mutation, but there is no recommendation for the duration of treatment or dosage.[84] It is suggested that erlotinib use can be continued for patients with NSCLC until the disease progresses or there is unacceptable toxicity. Moreover, docetaxel or pemetrexed can be used as a second-line monotherapy for NSCLC.[84]

In 2006, the FDA approved dose of thalidomide is 200 mg in combination with dexamethasone for multiple myeloma treatment.[85] Subsequently, NCCN guidelines recommend using thalidomide in combination with bortezomib and dexamethasone as one of the preferred regimens of primary therapy for patients who anticipated undergoing stem cell transplant. Thalidomide is recommended with melphalan and prednisolone in patients not eligible for stem cell transplant. Additionally, thalidomide in combination with dexamethasone has been shown effective as maintenance treatment for multiple myeloma.[86] There is no recommendation for the duration of treatment with thalidomide

for multiple myeloma. However, the median survival in thalidomide users was 65.5 months.[87]

Conceptual Framework

This study has been derived from the conceptual framework of cost-related nonadherence (CRN).[88] The conceptual framework for medication discontinuation can be adapted from the CRN model offered by Piette et al. The framework shown in Figure 1 was used to estimate the relationship between total OOP spending and medication discontinuation. The relationship between OOP costs of prescription drugs and adherence is complex; nonadherence due to costs of medications cannot be estimated solely based on patients' financial burden. Piette included financial and non-financial factors associated with nonadherence into the model. These factors were financial characteristics, regimen complexity, and characteristics of disease, patients and medication. Financial characteristics involve prescription costs, OOP costs, total household income, and prescription drug coverage. Regimen complexity is defined as numbers of prescriptions and frequency of refills. Moreover, clinician and health system factors influence the effects of medication costs on patients' adherence. Cost pressures and regimen complexity are possibly minimized by those factors.[88]

This study evaluated the influence of regimen complexity, financial factors, patient characteristics, disease characteristics, and prescription characteristics on medication discontinuation. Clinician and health system factors were excluded because no data are available in the Medicare Part D data related to these factors.

The model indicates that pressures from financial factors are one of the reasons leading patients to not adhere to their medication. Financial factors include income, prescription coverage, OOP prescription costs, and other health costs. It was hypothesized that patients with high OOP spending were more likely to discontinue their medications. This relationship may be stronger in cancer patients because of the high cost of these drugs. On the other hand, the relationship might be weaker because cancer drugs are perceived to be life-saving treatments.[88]

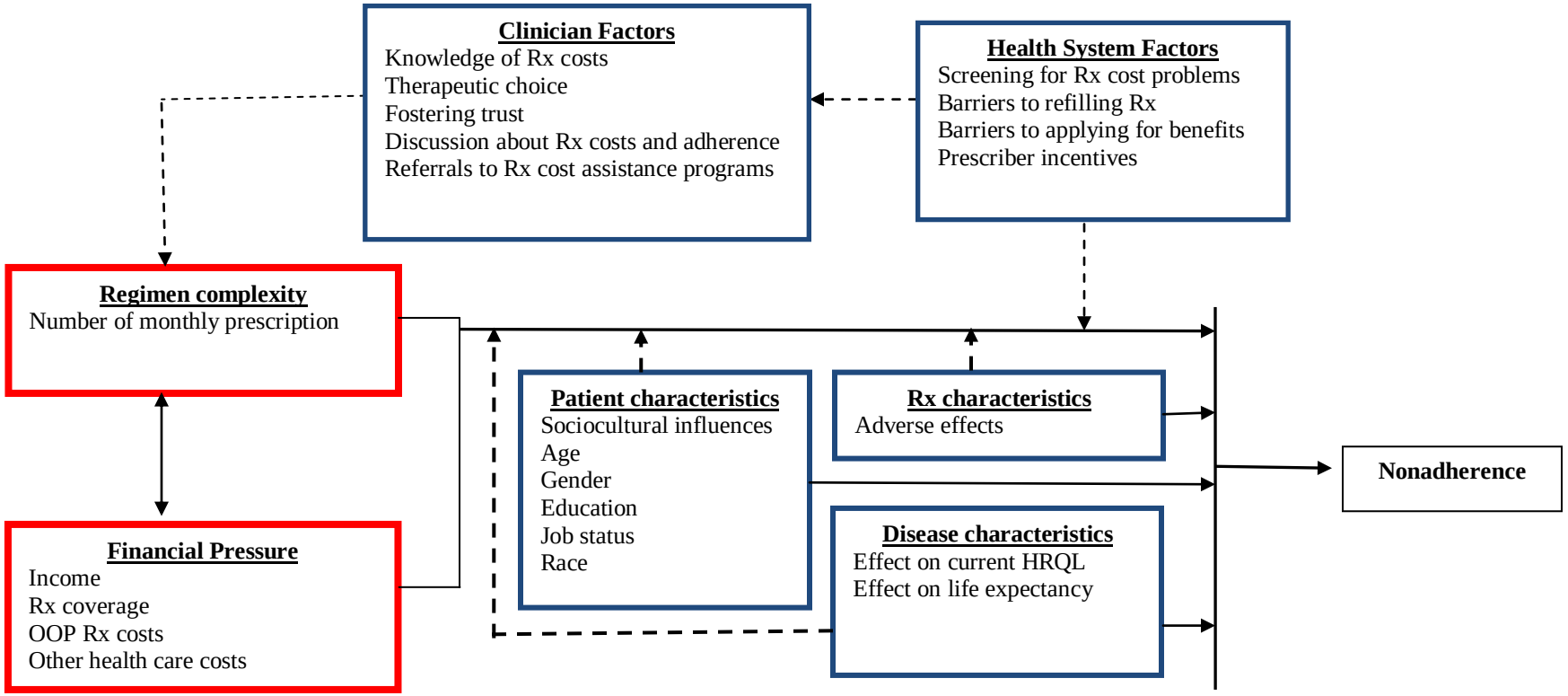
There is a positive correlation between income and prescription use.[89] It was hypothesized that patients with low income are less likely to adhere to their medications.[90]

Regimen complexity includes numbers of prescriptions and the frequency of refills that patients have had. Both of these factors affect medication adherence. It was hypothesized that patients with high numbers of prescriptions and refills would be more likely to have medication nonadherence.[91,92]

The Piette et al model includes socio-cultural influences, perceived benefits of treatment, mental status, self-efficacy, and health literacy as patient characteristics that influence nonadherence due to prescription cost.[88] Because of the availability of information in Part D claims data, only variables regarding socio-cultural influences and mental status were included in our analysis. Differences in socio-demographics, including race, age, and gender, may have an impact on adherence to medication. For instance, non-white patients were more likely to forgo medication use due to cost and used less medication than white individuals.[93] Patients with depression had more risk of underuse of medication due to cost than non-depressed patients.[88]

Prescription characteristics include adverse effects, dosing complexity and perceived need. We were unable to incorporate prescription characteristics into the analysis. Disease characteristics have some effects on current health related quality of life (HRQL) and life expectancy. Patients' comorbidities will be used as the indicators for this effect. Comorbidities will be determined from the variables indicating the chronic conditions from which patients suffered during the study period. These include acute myocardial infarction, stroke, Alzheimer's disease, chronic kidney, chronic obstructive pulmonary disease, heart failure, stroke, glaucoma, rheumatoid arthritis, osteoporosis, and diabetes.

Figure 1 Conceptual framework for the factors influencing rates of cost-related medication underuse.[88]



(Rx = Prescription drug; OOP = Out-of-Pocket; HRQL = Health-Related Quality of Life)

CHAPTER 2

LITERATURE REVIEW

Cost and use of oral cancer medications

A recent study conducted by Raborn et al. identified the total OOP payments by payer type for 21 oral chemotherapies in managed care plans.[94]

They used patient-level medical and pharmacy claims data provided by the IMS LifeLink: Health Plan Claims Database. The inpatient and outpatient diagnoses (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)) files and Current Procedural Terminology (CPT) Fourth Edition Coding System formats were used to identify cancer type. Demographic variables, payer type, provider specialty, charges, allowed and paid amounts, and plan enrollments were included. Adult patients aged 18 years and older who had at least one claim for one of the study drugs were included. The 21 drugs in the study included: altretamine, bexarotene, capecitabine, cyclophosphamide, dasatinib, erlotinib, etoposide, everolimus, gefitinib, imatinib, isotretinoin, lapatinib, lenalidomide, nilotinib, sorafenib, sunitinib, temozolomide, thalidomide, topotecan, tretinoin, and vorinostat. The index date for each patient was the date of his/her first prescription filled. Each patient was required to have continuous health plan enrollment for 6 months before and after the index date. Patients who were 65 years or older were included if they were in a "Medicare Risk (private Medicare) plan." Medicare Part D data were not available in their database. The primary outcome was the OOP costs for oral cancer drugs in 2009. They calculated OOP costs as the allowed amount minus the paid amount. Per claim OOP costs were identified in aggregate for each medication. OOP payments were classified by payer type, including commercial,

Medicaid, Medicare Risk, self-insured, and unknown. Patient demographics, including age, gender, geographic region, health plan and payer types, and clinical characteristics, including cancer type, were evaluated.

Descriptive statistics: means, median, and standard deviation were reported. Differences in OOP payments were measured using analysis of variance. A total sample of 6,094 patients was included. The mean age was 53 years and 54% of the total sample were women. The lowest mean OOP cost per claim was $15 for cyclophosphamide and the highest was at $527 for dasatinib. Mean OOP costs were $225 for erlotinib, $154 for imatinib, and $193 for thalidomide. They classified study drugs in two groups: medications with available generics and without available generics. The mean OOP cost was lower for drugs with available generic substitutes with a mean cost of $31 versus $171 for drugs without available generic drugs. Overall, 66% of the patients paid less than $50 per claim, for 21% OOP costs exceeded $100. Patients with Medicare Risk (private Medicare) plans paid significantly higher OOP payment than patients with other payers ($p<0.001$).[94]

Goldman et al. studied the utilization of specialty cancer drugs by evaluating the relationship of patients' incomes and their OOP payments to drug use.[95] This study used regression to estimate the association between cost-sharing and the probability of initiating therapy and the number of claims. Administrative claims data were selected from the health plans offered by 15 employers, from claims collected between 1997 and 2005. Data were collected from more than 50 health plans. The five oncolytic agents studied included both oral and injectable products. The oral agents were erlotinib (Tarceva®) and imatinib mesylate (Gleevec®), and the injectible products were

bevacizumab (Avastin®), trastuzumab (Herceptin®), and rituximab (Rituxan®). They studied the elasticity of demand in rituximab and the remaining drugs in two groups: all eligible patients and metastatic cancer patients. In the all eligible patient group, they found that the estimated elasticity of demand for rituximab was -0.258 ($p<.05$), and was -0.189 for the other drugs. The elasticity of demand was less in metastatic patients: -0.0367 ($p<.01$) for rituximab and -0.108 ($p<.05$) for non-rituximab drugs. A twenty-five percent lower OOP spending was associated with a 6.4 percent higher initiation of rituximab treatment in the all eligible patients group. In the remaining drugs, twenty-five percent lower OOP was associated with 4.7 percent higher initiation.[95]

A study done in 2006 by Bowman et al. looked at variation in the coverage and cost-sharing for cancer drugs covered by Medicare Part D.[96] They focused on cost-sharing of beneficiaries and comparison of formulary coverage across the plans. However, the use of cancer drugs and the impact of coverage were not studied. The "1 February 2006 extract of the CMS Prescription Drug Plan Formulary and Pharmacy Network Files" was used. Cancer drugs were stratified by type of plan: local MA-PD, regional MA-PD, and PDP. They examined average tier position, median coinsurance or copayments in the initial coverage phase, variation in coverage across benefit plans, and frequencies with which the cancer drugs were covered in the formularies. The percentage of generic cancer drugs that was covered was higher than that of brand name drugs. Regional MA-PD plans covered ($p<0.01$) significantly more of the cancer drugs, more frequently covered both generic and brand-name drugs, and less frequently used prior authorization than those of PDPs and local MA-PD plans. Fifteen out of twenty drugs most frequently covered on the formularies were brand-name drugs. Each of those twenty

drugs was listed on the formularies of all PDPs and more than 99 percent of MA-PD plans.

Most Part D plans have a tiered-cost-sharing structure in their formularies. Brand-name medications are mostly covered on higher tiers with higher coinsurance or copayment while generic drugs are on lower tiers with lower cost sharing. For example a typical tier structure might include generic drugs on the first tier, preferred brand-name drugs on the second tier, non-preferred brand-name drugs on the third tier, and specialty drugs on a fourth tier.[97]

The average cost-sharing tier was 2.1-3.1 for brand name versus 1.0-1.2 for generics. Most Part D benefit plans use a fixed copayment rather than coinsurance. However, most PDPs used coinsurance for imatinib and erlotinib. The median copayments for a thirty-day supply were $5-40 for PDPs versus $5-35 for MA-PD plans. The median coinsurance rate for both PDPs and MA-PD plans was 25 percent.[96]

Streeter et al. examined the abandonment rate of oral cancer medications and the factors associated with abandonment.[60] Administrative claims data from the Wolters Kluwer Dynamics Claim Lifecycle Database, a nationally representative pharmacy utilization data source, were used. The sample included data for 10,508 patients who met the inclusion criteria between January 1, 2007 and June 30, 2009. The inclusion criteria were as follows: 1) patients who were enrolled in non-Medicare commercial plans or Medicare plans, 2) patients who had at least one claim for any medication at least 120 days before the first oral cancer drug claim and at least 90 days after the first oral cancer agent claim, 3) patients who had a claim for at least one of these eight agents: capecitabine, imatinib, sorafenib, lenalidomide, sunitinib, erlotinib, temozolomide, and

lapatinib. Abandonment status was determined within 90 days after a claim for an oral oncolytic agent was initiated. An abandoned claim was defined as a prescription which had been prescribed, submitted by the pharmacy for third party reimbursement then reversed after adjudication, and which had not been followed up with a subsequent drug within 90 days. Ten percent of the total sample abandoned their oral cancer medication. The factors that were significantly associated with the abandonment rate were number of claims and pharmacy benefit design. Patients with cost-sharing of more than $500 (OR=4.46, P<0.001) and patients with five or more claims (OR=1.50, p<0.001) were more likely to abandon oral cancer drugs than those with cost-sharing less than $100 and those with no claims, respectively. In addition, patients with Medicare coverage had significantly higher OOP spending than those with commercial coverage (p<0.001) and rates of abandonment were higher after the second quarter of the year (between April and December) than in the first quarter (p<0.05).[60]

Recently, Short et al. estimated medical expenditures for adult cancer survivors who were less than 65 years old.[98] A cancer survivor is defined by the National Cancer Institute (NCI) as a living individual diagnosed with cancer.[99] Data from the Household Component of the Medical Expenditure Panel Survey (MEPS-HC) were linked with data from the National Health Interview Survey (NHIS) data to calculate the estimated expenditures for cancer survivors. Pooled data from 2001 to 2007 were included and weighted to be representative of the U.S. adult population. The total sample of individuals aged 25-64 years was categorized into three groups: 1) newly diagnosed survivors (n=361), 2) previously diagnosed survivors (n=2,119), and 3) not a survivor (i.e., patients with no history of cancer) (n=47,690). Propensity score matching

techniques were used to estimate the effect of cancer on the expenditures of cancer population. Probit models were developed to estimate the effects of cancer on the distribution of total and OOP expenditures. Mean annual expenditure for all services was $16,910 ± $3,911 for newly diagnosed survivors, $7,992 ±$972 for previously diagnosed survivors, and $3,303 ± $103 for individuals without a history of cancer. The mean of prescription expenditures was $2,347 for newly diagnosed survivors, $1,691 for previously diagnosed survivors, and $754 for adults with no history of cancer. The mean of OOP expenditures for prescriptions was $808 for newly diagnosed survivors, $607 for previously diagnosed survivors, and $265 for adults with no history of cancer. They estimated that cancer added $832 ± $286 to the average annual prescription expenditure for female cancer survivors and $1,219 ± $637 for male survivors. It was estimated that approximately twenty percent of previously diagnosed survivors aged 40-64 years old paid more than $2,000 OOP. This study showed that cancer is significantly associated with higher total medical expenditures and higher OOP spending, especially for those who were newly diagnosed.[98]

Cost-related nonadherence

Most cost-related nonadherence (CRN) studies have been conducted using self-reported survey data. There is no gold standard definition of CRN. Previous studies have defined CRN as the self-reported behaviors relating to cost of prescriptions. According to this definition, patients who reported any of the following behaviors were labeled as experiencing CRN: 1) delayed or stopped filling or refilling of a prescription because it was expensive, 2) skipped doses to make the prescription last longer, and 3) used less medication than prescribed to make it last longer.[100-104]

Cost-related nonadherence in cancer patients

We found only one study examining CRN in Medicare cancer patients. Nekhlyudov et al. conducted a CRN study in elderly Medicare beneficiaries.[100] CRN was compared between the Medicare enrollees with or without cancer using 2005 Medicare Current Beneficiary Survey (MCBS) data. They categorized the sample into two groups: enrollees with and without cancer based on the ICD-9 claim codes for any cancer. The outcomes of interest included the self-reported CRN, spending less on basic needs to afford medicine, and cost reduction strategies. The cost reduction strategies used to offset medication costs included: using generic substitution, requesting free samples, using mail-order or internet, obtaining medication from outside the US, and comparing prices before filling prescriptions. Descriptive statistics and logistic regression were used to measure CRN and cost-reduction strategies. Covariates included demographic and socio-economic variables, self-reported health status, type of drug coverage, number of years participating in MCBS, and the year of survey. Of 9,818 non-institutionalized elderly Medicare enrollees, 14% had at least one cancer claim. Cancer survivors were more likely to be male, non-Hispanic, older, more educated, and have multiple comorbidities, poor health status, and employer based insurance coverage. Of the total cancer survivors, 10.3% reported CRN and 6.3% reported forgoing basic needs. Cancer survivors who reported CRN were more likely to be African American, have income <$25,000, and do not have drug insurance coverage, compared to cancer survivors without CRN. Moreover, cancer survivors who reported spending less on basic needs were more likely to be African American, female, have incomes less than $25,000, and not have a high school education than those who did not report spending less on basic needs. For cost-

reduction strategies, approximately half of all enrollees reported that they used generic substitution or requested free samples. Cancer survivors were more likely to use mail-order or obtain their medications from internet compared to non-cancer patients.[100]

Cost-related nonadherence in Medicare Part D program

A recent study was conducted by Williams et al. using data from the Translating Research into Action for Diabetes (TRIAD) survey of patients in 8 western states.[101] The TRIAD survey randomly selected Medicare beneficiaries who 1) were 65 years or older by January 1, 2005, 2) had total prescription costs that exceeded $2,250 by October 1, 2006, and 3) were continuously enrolled in an MAPD plan between January 1, 2005 and December 31, 2006. Beneficiaries who had full prescription coverage in the coverage gap and LIS beneficiaries were excluded because they did not have a coverage gap.

Telephone interviews were conducted among elderly Medicare Part D beneficiaries with diabetes who entered the coverage gap in 2006. CRN was identified based on pharmacy claims data records and telephone interviews. The interviewers identified nonadherence to medications that were not recorded in pharmacy claims by asking each participant to bring their medications to the phone during the interview. A total of 1,264 participants were asked whether they had any CRN to any medication they took during 2006. The specific drugs were identified if participants took less because of cost. Multivariate logistic regression analyses were used to examine CRN controlling for other variables, including comorbidity count, OOP costs in the first quarter of 2006, sex, race, gender, educational attainment, annual income, plan type, and medication coverage during the coverage gap. The type of medications was created as indicator variables,

including: diabetes, hypertension, cholesterol-lowering, symptom relief, and others. These indicators were used as the main predictors in the analyses. The authors found a 16% prevalence of CRN occurred with any medication. CRN was higher with cholesterol-lowering medication (Relative Risk (RR), 1.54; 95% CI, 1.01-2.32), or an annual income less than $25,000 (RR, 3.05; 95% CI, 1.99-4.65). As age increased, rates of CRN decreased.[101]

Frankenfield et al. conducted a CRN study among Medicare Part D beneficiaries with end-stage renal disease (ESRD).[102] The 2007 Medicare Consumer Assessment of Health Providers and Systems Survey (CAHPS) was used to obtain CRN information. This is a national survey of a randomly selected sample of community dwelling Medicare beneficiaries. CRN was evaluated based on whether participants delayed filling a prescription because of cost in the last six months. Covariates included socio-demographics, health status measures, selected health behaviors, accessibility to the healthcare system and providers, chronic condition risk scores, and whether they were a new Medicare enrollee. Multivariate logistic regression was used to estimate the CRN risk, controlling for demographic characteristics, socio-economic status, chronic conditions, and health behaviors. Sixteen percent of the total sample reported CRN. Furthermore, for the total Medicare beneficiary sample, CRN was found to be significantly associated with the following variables: chronic conditions, including ESRD, diabetes, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and mental disorders; race, including American Indian, black, or Hispanic; low educational attainment (less than high school), lower socio-economic status (SES) score, female, younger than 65 years old, smoking, poor self-reported health status, lower

personal-physician rating, and filling six or more prescriptions in the past six months. Respondents with ESRD were more likely to report CRN than those without ESRD. Of the 1,329 respondents with ESRD, 31% reported CRN. Respondents with ESRD were 23% more likely to report CRN than those without ESRD. The odds ratio for CRN in respondents with ESRD was 2.34 (95% CI, 2.0-2.75) for the unadjusted model and 1.23 (95% CI, 1.07-1.41) for the adjusted model. Respondents who identified as Black and those receiving LIS were significantly more likely to report CRN.[102]

Kennedy et al. conducted a CRN study in Medicare Part D beneficiaries. They examined how CRN changed with Part D implementation and whether the extent of CRN changed from 2005 to 2006 among three groups.[103] The three groups included newly insured beneficiaries, continuously insured beneficiaries and continuously uninsured beneficiaries. MCBS access to care files were used to compare rates of CRN and changes in CRN. Multinomial logistic regression was used to estimate changes in CRN by insurance status controlling for other covariates. They categorized CRN changes into 4 levels, including: 1) Resolved CRN (CRN was reported in 2005 but not in 2006), 2) Unresolved CRN (CRN was reported in 2005 and 2006), 3) New CRN (CRN was reported only in 2006), and 4) No CRN (CRN was not reported in either 2005 or 2006).

After the introduction of Medicare Part D, CRN rates decreased from 15.4% in 2005 to 11.3% in 2006. Newly insured beneficiaries were more likely to have resolved CRN (OR=1.6; 95% CI 1.3-2.2), and unresolved CRN (OR=2.1; 95% CI, 1.5-2.9) than continuously insured beneficiaries. Continuously uninsured beneficiaries were more likely to report unresolved CRN (OR=1.8; 95% CI, 1.3-2.4) than continuously insured enrollees. Moreover, disabled Medicare beneficiaries who were younger than 65 years

old were more likely to report all CRNs (resolved, unresolved, and new CRN) than elderly beneficiaries. Beneficiaries with fair or poor health were more likely to report resolved (OR=1.3, 95% CI, 1.1-1.6), unresolved (OR=1.7; 95%CI, 1.3-22) and new CRN (OR=1.4; 95% CI, 1.1-1.9). Beneficiaries with multiple chronic diseases or depression were more likely to report CRN.[103]

Madden et al.estimated the changes in CRN following Part D implementation using longitudinal MCBS data from 2004 to 2006.[104] Data from community dwelling respondents from the MCBS access to care files were included. The CRN measure was obtained from the three questions in the MCBS data as mentioned previously. In addition, they measured whether beneficiaries spent less on food, heat, or other basic needs for medicine. They used logistic regression models to estimate changes in CRN and whether beneficiaries spent less on basic needs over time. The models were weighted and controlled for the interview sequence, demographic characteristics, and health status. Changes in CRN and spending less on basic needs declined significantly after Part D implementation. The adjusted odds ratio for CRN was 0.85 (95%CI, 0.74-0.98) and the OR for spending less on basic needs was 0.59 (95%CI, 0.48-0.72). The decline in CRN was significantly associated with elderly status, good or excellent self-reported health status, fewer comorbidities (2-3 diseases), and lower income. The tendency to forgo basic needs significantly decreased among all subgroups except nonelderly disabled beneficiaries.[104]

Duru et al. assessed the association between generic-only gap coverage and cost-cutting behaviors of diabetic beneficiaries who used and did not use insulin.[105] The study sample was selected from the TRIAD survey including diabetic beneficiaries who

reached the coverage gap by October 2006. The primary predictor was no gap coverage or generic-only gap coverage. Multivariate logistic models were used to measure seven medication cost-cutting behaviors, controlling for other covariates. The cost-cutting behaviors included: 1) CRN, 2) forgoing necessities because of financial hardship, 3) generic substitution, 4) split pills according to their doctor's advice, 5) used an over-the-counter (OTC) substitute, 6) used a mail-order pharmacy, and 7) called a different pharmacy to find the lowest price. In the insulin user group, beneficiaries with generic-only gap coverage were less likely to report CRN than beneficiaries without gap coverage (16% vs. 29%; p= 0.03). CRN was not different between beneficiaries with or without gap coverage among non-insulin users. However, non-insulin users with generic-only gap coverage were less likely to switch to a cheaper medicine (36% vs 46%; p=0.01) or to call a different pharmacy to find a lower price than those who had no gap coverage (22% vs 36%; p<0.001). Medicare beneficiaries who used insulin were at high risk of reporting CRN.[105]

Zivin et al. estimated changes in CRN two years before and one year after Part D initiation.[106] MCBS data were used to determine the annual prevalence and changes in CRN among Medicare beneficiaries with and without depressive symptoms following Part D implementation. The following self-reports of CRN were the main outcome measure: 1) "skipping doses to make medication last longer, 2) taking smaller doses of a medicine to make medicine last longer, 3) not obtaining prescribed medicine because it would cost too much, 4) not filling or refilling prescription because it was too expensive, and 5) spent less money on food, heat, and other basic needs so that they would have money for medicine."

In beneficiaries with depression, spending less on basic needs declined significantly after part D implementation (adjusted ratio of ORs, 0.72; 95%CI, 0.52-0.99), but CRN was not significantly different after Part D implementation (adjusted ratio of ORs, 0.85; 95%CI, 0.65-1.12). In non-depressed beneficiaries, spending less on basic needs declined significantly (adjusted ratio of ORs, 0.50; 95% CI, 0.40-0.63), and CRN decreased significantly (adjusted ratio of ORs, 0.83; 95%CI, 0.70-0.97) after Part D implementation. However, the risk of CRN persisted in depressive beneficiaries.[106]

Madden et al. analyzed CRN after Medicare Part D implementation to determine whether the nationwide reduction in CRN among Medicare part D beneficiaries remained stable in 2007.[107] All total community-dwelling respondents with MCBS data between 2004 and 2007 were included and categorized into 4 subgroups: 1) elderly with 0-2 morbidities, 2) elderly with 3 or more morbidities, 3) non-elderly disabled with 0-2 morbidities, and 4) non-elderly disabled with 3 or more morbidities. Self-reported CRN included "skipping or taking smaller doses to make a medicine last longer, or not filling a prescription because it was too expensive."[104] Moreover, other behaviors related to cost-cutting were included, such as "spending less on food, heat, or other basic needs to afford medicine."[107] CRN and forgoing basic need outcomes were compared for 2007 vs 2006 and 2007 vs 2005. Between 2006 and 2007, the prevalence of CRN decreased significantly for the overall population (OR=0.71, $p<0.001$) and in the disabled with 3 or more morbidities (OR=0.74, $p<0.01$). Between 2005 and 2007, CRN and forgoing basic needs declined significantly for the overall population (OR=0.71, $p<0.001$; OR=0.66, $p<0.001$) and for all subgroups (ORs between 0.58 and 0.77, $p<0.05$).

This study demonstrated that reductions in CRN and forgoing basic needs were maintained in the year following Part D implementation.[107]

Castaldi et al. determined the relationship between inhaler out-of pocket costs and CRN among elderly beneficiaries with Chronic Pulmonary Disease (CPD).[33] The 2006 national survey data of non-institutionalized Medicare beneficiaries provided by the CMS were used. The amounts that participants spent on inhalers over the previous 30 days were determined as OOP inhaler costs. Participants were classified into 4 groups: "those with CPD using inhalers, those with CPD not using inhalers, those without a diagnosis of CPD on inhalers, and those without either CPD or inhaler use." CRN was determined by these three behaviors: not filling a prescription because of cost, skipping doses to make a prescription last longer, or taking smaller-than prescribed doses to make a prescription last longer. The CRN rate in enrollees with CPD using inhalers was 31%. CRN was found to have a strong association with OOP inhaler costs in Medicare enrollees diagnosed with CPD using inhalers. This study demonstrated that Medicare beneficiaries with CPD and high OOP costs for inhalers were at risk of CRN.[33]

Overall, as this review indicated, Medicare beneficiaries experienced a high risk of CRN. CRN rates among Medicare Part D beneficiaries ranged between 10.3% and 31%.[33,100-102] CRN was higher in patients with chronic diseases, including ESRD, diabetes, COPD, CHF, mental disease, and high cholesterol. The risk of CRN decreased after Medicare Part D implementation; however, it remained unchanged in some groups of patients, such as depressed beneficiaries or elderly beneficiaries with comorbidities. The significant factors associated with increased risk of CRN included age, race, gender,

poor health status, low income, lack of prescription coverage, comorbidities, high OOP costs, and not having generic gap coverage.

Adherence to oral cancer drugs

A number of studies have examined adherence in patients taking imatinib and the aromatase inhibitors (anastrozole and letrozole).

Wu et al. examined the association between adherence with imatinib and healthcare costs and utilization, controlling for comorbidities and disease severity.[108] They used the MedstatMarketScan Commercial Claims and Encounters database, a large commercial claims database. The database includes enrollment history and medical and pharmacy claims of employees aged 18-65 years old from large employers and health plans. All imatinib users treated for CML between January 1 2002 and July 31, 2008 were identified using ICD-9-CM codes. The date of the first imatinib prescription was the index date. Patients were included in the study if they were continuously enrolled in a private plan at baseline and 12 months after the index date. The baseline was defined as a 4 month period before the index date. ICD-9-CM codes were used to identify severity of CML and comorbidities. Adherence was measured using the medication procession ratio (MPR). MPR was calculated as "the total days' supply of imatinib possessed by the patient during 12 months following the first imatinib prescription divided by 365 days."[108] Patients with an MPR equal to 85% or higher were classified as high MPR. Otherwise, they were categorized as low MPR. Utilization was measured as "numbers of inpatient visits, emergency visits, total inpatient days, days per stay, outpatient visits, emergency room visit, and non-imatinib and imatinib prescriptions."[108] They included the costs of medical claims in which CML was a primary or secondary diagnoses and

pharmacy claims for imatinib as CML-related costs. Generalized linear models (GLM) with log link and gamma distributions were conducted to examine the relationship between healthcare costs and adherence. Age, gender, non-adult (aged <18 years old) indicator, health plan type at index date, comorbidity index, year of treatment initiation, severity of CML, total number of concurrent medications, and total baseline costs were controlled in the models. A total of 592 patients was included.

Overall, the mean MPR was 79% (95% CI, 76-81%) and 41% of the sample had low MPR. Patients with low MPR had higher inpatient care costs ($44,498 vs. $3,758; p<0.001) and higher non-imatinib medication costs ($5,652 vs. $2,743; p<0.001) than patients in the high MPR group. However, patients with low MPR had lower imatinib costs ($22,846 vs. $40,164; p<0.001). The number of inpatient visits and total inpatient days were greater in patients with low MPR (p<.0.001). Low MPR was significantly associated with increased total costs (p<0.001). After controlling for baseline costs, CML severity, concomitant medications and other covariates, total medical costs were 26% higher and total non-imatinib costs were 178% higher in low MPR patients (p<0.001).[108]

Darkow et al. examined the association between treatment interruptions and nonadherence with imatinib and health care costs among managed care patients with CML.[19] The retrospective study used pharmacy and medical claim data from a managed care provider for the period between January 1, 2001 and March 31, 2005. Inclusion criteria were, 1) Patients aged 18 years and older with one prescription filled for imatinib from June 1, 2001 to March 31, 2004, 2) continuously enrolled in the plan 3 months before the index date and 12 month following the index date. The index date was the date of the first imatinib fill during the study period. The baseline period was assigned as 3

months prior to the index date. Patients were stratified into usual, moderate or high cancer complexity categories. Treatment interruption was defined as "failure to refill imatinib within 30 days from the end of supply of the prior prescription."[19]

MPR was calculated and stratified to low MPR (<50%), intermediate MPR (between 50 and 90%), high MPR (between 90-95%), and very high MPR (greater than 95%). Total healthcare costs (medical services and prescription costs), imatinib costs, and medical costs were examined.

Mean MPR in the first year was 77.7% (SD 27.5%). Forty-five percent of the sample had a very high MPR and 20% had a low MPR. Overall, 30.7% had a treatment interruption. MPR decreased significantly as number of unique prescriptions increased (p=0.002). Patients with high cancer complexity had a lower MPR (p=0.003). Female patients had a lower MPR (p=0.003) than male patients. Higher rates of emergency room visits and urgent care use were found in patients with low MPRs. MPR was not associated with total healthcare costs including imatinib after adjusting for other factors (p=0.08), but was associated with total healthcare costs excluding imatinib (p<0.001). A 10% decrease in MPR was associated with a 14% increase in medical and prescription costs, excluding imatinib costs, and 15% increase in medical costs.[19]

Patridge et al. conducted an adherence study of anastrozole using longitudinal pharmacy and claims data from two large commercial health plans and MarketScan, an employer-based database.[109] Patients with MPR greater than 80% were defined as adherent. Moreover, they also conducted a persistency analysis to identify patterns of prescriptions filled in nonadherent patients. Nonpersistent (i.e. discontinued) was defined as failure to fill prescriptions over a continuous 4-month period.

A total of 12,391 patients were included in the study. The mean MPR of patients in the 12 month follow-up group was between 82%-88%. The mean MPR declined after the first year of therapy. In patients with 36 month follow-up, the MPR decreased from 78%-86% in year 1 to 62%-79% in year 3. The mean MPR in nonadherent patients was 42% in the first 12 months of therapy. The average gap between consecutive fills was 20 days. Of 184 patients with nonadherence, 76% were nonpersistent and the discontinuation rate was 13% during the first 12-months period.[109]

Sedjo and Devince examined risk factors for nonadherence to three aromatase inhibitors (exemestane, anastrozole, and letrozole) using data from the MarketScan Commercial Claims and Encounters Database.[110] Females enrolled for at least two years during the study period (January 1, 2005 to December 31 2007) and who had a claim for a primary or secondary breast cancer diagnosis in the first year were included in the study. Adherence was defined as an MPR greater than or equal to 80%. Multivariate logistic regression was used to determine the relationship between adherence and potential predictors that included "age, initial aromatase inhibitor treatment claim in 2006, switching to another AI or tamoxifen, previous endocrine treatment, total OOP prescription costs, total medical OOP cost, mail order pharmacy use, outpatient visits, ER and/or urgent care use, oncology visit, mastectomy, and any use of a preventive health visit cancer diagnosis other than breast"[110] Overall, the prevalence of nonadherence to AI treatment was 23%. Younger age, OOP cost greater than or equal to $30 per AI prescription, switching to another AI or tamoxifen, no mastectomy, and higher Charlson Comorbidity Index significantly increased the likelihood of nonadherence.[110]

A clinical trial was conducted by Noens et al. to assess the prevalence of imatinib nonadherence over a 90-day period among patients with CML.[27] A prospective, observational multicenter noninterventional study was designed to examine the factors associated with nonadherence and to assess whether treatment response was associated with adherence levels. Treatment response was defined using hematologic cytogenetic and molecular response rates. Nonadherence was measured using self-report: "Basel Assessment of Adherence Scale (BAAS) with Immunosuppressive Medication adapted to imatinib."[27] Given a positive answer to any of the 4-questions on the adapted BAAS, a patient was defined as nonadherent. Pill count for a 90-day period was used to identify the "percent not taken of percent prescribed."[27]

A total of 169 patients were included. Nonadherence based on the BAAS was reported at 32.7% at the follow-up compared with 36.1% at baseline. On average, patients with suboptimal response had a higher mean percentage of not taking imatinib (23.2%, S.D. =23.8) compared with patients with optimal response (7.3%, SD=19.3; p=.005). For patients treated with imatinib for at least 12 months, patients with complete cytogenetic response (CCyR) had a significantly lower mean percentage of not taking imatinib (9%, S.D. = 18.6) than those with incomplete response (26.0%, S.D. = 24.4; p=0.012). In all patients and those with at least 18 months of therapy, no significant difference was found in the mean percentages of pill count between complete and incomplete hematologic response patients.[27]

Marin et al. conducted a study to examine the relationship between imatinib adherence and degree of molecular response in CML patients.[28] Eighty-seven patients with CML who received imatinib as first therapy for at least 2 years were included in the

study. All patients had achieved complete cytogenetic response at the time of recruitment. Patients were required to tolerate at least 400 mg of imatinib. However, if patients failed to achieve major molecular response (MMR), the dose was increased to 600 mg. Adherence was measured using microelectronic monitoring system (MEMS) and blood sample test. MEMS was used to monitor adherence in patients for a median of 91 days (range 84 to 120 days). Logistic regression was used to determine the relationship between adherence and prognostic factors and the response in patients. The median adherence rate was 97.6% (range 22.6%-103.8%). Adherence was significantly associated with prior MMR achievement (RR, 1.093, $p<0.001$). The median adherence rate was significantly lower for patients who took the 600 mg dose than patients who remained on 400 mg (86% vs. 98.8%, $p=0.21$). Younger patients were more likely to have lower adherence rate than older. Other conditions associated with lower adherence rate included asthenia, nausea, muscle cramps, and bone or joint pain. The results of this group of studies indicated that nonadherence to oral cancer medications was between 3%-41%. Low adherence was associated with negative consequences, including increased inpatient and non-cancer drug costs, higher number of inpatient and emergency room visits and inpatient days, and higher total health care costs. Factors found to be significantly associated with low adherence included high OOP costs, higher numbers of comorbidities, polypharmacy, and cancer complexity.[28]

Summary of Literature Review

Overall, the review of literature indicates that high OOP costs of oral cancer drugs decrease patients' adherence. Other factors that have been found to be associated with adherence include variation of pharmacy benefit design and cost-sharing structure. The findings from previous studies also indicate that patients with cancer experienced a high prevalence of nonadherence and could be at higher risk for cost-related discontinuation.

Many studies have been conducted using pharmacy claims data from employer-based insurance plans, private health insurance plans and managed care. These studies found rates of nonadherence to cancer medicines that ranged from 19 to 41%. The beneficiaries in these plans are, for the most part, under 65 years of age. Medicare data, or other data on elderly patients, have rarely been used to estimate adherence in oral cancer drug users. Another group of studies has measured patient adherence to oral cancer drugs in clinical trials. Rates of nonadherence in these studies ranged from 3 to 33%. Nonadherence rates from those studies may not accurately represent adherence to oral cancer drugs in real world medical practice because patients in trials are closely monitored and treated in a more controlled environment. Further, patients using oral cancer drugs in actual practice may have high OOP costs for these agents and this may increase the likelihood of nonadherence.

Overall, as this review indicates, there has been a limited amount of research on costs of oral cancer drugs, especially in the Part D population. Similarly, there have been few published studies focusing on nonadherence to oral chemotherapy due to cost.

Our study was the first to examine the costs associated with the use of oral cancer medication and the impact of OOP costs and prescription drug coverage on medication discontinuation in a nationally representative Medicare Part D elderly population.

CHAPTER 3

RESEARCH OBJECTIVES

Objective1: To identify demographic characteristics and types of prescription drug subsidies for Part D beneficiaries who used oral cancer drugs in 2008

Objective 2: To identify total costs, patient out-of-pocket costs, and plan costs relating to use of oral cancer medications in elderly Medicare Part D population in 2008

Objective 3: To determine the percentage of patients entering the Medicare Part D coverage gap, the time they entered the gap in 2008, and the duration of time they spent in the gap in 2008.

Objective 4: To determine the number and percentage of Medicare Part D patients who discontinued or delayed their oral cancer drug therapy in 2008.

Objective 5: To examine the extent to which total out-of-pocket costs for oral cancer medications are associated with the discontinuation or delay of oral cancer medications, adjusted for factors associated with medication nonadherence including, polypharmacy, prescription drug subsidies, and socio-demographic factors.

CHAPTER 4

METHODS

This chapter describes the methods used in conducting this study. It provides the complete details of all procedures performed in this study, including study design, sample preparation, and statistical analyses. In this chapter, the methods will be presented for each objective.

Study Design

This study was a cross-sectional retrospective study of spending on oral cancer drugs in the Medicare Part D population. All statistical analyses were performed with SAS software version 9.3 (Cary, NC).

Data and Sample Preparation

The data used in this study were selected from the 2008 Medicare Part D database compiled by the Centers for Medicare and Medicaid Services (CMS) provided by the Research Data Assistance Center (ResDAC). A 5% random sample of 2008 Medicare beneficiaries was used. The sample included the Beneficiary Summary File with Part D denomination, Beneficiary Annual Summary File, Part D Event File with drug characteristics, and the Plan Characteristics File.[111]

The Beneficiary Summary File

The Beneficiary Summary File with Part D denomination contains demographic eligibility and Part D enrollment information about beneficiaries who are eligible for Medicare. Table 1 shows the variables utilized from this file.

Table 1: Variables from the Beneficiary Summary File[112,113]

Variable	SAS Variable Name	Description
Beneficiary ID	**BENE_ID**	A unique encrypted beneficiary identification number The BENE_ID is used to link data for each beneficiary across all claim and assessment data files.
State code	**STATE_CD**	State of residence of a beneficiary
Zip code of residence	**BENE_ZIP**	Zip code of residence based on the mailing address of a beneficiary. Each code is represented by a 9-digit code.
Gender	**SEX**	Gender
Race	**RACE**	Beneficiary race code
Date of birth	**BENE_DOB**	Date of birth of the beneficiary
Date of death	**BENE_DOD**	Date of death of the beneficiary

Cost share group	**CST_SHR_GRP_CD_01 – 12**	Beneficiary's cost-sharing for each month. This code indicates subsidy and dual eligible status of the beneficiary.
Retiree drug subsidy	**RDS_CVRG_MOS_NUM**	Retiree drug subsidy coverage months number
Dual eligible months number	**DUAL_ELGBL_MOS_NUM**	Total number of months of dual eligibility for each beneficiary
Plan coverage months number	**PLAN_CVRG_MOS_NUM**	Total number of months of Part D plan coverage

The Beneficiary Annual Summary File (BASF)

The BASF provides diagnosis and date of diagnosis of 21 chronic conditions. This file was used to identify whether beneficiaries had any comorbidities while they received chemotherapy and to identify the history of any indications of cancer of each enrollee. However, only five selected cancers are on this list. Table 2 presents all variables utilized from the BASF file. This file was linked with the Beneficiary Summary File by using beneficiary identification number (BENE_ID).

Table 2: Variables used to identify beneficiaries' comorbidities and history of any caner conditions[112,113]

SAS Variable Name	Description
AMI	CCW: Acute Myocardial Infarction
ALZH	CCW: Alzheimer's Disease
ALZHDMTA	CCW: Alzheimer's Disease and Related Disorder
ATRIALFB	CCW: Atrial Fibrillation
CATARACT	CCW: Cataract
CHRNKIDN	CCW: Chronic Kidney Disease
COPD	CCW: Chronic Obstructive Pulmonary Disease
CHF	CCW: Heart Failure
DIABETES	CCW: Diabetes
GLAUCOMA	CCW: Glaucoma
HIPFRAC	CCW: Hip/Pelvic Fracture
ISCHMCHT	CCW: Ischemic Heart Disease
DEPRESSN	CCW: Depression
OSTEOPRS	CCW: Osteoporosis
RA_OA	CCW: Rheumatoid Arthritis/Osteoarthritis
STRKETIA	CCW: Stroke / Transient Ischemic Attack
CNCRBRST	CCW: Female Breast Cancer
CNCRCLRC	CCW: Colorectal Cancer
CNCRPRST	CCW: Prostate Cancer

CNCRLUNG	CCW: Lung Cancer
CNCRENDM	CCW: Endometrial Cancer
CNCRBRSE	Earliest indication of Female Breast Cancer
CNCRCLRE	Earliest indication of Colorectal Cancer
CNCRPRSE	Earliest indication of Prostate Cancer
CNCRLNGE	Earliest indication of Lung Cancer
CNCENDME	Earliest indication of Endometrial Cancer

*CCW- Chronic Condition Data Warehouse is a research database providing Medicare, Medicaid, Assessment, and Part D prescription drug event data

Part D Event (PDE) File

(1) Drug event and characteristics file

The Part D event (PDE) data, including the Drug and Plan Characteristics Files provide information on demographics and characteristics of drug, plan, and payment. Both drug and plan characteristic files were linked by using the encrypted beneficiaries' identification number (Bene_ID) variable. Table 3 presents the variables obtained from the drug event and characteristics file. This file was used to identify the details of prescriptions, the payment amount for each fill, and to identify whether patients discontinued their oral cancer medication.

Table 3: Variables used from drug characteristics file[112,113]

SAS Variable Name	Description
BENE_ID	Encrypted Beneficiary ID
SRVC_DT	Prescription service date
QTY_DSPNSD_NUM	Quantity dispensed
DAYS_SUPPLY_NUM	Number of days' supply of medication dispensed
PTNT_PAY_AMT	Patient paid amount
OTHR_TROOP_AMT	Third party payments that contribute to true out-of pocket amount
CVRD_D_PLAN_PD_AMT	Net amount the plan paid for covered Part D drugs
BENEFIT_PHASE	Benefit phase of the Part D event
BN	Brand name of the drug
GNN	Generic name of the drug
STR	Drug strength

(2) Plan Characteristics File

We used the plan characteristics file to determine the Part D benefit structure. The types of benefit structures include defined standard, actuarially equivalent standard, basic alternative, and enhanced alternative. The defined standard benefit includes an initial deductible of $275, pre-ICL in which the patient pays 25% coinsurance, coverage gap in which the patient pays 100% coinsurance, and catastrophic phase in which the patient pays 5% coinsurance. The actuarially equivalent standard benefit includes the same deductible as the standard benefit, but offers different cost-sharing. The basic alternative structure includes a lower deductible than the standard benefit and uses tiered cost-sharing for covered prescriptions. The enhanced alternative benefit offers coverage for some medications during the coverage gap, lower cost-sharing, or covers more medications than the standard benefit.[46]

Calculating Median Household Income

Several studies show that income is one of the potential factors that indicate which patients would discontinue or not adhere to their medications.[88,89,100,104,114] Medicare Part D data do not provide beneficiaries' incomes. Therefore, to estimate patients' incomes we had to use a proxy variable. We used the median household income of the beneficiary's zip code of residence. We obtained the income information from the Zip Code Tabulation Areas (ZCTA) level geography 2000: Version 4 dataset.[115] The income data contained the beneficiary's zip code and was calculated from the US Census 2000 data. The ZCTA median household income information was provided by age range. We used the median household income for householders aged 65-74 years

old and aged 75 years or older in 1999 dollars. The 1999 median household income in the zip code of residence was linked with the Medicare data set by using the 5-digit zip code of residence. The income data were converted to 2008 US dollar values by adjusting for inflation using the Consumer Price Index (CPI).

Adjusting for inflation

The Consumer Price Index (CPI) is commonly used to measure the average change in prices over a period of time for a market basket of consumer products and services.[116] The percentage annual inflation rate is used to calculate the change in price.[116] This study used median household income values from 1999. As a result, we needed to adjust the value of 1999 dollars to their 2008 value. Table 4 illustrates the CPI from 2000 to 2008.[117,118]

Current dollars is a term used to describe income in the year that an individual received it. After adjusting for price changes, the value expressed in dollars is called real dollars, constant dollars, or real income.[119]

The following section illustrates the adjustment for inflation and inflation adjusted income.

Calculation for inflation using CPI and inflation adjusted income

(a) Inflation rate

The following formula was used for calculating the inflation rate by using CPI.

$$i = \frac{CPI_{\text{Current year}} - CPI_{\text{Base year}}}{CPI_{\text{Base year}}} \text{ x } 100 \qquad \text{..... (1)}$$

Where:

i = Inflation rate (%)

$CPI_{\text{Current year}}$ = Consumer Price Index at the given year

$CPI_{\text{Base year}}$ = Consumer Price Index at the base year

Example:

According to equation 1, the inflation rate for year 2000 was calculated as

$$i = \frac{252.9 - 244.7}{244.7} \text{ x } 100$$

$$i = 0.0335 \text{x} 100$$

$$i = 3.35\ \%$$

(b) Inflation adjusted income

To assess the value of income accurately, income should be adjusted for changes in the cost of living over time. For example, if we compare the median household income of $25,000 in 1999 with the 2001 median income of $26,000 without adjusting for inflation, it would appear to have increased. However, if we convert the 1999 current dollars to 2001 real dollars, the adjusted income is $26,574. This indicates a decrease in income from 1999 to 2001.

The following formula was used to calculate the adjusted household income.

$$FV = PV\,(1+r) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

Where:

*FV (*Future value) = Real dollars (Inflation adjusted income)

PV (Present value) = Current dollars (unadjusted income)

r = Decimal inflation rate

Example:

According to equation 2, the inflation adjusted income of $35,000 for year 2008 was calculated as:

$$\mathbf{FV_{2008}} = \mathbf{PV_{1999}}\ [(1+\boldsymbol{r}_{2000})(1+\boldsymbol{r}_{2001})(1+\boldsymbol{r}_{2002})\ (1+\boldsymbol{r}_{2003})\ (1+\boldsymbol{r}_{2004})\ (1+\boldsymbol{r}_{2005})\ (1+\boldsymbol{r}_{2006})\ (1+\boldsymbol{r}_{2007})\ (1+\boldsymbol{r}_{2008})]$$

$$\mathbf{FV_{2008}} = 35{,}000\ [(1+0.0335)\ (1+0.0280)\ (1+0.0161)\ (1+0.0223)\ (1+0.0270)\ (1+0.0335)\ (1+0.0328)\ (1+0.0283)\ (1+0.0384)]$$

= 35,000 x 1.292

$\mathbf{FV_{2008}}$ = 45,220

The real dollars for the 1999 income of $35,000 in 2008 was $45,220 after adjusting for inflation rates.

Table 4: Annual average Consumer Price Index Research Series (CPI-U-RS) using current methods all items: 1999-2008[117]

Year	CPI-U-RS index	Decimal inflation	Inflation rate (%)
1999	244.7	-	-
2000	252.9	0.0335	3.35
2001	260.0	0.0280	2.80
2002	264.2	0.0161	1.61
2003	270.1	0.0223	2.23
2004	277.4	0.0270	2.70
2005	286.7	0.0335	3.35
2006	296.1	0.0328	3.28
2007	304.5	0.0283	2.83
2008	316.2	0.0384	3.84

A modified income variable was created using cost sharing status information from the Beneficiary Summary File and the median household income adjusted to 2008 dollars. The cost sharing status variable (cost share group code) indicated the subsidy status of each beneficiary. We used the subsidy eligibility status of each beneficiary as of January 2008 to create the modified income variable. This was possible because the Medicare program determines eligibility for subsidies for cost sharing and premiums based on beneficiaries' income and financial resources.[120,121] Table 5 shows the income - as a FPL threshold - and financial resource limits for each type of subsidy.

Table 5: Subsidy/Dual eligibility status and copayment amount[115,120-123]

Cost share group code		Copayment	Eligibility status	Assets Limit*	Annual Income percentage of Federal Poverty Level (FPL)
01	Beneficiaries living in long term care is qualified with 100% premium subsidy and no copayment	0	Full Dual/Full subsidy	$2,000 (individual) $3,000 (couple)	<100%
02	Beneficiaries is qualified with 100% premium subsidy and low copayment	$3.10	Full Dual/Full subsidy	$2,000 (individual) $3,000 (couple)	<100% (56%-100%)
03	Beneficiaries is qualified with 100% premium subsidy and high copayment	$5.60	Partial Dual/Full subsidy	$4,000 (individual) $6,000 (couple)	100-135%
04	Beneficiaries with LIS, 100% premium-subsidy and high copayment	$5.60	Full subsidy	Resources ≤ $6,290 (individuals) or ≤ $9,440 (couples)	< 135%
05	Beneficiaries with LIS, 100% premium-subsidy and 15% copayment	15%	Full subsidy	Resources between $6,290-$10,490 (individuals) or $9,440-$20,970 (couples)	<135%
06	Beneficiaries with LIS, 75% premium-subsidy and 15% copayment	15%	Partial Subsidy	Resources below $10,490 (individuals) or $20,970 (couples)	135% - 140%

Cost share group code		Copayment	Eligibility status	Assets Limit*	Annual Income percentage of Federal Poverty Level (FPL)
07	Beneficiaries with LIS, 50% premium-subsidy and 15% copayment	15%	Partial Subsidy	Resources below $10,490 (individuals) or $20,970 (couples)	140% - 145%
08	Beneficiaries with LIS, 25% premium-subsidy and 15% copayment	15%	Partial Subsidy	Resources below $10,490 (individuals) or $20,970 (couples)	145%- 150%
09	No premium-subsidy nor cost sharing		No Subsidy	Not Applicable	≥ 150%

*These resource limits excluded the burial expenses for $1,500 (individual) and $3,000 (couple).

According to the 2008 Department of Health and Human Services (HHS) Poverty Guidelines, the FPL was calculated based on the number of people in a family or household (shown in Table 6).[124] We estimated income from the FPL by assuming two people in each household because that is the minimum number needed to make up a family household as defined by census.[125] We used a weighting system method to estimate the income for patients in different subsidy groups as described below.

Table 6: 2008 Department of Health and Human Services Poverty Guidelines[124]

Persons in Family or Household	48 Contiguous States and D.C.	Alaska	Hawaii
1	$10,400	$13,000	$11,960
2	14,000	17,500	16,100
3	17,600	22,000	20,240
4	21,200	26,500	24,380
5	24,800	31,000	28,520
6	28,400	35,500	32,660
7	32,000	40,000	36,800
8	35,600	44,500	40,940
For each additional person, add	3,600	4,500	4,140

Estimation of modified income variable using FPL weighting

We estimated the income for beneficiaries in each subsidy group by using the 2008 HHS Poverty guidelines for two householders based on the state in which they resided. In 2008, the FPL for two people who lived in the contiguous 48 states and the District of Columbia was $14,000; in Alaska it was $17,500 and in Hawaii it was $16,100.

Table 7 presents the calculation of the modified income variable using the weighting. Since the cost share group code was ranked by beneficiaries' income levels, we weighted the FPL to estimate their incomes based on the code orders. Being eligible

for cost share group code 01 required that beneficiaries have annual incomes less than 100% FPL, and resources less than $2,000 (individual) and $3,000 (Couple). In 2008, the income standard was $637 per month for an individual and $956 per month for a couple.[126] This income standard for a couple was 82% of the FPL. As a result, we estimated these beneficiaries' incomes as 82% of the FPL.[122]

Beneficiaries in cost share group code 02 were required to have annual incomes less than 100% of the FPL. Financial eligibility standards for full dual eligibility vary significantly across states between 56% FPL in Connecticut and 109% FPL in Alaska.[127] However, these two values were only the maximum and minimum values. The majority of states set the eligibility at 75% FPL and 100 % FPL.[127] As a result, we weighted the incomes of beneficiaries in this group as 87.5% of the FPL, which was the average of the income limit levels.

Beneficiaries in cost share group code 03 were required to have annual incomes greater than or equal to 100%, but less than 135% FPL. There are several types of Medicare Savings Programs (MSPs) for partial dual eligible beneficiaries.[122] These programs include Specified Low-Income Medicare Beneficiaries (SLMB) and Qualifying Individuals (QI). The SLMB require beneficiaries' incomes being between the ranges of 100-120% FPL and the QI require beneficiaries' income between 120-135% FPL. We estimated the incomes of beneficiaries in this group with the average of the lower and upper income levels, which was 117.5% of the FPL.

Beneficiaries in cost share group code 04 were required to have annual incomes less than 135% FPL and resources less than $9,440 (for couples). The resource limit for

these eligibility criteria was higher than the one for partial dual eligible beneficiaries. We weighted the income of beneficiaries who were in this group with 125% FPL.

Beneficiaries in cost share group code 05 were required to have annual incomes less than 135% FPL and resources between $9,440 and $20,970 (for couples). Since the resource criteria for this group were higher than the previous group, we weighted the incomes of beneficiaries in this group with 130% of the FPL.

Beneficiaries in cost share group code 06, 07, and 08 were required to have annual incomes in the ranges of 135-140%, 140-145%, and 145-150% of the FPL. Since the income levels were in ranges, we weighted beneficiaries' incomes by using the average of the lower and upper limits.

Lastly, since beneficiaries in cost share group code 09 were ineligible for a subsidy, there were no criteria for their income level limits. As a result, we assigned the median household income by the zip code of residence and age range as their incomes.

Table 7: Modified income variable for beneficiaries [120-124]

Cost share group code		Annual Income as a percentage of Federal Poverty Level (FPL)	100% FPL for 2 people in household	Generating modified income variable
01	Beneficiaries qualified with 100% premium subsidy and no copayment	<100%	▪ $14,000 (48states+D.C.) ▪ $17,500 (Alaska) ▪ $16,100 (Hawaii)	▪ 0.82x14,000 =$11,480 ▪ 0.82x17,500 =$14,350 ▪ 0.82x16,100 = $13,202
02	Beneficiaries qualified with 100% premium subsidy and low copayment	< 100%	▪ $14,000 (48states+D.C.) ▪ $17,500 (Alaska) ▪ $16,100 (Hawaii)	▪ 0.875x14,000 =$12,250 ▪ 0.875x17,500=$15,313 ▪ 0.875x16,100 = $14,088
03	Beneficiaries qualified with 100% premium subsidy and high copayment	100%-135%	▪ $14,000 (48states+D.C.) ▪ $17,500 (Alaska) ▪ $16,100 (Hawaii)	▪ 1.175x14,000 =$16,450 ▪ 1.175x17,500 = $20,563 ▪ 1.175x16,100 = $18,918
04	Beneficiaries with LIS, 100% premium-subsidy and high copayment	< 135%	▪ $14,000 (48states+D.C.) ▪ $17,500 (Alaska) ▪ $16,100 (Hawaii)	▪ 1.25x14,000 =$17,500 ▪ 1.25x17,500 =$21,875 ▪ 1.25x16,100= $20,125
05	Beneficiaries with LIS, 100% premium-subsidy and 15% copayment	<135%	▪ $14,000 (48states+D.C.) ▪ $17,500 (Alaska) ▪ $16,100 (Hawaii)	▪ 1.30x14,000 = 18,200 ▪ 1.30x17,500=22,750 ▪ 1.30x16,100= 20,930
06	Beneficiaries with LIS, 75% premium-subsidy and 15% copayment	135% - 140%	▪ $14,000 (48states+D.C.) ▪ $17,500 (Alaska) ▪ $16,100 (Hawaii)	▪ 1.375 x14,000=19,250 ▪ 1.375 x17,500=24,063 ▪ 1.375 x16,100=22,138
07	Beneficiaries with LIS, 50% premium-subsidy and 15% copayment	140% - 145%	▪ $14,000 (48states+D.C.) ▪ $17,500 (Alaska) ▪ $16,100 (Hawaii)	▪ 1.425x14,000=19,950 ▪ 1.425 x17,500= 24,938 ▪ 1.425 x16,100=22,943

08	Beneficiaries with LIS, 25% premium-subsidy and 15% copayment	145%-150%	▪ $14,000 (48states+D.C.) ▪ $17,500 (Alaska) ▪ $16,100 (Hawaii)	▪ 1.475x14,000=20,650 ▪ 1.475 x17,500=25,813 ▪ 1.475 x16,100=23,748
09	No premium-subsidy nor cost sharing	≥ 150%	-	Median household income by zip code and age range

Study Sample

The study examined the costs and use of the top selling five oral cancer drugs covered by Part D in 2008. These drugs included anastrozole (Arimidex®), imatinib (Gleevec®), letrozole (Femara®), erlotinib (Tarceva®), and thalidomide (Thalomid®).[78] The sample included beneficiaries who met the following inclusion criteria:

- 65 years of age or older at the beginning of 2008
- Enrolled in Medicare Part D program for the entire 12-month period from January 1, 2008 through December 31, 2008
- Did not die by the end of 2008
- Filled at least one of the above mentioned oral cancer medications

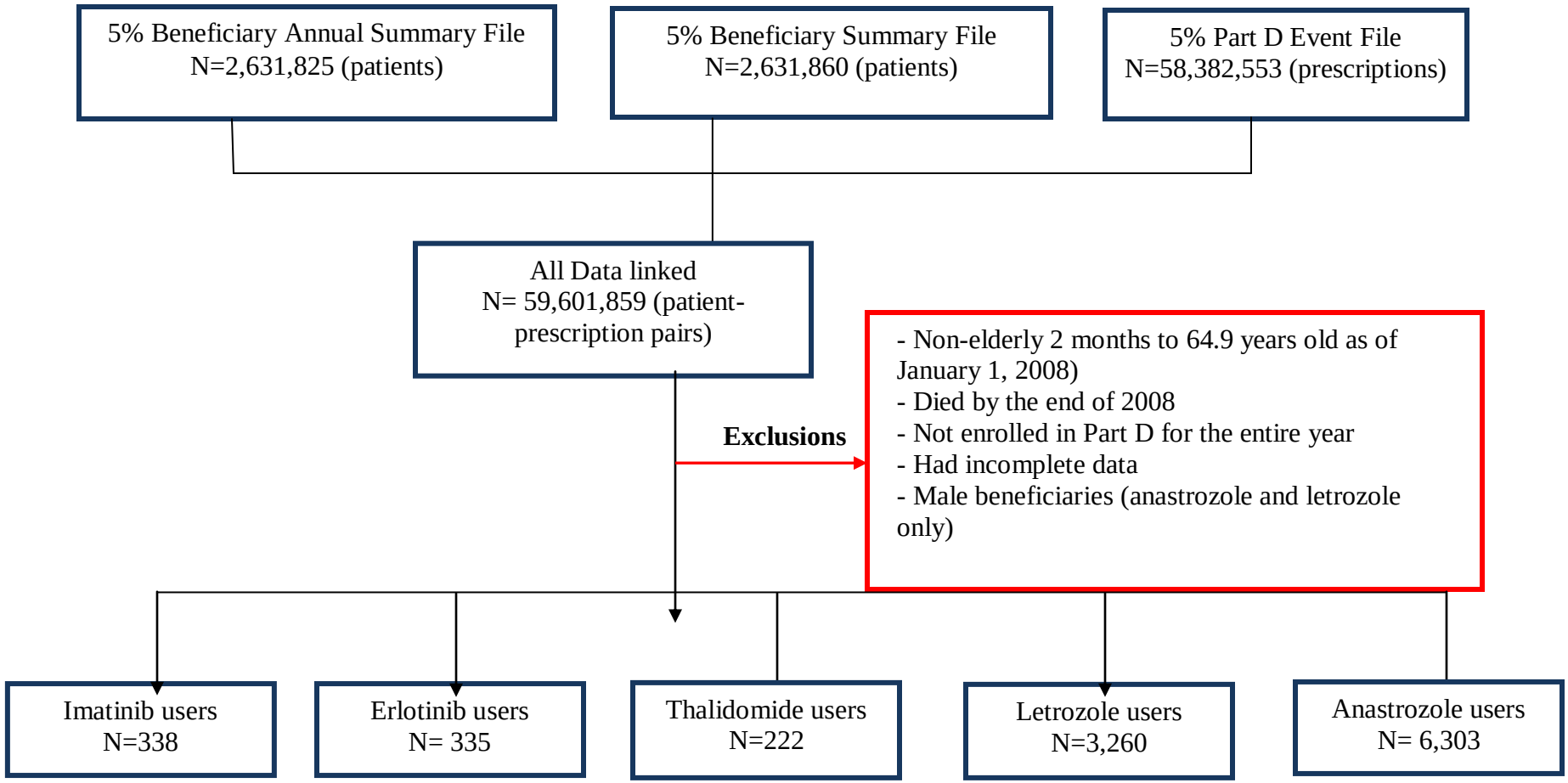
We further excluded beneficiaries who met the following criteria from the samples used for the regression analyses (Objective 5):

- Lack of data available for all variables used in the analyses. For example, income and coverage.

- Started filling the prescription after June 30th, 2008. We included only beneficiaries who started filling their prescriptions in the first six months of 2008 to ensure that we had at least six months to identify medication discontinuation.
- Male Beneficiaries who used anastrozole and letrozole.
- Diagnosed with breast cancer by January 1, 2004 (anastrozole and letrozole only)
- Switched between anastrozole and letrozole

Figure 2 illustrates the selection of the sample and dataset preparation for the analyses. Beneficiaries were divided into five subgroups based on their oral cancer medication use: imatinib, erlotinib, anastrozole, letrozole, and thalidomide.

Figure 2: Flow diagram for identifying the sample



This section presents the methods used to conduct the analyses for each objective.

Objective 1:

The first objective was to identify the demographics and prescription drug subsidy status of Part D beneficiaries who used oral cancer drugs.

The demographic characteristics of all oral cancer drug users were identified for each drug. The ages of beneficiaries were reported as means, ranges, and standard deviations. The gender and race of beneficiaries were reported in terms of frequency counts and percentages. We identified and reported the frequency counts and percentages of the type of prescription drug subsidies of all beneficiaries who used oral cancer drugs. The types of prescription drug subsidies included Medicaid and Medicare dual eligibility; low income subsidy (LIS): partial and full subsidies; and no subsidy.

Objective 2:

The second research objective was to identify the OOP cost and plan liability for oral cancer medications in the Medicare Part D program in 2008. OOP costs are the expenditures that enrollees were required to pay for their prescriptions excluding their premiums. The OOP cost was the sum of deductibles, cost sharing during the initial coverage phase, full cost of the drugs during the coverage gap, and 5% coinsurance during the catastrophic phase. Plan liability is the total expenditures for each beneficiary that plans were responsible for paying. Descriptive statistics were used to report the range, mean, median, and standard deviation of costs.

We examined the mean costs that patients paid per day, the costs that plans paid per day, and total OOP costs for the entire year for each drug. The variables utilized to calculate costs relating to oral cancer use included prescription filled date (SRVC_DT), days supply (DAYS_SUPPLY_NUM), the amount that patients paid OOP (PTNT_PAY_AMT), the amount that third party paid that contributed to true out-of pocket (OTHR_TROOP_AMT), and the amount that Part D plans paid (CVRD_D_PLAN_PD_AMT).

We included only beneficiaries who filled a prescription between January 1, 2008 and June 30, 2008 in our sample. The patients who received third party payments that contributed to OOP amount were excluded. We calculated the costs for each strength of each medication. However, the differences between the average wholesale prices (AWP)[128] of the 100 mg and 150 mg strengths of erlotinib and the 100 mg, 150 mg, and 200 mg strengths of thalidomide were very small. Because of this, and to increase the cell sample sizes for these combinations, we combined observations for these strengths of each of these drugs when calculating costs.

1) OOP cost

The OOP cost for each beneficiary was calculated as a daily cost. The cost was calculated using the patient paid amount (PTNT_PAY_AMT) and days supply variables (DAYS_SUPPLY_NUM). Total OOP cost was the sum of the total amount patients paid for their OOP divided by the total days supply. We calculated the total annual OOP cost by multiplying the daily cost by 365.

2) Plan liability

Plan liability for each beneficiary was calculated based on the total costs that plans were responsible for paying per beneficiary per day. The cost was calculated by summing the total Part D plans paid amount (CVRD_D_PLAN_PD_AMT) divided by the total days supply (DAYS_SUPPLY_NUM). We calculated the annual plan cost by multiplying the daily cost by 365.

Objective 3

The high cost of oral cancer drugs could lead to patients quickly falling into the coverage gap. Therefore, the third objective of this study was to determine the percentage of beneficiaries who entered the coverage gap, to identify when beneficiaries fell into the gap, and to identify the length of time they stayed in the gap.

We first assessed the percentage of patients who entered the Medicare Part D coverage gap. All beneficiaries who fell into the coverage gap - regardless of whether they stayed in the coverage gap or entered the catastrophic phase - were included in this analysis. The variable used to identify the coverage gap entry was the benefit phase of the prescription drugs event (BENEFIT_PHASE). This variable indicates the benefit phase based on the beneficiary's accumulated expenses. Some pharmacy claims overlapped between phases; for example, the first fill of a prescription that cost $1,000 would take the patient through the deductible phase and into the ICL phase. Prescription fills that are part of more than one benefit phase are called the straddle PDEs.

The benefit phase variable includes ten codes: deductible phase (DD), deductible to Pre-ICL straddle PDE (DP), deductible to ICL straddle PDE (DI),

deductible to catastrophic straddle PDE (DC), Pre-ICL phase (PP), Pre-ICL to ICL Straddle PDE (PI), Pre-ICL to catastrophic straddle PDE (PC), ICL phase (II), and catastrophic phase (CC). We categorized the codes into 1) Deductible phase, 2) Pre-ICL phase, 3) ICL or coverage gap phase, and 4) catastrophic coverage phase. We collapsed the benefit phase into four categories based on the Part D standard benefit phases. In our collapsed categories, we categorized the benefit phase based on the last digit of the benefit phase variable code.[129] The last digit of the code represented the benefit phase where beneficiaries fell at that fill. After recoding, the deductible phase included the code of DD; the Pre-ICL phase included the codes DP and PP: and the ICL phase contained DI, PI, and II. The catastrophic phase included DC, PC, IC, and CC. Frequency counts and percentages of enrollees who entered the coverage gap were reported.

Next we identified when patients entered the coverage gap in 2008. We determined how long it took each patient to enter the coverage gap from the date that his or her initial prescription was filled. We identified the amount of time it took to reach the coverage gap in terms of months. The numbers and percentages of patients who entered the coverage gap each month were reported.

Finally, we identified the duration of time spent in the coverage gap. We calculated the average duration of time that patients spent in each benefit phase, including: deductible, pre-ICL, ICL, and catastrophic phases. Means and standard deviations were reported.

Objective 4

We identified the number and percentage of patients who discontinued or delayed therapy during 2008. Medication discontinuation or delay was defined as at least a 30 day delay for a scheduled refill.[130,131] We identified patients who discontinued their medication, as those who had a gap of at least 30 days between the time the patient should have run out of medication, based on the time of his/her last refill, and the time he/she obtained the next refill (or December 31, 2008 if it was the patient's last fill of the year). Discontinuation was defined as the patient being without medication for at least 30 days and not having another refill during the study period. Delay was identified from the gap as the period of time between the date that the patient's supply of the medication expired and the date that the patient obtained the next refill. Beneficiaries who delayed could resume refilling their prescription after the delay.

We identified the total number of beneficiaries who discontinued or delayed their therapy in each benefit phase. Frequency counts and percentages were reported for each drug.

Objective 5

The last objective was to examine the association between total OOP expenditures and medication discontinuation or delay, as adjusted for polypharmacy, prescription drug subsidies, and socio-demographic factors.

Several studies have indicated that cost is one of the reasons that patients discontinued or did not adhere to their medication.[67,68,132-134] According to these studies, a patient with high OOP spending has a higher risk of drug discontinuation.[70,132,133]

We performed multinomial logistic regression to examine whether OOP spending was associated with oral cancer medication discontinuation or delay. We included patients who started filling their prescription in the first six months of 2008, so that we would have a sufficient number of patients and amount of time to determine patients' discontinuation of medication. Medication discontinuation or delay was the outcome or dependent variable and was coded as 1 for delay and 2 for discontinuation. Otherwise, medication continuation was coded 0. The analysis included potential predictors that were available in the dataset that could influence medication discontinuation or delay.

National Comprehensive Cancer Network (NCCN) guidelines recommend using anastrozole or letrozole as adjuvant endocrine therapy for five years.[79] Therefore, to ensure that delay or discontinuation was not from completion of treatment, we included only anastrozole and letrozole users who were diagnosed with breast cancer since January 1, 2004. In addition, patients who switched between letrozole and anastrozole were excluded.

Logistic regression provided the odds of discontinuation or delay for every $1 increase in OOP per month. We calculated the odds of discontinuation or delay for increase in total OOP costs per $10 and $100 by raising the odds ratio to the 10^{th} power or 100^{th} power, respectively.

For example:

Odds of discontinuation for every $1 increase in OOP cost = 1.005

Odds of discontinuation for every $10 increase in OOP cost = 1.005^{10}

Odds of discontinuation for every $100 increase in OOP cost = 1.005^{100}

The following section presents the independent variables that were in the model.

a) OOP costs

We used OOP cost per month as a primary predictor in the regression analyses. The variables we used to calculate OOP costs included the amount that patients paid OOP for their medication costs (PTNT_PAY_AMT) and days supply (DAYS_SUPLY_NUM).

The OOP costs were calculated based on types of discontinuation: delay, discontinuation, or continuation.

1.) **Delay**: We defined the gap as the period of time between the date that the patient's supply of the medication expired and the date that the patient obtained the next refill. The OOP cost was calculated as the total OOP costs that the patient paid until the last claim before the delay. This was divided by the total days supply for the period before the delay.

2) **Discontinuation**: we defined discontinuation as prescriptions were filled consecutively every month but had discontinued by the end of 2008. A gap of 30 days or greater between the date that the patient's supply of the medication expired and December 31, 2008 was determined as discontinuation. We calculated OOP costs by summing total OOP costs that the patient paid until the last claim divided by the total days supply.

Otherwise, all OOP costs for oral cancer drugs that a patient paid were summed and divided by the total days supply that they had the prescriptions filled for. We calculated monthly OOP costs by multiplying by 30.

The following three examples illustrate how we calculated the OOP costs used in the analyses for delay, discontinuation, and continuation.

Case 1 (Delay)

A patient filled their prescriptions each month, consecutively, for a 30-day supply of their medications. However, the gap between the second and third fills was greater than 30 days. (The gap is defined as the period of time between the date that the patient's supply of the medication expired and the date that the patient obtained the next refill.) The OOP cost per day was calculated as the total OOP costs that the patient paid until the last claim before the delay. This was divided by the total days supply for the period before the delay. That is, we included all OOP costs that the patient paid for the first and second prescription divided by total days supply for the first and second prescription. The patient could resume his/her therapy any time after the delay. However, we considered this patient as a delay because effective chemotherapy requires that the

patient strictly follow the regimen and continue the treatment. This is especially important for long term chemotherapy. Table 8 shows the fill dates and OOP costs for a patient who delayed filling their prescription and later resumed therapy.

Calculation

OOP cost per month = (OOP costs for 1st fill +2nd fill) x 30/ (total days supply)

= ($2,250 +$1,750) x 30/ (30+30)

OOP cost = $2,000 per month

Table 8: Fill dates and OOP costs for a patient who delayed filling their prescription between fills

Rx	Fill date	Days supply	Expected next fill date	OOP Cost ($)
1st	January 15, 2008	30	February 14, 2008	2,250
2nd	February 12, 2008*	30	March 13, 2008	1,750
3rd	May 18, 2008	30	June 17, 2008	156
4th	June 18, 2008	30	July 18, 2008	156

Rx= Prescription, OOP =Out-of-Pocket cost

* February had 29 days in 2008

Case 2 (Continuation)

A patient filled their prescription consecutively every month for 12 times in 2008 (Table 9). This patient was defined as a continuation. We calculated the OOP cost for this patient as shown below.

Calculation

OOP cost per month = (OOP costs for 1^{st} +2^{nd} +3^{rd} +4^{th} +5^{th} +6^{Th} +7^{th} +8^{th+} 9^{th}+ 10^{th} + 11^{th} +12^{th} fills) x 30/ (total days supply)

= ($2,595+$1,320+159+159+159+159+159+170+170+170+ 170+170) x 30/ (12x30)

OOP cost = $463.3 per month

Table 9: Fill dates and OOP costs for a patient who filled oral cancer prescription drug consecutively.

Rx	Fill date	Days supply	Expected next fill date	OOP Cost ($)
1^{st}	January 25, 2008	30	February 24, 2008	2,595
2^{nd}	February 23, 2008*	30	March 24, 2008	1,320
3^{rd}	March 23, 2008	30	April 22, 2008	159
4^{th}	April 20, 2008	30	May 20, 2008	159
5^{th}	May 20, 2008	30	June 19, 2008	159
6^{th}	June 20, 2008	30	July 20, 2008	159

7th	July 19, 2008	30	August 18, 2008	159
8th	August 17, 2008	30	September 16, 2008	170
9th	September 17, 2008	30	October 17, 2008	170
10th	October 17, 2008	30	November 16, 2008	170
11th	November 15, 2008	30	December 15, 2008	170
12th	December 15, 2008	30	-	170

Rx= Prescription, OOP =Out-of-Pocket cost. *In 2008, February had 29 days

Case 3 (Discontinuation)

A patient filled their prescription consecutively every month but had discontinued by the end of 2008 (Table 10). We defined the discontinuation here as a gap of more than 30 days between the date that the patient's supply of the medication expired and December 31, 2008. We calculated OOP costs for these patients as shown below.

Calculation

OOP cost per month = (OOP costs for 1^{st} +2^{nd} +3^{rd} +4^{th} +5^{th} +6^{Th} +7^{th} +8^{th+} 9^{th} fills) x 30/ (total days supply)

= ($2,690+$1,350+163+163+163+163+174+174+174) x 30/ (9x30)

OOP cost = $579.3 per month

Table 10: Fill dates and OOP costs for a patient who filled oral cancer prescription drug consecutively but discontinued by the end of 2008.

Rx	Fill date	Days supply	Expected next fill date	OOP Cost ($)
1st	February 13, 2008*	30	March 14, 2008	2,690
2nd	March 13, 2008	30	April 12, 2008	1,350
3rd	April 12, 2008	30	May 12, 2008	163
4th	May 11, 2008	30	June 10, 2008	163
5th	June 10, 2008	30	July 10, 2008	163
6th	July 10, 2008	30	August 9, 2008	163
7th	August 8, 2008	30	September 7, 2008	174
8th	September 7, 2008	30	October 7, 2008	174
9th	October 7, 2008	30	November 7, 2008	174

Rx= Prescription, OOP =Out-of-Pocket cost

*February had 29 days in 2008.

b) Polypharmacy [66,88,102]

We measured polypharmacy by counting the number of concurrent medications that patients were taking during treatment. We used generic drug names (GNN) to count the total number of unique prescription drugs. Polypharmacy may cause adverse events and increase patients' prescription costs leading patients to discontinue or delay their oral chemotherapy.

c) Comorbidities[88]

The total numbers of chronic conditions that patients had were included in the analyses. We identified chronic conditions that patients had from the variables provided by the CCW dataset.[112,135] These variables included Alzheimer's disease (ALZH), acute myocardial infarction (AMI), Alzheimer's disease or senile dementia (ALHDMTA), atrial fibrillation (ATRIALFB), cataract (CATARACT), chronic kidney disease (CHRNKIDN), chronic obstructive pulmonary disease (COPD), depression (DEPRESSN), diabetes (DIABETES), glaucoma (GLAUCOMA), heart failure (HF), hip/pelvic fracture (HIPFRAC), colorectal cancer (CNCRCLRC), endometrial cancer (CNCRENDM), breast cancer (CNCRBRST), lung cancer (CNCRLUNG), prostate cancer (CNCRPRST), ischemic heart disease (ISCHMCHT), osteoporosis (OSTEOPRS), rheumatoid arthritis/osteoarthritis (RA_OA), and stroke/transient ischemic attack (STRKETIA). Chronic conditions were determined based on information obtained through Fee-for-Service (FFS) administrative claims data, including International Classification of Diseases Ninth Revision (ICD-9-CM), Current Procedural Technology (CPT-4) 4th edition, and Healthcare Common Procedure Coding System (HCPCS). Each variable had four values: 0 = neither claims nor coverage met; 1= claims met, coverage

not met; 2 = claims not met, coverage met; and 3 = claims and coverage met. Patients with value of 1 and 3 were determined to have chronic conditions because they indicated whether a beneficiary received services in 2008.[135]

d) Drug subsidy status [132,133]

Drug subsidy status was included in the model as an indicator variable. It was coded as 1 to indicate the patient received a subsidy (DE, full LIS, or partial LIS) and 0 for no subsidy.

e) Drug benefit type[88]

This variable indicates the type of Part D benefit structure, including 1) defined standard benefit, 2) actuarially equivalent standard, 3) basic standard, and 4) enhanced alternative. The variable was included in the model as a categorical variable.

f) Income[88,114]

A proxy income variable was created and included in the analyses. The details of generating the income variable were described previously in the data preparation section.

g) Total OOP costs for other non-cancer prescription drugs

We calculated the total OOP costs for other medications that patients were taking concurrently during oral cancer drug treatment until oral cancer medication discontinuation or delay. We determined total OOP costs for other medications in the same process that we calculated OOP spending for oral cancer drugs.

h) Mental status [88]

We created binary variables that identified patients who had Alzheimer's disease or depression condition. We used the variables of Alzheimer's disease (ALZH) and senile dementia (ALHDMTA) indicating Alzheimer's disease and were coded as 1. If patients had depression (DEPRESSN), they were coded as 1, otherwise as zero.

i) A history of cancer

A dummy variable was created as to indicate whether the patient was previously diagnosed with any of the cancer conditions included on the Part D dataset. The cancer conditions included colorectal cancer (CNCRCLRE), endometrial cancer (CNCENDME), breast cancer (CNCRBRSE), lung cancer (CNCRLNGE), and prostate cancer (CNCRPRSE). The variable of diagnosed dates of the earliest indication of cancer was used to identify whether patient had been diagnosed with any of these cancers before 2008. The previously diagnosed cancer variable was assigned a value of 1 if the beneficiary had been diagnosed with cancer and 0 if they had not been diagnosed.

j) Patient demographic variables [26,88,130]

Gender and race variables were included in the analyses. Female and white race variables were used as referent groups. Age was generated from the patients' dates of birth.

The age variable was created based on the tertiles of age for each drug and incorporated as a categorical variable in the analyses. The categories were based on boundaries at the 33th and 66th percentiles of the distribution (Table 11).

Multicollinearity is a common problem in multivariate regression. Multicollinearity occurs when predictors are correlated. This could become a serious problem and it could provide inaccurate results and large standard errors for the estimation.[136,137] We determined collinearity by checking the variance inflation factor (VIF) for all independent variables. If a VIF for one of independent variables is greater than 4, it indicated a strong collinearlity between that variable with others. As a result, we removed it from the analysis. For any two or more variables with a VIF greater than 4, we checked the correlations among those variables. If the high correlations were detected, the intercorrelated variables must be removed from the analysis.

Table 11: Tertile categories of age

Medication / Tertile	**Imatinib (years)**	**Erlotinib (years)**	**Thalidomide (years)**	**Anastrozole (years)**	**Letrozole (years)**
1st	65.0-71.49	65.0-72.90	65.0-71.20	65.0-71.28	65.0-70.52
2nd	71.50-78.43	72.91-79.16	71.21-77.60	71.29-78.70	70.53-77.88
3rd	>78.43	>79.16	>77.60	>78.71	>77.88

CHAPTER 5

RESULTS

This chapter presents the results for each objective.

Objective 1: To identify demographic characteristics and prescription drug coverage of Part D beneficiaries who used oral cancer drugs in 2008.

Overall, beneficiaries who used oral cancer medications had mean ages between 74 and 76 years. Over half of oral cancer medication users were Caucasian and female. Over two-thirds of all oral cancer medication users received no subsidies for their prescription coverage. Approximately a quarter of all oral cancer medication users were dual eligible beneficiaries. No beneficiary in our sample received a retiree drug subsidy. More detailed information is shown in Table 12 and Table 13.

Table 12: Type of prescription drug subsidy by medication

Total (%)	**Imatinib** (N=338)	**Erlotinib** (N= 335)	**Anastrozole** (N=6,303)	**Letrozole** (N= 3,260)	**Thalidomide** (N= 222)
Dual eligible	83 (24.56)	87 (25.97)	130 (20.75)	696 (21.35)	54 (24.32)
Low Income Subsidy (LIS)					
▪ Full subsidy	10(2.96)	10(2.99)	243 (3.86)	121(3.71)	9 (4.05)
▪ Partial subsidy	11(3.25)	2 (0.60)	118 (1.87)	53 (1.63)	3 (1.35)
No Subsidy N (%)	234 (69.23)	236 (70.45)	4,634 (75.52)	2,390 (73.31)	156 (70.27)

Table 13: Demographic characteristics of beneficiaries by type of oral cancer medication used

	Imatinib (N=338)	Erlotinib (N= 335)	Anastrozole (N=6,303)	Letrozole (N= 3,260)	Thalidomide (N= 222)
Age					
Mean (S.D.)	75.7 (6.83)	76.0(6.55)	76.04 (7.20)	75.9(7.04)	74.8 (6.40)
Range	65.2-97.2	65.0-96.0	65.0-105.7	65.0-98.8	65.0-94.5
Gender					
Male (%)	143 (42.31)	92(27.46)	50 (0.79)	19 (0.58)	101 (45.5)
Female (%)	195 (57.69)	243(72.54)	6,253 (99.21)	3,241 (99.42)	121 (54.5)
Race					
Unknown	-	-	6(0.1)	4(0.12)	1 (0.45)
Caucasian (%)	267 (78.99)	269 (80.30)	5482 (86.97)	2,827 (86.72)	168 (75.68)
African-American (%)	37 (10.95)	29 (8.66)	519 (8.23)	276 (8.47)	34 (15.32)
Other (%)	7 (2.07)	8 (2.39)	78 (1.24)	41(1.26)	3 (1.35)
Asian (%)	15 (4.44)	20 (5.97)	80 (1.27)	36 (1.10)	5 (2.25)
Hispanic (%)	9 (2.66)	7 (2.09)	125 (1.98)	69 (2.12)	9 (4.05)
Native American (%)	3 (0.89)	2 (0.60)	13 (0.21)	7 (0.21)	2 (0.90)

Objective 2:

To identify patient out-of-pocket and plan costs relating to use of oral cancer medications in the elderly Medicare Part D population in 2008

We categorized oral cancer medication users in four categories: 1) Dual Eligible (DE), 2) full Low Income Subsidy (LIS), 3) partial LIS, and 4) no subsidy. The details of the costs for all cancer medications are shown in Tables 14 to Table 17. We included only beneficiaries who filled their first prescription during the first six months of 2008. As a result, the sample sizes for some combinations of drug, strength, and subsidy type were small or missing.

Mean OOP costs per day were between $0.03 and $0.09 for DE beneficiaries, between $0.04 and $0.23 for full LIS beneficiaries, between $1.17 and $6.34 for partial LIS beneficiaries and between $2.93 and $36.84 for beneficiaries who did not receive a subsidy.

Mean plan costs per day per beneficiary were between $4.67 and $140.44 for DE beneficiaries, between $4.52 and $177.36 for full LIS beneficiaries, between $4.39 and $172.62 for partial LIS, and between $5.21 and $145.65 for beneficiaries who did not receive a subsidy.

Table 18 shows details for annual patient costs and plan costs.

Table 14: **Costs of oral cancer medications for dual eligible beneficiaries**

Costs($)	Imatinib		Erlotinib		Thalidomide		Anastrozole	Letrozole
	100 mg (N=27)	400 mg (N=46)	25 mg (N= 2)	100, 150 mg (N =45)	50 mg (N=14)	100,150, 200 mg (N=32)`	1 mg (N= 1,134)	2.5 mg (N=597)
OOP cost/day								
Mean (S.D.)	0.08 (0.24)	0.03 (0.03)	0.08 (0.04)	0.05 (0.05)	0.04 (0.04)	0.05 (0.05)	0.09 (0.06)	0.09 (0.07)
Median ($)	0.03	0.02	0.08	0.03	0.03	0.04	0.09	0.10
Range	[0,1.28]	[0, 0.12]	[0.05,0.10]	[0, 0.19]	[0, 0.11]	[0, 0.20]	[0,0.65]	[0, 1.04]
Plan cost/day								
Mean (S.D.)	71.69 (40.14)	95.85 (37.28)	74.64 (26.54)	81.44 (23.75)	111.97 (58.22)	140.44 (49.60)	4.67 (1.53)	5.00 (1.76)
Median	70.77	94.84	74.64	89.08	93.13	148.05	4.46	4.82
Range	[8.07,170.06]	[5.31,203.04]	[55.88,93.41]	[17.59, 113.63]	[38.08, 243.88]	[59.87, 317.33]	[0, 9.04]	[0, 12.12]

Table 15: Costs of oral cancer medications for full low income subsidy beneficiaries

Costs	Imatinib		Erlotinib		Thalidomide		Anastrozole	Letrozole
	100 mg (N= 1)	400 mg (N=11)	25 mg (N= 0)	100, 150 mg (N= 6)	50 mg (N= 5)	100,150, 200 mg (N= 4)`	1 mg (N=216)	2.5 mg (N=102)
OOP cost/day								
Mean ($) (S.D.)	-	0.07 (0.06)	-	0.12 (0.07)	0.10 (0.09)	0.04 (0.04)	0.23 (0.48)	0.21 (0.41)
Median ($)	-	0.05	-	0.08	0.06	0.03	0.16	0.19
Range	-	[0.03,0.19]	-	[0.03, 0.19]	[0.01, 0.20]	[0, 0.10]	[0.03, 3.74]	[0.03, 3.81]
Plan cost/day								
Mean (S.D.)	-	76.70 (25.82)	-	68.84 (23.81)	177.36 (116.60)	161.92 (37.28)	4.52 (1.56)	4.79 (1.69)
Median	-	89.60	-	74.63	218.52	174.83	4.22	4.52
Range	-	[25.54, 96.50]	-	[36.24, 92.31]	[46.72, 294.90]	[107.28, 190.76]	[0, 10.85]	[0.88, 9.10]

Table 16: **Costs of oral cancer medications for partial low income subsidy beneficiaries**

Costs	Imatinib		Erlotinib		Thalidomide		Anastrozole	Letrozole
	100 mg (N= 4)	400 mg (N=6)	25 mg (N= 0)	100,150 mg (N= 1)	50 mg (N= 2)	100, 150, 200 mg (N= 1)`	1 mg (N=92)	2.5 mg (N=40)
OOP cost/day								
Mean ($) (S.D.)	2.58 (1.07)	5.96 (5.82)	-	6.34	4.19 (1.14)	3.51	1.26 (1.04)	1.17 (0.33)
Median ($)	2.90	3.98	-	6.34	4.19	3.51	1.15	1.20
Range	[1.13, 3.39]	[2.66, 17.74]	-	-	[3.39, 5.0]	-	[0.34, 9.24]	[0.06, 1.56]
Plan cost/day								
Mean (S.D.)	81.40 (40.81)	85.53 (15.12)	-	87.28	148.56 (38.33)	172.62	4.39 (1.56)	5.35 (1.85)
Median	78.99	89.90	-	87.28	148.56	172.62	4.14	5.28
Range	[44.41,123.20	[55.88,97.56]	-	-	[121.46, 175.67]	-	[0, 8.64]	[1.60, 9.27]

Table 17: Costs of oral cancer medications for beneficiaries who did not receive a subsidy

	Imatinib		Erlotinib		Thalidomide		Anastrozole	Letrozole
	100 mg (N= 49)	400 mg (N=97)	25 mg (N= 11)	100-150 mg (N=106)	50 mg (N= 51)	100,150, 200 mg (N= 60)	1 mg (N=3,189)	2.5mg (N=1,612)
OOP cost/day								
Mean ($) (S.D.)	29.00 (28.60)	20.03 (12.07)	15.66 (16.74)	28.60 (17.03)	36.84 (30.80)	36.83 (29.79)	2.93 (1.86)	3.15 (2.05)
Median ($)	16.25	16.07	14.79	21.14	27.81	24.31	2.74	2.80
Range	[7.17,129.57]	[4.04,73.32]	[1.90,61.47]	[2.67, 84.29]	[5.49, 147.78]	[8.08,129.29]	[0.31, 9.74]	[0.33, 10.36]
Plan cost/day								
Mean (S.D.)	69.92 (26.64)	93.78 (27.82)	74.73 (38.83)	81.94 (19.24)	108.24 (81.12)	145.65 (49.75)	5.21 (1.69)	5.75 (1.92)
Median	61.64	93.50	86.66	86.41	89.63	146.80	5.20	5.76
Range	[19.52,162.94]	[12.02,203.56]	[21.68,133.72]	[22.68, 124.06]	[29.93, 492.43]	[52.53, 316.46]	[0, 12.47]	[0, 13.96]

Table 18: **Estimated annual costs for all types of prescription drug subsidy**

Annual Cost ($)	**Imatinib**		**Erlotinib**		**Thalidomide**		**Anastrozole**	**Letrozole**
	100 mg	400 mg	25 mg	100-150 mg	50 mg	100,150,200 mg	1 mg	2.5 mg
Dual Eligible								
Patient	29.20	10.95	29.20	18.25	14.60	18.25	32.85	32.85
Plan	26,166.85	34,985.25	27,243.60	29,725.60	40,869.05	51,260.60	1,704.55	1,825.00
Full Low Income Subsidy								
Patient	-	25.55	-	43.80	36.50	14.60	83.95	76.65
Plan	-	27,995.50	-	25,126.60	64,736.40	59,100.80	1,649.80	1,748.35
Partial Low Income Subsidy								
Patient	941.70	2,175.40	-	2,314.10	1,529.35	1,281.15	459.90	427.05
Plan	29,711.00	31,218.45	-	31,857.20	54,224.40	63,006.30	1,602.35	1,952.75
No Subsidy								
Patient	10,585	7,310.95	5,715.90	10,439.00	13,446.60	13,442.95	1,069.45	1,149.75
Plan	25,520.80	34,229.70	27,276.45	29,908.10	39,507.60	53,162.25	1,901.65	2,098.75

Objective 3:

To determine the number and percentage of patients entering the Medicare Part D coverage gap, the time that they entered the gap, and the duration of time spent in the gap

(a) Number and percentage of patients entering the Medicare Part D coverage Gap

Table 19 illustrates, by drug, the number and percentage of oral cancer medication users who entered the coverage gap. Approximately 99% of the beneficiaries who used imatinib, erlotinib and thalidomide entered the coverage gap. In contrast, approximately 70% of beneficiaries using the less expensive drugs (anastrozole and letrozole) entered the coverage gap.

Table 19: **Number of patients who entered the Part D coverage gap by drug**

Medication	Entered the Gap N (%)	Did not enter the Gap N (%)
Imatinib **(N=288 patients)**	284 (98.61)	4 (1.39)
Erlotinib **(N=298 patients)**	295 (98.99)	3 (1.01)
Anastrozole **(N=5,585 patients)**	3964 (70.95)	1623 (29.05)
Letrozole **(N=2,902 patients)**	1,975 (68.06)	927(31.94)
Thalidomide **(N= 195 patients)**	194 (99.49)	1 (0.51)

(b) Time of Part D coverage gap entry

A majority of beneficiaries who used costly medications - imatinib, erlotinib, and thalidomide - entered the coverage gap at the time of their first fill. In contrast, beneficiaries who filled anastrozole or letrozole entered the coverage gap later; less than 7% entered the coverage gap in the first fill.

Table 20 presents the time that beneficiaries entered the Part D coverage gap for each medication.

(c) Duration of time spent in the Part D coverage gap

We found that there were two patterns of time spent in each benefit phase. For costly medications, including imatinib, erlotinib, and thalidomide, beneficiaries spent approximately a month in the coverage gap. Most of their time was spent in the catastrophic phase. For less expensive medications, anastrozole and letrozole, the time that beneficiaries spent in the pre-ICL and ICL phases were four to five times greater than those of beneficiaries using expensive oral cancer drugs (Table 21).

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Table 20: Time of coverage gap entry

Duration* (month)	Imatinib (N=288) N (%)**	Erlotinib (N=298) N (%)**	Thalidomide (N=195) N (%)**	Anastrozole (N=5,585) N (%)**	Letrozole (N=2,902) N (%)**
0* **	254 (89.44)	289 (97.97)	191 (98.45)	220(5.55)	127 (6.43)
1	26 (9.15)	5 (1.69)	2 (1.03)	73(1.84)	52 (2.63)
2	4(1.41)	1(0.34)	1 (0.52)	210 (5.30)	137 (6.94)
3	-	-	-	495 (12.49)	267 (13.53)
4	-	-	-	521 (13.14)	276 (13.98)
5	-	-	-	612 (15.44)	300 (15.20)
6	-	-	-	740 (18.67)	350 (17.73)
7	-	-	-	487 (12.29)	256 (12.97)
8	-	-	-	350 (8.83)	117 (5.93)
9	-	-	-	163(4.11)	54 (2.74)
10	-	-	-	64 (1.61)	28 (1.42)
11	-	-	-	29 (0.73)	10 (0.51)
Did not enter the coverage gap	4	3	1	1,623	927

*Duration is the time in months from the first prescription beneficiaries filled to the time that they entered the coverage gap.
** %- presents the percentage of the total number of oral cancer drug users for each drug who entered the coverage gap
***The patient entered the coverage gap at the time he or she filled the first prescription.

Table 21: Mean time beneficiaries spent in each benefit phase

	Imatinib	Erlotinib	Thalidomide	Anastrozole	Letrozole
Benefit Phase	**Days (S.D.)**	**Days (S.D.)**	**Days (S.D.)**	**Days (S.D.)**	**Days (S.D.)**
Deductible	30	-	-	28.80 (5.60)	28.29 (4.71)
Pre-ICL	29.30 (8.83)	15.93 (10.32)	28 (0)	156.68 (72.73)	147.64 (71.10)
ICL	36.80 (19.30)	32.98 (23.92)	33.14 (16.98)	130.38 (61.78)	129.15 (62.67)
Catastrophic phase	244.55 (107.65)	159.90 (112.90)	188.03 (112.10)	108.66 (63.65)	112.95 (64.39)

ICL =Initial Coverage Limit

Objective 4:

To determine the number and percent of patients who discontinued oral cancer therapy

The total number of beneficiaries who used oral cancer medication and discontinued or delayed their treatment was 97 (33.45%) for imatinib, 142 (47.65%) for erlotinib, 117 (60%) for thalidomide, 2,690 (48.15%) for anastrozole and 1,495 (51.52%) for letrozole. Table 22 presents the total number of oral cancer drug users who discontinued or delayed their therapy in each benefit phase. The highest percentage of patients who used imatinib, erlotinib, and thalidomide delayed or discontinued their therapies in the catastrophic phase. In contrast, the highest percentage of anastrozole and letrozole users delayed or discontinued filling their medications permanently during the pre-ICL phase and coverage gap.

Table 22: Total number of oral medication users who discontinued or delayed their therapy by benefit phase

Benefit Phase	Imatinib N (%)*	Erlotinib N (%)*	Thalidomide N (%)*	Anastrozole N (%)*	Letrozole N (%)*
Deductible					
Delay	-	-	-	-	-
Discontinuation	-	-	-	6 (0.11)	1 (0.03)
Pre-ICL					
Delay	-	-	-	152 (2.72)	87 (3.00)
Discontinuation	3 (1.03)	1(0.34)	1 (0.51)	1,100 (19.69)	639 (22.02)
ICL					
Delay	16(5.52)	1 (0.34)	-	491 (8.79)	257 (8.86)
Discontinuation	-	35 (11.74)	18 (9.23)	768 (13.75)	418 (14.40)
Catastrophic phase					
Delay	39 (13.45)	23 (7.72)	24 (12.31)	140 (2.51)	76 (2.62)
Discontinuation	39 (13.45)	82 (27.52)	74 (37.95)	33 (0.59)	17 (0.59)
Total	97 (33.45)	142 (47.65)	117(60.0)	2,690 (48.15)	1, 495 (51.52

*% - presents the percentage of the total number of oral cancer drug users for each drug
ICL= Initial Coverage Limit

Objective 5:

To examine the association between OOP costs and medication discontinuation or delay

We used multinomial logistic regression to examine the association between OOP costs and medication discontinuation or delay. The reference groups were the groups of beneficiaries who continued using the therapy for each drug. We controlled for all variables which were discussed previously in the methods section in the adjusted models.

We had a small sample size and many variables included in the model. We checked the events per variable (EPV) in drugs with a small sample size: imatinib, erlotinib, and thalidomide.[138] A common rule of thumb indicates that a regression should include ten events (or observations) for each independent variable.[138] The EPVs were 5.8 for imatinib, 7.6 for erlotinib, and 7.3 for thalidomide. Even though the EPVs were below the rule of thumb, they were, according to Vittinghoff's and McCulloch's study, within the acceptable level.[139]

Table 23 and Table 24 show the unadjusted and adjusted logistic regression analyses comparison for each drug. We found a significant relationship between OOP costs and medication discontinuation or delay. The odds of discontinuation and delay significantly increased as OOP costs increased for all study drugs. In the adjusted models, the odds of medication discontinuation were 1.007 ($p<0.0001$) for imatinib users, 1.010 ($p =0.0002$) for erlotinib users, 1.013 ($p=0.0002$) for thalidomide users, 1.009 ($p<0.0001$) for anastrozole users, and 1.006 ($p=0.0348$) for letrozole users. The odds of delay were 1.007 ($p<0.0001$) for imatinib users, 1.010 ($p =0.0005$) for erlotinib users, 1.013 ($p=0.0003$) for thalidomide users, 1.010 ($p<0.0001$) for anastrozole users, and 1.008

(p=0.0133) for letrozole users. For every one dollar increase in OOP cost per month, the odds of medication discontinuation increased 0.7% for imatinib users, 1% for erlotinib users, 1.3% for thalidomide users, 0.9% for anastrozole users, and 0.6% for letrozole users. The increases in odds were similar for delays in therapy for imatinib, erlotinib, and thalidomide. For every one dollar increase in OOP cost per month, the odds of delay increased 1% for anastrozole users and 0.8% for letrozole users (Table 24).

We calculated the increase in the odds of discontinuation and delay for every $10 and $100 increase in the total OOP cost per month. For each $100 increase in OOP cost, the odds of discontinuation increased 101% for imatinib, 170% for erlotinib, and 264% for thalidomide users. The increases in odds were similar for delays in therapy. Moreover, for every $10 increase in OOP cost, the odds of discontinuation increased 9% for anastrozole users and 6% for letrozole users. For every $10 increase in OOP cost, the odds of delay increased 10% for anastrozole users and 8% for letrozole user (Table 25).

As the number of non-cancer drugs a beneficiary used increased, the odds of discontinuation increased significantly for imatinib, thalidomide, anastrozole, and letrozole users. The number of non-cancer drugs increased the odds of delay for anastrozole and letrozole users. Surprisingly, the odds of discontinuation and delay decreased with higher OOP costs for other non-cancer drugs for all patients. Moreover, higher numbers of comorbidities significantly increased the odds of discontinuation in letrozole users, but decreased the odds of discontinuation in thalidomide and erlotinib users. The drug benefit type had a significant impact on letrozole and anastrozole users in increasing the odds of discontinuation in patients with less generous coverage.

We found multicollinearity between the prescription drug subsidy variable and OOP costs for imatinib, erlotinib, and thalidomide. As a result, the prescription drug subsidy variable was excluded from the analyses for these medications. The odds of medication discontinuation or delay decreased in anastrozole and letrozole users who received prescription drug subsidies. We found that Alzheimer's disease, depression, previous history of cancer, age, gender, income, and race were not associated with medication discontinuation or delay.

Table 23: Unadjusted multinomial logistic regression of medication discontinuation or delay

Predictor	Discontinuation or delay	Imatinib OR (p-value) (95% CI)	Erlotinib OR (p-value) (95% CI)	Thalidomide OR (p-value) (95% CI)	Anastrozole OR (p-value) (95% CI)	Letrozole OR (p-value) (95% CI)
OOP cost	Discontinuation	1.001* (0.0011) [1.001,1.002]	1.002* (<0.0001) [1.001,1.002]	1.001* (0.0005) [1.001,1.002]	0.992* (<0.0001) [0.991,0.994]	0.994* (<0.0001) [0.992,0.995]
	Delay	1.002* (<0.0001) [1.001,1.002]	1.001* (0.0041) [1.000,1.002]	1.001* (0.0030) [1.000,1.002]	0.992* (<0.0001) [0.990,0.994]	0.992* (<0.0001) [0.989,0.994]

* Significant at 0.05

Table 24 : Multinomial logistic regression for medication discontinuation or delay

Predictor	Discontinuation or delay	Imatinib OR (p-value) (95% CI) N= 227	Erlotinib OR (p-value) (95% CI) N= 163	Thalidomide OR (p-value) (95% CI) N =149	Anastrozole OR (p-value) (95% CI) N=3,716	Letrozole OR (p-value) (95% CI) N= 1,697
OOP cost	Discontinuation	1.007* (<0.0001) [1.004,1.009]	1.010* (0.0002) [1.005, 1.016]	1.013* (0.0002) [1.006, 1.021]	1.009* (<0.0001) [1.005, 1.013]	1.006* 0.0348) [1.002, 1.012]
	Delay	1.007* (<0.0001) [1.004,1.010]	1.010* (0.0005) [1.004, 1.015]	1.013* (0.0003) [1.006, 1.020]	1.010* (<0.0001) [1.005, 1.014]	1.008* (0.0133) [1.002,1.015]
Male	Discontinuation	0.635 (0.3676) [0.237, 1.704]	1.079 (0.9074) [0.301, 3.863]	1.361 (0.6251) [0.395, 4.685]	-	-
	Delay	0.622 (0.3841) [0.214, 1.811]	1.514 (0.6040) [0.316, 7.258]	7.509* (0.0147) [1.485, 37.960]	-	-
Black	Discontinuation	2.569 (0.1144) [0.796, 8.289]	0.917 (0.9133) [0.192, 4.377]	0.262** (0.0773) [0.059, 1.158]	1.105 (0.5496) [0.796, 1.535]	1.096 (0.7005) [0.687, 1.749]
	Delay	1.387 (0.6610) [0.321, 5.985]	0.972 (0.9791) [0.117, 8.059]	0.209 (0.1063) [0.031, 1.397]	1.470* (0.0350) [1.028, 2.103]	0.990 (0.9716) [0.575, 1.705]

Other races	Discontinuation	1.135 (0.8583) [0.282, 4.573]	0.360 (0.1883) [0.079, 1.649]	0.083* (0.0094) [0.013, 0.543]	0.768 (0.2277) [0.500, 1.180]	0.956 (0.8886) [0.510, 1.793]
	Delay	2.935 (0.1327) [0.721, 11.938]	0.163 (0.1510) [0.014, 1.938]	0.239 (0.2319) [0.023, 2.495]	1.252 (0.3284) [0.798, 1.965]	0.757 (0.4649) [0.358, 1.598]
Age(T1)	Discontinuation	0.436 (0.1347) [0.147, 1.293]	0.629 (0.4540) [0.187, 2.118]	0.627 (0.5672) [0.127, 3.104]	1.007 (0.9495) [0.801, 1.267]	0.735** (0.0768) [0.522, 1.034]
	Delay	0.315** (0.0772) [0.088, 1.134]	0.631 (0.5378) [0.146, 2.733]	0.675 (0.6908) [0.097, 4.688]	0.807 (0.1157) [0.617, 1.054]	0.680** (0.0561) [0.458, 1.010]
Age(T2)	Discontinuation	0.611 (0.3781) [0.205, 1.827]	0.883 (0.8462) [0.251, 3.104]	1.384 (0.6554) [0.332, 5.778]	0.865 (0.1975) [0.693, 1.079]	1.116 (0.5109) [0.804, 1.549]
	Delay	0.786 (0.6877) [0.243, 2.542]	0.218 (0.1046) [0.035, 1.372]	1.648 (0.5802) [0.281, 9.667]	0.740* (0.0217) [0.572, 0.957]	0.795 (0.2468) [0.540, 1.172]
Drug benefit type	Discontinuation	1.035 (0.8743) [0.672, 1.595]	0.853 (0.5181) [0.526, 1.383]	0.925 (0.7466) [0.575, 1.488]	1.173* (0.0025) [1.058, 1.301]	1.183* (0.0376) [1.010, 1.386]
	Delay	1.093 (0.7257) [0.672, 1.595]	1.049 (0.8806) [0.562, 1.960]	0.987 (0.9648) [0.541, 1.800]	1.194* (0.0050) [1.055, 1.351]	1.047 (0.6203) [0.873, 1.257]
Comorbidities	Discontinuation	0.955 (0.7376) [0.727,1.253]	0.723** (0.0616) [0.515, 1.016]	0.662* (0.0310) [0.455, 0.963]	1.023 (0.4911) [0.959, 1.091]	1.113* (0.0325) [1.009, 1.229]
	Delay	1.082 (0.6053)	1.064 (0.7650)	0.732 (0.1887)	1.034 (0.3697)	1.085 (0.1606)

		[0.803,1.458]	[0.709, 1.597]	[0.460, 1.165]	[0.961, 1.114]	[0.968, 1.217]
Income	Discontinuation	1.000 (0.1782) [1.00, 1.00]	1.00 (0.4247) [1.00, 1.00]	1.00 (0.5830) [1.00, 1.00]	1.00* (0.0474) [1.00, 1.00]	1.00 (0.1492) [1.00, 1.00]
	Delay	1.000 (0.4034) [1.00, 1.00]	1.00 (0.8966) [1.00, 1.00]	1.00 (0.8701) [1.00, 1.00]	1.00* (0.0317) [1.00, 1.00]	1.00 (0.8501) [1.00, 1.00]
Cancer	Discontinuation	1.516 (0.4720) [0.488, 4.716]	3.639 (0.1069) [0.757, 17.497]	5.708** (0.0527) [0.980, 33.240]	1.049 (0.7282) [0.802, 1.371]	1.021 (0.9170) [0.687, 1.518]
	Delay	1.331 (0.6542) [0.381, 4.656]	1.119 (0.9081) [0.167, 7.512]	3.694 (0.2196) [0.459, 29.757]	1.254 (0.1658) [0.911, 1.725]	1.144 (0.5813) [0.709, 1.846]
Alzheimer	Discontinuation	1.097 (0.9294) [0.142, 8.441]	1.798 (0.5262) [0.293, 11.044]	0.333 (0.3577) [0.032, 3.463]	1.351 (0.1242) [0.921, 1.984]	0.980 (0.9499) [0.525, 1.829]
	Delay	1.482 (0.7055) [0.193, 11.394]	0.596 (0.7152) [0.037,9.627]	1.095 (0.9457) [0.080, 15.009]	1.320 (0.2049) [0.859, 2.026]	0.649 (0.2535) [0.309, 1.363]
Depression	Discontinuation	1.957 (0.4105) [0.396, 9.675]	0.837 (0.8502) [0.131,5.332]	1.375 (0.7679) [0.166, 11.385]	1.012 (0.9453) [0.717, 1.430]	0.851 (0.5221) [0.519, 1.395]
	Delay	2.485 (0.3033) [0.439, 14.064]	0.202 (0.2557) [0.013, 3.181]	4.376 (0.2738) [0.311, 61.566]	0.936 (0.7437) [0.629, 1.393]	1.146 (0.6262) [0.662, 1.985]
Polypharmacy	Discontinuation	1.084* (0.0144)	1.073 (0.1281)	1.160* (0.0076)	1.096* (<.0001)	1.074* (<0.0001)

		[1.016, 1.156]	[0.980, 1.175]	[1.040, 1.294]	[1.076, 1.117]	[1.047, 1.102]
	Delay	1.051 (0.1780) [0.978, 1.129]	0.994 (0.9160) [0.886, 1.115]	1.062 (0.3968) [0.925, 1.219]	1.091* (<.0001) [1.068, 1.114]	1.085* (0.0008) [0.968, 1.217]
Subsidy	Discontinuation	-	-	-	0.058* (<0.0001) [0.043, 0.080]	0.048* (<.0001) [0.030, 0.077]
	Delay	-	-	-	0.117* (<0.0001) [0.082, 0.169]	0.122* (<.0001) [0.071, 0.210]
Costs of non-cancer medications	Discontinuation	0.999* (<0.0001) [0.999, 1.000]	0.998* (<0.0001) [0.998, 0.999]	0.998* (<0.0001) [0.997, 0.999]	0.998* (<.0001) [0.997, 0.998]	0.998* (<0.0001) [0.997, 0.998]
	Delay	0.999* (<0.0001) [0.999, 1.000]	0.999** (<0.0001) [0.998, 0.999]	0.998* (<0.0001) [0.99, 0.999]	0.998* (<.0001) [0.997, 0.998)	0.998* (<0.0001) [0.997, 0.998]

Age (T1), (T2) = age (indicator variable) in 1st tertile and 2nd tertile (3th tertile-reference group); **Alzheimer** = patients had an Alzheimer's disease; **Cancer** = had a previous history of cancer; **Comorbidities** = number of medical conditions; **Depression** = patients had depression condition; S**ubsidy** = received a prescription subsidy (did not received a subsidy - reference group); **OR** = Odds Ratio; **OOP cost** = Out-of-Pocket cost; **Polypharmacy** = number of other medications used; **95% CI** =95% Confident Interval

* Significant at 0.05; ** significant at 0.10

Table 25: Odds of discontinuation or delay for increase in total out-of-pocket costs per month[a]

Predictor	Discontinuation or delay	Imatinib (Adjusted OR)	Erlotinib (Adjusted OR)	Thalidomide (Adjusted OR)	Anastrozole (Adjusted OR)	Letrozole (Adjusted OR)
		Each $100 increase			Each $10 increase	
OOP cost	Discontinuation	2.01	2.70	3.64	1.09	1.06
	Delay	2.01	2.70	3.64	1.10	1.08

[a]The odds of discontinuation or delay for increase in total OOP costs were calculated by raising the odds ratio to the 10^{th} power or 100^{th} power.

CHAPTER 6

DISCUSSION

This chapter discusses the results, strengths and limitations of the study. It further presents implications of this study and suggests directions for future study.

This study hypothesized that beneficiaries with higher OOP spending were more likely to discontinue or delay their medications. We identified discontinuation or delay as an instance in which the patient was more than 30 days overdue for a refill. Discontinuation was defined as situations in which beneficiaries did not receive another refill during the study period. Delay was defined as situations in which they did receive another refill after the gap in therapy.

We found a significant relationship between OOP costs and medication discontinuation or delay. The findings from the multinomial logistic regression showed that the odds of discontinuation or delay were higher at higher levels of OOP spending. The odds for discontinuation and the odds of delay for each $100 increase in OOP are as follows. For each $100 increase in OOP cost, the odds of discontinuation or delay increased 101% for imatinib, 170% for erlotinib, and 264% for thalidomide users. The odds of discontinuation were slightly lower than the odds of delay among anastrozole and letrozole users. For every $10 increase in OOP cost, the odds increased 9% for anastrozole users who discontinued and 10% for those who delayed, and 6% for letrozole users who discontinued and 8% for those who delayed.

The results also indicated that between 33% and 60% of Medicare Part D beneficiaries who used oral cancer medication discontinued their treatment. Previous

studies have found nonadherence rates of 12%-33% for oral cancer therapy,[27,36,109,140-142] 2%-40% for parenteral cancer drugs,[143-147] and 7%-20% for chronic diseases.[16-18,148-154]

In our findings, approximately 33% of total imatinib users discontinued or delayed their treatment. This finding was slightly higher than previous studies in which the nonadherence rates among CML patients who used imatinib were between 26%-29%.[28,29,166] However, these studies were clinical trials and a majority of imatinib users were male and younger than 65 years old. The mean OOP costs of imatinib treatment in our findings were between $600-$870 per month. The difference in our nonadherence rate and in those found in these studies could reflect the effects of high OOP costs, because patients in trials were not required to pay OOP for their medications.

Our results showed the highest discontinuation rates among thalidomide users. Discontinuation rates were 60% among thalidomide users in our study. According to previous studies, the discontinuation rates due to intolerance in thalidomide usage were between 8%-15%.[155-158] However, these studies were clinical trials and they reported that a majority of patients were male[158] and younger than 65 years old.[155,158] The difference in our higher rates and the discontinuation rates found in these studies may be due to the strong association between OOP costs and discontinuation. Patients in the previous studies did not pay OOP for their medications. Our results found the mean OOP costs for thalidomide treatment were approximately $1,100 per month. As a result, the high OOP cost could influence patients' decision on discontinuing their therapies.

We found a 48% rate of discontinuation in erlotinib users. Clinical trials have found 5%-10% discontinuation rates of erlotinib use due to its side effects.[159,160] A majority of patients in previous studies were male and younger than 65 years old.[159,160]

The mean OOP costs of erlotinib treatment in our findings were between $470-$858 per month. Again, the higher rate found in our study could reflect the effects on high OOP costs.

Discontinuation rates for anastrozole and letrozole in this study were 48% and 52%, respectively. These rates were higher than those found in previous studies, where the discontinuation rates in patients with breast cancer who used oral cancer drugs ranged between 19%-31%[36,109,140,161,167] and a majority of patients were younger than 65 years old.[36,109,140,161] In our findings, the mean OOP costs per month were $88 for anastrozole and $95 for letrozole. Even if the OOP costs per month for anastrozole and leterozole were not high, we found the odds of discontinuation increased 7%-10% for every $10 increase in OOP cost per month. These results revealed that OOP costs could have lead to the higher discontinuation rates in our study.

The odds of discontinuation or delay among beneficiaries who used anastrozole and letrozole and who received any prescription drug subsidy were significantly lower than for those who did not receive subsidies. We also found that the number of non-cancer medications that the patients were taking during cancer treatment and their costs had a significant impact on discontinuation. Surprisingly, higher costs of non-cancer medication decreased the odds of discontinuation and delay for all study drugs. However, the number of non-cancer drugs increased the odds of delay for anastrozole and letrozole users and increased the odds of discontinuation for all patients except erlotinib users.

Comorbidities were associated with decreased odds of discontinuation in erlotinib and thalidomide users; however, the odds of discontinuation increased among letrozole users.[161]

The income variable used in our study was not associated with discontinuation, possibly because the measure we used was based on income in a zip code rather than the individual's actual income. Age, gender, race, Alzheimer's disease and depression were not associated with medication discontinuation or delay.

Beneficiaries in our study were 65 years and older, with the average ages were between 74 and 76 years. A majority of patients in our study were female. In previous studies, most oral cancer medication users were male and younger than 65 years old. Because of the differences in age and gender, the results from previous studies may not accurately compare with our sample. Moreover, the nonadherence rates from clinical trials were not able to represent the nonadherence to oral cancer drugs due to OOP costs because patients in previous studies did not pay high OOP costs.

Strengths and Limitations

The strengths of this study are the following:

First, this study used prescription claims data from the Medicare Part D population. At this time, this is the first study to examine the costs relating to the use of oral chemotherapy and the impact of cost-sharing on the use of oral chemotherapy in the Medicare Part D population.

Second, the study results were nationally generalizable since this study used nationally representative Medicare claims data. The results were generalizable for oral cancer medication costs and adherence of Medicare cancer survivors across the United States.

The limitations of this study include the following.

First, the available data did not allow us to determine whether medication discontinuation occurred because patients discontinued their cancer treatment on their own or as a result of their physicians' advice. Oral cancer drugs are self-administered outside providers' offices and are taken without close monitoring by physicians. As a result, patients could potentially stop their medications due to side effects associated with drugs.[47,67,161] We did not have drug adverse event information in our dataset. As a result, we cannot identify whether beneficiaries discontinued their therapies because of high OOP costs or because of side effects of oral chemotherapy. However, we found that the rates of discontinuation in our study were higher than those found in clinical trials.[27,28,160,161,162] Given that patients in clinical trials do not pay OOP for their

chemotherapy, this suggests that at least some of the differences in discontinuation rates could be due to cost.

Moreover, we lacked cancer stage information in the data. We did not know if patients were in the later or at the beginning stages of cancer. Late stage or severely ill patients might decide to stop their therapy and switch to palliative care. Moreover, late stage patients with high OOP payments might believe the treatment has less benefit to them and discontinue the therapy by themselves.

Second, this study used only Part D data and did not have information about cancer drugs that were covered by Part B. Consequently, we were unable to determine the extent to which patients switched from oral medications to injections or the extent to which patients who received cancer drugs under both Part B and Part D continued their Part B medication without taking their Part D medication. This limitation should have only a limited impact on our results because the amount of switching between oral and parenteral therapy is not likely to be large. Most practice guidelines recommend prescribing intravenous drugs as the first-line therapy, Part D covered oral cancer drugs are used primarily as alternative or adjuvant treatment.[79,84,86] In our study, docetaxel (injection) or pemetrexed (injection), and bortezomib (injection) are substitutes covered by Part B for erlotinib and thalidomide, respectively. However, docetaxel (injection) or pemetrexed are second line therapies for NSCLC and bortezomib is an alternative drug for maintenance therapy for multiple myeloma.

Third, Medicare Part D data did not include personal income data, so median household income data by zip code were used as proxies for beneficiaries' household income. We attempted to increase the accuracy of the income variable by incorporating

the eligibility income limits for patients who received subsidies; however, this was not a good measure for beneficiaries' incomes because it did not represent beneficiaries' actual income.

Fourth, this study was a cross-sectional design in which only 2008 Part D data were used. The impact of OOP spending should be investigated in the long-term to examine the outcomes of discontinuation and delay. Because we used only one year's data, it is unable to determine whether beneficiaries that delayed or discontinued their therapy late in the year had completely discontinued or whether resumed therapy in the following year.

Fifth, Medicare Part D enrollees who have a high demand for prescriptions may have strong incentives to enroll in plans with more generous coverage, and adverse selection could arise as a result.[164] Beneficiaries who do not have any subsidy can switch their plan during the open enrollment period by the end of the year (October 15 to December 7, of each year). Only dual eligible or LIS beneficiaries can switch to a new plan any time during the year. In our study, all five medications are used in the long term. If beneficiaries were diagnosed with cancer and prescribed any of the oral drugs by the open enrollment period, they could switch to plans with more comprehensive coverage and pay higher premiums. However, this limitation should have limited impact on our discontinuation results because we used only one year of data and included only beneficiaries who filled oral cancer drugs in the first sixth months of 2008, which was immediately after the open enrollment period. As a result, the amount of switching to a new plan is not likely to be large. Subsidy patients would be unlikely to experience adverse selection because of the low OOP costs associated with the subsidies.

Sixth, we included only those beneficiaries who filled prescriptions in the first six months of the year to calculate the costs of oral cancer drug treatment. We had a small sample for a number of drug, strength, and subsidy type combinations. For example, we did not have any cost data for erlotinib 25 mg for beneficiaries who received subsidies and imatinib 100 mg for beneficiaries with full LIS.

Moreover, according to the logistic regression assumptions,[165] we could overspecify the confounders in the model because of the small sample size and the number of variables that we included to fit the model. We had fewer than 10 events per variable in our study, which violates the rule of thumb.[138] However, the relative bias was within an acceptable level.[139]

Implications

The findings of this study provide policymakers with estimates of the total annual OOP costs that patients pay for oral cancer drugs and of the substantial effects that these costs have on medication adherence. The time that patients enter the coverage gap and the duration of time they spend in the coverage gap affect OOP costs and, consequently, adherence.

From our findings, the cost of cancer treatment plays an important role in nonadherence. We found that high OOP costs increase the risk that patients will stop taking oral chemotherapy. This could result in progression or increased severity of disease, leading to hospitalization, mortality and increasing health care expenditures.[15,19-21] Moreover, policymakers should be aware of the negative consequences of the Medicare Part D coverage gap. We found that a majority of cancer drug users entered the coverage gap in the first fill of their prescriptions, resulting in a significantly high discontinuation rate after they reached the coverage gap. Medicare Part D beneficiaries with higher OOP medication spending had higher rates of cost-related nonadherence. The Affordable Care Act provides expanded coverage for Medicare Part D beneficiaries such that the coverage gap will be fully closed by 2020. Part D beneficiaries will pay only 25% for covered prescriptions after meeting the deductible and before reaching the catastrophic phase.[165] OOP costs will be decreased, in the best case, to one-fourth of the amount of OOP costs that the beneficiaries in this study paid. However, OOP costs will continue to be high, especially for beneficiaries using brand name medications without generic equivalents, because of the high cost of these products and the substantial coinsurance rates. Discontinuation could be the only choice for patients

who cannot afford the high costs of the therapy and lack lower-priced alternatives. According to our finding, for every $100 increase in the OOP cost, the odds of discontinuation increased 101%-264% for expensive oral cancer drug users. The increased likelihood of discontinuation will exist among beneficiaries on oral cancer drug treatment even after coverage gap is closed.

Future Research

Future research should study the effects of total OOP costs on adherence and discontinuation on a long-term basis. To detect the effects of high OOP spending over several years, a longitudinal study design should be employed. Medication discontinuation can be identified more accurately in a longer period of time, because it would provide enough time to examine if beneficiaries discontinued their therapies completely. Moreover, the time to discontinuation can be measured if the researchers have several years of data. In addition, the effects of OOP costs and medication adherence can be measured by examining medication possession ratios (MPR) or proportion of days covered (PDC) and the OOP costs.

More research can be conducted to examine the OOP costs and nonadherence in cancer drugs by using both Part B and Part D data. OOP costs for cancer treatment could be compared between Part B and Part D covered drugs to identify the differences in OOP costs between the benefits or to compare the costs of oral therapy and parenteral therapy. Moreover the effects of OOP on adherence could be analyzed to examine the nonadherence due to high OOP costs and compare the extent and impact of OOP costs between Part B and Part D covered oral cancer drugs. Moreover, both Part B and Part D

data can be used to evaluate the extent of switching between parenteral and oral cancer therapy. The costs for oral and parenteral cancer therapy can be estimated to gain insights into the total costs relating to cancer treatment.

Conclusions

In conclusion, approximately 33-60% of total oral cancer drug users discontinued or delayed their therapies and most discontinued or delayed during the catastrophic phase. There was a significant association between OOP costs and medication discontinuation or delay. As OOP costs increased, the odds of medication discontinuation or delay increased.

REFERENCES

1. Hoyert DL. Xu J. Deaths: Preliminary Data for 2011. *National Vital Statistics Reports.*2012;61(6). Available at http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_06.pdf. Accessed October 15, 2012.

2. National Cancer Institution (NCI). The Cost of Cancer. Available at http://www.cancer.gov/aboutnci/servingpeople/cancer-statistics/costofcancer. Updated February 18, 2011. Accessed September 12, 2012.

3. Moseley WG, Nystrom JS. Dispensing Oral Medications: why now and how? *Community Oncology.*2009;6:358-361. Available at http://www.oncologypractice.com/co/journal/articles/0608358.pdf Accessed October 1, 2011

4. Reese DW, Skyberg JT, Kuntz GA. Oral oncology treatment regimens and the role of Medication Therapy Management on patient adherence and compliance. 2009. Available at http://accc-cancer.org/publications/pdf/usoncologywhitepaper.pdf. Accessed November 13, 2011

5. Weingart SN, Brown E, Bach PB, et al. NCCN Task Force Report: Oral chemotherapy. *J Natl Compr Canc Netw.* Mar 2008;6 Suppl 3:S1-14.

6. Campbell ML KM, Bendix J. Oral oncology. 2009. Available at http://drugtopics.modernmedicine.com/Cancer. Accessed August 5, 2012

7. Lau DT, Nau DP. Oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. *Diabetes Care.* Sep 2004;27(9):2149-2153.

8. Yang Y, Thumula V, Pace PF, Banahan BF, 3rd, Wilkin NE, Lobb WB. Predictors of medication nonadherence among patients with diabetes in Medicare Part D programs: a retrospective cohort study. *Clin Ther.* Oct 2009;31(10):2178-2188; 2150-2171.

9. Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med.* Sep 25 2006;166(17):1836-1841.

10. Blackburn DF, Dobson RT, Blackburn JL, Wilson TW. Cardiovascular morbidity associated with nonadherence to statin therapy. *Pharmacotherapy.* Aug 2005;25(8):1035-1043.

11. Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. *Circulation.* Feb 26 2008;117(8):1028-1036.

12. Ettinger AB, Manjunath R, Candrilli SD, Davis KL. Prevalence and cost of nonadherence to antiepileptic drugs in elderly patients with epilepsy. *Epilepsy Behav.* Feb 2009;14(2):324-329.

13. Modi AC, Rausch JR, Glauser TA. Patterns of nonadherence to antiepileptic drug therapy in children with newly diagnosed epilepsy. *JAMA.* Apr 27 2011;305(16):1669-1676.

14. Faught RE, Weiner JR, Guerin A, Cunnington MC, Duh MS. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: findings from the RANSOM study. *Epilepsia.* Mar 2009;50(3):501-509.

15. Davis KL, Candrilli SD, Edin HM. Prevalence and cost of nonadherence with antiepileptic drugs in an adult managed care population. *Epilepsia.* Mar 2008;49(3):446-454.

16. Martin MY, Kohler C, Kim YI, et al. Taking less than prescribed: medication nonadherence and provider-patient relationships in lower-income, rural minority adults with hypertension. *J Clinical hypertens.* Sep 2010;12(9):706-713.

17. Bailey JE, Hajjar M, Shoib B, Tang J, Ray MM, Wan JY. Risk Factors Associated with Antihypertensive Medication Nonadherence in a Statewide Medicaid Population. *Am J Med Sci.* Aug 9 2012.

18. Evans CD, Eurich DT, Remillard AJ, Shevchuk YM, Blackburn D. First-fill medication discontinuations and nonadherence to antihypertensive therapy: an observational study. *Am J Hypertens.* Feb 2012;25(2):195-203.

19. Darkow T, Henk HJ, Thomas SK, et al. Treatment interruptions and non-adherence with imatinib and associated healthcare costs: a retrospective analysis among managed care patients with chronic myelogenous leukaemia. *Pharmacoeconomics.* 2007;25(6):481-496.

20. Egede LE, Gebregziabher M, Dismuke CE, et al. Medication Nonadherence in Diabetes: Longitudinal effects on costs and potential cost savings from improvement. *Diabetes care.* Aug 21 2012.

21. Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. *Am J Psychiatry.* Apr 2004;161(4):692-699.

22. Bhatia S, Landier W, Shangguan M, et al. Nonadherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: a report from the children's oncology group. *J Clinical Oncol.*2012;30(17):2094-2101.

23. Subotnik KL, Nuechterlein KH, Ventura J, et al. Risperidone nonadherence and return of positive symptoms in the early course of schizophrenia. *Am J Psychiatry.* Mar 2011;168(3):286-292.

24. Butler RJ, Davis TK, Johnson WG, Gardner HH. Effects of nonadherence with prescription drugs among older adults. *Am J Manag Care.* Feb 2011;17(2):153-160.

25. Fitzgerald AA, Powers JD, Ho PM, et al. Impact of medication nonadherence on hospitalizations and mortality in heart failure. *J Card Fail.* Aug 2011;17(8):664-669.

26. Tuppin P, Neumann A, Danchin N, et al. Evidence-based pharmacotherapy after myocardial infarction in France: adherence-associated factors and relationship with 30-month mortality and rehospitalization. *Arch Cardiovasc Dis.* Jun-Jul 2010;103(6-7):363-375.

27. Noens L, van Lierde MA, De Bock R, et al. Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: the ADAGIO study. *Blood.* May 28 2009;113(22):5401-5411.

28. Marin D, Bazeos A, Mahon FX, et al. Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. *J Clin Oncol.* May 10 2010;28(14):2381-2388.

29. Ganesan P, Sagar TG, Dubashi B, et al. Nonadherence to imatinib adversely affects event free survival in chronic phase chronic myeloid leukemia. *Am J Hematol.* Jun 2011;86(6):471-474.

30. Wu JR, Frazier SK, Rayens MK, Lennie TA, Chung ML, Moser DK. Medication Adherence, Social Support, and Event-Free Survival in Patients With Heart Failure. *Health Psychol.* Jul 2 2012.

31. Kennedy J, Tuleu I, Mackay K. Unfilled prescriptions of medicare beneficiaries: prevalence, reasons, and types of medicines prescribed. *J Manag Care Pharm.* Jul-Aug 2008;14(6):553-560.

32. Ellis JJ, Erickson SR, Stevenson JG, Bernstein SJ, Stiles RA, Fendrick AM. Suboptimal statin adherence and discontinuation in primary and secondary prevention populations. *J Gen Intern Med.* Jun 2004;19(6):638-645.

33. Castaldi PJ, Rogers WH, Safran DG, Wilson IB. Inhaler costs and medication nonadherence among seniors with chronic pulmonary disease. *Chest.* Sep 2010;138(3):614-620.

34. Riley GF, Warren JL, Harlan LC, Blackwell SA. Endocrine therapy use among elderly hormone receptor-positive breast cancer patients enrolled in Medicare Part D. *Medicare Medicaid Res Rev.* 2011;1(4).

35. Neugut AI, Subar M, Wilde ET, et al. Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. *J Clin Oncol.* Jun 20 2011;29(18):2534-2542.

36. Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. *J Clin Oncol.* Sep 20 2010;28(27):4120-4128.

37. Partridge AH, Wang PS, Winer EP, Avorn J. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *J Clin Oncol.* Feb 15 2003;21(4):602-606.

38. Owusu C, Buist DS, Field TS, et al. Predictors of tamoxifen discontinuation among older women with estrogen receptor-positive breast cancer. *J Clin Oncol.* Feb 1 2008;26(4):549-555.

39. National Cancer Institute (NCI). US cancer survivors grows to nearly 12 million. http://www.cancer.gov/newscenter/pressreleases/2011/survivorshipMMWR2011. Accessed August 11, 2011.

40. American Cancer Society. Cancer Treatment& Survivorship Facts & Figures 2012-2013. Available at

http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-033876.pdf. Accessed November 1, 2012

41. National Cancer Institute (NCI). Browse the SEER Cancer Statistics Review 1975-2008: Table 2.7 all cancer sites (Invasive). Available at http://seer.cancer.gov/csr/1975_2008/browse_csr.php?section=2&page=sect_02_table.07.html#a. Accessed September 7, 2011.

42. Agency for Healthcare Research and Quality (AHRQ). Medicare Part D enrollees have higher cost-sharing amounts for brand name prescription drugs than those in employer plans. Avilable at http://origin.www.ahrq.gov/news/newsletters/research-activities/apr11/0411RA17.html. Accessed January 7, 2012.

43. Cubanski J, Huang J, Damico A, Jacobsen**.** *Medicare Chartbook.*Fourth Edition. Kaiser Family Foundation;2010. Available at http://facts.kff.org/chartbooks/Medicare%20Chartbook,%20Fourth%20edition,%202010.pdf. Accessed January 7, 2012.

44. Medicare Payment Advisory Commission. Health Care Spending and the Medicare Program. *A Data Book.*2012. Available at http://www.medpac.gov/documents/Jun12DataBookEntireReport.pdf. Accessed August 7, 2012.

45. Millett C, Everett CJ, Matheson EM, Bindman AB, Mainous AG, 3rd. Impact of Medicare Part D on seniors' out-of-pocket expenditures on medications. *Arch Intern Med.* Aug 9 2010;170(15):1325-1330.

46. O'Sullivan J. Medicare Part D Prescription Drug Benefit:A Primer.2008. Available at http://aging.senate.gov/crs/medicare12.pdf. Accessed October 7, 2012.

47. Barnes L BM, Little A, Nowak M Haroldson B. Oral oncolytics: Addressing the barriers to access and identifying areas for engagement. February 2010. Available at http://admin.communityoncology.org/UserFiles/files/e6c14902-aebb-4368-8d8f-b14234f95161/Avalere%20COA%20Oral%20Oncolytics%20Study%20Summary%20Report.pdf. Accessed November12, 2012.

48. Q1Group LLC. How does the 2008 Part D Model plan compare to 2007 and 2006? Available at http://www.q1medicare.com/PartD-The-2008-Medicare-Part-D-Outlook.php. Accessed June 26, 2011.

49. Medicare. What is Part D (Medicare prescription coverage)? Available at http://www.medicare.gov/navigation/medicare-basics/medicare-benefits/part-d.aspx#other. Accessed December 17, 2011.

50. Q1Group LLC. PDP-facts: 2008 Medicare Part D plan statistics- State and national. Available athttp://www.q1medicare.com/PartD-2008MedicarePartD-PlanStatistics.php?crit=National. Accessed June 26, 2011.

51. Hoadley J T, Hargrave E. et al. Medicare Part D 2008 data spotlight: The coverage gap. November 2007. Available at http://www.kff.org/medicare/upload/7707.pdf. Accessed March 8, 2012.

52. Hargrave E, Hoadley J, Merrell K. Drugs on specialty tiers in Part D.Final Report.*NORC Project No.6388.12*.2009. Available at http://www.medpac.gov/documents/feb09_drugsonspecialtytiers_contractor_rs.pdf. Accessed January 21, 2012.

53. Center for Medicare and Medicaid Services (CMS). Medicare Prescription drug benefit manual: chapter 6 Part D drugs and formulary requirement. Available at http://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/downloads/Chapter6.pdf. Accessed August 21, 2011

54. Center for Medicare and Medicaid Services (CMS). Medicare drug coverage under Medicare Part A, Part B, and Part D. August 2007;11315.

55. Center for Medicare and Medicaid Services (CMS). Clarification of LTE DESI drugs and oral anti-cancer agents. Memorandum to all Part D sponsors.2006. Avilable at http://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/QADESICancer_120506.pdf. Accessed September 29, 2011.

56. Academy of Managed Care Pharmacy (AMCP). The future of Medicare Part D. Available at http://amcp.org/WorkArea/DownloadAsset.aspx?id=9517. Accessed September 29, 2012.

57. Charatan F. Medicare is likely to pay for anti-cancer drugs. *BMJ.* 2002;324(7346):1118.

58. Twombly R. Medicare cost containment strategy targets several oncology drugs. *JNCI J Natl Cancer Inst.* 2004;96(17):1268-1270.

59. Fitch K, Iwasaki K, Pyenson B. Parity for oral and intravenous/injected cancer drugs. Milliman; 2010. Available at http://publications.milliman.com/research/health-rr/pdfs/parity-oral-intravenous-injected.pdf. Accessed August 21, 2011

60. Streeter SB, Schwartzberg L, Husain N, Johnsrud M. Patient and plan characteristics affecting abandonment of oral oncolytic prescriptions. *J Oncol Pract.* May 2011;7(3 Suppl):46s-51s.

61. Aisner J. Overview of the changing paradigm in cancer treatment: oral chemotherapy. *Am J Health Ssys Pharm.* 2007;64(9 Suppl 5):S4-7.

62. Liu G FE, Fitch M, et al. Patient preference for oral versus intravenous palliative chemotherapy. *J Clin Oncol.* 1997;15:110-115.

63. O'Neill VJ, Twelves CJ. Oral cancer treatment: developments in chemotherapy and beyond. *Br J Cancer.* Oct 21 2002;87(9):933-937.

64. Borner M, Scheithauer W, Twelves C, Maroun J, Wilke H. Answering patients' needs: oral alternatives to intravenous therapy. *Oncologist.* 2001;6 Suppl 4:12-16.

65. Palmieri FM, Barton DL. Challenges of oral medications in patients with advanced breast cancer. *Semin Oncol Nurs.* Nov 2007;23(4 Suppl 2):S17-22.

66. Spoelstra SL, Given CW. Assessment and measurement of adherence to oral antineoplastic agents. *Semin Oncol Nurs.* May 2011;27(2):116-132.

67. Kirk MC, Hudis CA. Insight into barriers against optimal adherence to oral hormonal therapy in women with breast cancer. *Clin Breast Cancer.* Apr 2008;8(2):155-161.

68. Conwell LJ, Esposito D, Colby M, et al. Promising therapies, prohibitive costs: a qualitative assessment of the effects of the Medicare Part D doughnut hole on access to costly cancer medications. . *Community Oncol.* 2011;8:111-117.

69. California Health Benefits Review Program (CHBRP). Analysis of Senate Bill 961:Cancer Treatment.Report to California State Legislature.2010. Oakland, CA CHBRP 10-05. Available at http://chbrp.ucop.edu/index.php?action=read&bill_id=73&doc_type=2. Accessed August 28, 2011

70. Weaver KE, Rowland JH, Bellizzi KM, Aziz NM. Forgoing medical care because of cost: assessing disparities in healthcare access among cancer survivors living in the United States. *Cancer.* Jul 15 2010;116(14):3493-3504.

71. Piette JD, Heisler M, Wagner TH. Cost-related medication underuse: do patients with chronic illnesses tell their doctors? *Arch Intern Med.* Sep 13 2004;164(16):1749-1755.

72. Alexander GC, Casalino LP, Meltzer DO. Physician strategies to reduce patients' out-of-pocket prescription costs. *Arch Intern Med.* Mar 28 2005;165(6):633-636.

73. Neumann PJ, Palmer JA, Nadler E, Fang C, Ubel P. Cancer therapy costs influence treatment: a national survey of oncologists. *Health Aff.* Jan-Feb 2010;29(1):196-202.

74. O'Bryant CL, Crandell BC. Community pharmacists' knowledge of and attitudes toward oral chemotherapy. *J Am Pharm Assoc.* Sep-Oct 2008;48(5):632-639.

75. Bartel SB. Safe practices and financial considerations in using oral chemotherapeutic agents. *Am J Health Syst Pharms.* May 1 2007;64(9 Suppl 5):S8-S14.

76. The Henry J. Kaiser Family Foundation. Low-income Assistance under the Medicare drug benefit. 2008. Available at http://www.kff.org/medicare/upload/7327_04.pdf. Accessed October 29, 2012

77. Hsu J, Fung V, Price M, et al. Medicare beneficiaries' knowledge of Part D prescription drug program benefits and responses to drug costs. *JAMA.* Apr 23 2008;299(16):1929-1936.

78. Lamb E. Top 200 drugs of 2008. *Pharm Times.* 2009. Available at http://www.pharmacytimes.com/publications/issue/2009/2009-05/RxFocusTop200Drugs-0509. Accessed August 15, 2011

79. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Breast Cancer version 2.2011. Fort Washington, PA: National Comprehensive Cancer Network; 2011. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed September 21, 2011

80. Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. *J Clin Oncol.* Jun 10 2011;29(17):2342-2349.

81. National Comprehensive Cancer Network (NCCN). Clinical practice Guidelines in Oncology (NCCN Guidelines®), Chronic Myelogenous Leukemia version 2.2012. Fort Washington, PA: National Comprehensive Cancer Network (NCCN); 2012. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed October 21, 2012

82. O'Brien S, Berman E, Moore JO, et al. NCCN Task Force report: tyrosine kinase inhibitor therapy selection in the management of patients with chronic myelogenous leukemia. *J Natl Compr Canc Netw.* Feb 2011;9 Suppl 2:S1-25.

83. Food and Drug Administration (FDA). Erlotinib. Available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm209058.htm. Accessed October 11, 2012

84. National Comprehensive Cancer Network (NCCN). Clinical practice Guidelines in Oncology (NCCN Guidelines®), Non-small cell lung cancer version 2.2012. Fort Washington, PA2012. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed October 21, 2012

85. Food and Drug Administration (FDA). FDA Approves Thalomid (thalidomide) to Treat Multiple Myeloma. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm095651.htm. Accessed October 11, 2012

86. National Comprehensive Cancer Network (NCCN). Clinical practice Guidelines in Oncology (NCCN Guidelines®): Multiple Myeloma Version 1.2013. 2012. Available at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed November 1, 2012

87. Brinker BT, Waller EK, Leong T, et al. Maintenance therapy with thalidomide improves overall survival after autologous hematopoietic progenitor cell transplantation for multiple myeloma. *Cancer.* May 15 2006;106(10):2171-2180.

88. Piette JD, Heisler M, Horne R, Caleb Alexander G. A conceptually based approach to understanding chronically ill patients' responses to medication cost pressures. *Soc Sci Med.* Feb 2006;62(4):846-857.

89. Phelps C. The Demand for Medical Care: Conceptual Framework. *Health Economics.* 3 ed. Boston: Addison Wesley; 2003:100-135.

90. Zivin K, Ratliff S, Heisler MM, Langa KM, Piette JD. Factors influencing cost-related nonadherence to medication in older adults: a conceptually based approach. *Value Health.* Jun-Jul 2010;13(4):338-345.

91. Kennedy J, Erb C. Prescription noncompliance due to cost among adults with disabilities in the United States. *Am J Public Health.* Jul 2002;92(7):1120-1124.

92. Willlams CM. Using medications appropriately in older adults. *Am Fam Physician.* Nov 15 2002;66(10):1917-1924.

93. Steinman MA, Sands LP, Covinsky KE. Self-restriction of medications due to cost in seniors without prescription coverage. *J Gen Intern med.* Dec 2001;16(12):793-799.

94. Raborn ML, Pelletier EM, Smith DB, Reyes CM. Patient Out-of-Pocket Payments for Oral Oncolytics: Results From a 2009 US Claims Data Analysis. *J Oncol Pract.* May 2012;8(3 Suppl):9s-15s.

95. Goldman DP, Jena AB, Lakdawalla DN, Malin JL, Malkin JD, Sun E. The value of specialty oncology drugs. *Health Serv Res.* Feb 2010;45(1):115-132.

96. Bowman J, Rousseau A, Silk D, Harrison C. Access to cancer drugs in Medicare Part D: formulary placement and beneficiary cost sharing in 2006. *Health Aff.* Sep-Oct 2006;25(5):1240-1248.

97. Hargrave E, Hoadley J, Summer L, Cubanski J, Neuman T. Medicare Part D 2010 Data Spotlight: Benefit design and cost-sharing. 2009. Available at http://www.kff.org/medicare/upload/8033.pdf

98. Short PF, Moran JR, Punekar R. Medical expenditures of adult cancer survivors aged <65 years in the United States. *Cancer.* Jun 15 2011;117(12):2791-2800.

99. Office of Cancer Survivorship NCI. About Cancer Survivorship Research: Survivorship Definitions. http://cancercontrol.cancer.gov/ocs/definitions.html. Accessed December 25, 2012.

100. Nekhlyudov L, Madden J, Graves AJ, Zhang F, Soumerai SB, Ross-Degnan D. Cost-related medication nonadherence and cost-saving strategies used by elderly Medicare cancer survivors. *J Cancer Surviv.* Dec 2011;5(4):395-404.

101. Williams J, Steers WN, Ettner SL, Mangione CM, Duru OK. Cost-related Nonadherence by Medication Type Among Medicare Part D Beneficiaries With Diabetes. *Medical Care.* Sep 29 2012.

102. 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;68(14):1339-1348.

103. Kennedy JJ, Maciejewski M, Liu D, Blodgett E. Cost-related nonadherence in the Medicare program: the impact of Part D. *Medical care.* May 2011;49(5):522-526.

104. Madden JM, Graves AJ, Zhang F, et al. Cost-related medication nonadherence and spending on basic needs following implementation of Medicare Part D. *JAMA.* Apr 23 2008;299(16):1922-1928.

105. Duru OK, Mangione CM, Hsu J, et al. Generic-only drug coverage in the Medicare Part D gap and effect on medication cost-cutting behaviors for patients with diabetes mellitus: the translating research into action for diabetes study. *J Am Geriatr Soc.* May 2010;58(5):822-828.

106. Zivin K, Madden JM, Graves AJ, Zhang F, Soumerai SB. Cost-related medication nonadherence among beneficiaries with depression following Medicare Part D. *Am J Geriatr Psychiatry.* Dec 2009;17(12):1068-1076.

107. Madden JM, Graves AJ, Ross-Degnan D, Briesacher BA, Soumerai SB. Cost-related medication nonadherence after implementation of Medicare Part D, 2006-2007. *JAMA.* Oct 28 2009;302(16):1755-1756.

108. Wu EQ, Johnson S, Beaulieu N, et al. Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients. *Curr Med Res Opin.* Jan 2010;26(1):61-69.

109. Partridge AH, LaFountain A, Mayer E, Taylor BS, Winer E, Asnis-Alibozek A. Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *J Clin Oncol.* Feb 1 2008;26(4):556-562.

110. Sedjo RL, Devine S. Predictors of non-adherence to aromatase inhibitors among commercially insured women with breast cancer. *Breast Cancer Res Treat.* Jan 2011;125(1):191-200.

111. Research Data Assistance Center (ResDAC). Medicare data documentation. Available at http://www.resdac.org/ddvh/index.asp. Accessed August 26, 2012

112. Chronic Condition Data Warehouse (CCW). Data dictionaries. Available at http://www.ccwdata.org/data-dictionaries/index.htm. Accessed August 26, 2011

113. Desai U. Impact of Medicare PART D coverage gap on beneficiairies' adherence to prescription medications. Richmond, VA: Department of Pharmacotherapy and Outcomes Science, Virginia Commonwealth University; 2011.

114. Shankaran V, Jolly S, Blough D, Ramsey SD. Risk factors for financial hardship in patients receiving adjuvant chemotherapy for colon cancer: a population-based exploratory analysis. *J Clin Oncol.* May 10 2012;30(14):1608-1614.

115. Research Triangle Institute (RTI). RTI Spatial impact factor data-download-data. Available at https://rtispatialdata.rti.org/Download/Data/tabid/56/Default.aspx.

116. Bureau of Labor Statistics. Consumer Price Index. Available at http://www.bls.gov/cpi/cpifaq.htm. Accessed August 26, 2012

117. Bureau of Labor Statistics. Consumer Price Index Research Series Using Current Methods (CPI-U-RS). Available at http://www.bls.gov/cpi/cpiursai1978_2010.pdf. Accessed August 26, 2012

118. DeNavas-Walt C, Proctor BD, Smith JC. Income, poverty and health insurance coverage in the United States: 2008. *U.S. Census Bureau, Current Population Reports*. 2009.60-236.

119. U.S. Census Bureau. Income: current versus Constant (or Real) Dollars. Available at http://www.census.gov/hhes/www/income/data/historical/dollars.html. Accessed August 26, 2012

120. United States Government Accountability Office (GAO). Medicare Part D low-income subsidy. *GAO-08-824, a report to congressional committees*.2008. Available at http://www.gao.gov/new.items/d08824.pdf. Accessed August 26, 2012

121. The Henry J. Kaiser Family Foundation. The role of Medicare for the people dually eligible for Medicare and Medicaid. *The Kaiser Family Foundation Program on Medicare Policy*. 2011. Available at http://www.kff.org/medicare/upload/8138.pdf. Accessed August 28, 2012

122. Young K, Garfield R, Musumeci M, Clemans-Cope L, Lawton E. Medicaid's Role for Dual Eligible Beneficiaries. 2012. Available at http://www.kff.org/medicaid/upload/7846-03.pdf

123. Jacobson G, Neuman T, Damico A, Lyons B. The Role of Medicare for the People Dually Eligible for Medicare and Medicaid. 2011. Available at http://www.kff.org/medicare/upload/8138.pdf. Accessed August 26, 2012

124. U.S. Department of Health and Human Services. The 2008 HHS Poverty Guidelines. Available at http://aspe.hhs.gov/poverty/08poverty.shtml. Accessed August 25, 2012

125. U.S. Census Bureau. Household and Families:2000. *Census 2000 Brief*. 2001. Available at http://www.census.gov/prod/2001pubs/c2kbr01-8.pdf. Accessed August 25, 2012

126. U.S. Social Security Administration. OASDI and SSI Program Rates & Limits, 2008. 2007. Available at http://www.ssa.gov/policy/docs/quickfacts/prog_highlights/RatesLimits2008.html. Accessed August 25, 2012

127. The Henry J. Kaiser Family Foundation. Medicaid Financial Eligibility: Primary Pathways for the Elderly and People with Disabilities. 2010. http://www.kff.org/medicaid/upload/8048.pdf. Accessed August 23, 2012.

128. Micromedex 2.0:Redbook online search.

129. Schneider K, O'Donnell B, O'Donnell J, Powers C. Technical Guidance for Researchers Summarizing and Describing Prescription Drug Utilization. 2010. Available at http://www.ccwdata.org/cs/groups/public/documents/document/ccw_part_d_tech_guidance.pdf

130. Vanelli M, Pedan A, Liu N, Hoar J, Messier D, Kiarsis K. The role of patient inexperience in medication discontinuation: a retrospective analysis of medication nonpersistence in seven chronic illnesses. *Clinical Therapeutics.* Nov 2009;31(11):2628-2652.

131. Reynolds RF, Walker AM, Obermeyer CM, Rahman O, Guilbert D. Discontinuation of postmenopausal hormone therapy in a Massachusetts HMO. *J Clin Epidemiol.* Oct 2001;54(10):1056-1064.

132. Melloni C, Alexander KP, Ou FS, et al. Predictors of early discontinuation of evidence-based medicine after acute coronary syndrome. *Am J Cardiol.* Jul 15 2009;104(2):175-181.

133. Curkendall S, Patel V, Gleeson M, Campbell RS, Zagari M, Dubois R. Compliance with biologic therapies for rheumatoid arthritis: do patient out-of-pocket payments matter? *Arthritis Rheum.* Oct 15 2008;59(10):1519-1526.

134. Daugherty KK, Butler JS, Mattingly M, Ryan M. Factors leading patients to discontinue multiple sclerosis therapies. *J Am Pharm Assoc (2003).* May-Jun 2005;45(3):371-375.

135. Chronic Condition Data Warehouse (CCW). Chronic Condition Data Warehouse User Guide Version 1.8. 2011. Available at http://www.ccwdata.org/cs/groups/public/documents/document/ccw_userguide.pdf. Accessed August 28, 2012

136. Stoltzfus JC. Logistic regression: a brief primer. *Acad Emerg Med.* Oct 2011;18(10):1099-1104.

137. Shen J, Gao S. A Solution to Separation and Multicollinearity in Multiple Logistic Regression. *J Data Sci.* Oct 1 2008;6(4):515-531.

138. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol.* Dec 1996;49(12):1373-1379.

139. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol.* Mar 15 2007;165(6):710-718.

140. Danilak M, Chambers CR. Adherence to adjuvant endocrine therapy in women with breast cancer. *J Oncol Pharm Pract.* Aug 15 2012.

141. Wigertz A, Ahlgren J, Holmqvist M, et al. Adherence and discontinuation of adjuvant hormonal therapy in breast cancer patients: a population-based study. *Breast Cancer Res Treat.* May 2012;133(1):367-373.

142. Bell RJ, Fradkin P, Schwarz M, Davis SR. Understanding discontinuation of oral adjuvant endocrine therapy by women with hormone receptor-positive invasive breast cancer nearly 4 years from diagnosis. *Menopause.* Aug 31 2012.

143. Salloum RG, Smith TJ, Jensen GA, Lafata JE. Factors associated with adherence to chemotherapy guidelines in patients with non-small cell lung cancer. *Lung Cancer.* Feb 2012;75(2):255-260.

144. Greer JA, Pirl WF, Park ER, Lynch TJ, Temel JS. Behavioral and psychological predictors of chemotherapy adherence in patients with advanced non-small cell lung cancer. *J Psychosom Res.* Dec 2008;65(6):549-552.

145. Markkula A, Hietala M, Henningson M, Ingvar C, Rose C, Jernstrom H. Clinical profiles predict early nonadherence to adjuvant endocrine treatment in a prospective breast cancer cohort. *Cancer Prev Res.* May 2012;5(5):735-745.

146. Richardson LC, Wang W, Hartzema AG, Wagner S. The role of health-related quality of life in early discontinuation of chemotherapy for breast cancer. *Breast J.* Nov-Dec 2007;13(6):581-587.

147. Llopis-Salvia P, Sarrio-Montes G, Garcia-Llopis P, Bargues-Ruiz A. Chemotherapy dose intensity reductions due to adverse drug reactions in an oncology outpatient setting. *J Oncol Pharm Pract.* Dec 2010;16(4):256-261.

148. Mostaza JM, Lahoz C, Martin-Jadraque R, et al. Factors associated with the discontinuation of evidence-based cardiovascular therapies in patients with stable coronary artery disease: a primary care perspective. *Eur J Cardiovasc Prev Rehabil.* Feb 2009;16(1):34-38.

149. Ferreira-Gonzalez I, Marsal JR, Ribera A, et al. Double antiplatelet therapy after drug-eluting stent implantation: risk associated with discontinuation within the first year. *J Am Coll Cardiol.* Oct 9 2012;60(15):1333-1339.

150. Swift JK, Greenberg RP. Premature discontinuation in adult psychotherapy: a meta-analysis. *J Consult Clin Psychol.* Aug 2012;80(4):547-559.

151. Kesten S, Plautz M, Piquette CA, Habib MP, Niewoehner DE. Premature discontinuation of patients: a potential bias in COPD clinical trials. *Eur Respir J.* Nov 2007;30(5):898-906.

152. de Vries L, Grushka Y, Lebenthal Y, Shalitin S, Phillip M. Factors associated with increased risk of insulin pump discontinuation in pediatric patients with type 1 diabetes. *Pediatr Diabetes.* Aug 2011;12(5):506-512.

153. Fortney JC, Pyne JM, Edlund MJ, et al. Reasons for antidepressant nonadherence among veterans treated in primary care clinics. *J Clin Psychiatry.* Jun 2011;72(6):827-834.

154. Rossini M, Bianchi G, Di Munno O, et al. Determinants of adherence to osteoporosis treatment in clinical practice. *Osteoporos Int.* 2006;17(6):914-921.

155. Cavo M, Zamagni E, Tosi P, et al. First-line therapy with thalidomide and dexamethasone in preparation for autologous stem cell transplantation for multiple myeloma. *Haematologica.* Jul 2004;89(7):826-831.

156. Prince HM, Schenkel B, Mileshkin L. An analysis of clinical trials assessing the efficacy and safety of single-agent thalidomide in patients with relapsed or refractory multiple myeloma. *Leuk Lymphoma.* Jan 2007;48(1):46-55.

157. Offidani M, Leoni P, Bringhen S, et al. Melphalan, prednisone, and thalidomide versus thalidomide, dexamethasone, and pegylated liposomal doxorubicin regimen in very elderly patients with multiple myeloma: a case-match study. *Leuk Lymphoma.* Aug 2010;51(8):1444-1449.

158. Zamagni E, Petrucci A, Tosi P, et al. Long-term results of thalidomide and dexamethasone (thal-dex) as therapy of first relapse in multiple myeloma. *Ann Hematol.* Mar 2012;91(3):419-426.

159. Kelly K, Azzoli CG, Zatloukal P, et al. Randomized phase 2b study of pralatrexate versus erlotinib in patients with stage IIIB/IV non-small-cell lung cancer (NSCLC) after failure of prior platinum-based therapy. *J Thorac Oncol.* Jun 2012;7(6):1041-1048.

160. Johnson JR, Cohen M, Sridhara R, et al. Approval summary for erlotinib for treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.*Clin Cancer Res.* Sep 15 2005;11(18):6414-6421.

161. Henry NL, Azzouz F, Desta Z, et al. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. *J Clin Oncol.* Mar 20 2012;30(9):936-942.

162. van Rhee F, Dhodapkar M, Shaughnessy JD, Jr., et al. First thalidomide clinical trial in multiple myeloma: a decade. *Blood.* Aug 15 2008;112(4):1035-1038.

163. Riley GF, Levy JM, Montgomery MA. Adverse selection in the Medicare prescription drug program. *Health Aff.* Nov-Dec 2009;28(6):1826-1837.

164. Kleinbaum DG. *Logistic Regression.* New York: Springer-Verlag; 1994.

165. Center for Medicare and Medicaid Services (CMS). Information Pharmacists Can Use on:closing the coverage gap. *Medicare Prescription Drug Coverage.* 2012. Available at http://www.cms.gov/Outreach-and-Education/Outreach/Partnerships/Downloads/11522-P.pdf. Accessed October 26, 2012

166. Ibrahim AR, Eliasson L, Apperley JF, et al. Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. *Blood*. 2011;117 (14):3733-6.

167. Ziller V, Kalder M, Albert US, et al. Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer. *Annals of Oncology*. 2009; 20: 431–436

CURRICULUM VITAE (CV)

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EDUCATION

Virginia Commonwealth University, (Medical College of Virginia Campus), Richmond VA,
Doctor of Philosophy in Pharmacy Administration (Pharmacoeconomics and Outcomes Research)
May 2013

University of South Carolina, Columbia SC,
Master of Health Administration
August 2008

Ramkhamhaeng University, Bangkok Thailand,
Master of Business Administration
November 2004

Mahidol University, Bangkok Thailand,
Bachelor of Pharmacy,
March 2002

WORK EXPERIENCE

Thai Food and Drug Administration, Bureau of Drug Control, Bangkok Thailand
Policy officer April 2002- July 2006

- Allocated the budget and created health care policies
- Collaborated with co-workers to develop 2004National List of Essential Medicines (NLEM) (Drug formulary of Thailand)
- Evaluated and reported drug use in National List of Essential Medicines (NLEM) of Thailand

Union Agri Phar Company Limited (pharmaceutical import company), Bangkok Thailand
Consultant December 2004- July 2006

- Evaluated and provided detailed information about veterinary products

The Boots Company (Thailand) Limited, (pharmacy) Bangkok Thailand
Part-time Pharmacist May 2002- May 2006

- Filled and dispensed prescriptions, counseled patients

Siam Makro Public Company Limited (drug retailer), Bangkok Thailand
Part-time Pharmacist May 2002- May 2006

- Filled and dispensed prescriptions, counseled patients

GNC (Thailand), Bangkok Thailand
Part-time Pharmacist May 2002- May 2006

- Counseled and educated customers and sale associates about dietary supplement products

PEER-REVIEWED PUBLICATIONS

Kaisaeng N., Zhang JX. Medicaid Pharmacy Cost-Containment Policy Actions and access to prescription drugs and medical care**,** *Drug Benefit Trends***.** November 2009; 21(10):301-308

PROFESSIONAL CONFERENCE PRESENTATIONS

- **Cost-Related Underuse of Medicine Due to Medicaid Pharmacy Cost-Containment Policy Actions:** 14th Annual International Meeting of the International Society for Pharmacoeconomics and Outcome Research (ISPOR), May16-20, 2009, Orlando, FL. (Poster presentation)

- **Medicaid Pharmacy Cost-Containment Policy Actions and Cost-Related Underuse of Medicine:** AcademyHealth Annual Research Meeting (ARM) June 28-30, 2009, Chicago, IL (Poster presentation)

- **The use of E-prescribing, physicians' perception of Medicaid payment and their willingness to accept new Medicaid patients**: 15th Annual international meeting of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) May 15-19, 2010, Atlanta, GA (Finalist award received)

- **Physicians' perception of Medicaid payments and their willingness to accept new Medicaid patients:** AcademyHealth Annual Research Meeting (ARM),June 27-29 2009, Boston, MA, (Poster presentation)

- **Use of Angiotensin II Receptor Blockers (ARBs) and Angiotensin-Converting Enzyme (ACE) Inhibitors among post-Myocardial Infarction (MI) patients and Insurance Status**. 16th Annual International Meeting of the International Society for Pharmacoeconomics and Outcome Research (ISPOR), May 23, 2011, Baltimore, MD (Poster presentation)

- **Insurance Status and the Use of Angiotensin II Receptor Blockers (ARBs) and Angiotensin-Converting Enzyme (ACE) Inhibitors among post-Myocardial Infarction (MI) patients**: Annual Research Meeting (ARM), June 13 2011, Seattle, WA (Poster presentation)

- **Costs and Use of Oral Anti-cancer medications among Senior Medicare Part D beneficiaries.** 17th Annual International Meeting of the International Society for Pharmacoeconomics and Outcome Research (ISPOR), May 21, 2013, New Orleans, LA (Poster presentation)

RESEARCH EXPERIENCE

- Use of Chitosan in Development of Theophylline Sustained Release Tablet (Project research), School of Pharmacy, Mahidol University, Thailand, 2001

- The Impact of Additional Breast and Cervical Cancer Screening Funds on South Carolina Medicaid Treatment Act Expenditures (Thesis research), Master of Health Administration, School of Public Health, University of South Carolina, SC, 2008

- Cost and Use of Oral Anti-Cancer Medications among Senior Medicare Part D Population (Dissertation research), PhD in Pharmacy Administration (Pharmacoeconomics and Outcomes Research)**,** School of Pharmacy, Virginia Commonwealth University, VA, 2012

BOOK REVIEW

Review of Health Care Research Done Right, by Kathleen A. Fairman, Denver: Outskirtspress,2012.

LEADERSHIPS

ISPOR Student Chapter President
Virginia Commonwealth University, Richmond, VA
May 2011 – June 2012

ISPOR Student Network,
Webmaster Committee Chair
May 2011- June 2012

INTERNSHIP

New Life Pharma Company (pharmaceutical manufacturer), Bangkok, Thailand (December 2001-March 2002)

- Formulated and developed pharmaceutical products in manufacturing department

Kasemras Hospital Bangkok (primary care hospital) and Rayong Hospital, Rayong (Secondary care hospital), Thailand (March 2001-July 2001)

- Residency practice: filled and dispensed prescriptions

Hi-Pex Company (pharmaceutical manufacturer), Bangkok Thailand (March-May 2000)

- Formulated and developed herbal products in Research and Development department

AWARDS

- 2011 Thai Scholar Innovation in USA and Canada Program
- 2012 ISPOR Distinguished Service Award as Webmaster Committee Chair/ Student Chapter President

PROFESSIONAL MEMBERSHIPS

- International Meeting of the International Society for Pharmacoeconomics and Outcome Research (ISPOR)
- AcademyHealth

TECHNICAL SKILLS

- Statistical software: Stata, SPSS and SAS
- Office computing programs: Word, Excel, Powerpoint