PRESCRIPTION WASTE AMONG HOSPICE PATIENTS

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DEDICATION

I dedicate this work to my incredible husband and my children, Rich, Juliana, and Ryker, whose unwavering support has sustained me every step of the way. To my parents and my in-laws, whose encouragement has been a constant source of support. Lastly, I extend my gratitude to Tim Coffin, Ph.D., and Jaime Smith, Ph.D., whose steadfast guidance, and motivation have been invaluable throughout this journey, from its inception to its culmination.

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LIST OF ABBREVIATIONS

Abbreviations

Area Under the Curve ..... AUC
Center for Medicare and Medicaid Services ..... CMS
Centers for Disease Control and Prevention ..... CDC
Clinical Classifications Software ..... CCS
Conditions of Participation ..... CoP
Department of Health and Human Service, Office of the Inspect General ..... DHHS OIG
Electronic health records ..... EHR
End Stage Renal Disease ..... ESRD
False negatives ..... FN
False positives ..... FP
Gaussian Naïve Bayes ..... GNB
Generalized estimating equations ..... GEE
K Nearest Neighbor ..... KNN
Karnofsky Performance Score ..... KPS
Least Absolute Shrinkage and Selection Operator ..... LASSO
Low-income subsidy ..... LIS
Medi-Span Generic Product Identifier ..... GPI
National Drug Codes ..... NDC
Negative likelihood ratio ..... NLR
Negative predictive value ..... NPV
Palliative Performance Scale ..... PPS
Positive likelihood ratio ..... PLR
Positive predictive valu***e*** ..... PPV
Prior authorizations ..... PA
Random Forest ..... RF
Random Survival Forest ..... RSF
Surveillance, Epidemiology, and End Results ..... SEER
Transaction Reply Reports ..... TRR
True negatives ..... TN
True positives ..... TP

ABSTRACT

PRESCRIPTION WASTE AMONG HOSPICE PATIENTS

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The purpose of this dissertation is to assess Part D prescription waste in hospice patients, in three related studies. This dissertation seeks to characterize Part D prescription waste among linked Surveillance, Epidemiology, and End Results (SEER) Medicare and a random 5% sample of Medicare fee-for-service hospice patients by examining policy intervention impacts, assess the quantity and type of prescription medication at time of death, use a novel methodologies such as random forests to identify factors that influence the likelihood of such prescriptions on hand at time of death, and assess life expectancy as a factor in determining prescription lengths that reduce prescriptions on hand at death.

Overview of Hospice and Part D Programs

Hospice was created with the goal of providing medical care that focuses on optimizing quality of life and mitigating suffering among people with terminal illness.

For eligible Medicare patients, hospice is covered under the Medicare Part A insurance benefits and includes care for an individual's terminal illness and related conditions. Hospice uses teams to provide doctor services, nursing care, medical supplies, prescription drugs, therapy (physical, occupational, and speech-language), social worker support, dietary counseling, grief counseling, and short-term inpatient or respite care.

Medicare Part D is a voluntary prescription drug benefit provided by private insurance sponsors for a monthly premium. The program aims to make prescription medications more affordable and accessible to Medicare recipients. The benefit covers patient's prescription drugs in most cases, but there are circumstances where drugs are covered instead under either Medicare Part A or Part B. One exception is when a patient elects hospice, and the prescription drugs related to the care of the terminal illness and conditions are covered under the Medicare Part A benefit. Medications unrelated to the patient's terminal illness may still be obtained through the Part D benefits.

In the past decade, hospice care has prioritized quality while aiming to reduce unnecessary waste. The Center for Medicare and Medicaid Services (CMS) defines waste as practices leading to unnecessary costs for the Medicare program. Since October 2010, CMS has issued several communications to Part D Sponsors and Hospice Providers highlighting the problem of Medicare paying for drugs under Part D that should be covered by hospice Medicare Part A. This inappropriate billing has led to significant costs and waste for the Medicare program. The following reviews the laws, practices,

and/or guidelines CMS has published from 2008 to present providing historical context for understanding Part D prescription waste among hospice patients.

Years 2008-2013

In June 2008, the CMS through the Federal Registrar released the first major revision of Medicare Hospice Conditions of Participation (CoPs) since the Medicare Hospice Benefit was established in 1983. The major revision related to hospice patient's prescriptions (including Part D medications) included:

CFR	**Explanation of Revision**
§ 418.106(e)	Added clarification that reiterates the requirement that hospices must provide all drugs and supplies related to a patient's terminal illness and related conditions and not expect patients to obtain drugs related to the terminal illness and related conditions through Medicare Part D. And that longstanding, preexisting conditions and comorbidities are included in the hospice bundle of services as written in the original implementing regulations of the Medicare hospice benefit. However, if a patient necessitates drugs unrelated to the terminal illness, they may seek coverage through Medicare Part D.

CFR	**Explanation of Revision**
§ 418.54(c)	Clarified the term "unnecessary drugs" as part of the content of the comprehensive assessment and reiterated that all medications should be included in the review in order to develop a plan of care. The ruling went on to clarify that as part of the drug profile review, the assessment should include a patient's prescription and over-the-counter drugs in use, drug effectiveness, side effects, drug interactions, duplicate therapies, and under or overdosing.

Following these changes and clarifications it wasn't until October 2010 that CMS released a Memorandum entitled Preventing Part D Payment for Hospice Drugs. The memorandum indicated there were concerns that Part D sponsors were paying for drugs that should be the responsibility of the Medicare hospice provider. Guidelines were released directing Part D sponsors to communicate with their network pharmacies to ensure Medicare hospice drugs were not billed to Part D. CMS indicated they would provide best practices for doing so by late 2011.

However, following an initial proposal (in February 2011), by April 2011 CMS issued as part of the Announcement of CY 2012 Medicare Advantage Capitation Rates and Medicare Advantage and Part D Payment Policies a section detailing the best practices for "Preventing Part D Payment for Hospice Drugs". The practices recommended Part D sponsors utilize patient-level transaction reply reports (TRR) they

had previously been receiving from CMS. These reports contained patient enrollment information and hospice election information. The best practices detailed how to utilize the included hospice indicators and data to ensure the claims processor is notified of an enrollee's hospice election and that processes are in place to prevent Part D payment for hospice drugs.

Then in June 2012, the Department of Health and Human Service, Office of the Inspect General (DHHS OIG) released a report titled "Medicare Could Be Paying Twice for Prescription Drugs for Hospice Patients" (which examined data from 2009). CMS concurred with two recommendations DHHS OIG made with regard to preventing the Part D benefit paying for medications already covered under the hospice Part A per diem payments. The accepted recommendations included: 1) Educating Part D sponsors, hospices, and pharmacies that it is inappropriate for Medicare Part D to pay for drugs related to hospice patients' terminal illnesses; and 2) Requiring Part D sponsors to develop controls that prevent Part D from paying for drugs that are already covered under the per diem payments.

Following additional TRR report guidance was provided by CMS in April 2013, CMS released a final rule in August 2013 requiring all Part D sponsors to have in place "means" to prevent duplicate payment of hospice medications as well as provided additional clarifications and explanations to sponsors, hospices, and pharmacies. CMS strongly recommended the Part D sponsors use of the TRR reports and have in place

controls to prevent the reimbursement for hospice medications. CMS indicated using prior authorizations (PA) for all hospice medications through Part D was best practice but wasn't required. However, CMS gave specific instruction for sponsors to implement PAs (or other approaches) for four categories of prescription drugs in hospice patients: analgesics, antinauseants, laxatives, and antianxiety drugs. These were identified by the DHHS OIG as typically used to treat the symptoms generally experienced by hospice patients during the end of life. CMS also provided additional guidance and practices for Part D sponsors, hospices, and pharmacies detailing terminal diagnosis and interrelated conditions. CMS reiterated the original intent of the hospice benefit was to have a Medicare benefit available that provided virtually all-inclusive care for terminally ill individuals, provide pain relief and symptom management, and offered the opportunity to die with dignity and comfort in one's own home rather than in an institutional setting.

At the end of 2013 in December, CMS released a memorandum seeking comments on new expectation for stakeholders related to "Part D Payment for Drugs for Beneficiaries Enrolled in Hospice". The memorandum provided a condensed overview of prior regulatory directives pertaining to the eligibility criteria and extent of benefits applicable to Medicare hospice services under Part A. CMS reiterated that patients should only very rarely be taking drugs that are not covered under the hospice per diem. CMS further stated that for prescription drugs to be covered under Part D when the enrollee has elected hospice, the drug must be for treatment of a condition that is completely unrelated to the terminal condition(s) or related conditions. In other words, the drug is unrelated to

the terminal prognosis of the individual. In addition, CMS communicated new expectations for Part D sponsors, aimed at preventing duplicate payments for medications covered within the hospice benefit or waived due to the beneficiary's hospice election. CMS expected for drugs covered under Part D for hospice patients to be extremely rare, the Part D sponsors should place patient-level PA requirements on the following four categories of prescription drugs: analgesics, antinauseants, laxatives, and antianxiety drugs for hospice patients to determine whether the drugs are coverable under Part D. The memorandum also provided guidance to Part D sponsors on making retrospective determinations of payment responsibility for drugs within these categories during the hospice election. The guidance to sponsors was to conduct outreach to the hospice provider to determine whether the drug is for treatment of a completely unrelated condition. CMS stated they expected the hospice provider to coordinate with the plan sponsor regarding these claims and provide the necessary written information, as requested by the sponsor.

Years 2014-Present

In March 2014, CMS issued guidance and established a standard Part D PA form, required for use by Part D sponsors, hospices, and prescribers. The following July, CMS issued a final rule memorandum regarding the "Determination of Payment Responsibility for Drugs for Hospice Patients". In this final memorandum, CMS provided updates to the March 2014 PA form and explanatory documentation and communicated their expectation for its universal implementation of their guidance by October 1, 2014.

In June 2015, the DHHS OIG issued a report titled "Ensuring the Integrity of Medicare Part D", providing a synthesis of investigations, audits, evaluations, and legal guidance related to weaknesses in the Part D program. It again identified highlights the 2012 DHHS OIG report discussing the inappropriate billing of hospice patient's drugs in 2009 to Part D that should be covered by hospice Medicare Part A. The DHHS OIG followed that report with a March 2016 report titled "Hospices Inappropriately Billed Medicare Over $250 Million for General Inpatient Care". CMS responded by concurring with the recommendation to increase its oversight of Part D payments for drugs for hospice patients. CMS began the process to procure a Hospice Recovery Audit contractor to conduct claim reviews and recoup payments as necessary. That November, CMS issued a memorandum titled "Update on Part D Payment Responsibility for Drugs for Beneficiaries Enrolled in Medicare Hospice", acknowledging, and thanking stakeholders for improvements in billing practices and noting the implementation of their Hospice Recovery Audit contractor for claim reviews.

Since 2013 stakeholders have raised concerns about the promptness of communications concerning the entitlement status of hospice patients. In response CMS, in August 2017, took additional action by outlining their strategy for introducing an electronic notice of election form for hospices to communication a patients election (OMB No. 0938-1269) as a component of the FY 2018 Hospice Wage Index and Payment Rate Update. The form went through updates before it was finalized in October 2018. In July 2018, the DHHS OIG recommended to CMS, via a report that assessed the

vulnerabilities in the Medicare hospice program, the need to execute a strategy to intervene with hospices to ensure they are providing the drugs covered under the hospice benefits and not inappropriately billed to Part D. CMS did not concur with this recommendation, which was similar to a recommendation from the June 2012 “Medicare Could Be Paying Twice for Prescription Drugs for Hospice Patients” report that they didn’t concur with then either.

Then the following year, in August 2019, the DHHS OIG conducted a follow-up audit to their 2012 findings. The DHHS OIG released their report titled “Medicare Part D Is Still Paying Millions for Drugs Already Paid for Under the Part A Hospice Benefit” [15]. The report, which examined data from 2016, detailed the ongoing inappropriate billing of prescriptions for hospice patients that the DHHS OIG found previously in its 2012 Report. In response, CMS commented that they would continue to engage in meaningful activities to reduce duplicate payment in this area, such as ensuring hospice providers are proactively educating patients on covered services and items (including drugs) and Part D drug plan sponsors are appropriately applying PA criteria and coordinating with hospice providers on drug coverage issues. To further address the ongoing problem of inappropriate billing documented in the 2012 and 2019 DHHS OIG reports, CMS through the Federal Registrar issued as part of the FY 2020 Hospice Wage Index and Payment Rate Update requires hospices disclose in an extensive written addendum to patients (and other health care providers) any care that would be deemed unrelated to hospice care as part of a Patient Notification of Hospice Non-Covered Items,

Services, and Drugs (OMB 0938-1153). The following year in August 2020, CMS made form OMB 0938-1153 a condition for payment for hospices.

Unfortunately, prescription waste can occur in many ways, not just through inappropriate billing. Estimates suggest up to $2 billion annually, in unused prescription medication, is being wasted in Medicare Part A long-term care facilities alone. A 2013 report by Visante found that around 14 million (approximately 1%) of all Part D prescriptions are wasted yearly. The study reported that most of this waste stems from therapy discontinuation, medication switching, dosage adjustments, and death. Regarding waste due to patient mortality, the study unearthed that, on average, patients had 50% of each prescription on hand at the time of their death.

Goals of this Dissertation

This dissertation seeks to characterize Part D prescription waste among SEER Medicare hospice patients by examining policy intervention impacts, assess the quantity and type of prescription medication at time of death, use a novel methodology such as random forests to identify factors that influence the likelihood of such prescriptions on hand at time of death, and assess life expectancy as a factor in determining prescription lengths that reduce prescriptions on hand at death compared to traditional prescribing methods. This will be accomplished through three related studies in hospice care and prescriptions.

The first study will utilize generalized estimating equations (GEE) with negative binomial regression analysis to understand the effects of hospice patient Part D billing policy guidance on linked SEER Medicare data of male hospice patients with prostate cancer and their Part D prescriptions. The second study seeks to examine Part D prescriptions waste in linked SEER Medicare data of hospice patients, with breast; lung; pancreas; prostate; and stomach cancer and identify any predictive characteristics. The methodology for this study consists of calculating the type and amount of medication on hand at time of death and the associated costs by year and then conducting predictive analyses of characteristics that influence Part D prescriptions waste using machine learning techniques. The third study will develop and test rule-based prescription durations for Medicare patients in hospice, with a particular focus on those with a survival of 90 days or less. This work will inform the development of a decision support tool that will describe Part D prescription durations that reduce potential waste related to the amount of prescription medication on hand at death compared to traditional prescribing methods. The methodology will use Random Survival Forest (RSF) calibrated with median trapezoidal rule to develop survival estimates, to simulate clinician predicted survival, which the rule-based prescription durations were applied to. Medication on hand at time of death was calculated and the resulting waste was compared between the rule-based prescription lengths and provider durations.

By employing generalized estimating equations, the first study was able to assess the (1) total monthly average prescriptions of all medications and (2) four categories of

commonly prescribed hospice medications in pre-and-post policy guidance. This study investigated the effects of guidance issued by CMS on April 4, 2011, targeting providers to prevent the improper billing of prescription drugs for hospice patients' terminal illness and related conditions to the Part D benefit. Using linked SEER Medicare data for male hospice patients between April 2009 and March 2013, the analysis found that hospice patients' monthly average total Part D prescriptions decreased from 7.3 pre-policy guidance to 6.5 medications following the issuing of the guidance, while the four categories of hospice-specific medications decreased from 0.57 to 0.49. The findings of this study show that CMS's guidance issued to providers to prevent the inappropriate billing of hospice patients' prescriptions to the Part D benefit may lead to decreases in improper billing as observed in this sample.

Summary statistics were applied in the second study to examine the type and quantity of Medicare Part D medications on hand at time of death in hospice patients. This analysis utilized a 5% subset of Medicare fee-for-service patient claims and linked SEER Medicare patient claims spanning from January 2015 to December 2019. Results indicated that cardiovascular medications accounted for 25% of prescriptions, followed by central nervous system medications at 20%. The mean prescription length was 36.65 days' supply with a mean of 62.18 quantity dispensed. Prescriptions resulting in medication on hand at time of death on average were dispensed 72.69 days after a patient's admission to hospice and resulted in a mean of 20.02 days' supply and 34.18 quantity wasted. Additionally, the study evaluated the predictive accuracy of four

classifiers in forecasting prescription waste at time of death, with Random Forest achieving the highest performance, boasting an area under the curve (AUC) exceeding 93%. Feature importance analysis revealed prescription days' supply and quantity dispensed as the most influential factors. Even after removing these predictive features, Random Forest still demonstrated a respectable AUC of 73.5%. The study demonstrates that medication on hand at time of death in hospice patients can be predicted and supports additional research should be done to identify ways to reduce the waste.

In the final study, rule-based prescription durations were developed and applied to each patient based on their simulated survival days. RSF calibrated with median trapezoidal rule was used to simulate clinician estimated patient survival days. Medication on hand at time of death was then calculated for the rule-based prescriptions and compared to the amount caused by the traditional clinician prescription durations. Two scenarios were conducted that compared the overage for (1) all prescriptions regardless of when the clinician determined prescription ended and (2) prescriptions where a threshold excluded prescriptions where either the clinician or rule-based prescriptions ended more than 3 days before the death date. In the initial scenario, the rule-based prescriptions reduced overage in 28% of cases, leading to a decrease of 29.1% to 36.1% in the amount of prescription medication on hand at the time of death. The second scenario saw similar success with the rule-based prescriptions reducing overage in 32% of cases, leading to a decrease of 32% to 45.5% in the amount of prescription waste.

Overall, in this sample the rule-based initial and refill prescription durations were effective in reducing waste.

The occurrence of Part D prescription waste in hospice has been well documented by CMS in memorandums and reports. However, few studies exist examining CMS implemented policy impacts to reduce waste, characteristics identification of Part D hospice prescription waste for predicting medication on hand at death, or novel methods to reduce medication waste at the source, i.e., the prescription. Each of these three related studies is significant in that it addresses a gap in hospice care and prescription waste using novel machine learning approaches.

The first study is significant in it addresses how government policy guidance has impacted the inappropriate billing of Part D prescriptions in hospice patients. While CMS has documented decreases in billing of Part D prescriptions in hospice patients, no study or analysis exists that definitively ties the decrease and policy together. This study addresses this gap using a GEE with negative binomial regression will address this gap and has the potential to bolster the findings of CMS.

The significance of the second study is twofold, as like the first paper, this study also addresses two gaps: 1) the review of Part D prescription waste patterns in hospice patients using individual hospice patient claim records, and 2) in its identification of characteristics that influence the likelihood of Part D prescription waste. Limited research

exists in exploring the type, quantity, and costs of medications on hand at time of death in hospice patients and no research exists that examines characteristics that influence the likelihood of prescription waste. Currently this gap in research exists as prior studies have only assessed the amount of hospice Medicare Part A prescription waste at individual hospice organizations. Using novel methods, such as K Nearest Neighbor, the study will assess the effects of hospice patient's characteristic on the likelihood of Part D medications on hand at time of death. This study is crucial as a first step to bring about further understanding and awareness of potential waste patterns in hospice patients' Part D prescriptions in order to better the prescribing patterns of physicians and improved care coordination between teams.

The use of average life expectancy to influence prescription lengths in hospice patients is a significant gap in the literature. While studies have explored the clinical and cost-effectiveness of longer and shorter (3-month vs 28 days) duration prescriptions to reduce waste, studies identifying prescription durations for reducing medication on hand at time of death in hospice patients do not. The use of machine learning methods in this study, e.g. RSF, to develop a rule-based decision support tool to assess prescription lengths that reduce waste in real time is novel. This study has the potential to influence how Part D prescriptions are prescribed to hospice patients in order to address ongoing issues of medical waste in terms of money and resources.

This work provides critical evidence on the scope of problematic medication waste at the end of life. The research should ideally be used to promote increased efforts around appropriate billing of prescription drugs in conjunction with identifying predictors of medication on hand at time of death to developed tailored medication prescription duration strategies that minimize burden without impacting quality of life during the patient's final weeks and months. Additionally, this work's implementation of novel machine learning approaches, using individual patient data, provides further evidence of need for these advanced models to be incorporated into provider's medical software to aide in decision making as well as providing personalized medicine to the patient. Until then, a more careful review of patients' prescription prescribed through Part D and the prescription duration at the time of hospice enrollment is warranted.

MANUSCRIPT ONE: ASSESSING THE IMPACT OF THE CENTER FOR MEDICARE AND MEDICAID SERVICES POLICY GUIDANCE ON PART D PRESCRIPTIONS AMONG HOSPICE PATIENTS

ABSTRACT

Hospice care facilities are required to provide prescription drugs related to a hospice patient's terminal illness. From October 2010 to present, the Center for Medicare and Medicaid Services (CMS) has issued a series of communications regarding Medicare paying for hospice patients' prescription drugs under Part D that should be covered under the hospice Medicare Part A benefit. On April 4, 2011, CMS issued specific policy guidance to providers aimed at preventing inappropriate billing. While CMS has documented Part D prescription decreases in hospice patients, no research exists that connects these decreases and the policy guidance. This study aims to evaluate the effect of the April 4, 2011, policy guidance on hospice patients' Part D prescriptions. This study employed generalized estimating equations to assess (1) total monthly average prescriptions of all medications and (2) four categories of commonly prescribed hospice medications in pre-and-post policy guidance. This research used the Medicare claims of 113,260 Part D-enrolled Medicare male patients aged 66 and older between April 2009 and March 2013, including 110,547 non-hospice patients and 2,713 hospice patients. Hospice patients' monthly average total Part D prescriptions decreased from 7.3 pre-policy guidance to 6.5 medications following the issuing of the guidance, while the four

categories of hospice-specific medications decreased from 0.57 to 0.49. The findings of this study show that CMS's guidance issued to providers to prevent the inappropriate billing of hospice patients' prescriptions to the Part D benefit may lead to Part D prescription decreases as observed in this sample.

Keywords: hospice, policies, prescription, SEER, Medicare, waste, Generalized estimating equations, negative binomial regression

INTRODUCTION

Hospice began in the United States in the early-1970s, as a way for individuals with terminal cancer to pass with dignity [1] and as a means to address the unmet needs for end-of-life care [2]. However, it wasn't until the Tax Equity and Fiscal Responsibility Act of 1982 that the Medicare hospice benefit was authorized [3]. The provisions dictated hospice qualifications and elections, certification and coverage, and payment methods and caps [4]. Noteworthy changes in the following years included increases in reimbursement rates in 1985, 1989, 2001, and 2002 and changes to the benefit limitation in 1990 and 1997. For eligible Medicare patients' hospice is covered under the Part A benefits and includes care for an individual's terminal illness and related conditions, the care includes doctor services, nursing care, medical equipment and supplies, prescription drugs, hospice aide services, physical and occupational therapy, speech-language pathology services, social worker services, dietary counseling, grief and loss counseling, and respite care [5].

Medicare Part D began in 2006, following its inception under the Medicare Prescription Drug and Modernization Act of 2003. The program provides patients with the option to elect to pay a monthly premium to CMS-approved private insurance sponsors and obtain coverage for their outpatient prescriptions [6]. The benefits were enacted as a response to the rising costs of prescription drugs and to protect senior citizens, who were the highest users and therefore the most vulnerable population [7]. Medicare Part D benefit provides tax breaks and subsidies to cover prescription drugs.

However, there are circumstances where drugs are covered under either Part A (prescriptions related to a hospital, skilled nursing facility, or hospice stay) or Part B (prescriptions administered by your provider or at a dialysis facility) [8]. The hospice Medicare Part A benefit covers prescription drugs related to the palliative treatment of terminal illness and related conditions [5]. Only medications unrelated to the palliation of the patient's terminal illness may still be obtained through the Part D benefits.

In the past decade, the focus for hospice has been not only on providing quality care but doing so while reducing unnecessary waste [9]. CMS defines waste as "the overutilization of services, or other practices that, directly or indirectly, result in unnecessary costs to the Medicare program. Waste is generally not considered to be caused by criminally negligent actions but rather the misuse of resources" [10]. Since October 2010, and most recently on April 14, 2021 [11], CMS has issued a series of call letters and memorandums [12] [13] [14] [15] [16] [17] [18], as well as reports [19] [20] [21] to Part D sponsors and hospice providers detailing the ongoing issue of Medicare paying for prescription drugs under Part D that should be covered under the hospice Medicare Part A benefit. This includes four common categories of prescription drugs (prescription analgesic, anti-nausea, laxative, and antianxiety drugs) typically used to treat hospice patients' symptoms [19]. This inappropriate billing has resulted in millions of unnecessary costs and waste for the Medicare program [19] [20] [21].

Limited research exists exploring the direct relationship between the inappropriate billing of hospice patient drugs and the communications released by CMS to hospice providers and Part D sponsors. The policies surrounding payer responsibility for drugs related to a hospice patient's terminal illness and conditions have never changed, but rather communications and process modifications have occurred. This study seeks to estimate the effect of CMS's policy communications to Part D sponsors in implementing control measures to prevent Part D payments for hospice drugs. Current research and reports that exist have assessed the percent changes of hospice Part D prescription fills over time [17] without addressing the effect CMS policy communications may have on Part D payments for hospice drugs. Therefore, by addressing this gap, there can be a better understanding of the impact released CMS notifications may have had. In addition, this research supports a statement made to the Department of Health and Human Services Office of the Inspector General (DHHS OIG) from CMS in 2019, following an audit, that "the control measures in place are working and should resolve the problems" [21].

Specifically, this study seeks to understand the effects that the April 4, 2011, guidance released by CMS to providers detailing the best practices for "Preventing Part D Payment for Hospice Drugs" [12] had on Part D prescriptions for male hospice patients between April 1, 2009 – March 31, 2013. The effects were measured by changes in overall Part D prescriptions, as well as by measuring the changes in the four common categories of prescription drugs (prescription analgesic, anti-nausea, laxative, and antianxiety drugs) typically used to treat hospice patients' symptoms.

METHODS

Data source and sample

This study used data from the Surveillance, Epidemiology and End Results (SEER) Program and Medicare linked database. This database covers approximately 34.6% of the U.S. population and provides detailed information about Medicare patients with cancer [22]. SEER-Medicare data includes two cohorts of patients, namely persons with cancer and a random sample of Medicare patients who do not have cancer. The cancer sample included 69,988 patients and was drawn from those who've had a history of prostate cancer. The "non-cancer" group contained 43,272 patients drawn from a random 5% sample of male Medicare fee-for-service patients (n=113,260) residing in the SEER areas [22]. The study sample included both the cancer and non-cancer groups and utilized their Medicare Part A/B/D claims and Medicare Enrollment data.

The study examined patient data between April 1, 2009 and March 31, 2013, with months prior to April 1, 2011 considered pre-policy guidance and the months after as post. The period chosen represents an equitable amount of time before and after the policy guidance, without including data prior to 2009 as they may have been impacted by the June 2008 Hospice Medicare Conditions of Participation (CoP) revision [23] or data that may have been impacted by the August 2013 final ruling on "means" to prevent inappropriate hospice prescription billing. April 2011 was selected as it was when CMS released guidance to providers detailing the best practices for "Preventing Part D Payment for Hospice Drugs" [12]. Patients were included in the study if they were at

least 66 years old and if they maintained continuous enrollment in Medicare Part A/B/D during the study or until their death. The sample included 113,260 patients after applying these criteria. Patients' hospice or non-hospice status was assessed monthly by checking for hospice claims and examining hospice admission and discharge dates for patients.

This study included a list of 469 prescription brand analgesic, antinausea, laxative, and antianxiety drugs names and their National Drug Codes (NDC) obtained from the DHHS OIG. The NDCs for these four categories of prescription medications were selected based on the methodology used by the DHHS OIG in their 2012 Report "Medicare Could Be Paying Twice for Prescription Drugs for Patients in Hospice" [19]. In this report, the DHHS OIG identified these four categories, 469 medications, as common drugs used to treat end-of-life symptoms in hospice patients.

Measures

Outcome Measures

Two measures of hospice prescription utilization were created, namely average monthly prescriptions of (1) all medications and (2) four categories of commonly prescribed hospice medications. The first measure of total monthly prescriptions of all medications is defined as the monthly total count of each prescription filled by a patient each month. The second measure utilized the list of 469 NDC's provided by the DHHS OIG and counted only those prescriptions filled by a patient each month. The inclusion of

a prescription in a month, within the study period, was determined by the "RX Service Date" on the claim, which is defined as the date on which the prescription was filled.

Policy and Hospice Measures

To examine the influence of the April 4, 2011, policy guidance [13], a measure was created to indicate the two time periods as *pre-* and *post-policy*. The pre-policy guidance time period ranged from April 1, 2009 through March 31, 2011, and the post-intervention time period run from April 1, 2011 through March 31, 2013. The patient's hospice status was recorded each month. The approach evaluated the effect of the policy guidance and compares pre- and post-policy guidance in outcomes between a treatment hospice group (exposed to policy guidance) and a comparison control non-hospice group (not exposed to policy guidance).

Covariates

The regression models were adjusted for covariates that included patient sociodemographic characteristics such as age, reported race, sex, the original reason for Medicare enrollment (Aged or Disabled/End Stage Renal Disease (ESRD)) and rural/urban residence. Patient clinical characteristics included prior history of prostate cancer and a count of comorbidities (Alzheimer's Disease, Chronic Heart Failure, Kidney Disease, Liver Disease, Stroke, Debility, Dementia, Chronic Obstructive Pulmonary Disease, and Heart Disease). These comorbidities were identified by examining the ICD-

9 diagnosis codes on the patient's claims for services that occurred during the study period.

Statistical Analysis

The total monthly average number of prescriptions for hospice and non-hospice were calculated. Line graphs were constructed to visually examine changes in the average number of prescriptions based on hospice status. The demographic and clinical characteristics of the sample patients were summarized. Regressions, with no constant, were conducted to assess the effects between different covariates and the hospice status variable on the two prescription outcome variables *pre-* and *post-policy*. GEE with negative binomial regression was conducted to estimate any significant changes in the two outcome measures (average monthly prescriptions and average monthly prescriptions of four specific categories of commonly prescribed hospice medications) pre-and-post policy guidance based on hospice status. These analyses were controlled for patient sociodemographic characteristics and comorbidities. The data was preprocessed in PSQL and then imported into STATA 14.0 [24] for analysis.

RESULTS

Summary statistics for the analysis are presented in Tables 1 and 2. In the overall sample of 113,260 patients, 2,713 (2.4%) enrolled in hospice care. The hospice group on average was 8 years older than the non-hospice group, with over 60% of the patients being 80+ years old whereas 60% of the non-hospice group were under 80 years old. The most common race among both groups was white followed by black. The non-hospice

group had a higher Medicare enrollment of DIB/ESRD patients (26%) compared to the 20% of hospice patients. While most of the individuals lived in urban settings the non-hospice group was 6% higher than the hospice one. More hospice patients had a history of prostate cancer than non-hospice patients, 72.9% versus 61.5%, respectively. Approximately 79% of the hospice patients and only 36% of the non-hospice ones had four or more comorbidities. Most patients lived in an urban setting but a larger percentage of the non-hospice group (97.5%) versus the hospice group (91.7%) was seen.

Figure 1 presents the pre and post-treatment trends of both the control and treated group's total average number of monthly Part D prescriptions. Figure 2 presents the trends of the four categories of hospice-specific medications pre- and post-policy. In both figures, the hospice group has a mostly downward trend following the policy intervention on April 4, 2011, while the non-hospice group trends upward. Therefore, the figures show that the hospice group could have followed a similar economic trajectory to the non-hospice group in the absence of the policy.

Table 2 presents the change in total monthly average prescriptions for both hospice and non-hospice patients, pre- and post-policy. In general, the hospice group saw a statistically significant decrease in both outcomes across the various characteristics. Specifically, those in hospice who were ages 80-84 saw an average monthly decrease of 3.29 for all medications post-policy and 0.06 for hospice-specific medications. Those with Medicare enrollment reason of DIB/ESRD had an average decrease of 2.42 for all

medications post-policy and 0.08 for hospice-specific medications. Whereas the non-hospice group, for the most part, saw both outcomes increase marginally over the same period.

Table 3 presents the results of the GEE with negative binomial regression. These results have been adjusted for patient age, race, Medicare enrollment reason, urban/rural, prior history of prostate cancer and number of comorbidities. The total average monthly Part D prescriptions for hospice patients is double that of non-hospice patients. However, there was an overall time trend of reduced prescriptions for both outcomes among the hospice patients; all medications decreased by 10% from 7.3 pre-policy guidance to 6.5 post-policy guidance. Similarly, hospice-specific medications decreased 14.0% from 0.57 pre-policy guidance to 0.49 post-policy guidance. The non-hospice patients saw an increase for both outcomes during the same period; 5% increase in all medications and a 12.5% increase in hospice-specific medications.

DISCUSSION

This is one of the first studies to assess the impact of CMS guidance on Part D prescription medication for hospice patients. The findings show that the guidance issued by CMS on April 4, 2011, to providers may had aided in the reduction of hospice patient's prescriptions being inappropriately billed to the Part D benefit and lead to the reduction of Part D prescriptions in this group. On April 4, 2011, CMS issued as part of the Announcement of CY 2012 Medicare Advantage Capitation Rates and Medicare Advantage and Part D Payment Policies a section detailing the best practices for

"Preventing Part D Payment for Hospice Drugs" [13]. The practices recommended Part D sponsors utilize patient-level TRR they had previously been receiving from CMS. These reports contained patient enrollment information and hospice election information. The best practices detailed how to utilize the included hospice indicators and data to ensure the claims processor is notified of an enrollees' hospice election and that processes are in place to prevent Part D payment for hospice drugs.

Medicare beneficiaries admitted to hospice should have all medications related to their terminal illness covered under the Part A benefit. This study presented the pre- and post-treatment Part D prescription trends of both the non-hospice and hospice groups and examined influential characteristics. The study found the non-hospice group trends upward, while the hospice group has a mostly downward trend following the policy intervention on April 4, 2011; indicating the hospice group could have followed a similar economic trajectory to the non-hospice group in the absence of the policy.

This study has several limitations. It is limited to male patients and those included in the SEER data with prostate cancer and those from the 5% Medicare fee-for-service patients residing in the SEER areas. Secondly, this study did not account for potentially influential factors of the hospice facilities and their providers such as the profit status, staffing levels, and age of the program, which are unknown due to data privacy limitations. Lastly, this study is focusing on a measurement period from 2009 to 2013. While CMS's first communication to sponsors and providers was in 2011, it was not until

2014 that a standardized prior authorization form for hospice patients' Part D prescriptions was required and implemented. Analysis of data after 2013 might provide additional insight into utilization patterns as CMS requirements were more clearly defined and standardized through additional communications. This additional period of data would further allow analysis that would complement, and support basic analyses already done by CMS in a report [17] from 2016 that showed decreases in hospice patient's Part D utilization between 2013-2016. Nevertheless, this study still shows that the CMS guidance to providers on Part D prescription medication for hospice patients may have impacted the reduction in inappropriate billing of hospice patients' prescriptions to Part D after April 4, 2011.

This research has implications most importantly for CMS, but also for the patient, the provider, and Part D sponsors. Existing research has not explored the relationship between Part D sponsor control measures and reduction in hospice drugs being inappropriately billed under the Part D benefit. By addressing this gap in research CMS can potentially demonstrate the causal impact of the control measures on the reduction of inappropriate billing of hospice medications. Studies that monitor the impact of CMS policy changes and issuance of guidelines are needed to support the control measures CMS has and is implementing to further reduce unnecessary prescriptions for populations such as those in hospices.

The findings of this study bring awareness to the prescribing behaviors of providers for hospice, who are responsible for supplying all medications related to the patient's terminal illness or related conditions [5]. Additionally, this study can provide hospice patients with a better understanding of what control measures are in place to protect them from paying for medications under Part D that should be covered under their hospice benefit. Policies and guidance for reducing waste are critical to the Medicare program as are policies, such as this that protect the hospice patient and reduce the burden on the patient to obtain a prescription through a pharmacy in a difficult time at the end of their life.

APPENDIX A. TABLES AND FIGURES

Table 1. Characteristics of Patients (n=113,260)

Characteristics	Hospice		Non-Hospice	
	n= 2,713	%	n= 110,547	%
Age mean (std)	79.9 (9.06)		71.8 (11.6)	
≤69	188	6.93%	25,421	23.00%
70-74	285	10.50%	23,318	21.09%
75-79	455	16.77%	26,625	24.08%
80-84	594	21.89%	19,154	17.33%
85-89	608	22.41%	11,101	10.04%
≥90	583	21.49%	4,928	4.46%
Race				
White	2,250	82.93%	84,886	76.79%
Black	273	10.06%	10,923	9.88%
Asian	82	3.02%	6,055	5.48%
Hispanic	67	2.47%	4,462	4.04%
Other/Unknown	41	1.51%	4,221	3.82%
Medicare Enrollment Reason				
Old age and survivor's insurance (OASI)	2,171	80.02%	81,811	74.01%
Disability insurance benefits (DIB) and/or End-stage renal disease (ESRD	542	19.98%	28,736	25.99%
Urban/Rural				
Urban	2,635	97.12%	107,822	97.53%
Prior History of Prostate Cancer				
Yes	1,969	72.58%	68,019	61.53%
Number of comorbidities, mean (std)	5.02 (1.84)		2.85 (1.99)	
0	22	0.81%	15,371	13.90%
1	70	2.58%	16,063	14.53%
2	172	6.34%	19,881	17.98%
3	296	10.91%	19,438	17.58%
4+	2,153	79.36%	39,794	36.00%

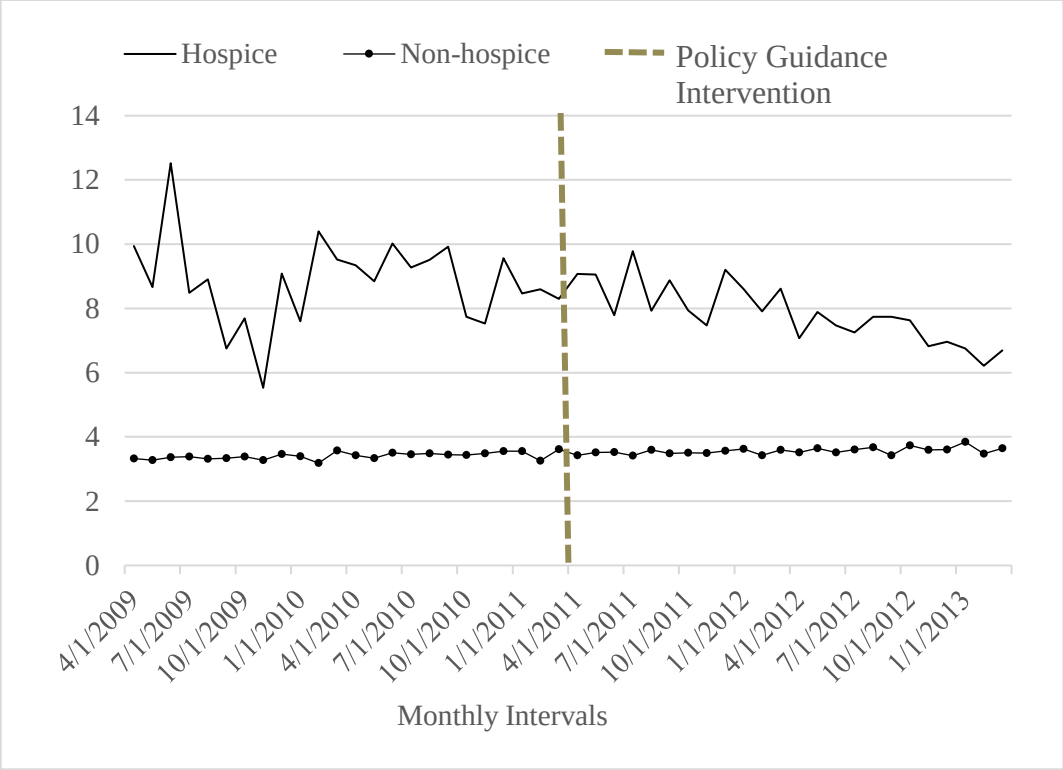

Figure 1. Total Monthly Average Part D Prescriptions - All Medication Pre and Post-Policy Intervention

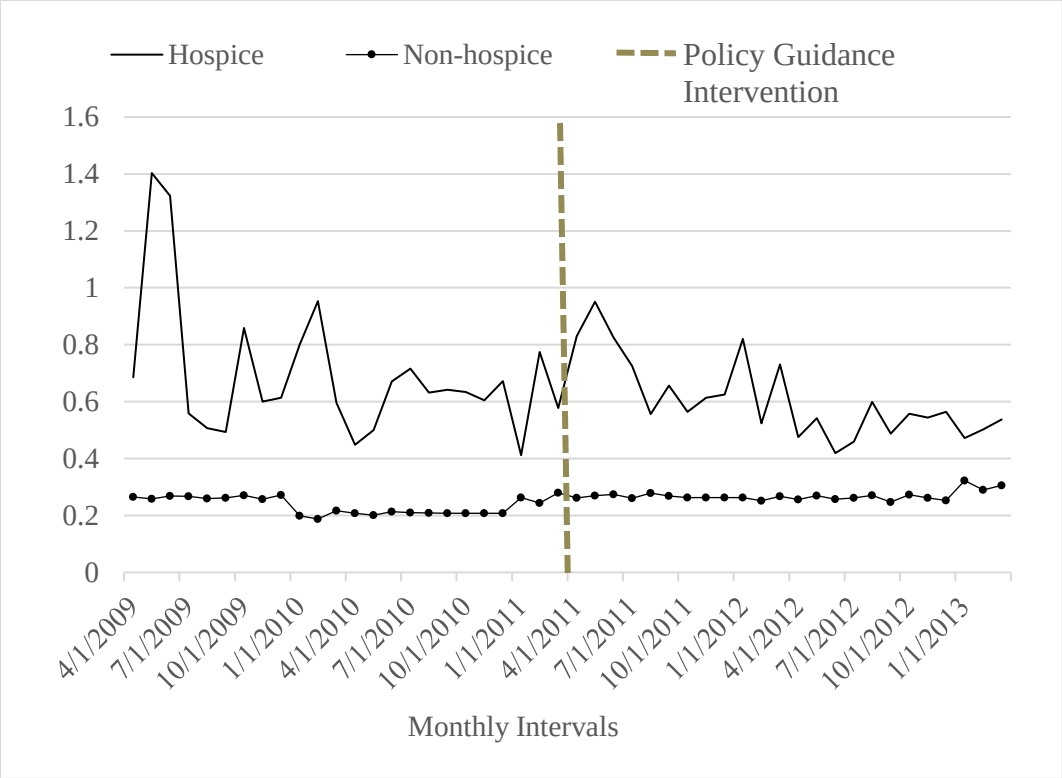

Figure 2. Total Monthly Average Part D Prescriptions -
Four Hospice Medication Categories Pre and Post-Policy Intervention

Table 2. Descriptive Statistics by Pre- and Post-policy and Hospice and Non-Hospice for All Prescriptions and Category Specific

Characteristics	Total Monthly Average Part D Prescriptions - All Medication				Total Monthly Average Part D Prescriptions - Four Hospice Medication Categories[a]			
	Non-Hospice		Hospice		Non-Hospice		Hospice	
	Pre-Policy[b]	Post-Policy[b]	Pre-Policy[b]	Post-Policy[b]	Pre-Policy[b]	Post-Policy[b]	Pre-Policy[b]	Post-Policy[b]
Age								
≤69	3.65*	4.00*	7.04*	6.54*	0.38*	0.54*	1.00*	1.00*
70-74	3.65*	3.32*	7.37*	6.76*	0.19*	0.22*	0.64*	0.65*
75-79	3.36*	3.47*	7.51*	6.72*	0.18*	0.20*	0.47*	0.50*
80-84	3.49*	3.67*	9.99*	6.70*	0.19*	0.20*	0.54*	0.48*
85-89	3.66*	3.80*	5.60*	5.89*	0.20*	0.21*	0.58*	0.39*
≥90	3.87*	4.09*	5.47*	6.77*	0.23*	0.27*	0.42*	0.39*
Race								
White	3.31*	3.48*	7.08*	6.18*	0.22*	0.26*	0.52*	0.44*
Black	3.99*	4.21*	7.97*	7.88*	0.37*	0.42*	0.66*	0.66*
Asian	4.27*	4.52*	10.6*	11.1*	0.19*	0.23*	1.11*	0.79*
Hispanic	4.11*	4.36*	7.8*	6.33*	0.31*	0.38*	0.68*	0.52*
Other	3.2*	3.35*	4.69*	5.1*	0.17*	0.21*	0.73*	0.32*
Medicare Enrollment Reason								
OASI	3.08*	3.26*	6.55*	6.24*	0.16*	0.18*	0.50*	0.42*
DIB/ESRD	4.74*	4.97*	10.2*	7.78*	0.62*	0.7*	0.89*	0.81*
Urban/Rural								
Urban	3.43*	3.61*	7.34*	6.56*	0.23*	0.28*	0.57*	0.48*
Rural	4.00*	4.31*	6.38*	4.30*	0.34*	0.40*	0.49*	0.80*
Prior History of Prostate Cancer								
Yes	3.00*	3.18*	8.02*	6.81*	0.16*	0.17*	0.49*	0.41*
No	4.57*	4.77*	5.31*	5.73*	1.48*	1.43*	1.56*	1.61*
Number of comorbidities								
0	1.63*	1.68*	3.57*	2.41*	0.07***	0.09**	0.31***	0.28**
1	2.48*	2.56*	4.07*	3.49*	0.17*	0.20*	0.50*	0.33*
2	2.89*	3.00*	5.24*	4.96*	0.20*	0.23*	0.55*	0.43*
3	3.35*	3.50*	4.72*	5.29*	0.23*	0.27*	0.40*	0.49*
4+	4.60*	4.93*	7.88*	6.89*	0.34*	0.39*	0.59*	0.50*

[a]DHHS OIG identified these four categories of analgesic, antinausea, laxative, and antianxiety medications (469 NDCs)

[b]Pre-Policy: April 2009 - March 2011 and Post-Policy April 2011-March 2013

*p-value = 0.000 **p-value = 0.003 ***p-value = 0.077

Table 3. Assessing the Impact of Policy Guidance on Total Monthly Part D Prescriptions for Hospice and non-Hospice patients Averages[1]

Interaction	Total Monthly Average Part D Prescriptions - All Medication			Total Monthly Average Part D Prescriptions - Four Hospice Medication Categories[a]		
	Average	IRR*	p-value	Average	IRR*	p-value
Not Hospice x Pre Policy	3.45	-		0.24	-	
Not Hospice x Post Policy	3.63	1.02	0.000	0.27	1.01	0.003
Hospice x Pre Policy	7.30	1.11	0.000	0.57	0.88	0.006
Hospice x Post Policy	6.54	1.04	0.000	0.49	0.71	0.000

[1]Results have been adjusted for patient age, race, Medicare enrollment reason, urban/rural, prior history of prostate cancer and number of comorbidities

[a]DHHS OIG identified these four categories of analgesic, antinausea, laxative, and antianxiety medications (469 NDCs)

*Incidence rate ratio (IRR) allows for the comparison of the incident rate between two different groups

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MANUSCRIPT TWO: A MACHINE LEARNING APPROACH TO ASSESSING PART D PRESCRIPTION MEDICATION WASTE IN HOSPICE PATIENTS

ABSTRACT

Research evidence shows that around 1% of all Part D prescriptions are wasted each year, which equates to about 14 million prescriptions per year. Patient death was one of the factors influencing waste with about 50% of medication on hand at time of death for each prescription. The objectives of this study were to (1) examine the type and quantity of Medicare Part D medications on hand at time of death in hospice patients, and (2) explore the features (e.g., patient characteristics) that are predictive of prescription waste on hand at time of death based on an estimated prescription threshold using Medicare claims data and a machine learning approach. Overall, the two most prescribed Part D medications to hospice patients were cardiovascular (25%) and central nervous (20%) medications. When a calculated threshold that considered a reasonable amount of medication left on hand at time of death was applied (where the days' supply was 30 days or greater and the dispensed quantity on hand at time of death was greater than 30) the most common dispensed medications were cardiovascular (30.6%) and central nervous (20.2%). On average patients were dispensed 36.7 days' supply of medications and on average had 20 days' supply on hand at time of death, with the threshold applied those amounts were 63.4- and 43.1-days' supply respectively. The most predictive features of prescription waste were prescription days' supply and quantity dispensed with most models achieving an area under the curve (AUC) over 93% and Random Forest (RF) still achieving 73.5% when these predictive features were removed. The study demonstrates

that medication on hand at time of death in hospice patients can be predicted but additional studies that monitor the factors, as well as the state and government prescribing guidelines are needed to support changes in Part D prescribing patterns in hospice patients. Policies and guidance for reducing waste are critical to the Medicare program, models such as this that can predict where waste is occurring and can help reduce the burden on the Medicare program.

Keywords: hospice, policies, prescription, Medicare, medication waste, SEER, deprescribing, end-of-life care, K-Nearest Neighbor, LASSO, Naïve Bayes Gaussian, and Random Forest.

INTRODUCTION

Hospice is covered under the Medicare Part A benefit and serves to provide medical care that focuses on optimizing quality of life and mitigating suffering among people with terminal illness. The medical care includes doctor services, nursing care, medical equipment and supplies, prescription drugs, hospice aide services, physical and occupational therapy, speech-language pathology services, social worker services, dietary counseling, grief and loss counseling, and short-term inpatient care or respite care [1]. Admission to a hospice facility requires the recommendation of the medical director in consultation with the patient's attending physician and that the patient's medical prognosis is terminal, i.e., the individual's life expectancy is 6 months or less if the illness runs its normal course [2]. Once the patient is certified as terminally ill, the individual must complete the process of electing hospice care to receive it [2]. This is done by signing an election statement that dictates the particular hospice to be providing care and the election date, the designated physician's information, that the patient understands they are to receive palliative hospice care, and that other Medicare services will be not be covered by the hospice benefit [3]. Medicare will still pay for any health problems that aren't part of a patient's terminal illness and related conditions.

Medicare Part D is a voluntary outpatient prescription drug benefit provided by The Centers for Medicare & Medicaid Services (CMS) and it is provided by private insurance sponsors for a monthly premium [4]. The benefit covers patient's prescription drugs in most cases, but there are circumstances where drugs are covered

instead under either Medicare Part A or Part B [5]. One of these situations is when a patient elects hospice, and the prescription drugs related to the care of the terminal illness and conditions are covered under the Medicare Part A benefit [1]. Medications unrelated to the patient's terminal illness may still be obtained through the Part D benefits. Many patients and their families question when it is appropriate to withdraw these regular medications, which a patient may still be filling under Medicare Part D. As the goal of hospice is to provide comfort, and neither hastening death or prolonging life, in most cases it is appropriate to continue regular medications [6]. Only when a patient enters the very last stage, known as the active phase of dying, is it then appropriate to withdraw care of regular medications or unless the care plan dictates withdrawal sooner. Otherwise, removing the medications from a patient, that is not at the end, is a form of hastening death or euthanasia [6].

At present the most common means of combating prescription waste is through pharmaceutical donation and reuse programs. These programs began with state legislative action in 1997 and have grown to be present in 38 states and Guam as of 2018 [7]. The three most significant issues with these programs are: 1) the lack of awareness about the programs; 2) they don't accept controlled drugs; and 3) all pharmaceuticals must be unopened and in sealed, tamper-evident packaging [8]. Since almost all Part D medications are controlled drugs and often the medications are opened and unsealed, hospice patient's medications are not candidates for these types of programs.

Limited research exists exploring the type and quantity of medications on hand at time of death in hospice patients. The two most relevant studies exploring this topic did so through retrospective case reviews of individual hospices and the medications related to the terminal diagnosis covered under the Medicare Part A hospice benefit [9] [10]. While Zueger et al. (2018, 2019) in two studies did explore Medicare Part D prescriptions in hospice patients, their research focused on the filling of prescriptions for limited benefit medications (LBM) [11] [12]. These LBM medications were described as those with questionable benefits as they do not increase the quality of life in hospice patients with limited life expectancies [12]. A report from Visante (2013) addressed the topic of Part D waste in hospice using secondary data and found death to be one of the largest contributors with 50% of medication on hand at time of death. Although these research studies have increased the understanding of Part D prescriptions in this population, they did not assess the patient and/or facility characteristics that can influence Part D prescription waste on hand at time of death [12] [11] [13] [14] [9] [10]. Therefore, the purpose of this study is to (1) examine the type and quantity of Medicare Part D medications on hand at time of death in hospice patients, and (2) explore the features (e.g., patient characteristics) that are predictive of prescription waste on hand at time of death and to predict Part D prescriptions medications on hand at time of death based on an estimated prescription threshold using Medicare claims data and a machine learning approach. Assessing Part D prescription waste patterns in hospice patients is essential in allocating available resources, including the prescriptions themselves and the Medicare program financials. Further understanding of Part D prescription potential waste patterns

in hospice patients can bring about awareness for better prescribing patterns and improved care coordination between teams.

METHODS

Data Source

This study uses secondary data from the 2015 to 2019 Surveillance, Epidemiology and End Results (SEER) Program and Medicare linked database. This database is a nationally representative, population-based source of data that provides detailed information about Medicare patients with cancer [15]. The registry covers approximately 34.6% of the U.S. population, with data coming from the SEER areas of Connecticut, Iowa, New Mexico, Utah, Hawaii, Alaska Natives, Arizona Indians, Cherokee Nation, Georgia, California, Idaho, Kentucky, Louisiana, Massachusetts, New York, Wisconsin, and the cities of Chicago and Seattle-Puget [15]. The SEER-Medicare data includes claims and patient entitlement information for two cohorts of patients; those with cancer from the SEER registry and a random 5% sample of Medicare patients who do not have cancer. The non-cancer group is drawn from Medicare fee-for-service patients residing in the SEER areas [15].

Study Sample

The process of identifying the sample was two-step. Initial, preprocessing identified 221,451 patients who died in hospice between January 1, 2015 and December 31, 2019 and who met the Medicare entitlement eligibility requirements of the model.

Died in hospice refers to having an active hospice benefit election (with a Medicare certified hospice) and receiving care at the time of the patient's death, patients who discharged before death were excluded. The patients needed to be continuously enrolled in Medicare Parts A and B the 6 months prior to their hospice admission and during their hospice care. These criteria were applied to ensure the data captures the most complete scope of a patient's healthcare interactions through claims. The patients must also have been continuously enrolled in the Medicare Part D prescription benefit the 6 months prior to their hospice election, as well as throughout their hospice care.

Secondly, the data were processed and limited to 76,777 patients (Table 1) with 204,952 prescriptions (Table 2) that resulted in medication on hand at time of death. This allowed the study to focus on patients and their prescribed medications leading up to death that resulted in medication on hand at death. The sample was split into cancer (n=60,920 patients who've had a history of prostate, stomach, pancreas, lung, and breast cancer) and non-cancer (15,857) cohorts to assess any biases of the dataset, which contains only those who've had cancer diagnoses as opposed to the non-care Medicare fee-for-service which is not limited. The study sample included both the cancer and non-cancer groups and utilized their Medicare Enrollment data, Medicare Part A and B claims, as well as their Part D prescription claims provided by non-hospice providers.

This study cross walked the Part D prescription Nation Drug Codes (NDCs) of medications to the Medi-Span Generic Product Identifier (GPI) - Drug Group created by

Wolters Kluwer's, which is an industry standard for grouping medications into therapeutic use categories for ease in disease grouping [16]. The Wolters Kluwer's Medi-Span database groups medications using a 14-character hierarchical classification based on the medications primary therapeutic use. The 14-character structure is used to identify a medication's drug group, class, sub-class, name, name extension, dosage, and strength [16]. The first six characters of the GPI define the therapeutic class code (two characters each for group, class, and sub-class), the next two pairs the drug name, and the last four define dosage and strength. A therapeutic class is a group of medications with certain similarities: 1) Mechanism of action: Specific changes they cause in your body; 2) Physiologic effect: How your body responds to them.; and 3) Chemical structure: What they're made of. This study used the highest level of the grouping hierarchy, the drug group, which categories the medications into one of 15 agents, products, or drug groups based on the condition or disease being treated/targeted.

The data were preprocessed in PostgreSQL and then imported into Jupyter Notebook for analysis with python.

Measures

Prescriptions

The Drug Enforcement Agency and the Department of Health and Human Services, as well as each state have different rules, regulations and laws related to prescribing medications [17] [18] [19]. Prescriptions are limited based on time (supply

based on hours and days), frequency filled, and dosage generally assigned by “schedule”. Medications are grouped based on drug schedules (schedule I, II, III, IV, & V), which is usually based on the accepted medical use and the likelihood that a drug will cause a person to develop a substance use disorder, or by their chemical makeup and the way they interact with the brain and body. Medications are also classified as long- or short-term medications. Long-term medications, sometimes referred to as maintenance drugs, have been described as those that are taken regularly for chronic conditions [20] [21]. Examples of chronic condition with medications that maybe taken regularly long-term, include high blood pressure, asthma, diabetes, or high cholesterol [21]. These medications usually have a 30, 60, 90-day supply or greater [20]. Short-term medications, sometimes referred to as acute medicines, are those that will only be used for a short time such as antibiotics which are the most common [22]. Short-term medications are usually prescribed a 1-month supply or less [23], with other common durations of 5, 7, 10, and 14-days [24] [25] [26]. Additionally, it is not uncommon guidance that insurance companies recommend that pharmacies should dispense a maximum 30-day supply or fraction thereof for first-time prescriptions of maintenance drugs [27]. The term “fraction thereof” in reference to a prescription means that any fraction of a dose is given over the full amount of time recommended [28].

Outcome Measures

Part D Prescription Medication on Hand at Time of Death

Waste is defined as the overutilization of services and/or the misuse of resources and is often the result of carelessness, inefficiency, or ignorance, but it is not a criminal act [29]. Under Medicare Part D, every time a patient fills a prescription, the plan sponsor must submit a summary record called the prescription drug event to CMS – these records make up the Part D claim files [30]. This study creates a calculated waste fields that makes conservative or "best case" assumptions and determines the least amount of medication on hand at time of death. Some of these assumptions, include (a) the patient begins the medication the day they picked it up; (b) the patient didn't stop the medication in the days before death; (c) another prescription wasn't given in its place; (d) that the dosage/frequency wasn't changed; and (e) that the prescription regimen isn't prescribed take as needed.

Medication on hand at time of death was identified by adding the prescription days' supply to the date the prescription was filled (service date) to obtain a prescription end date, taking into consideration where this prescription end date is greater than the date of death.

$$\text{bene}\_death\_dt < RX\ End\ Date = srvc\_dt\ +\ days\_suply\_num$$

bene_death_dt:	the date of death of the patient.
RX End Date:	the earliest date the prescription would be finished.
srvc_dt:	the date the prescription was filled.
days_supply_num:	the number of days' supply of medication dispensed by the pharmacy and will consist of the amount the pharmacy enters for the prescription.

A second calculated field was created to determine the amount of medication on hand at time of death. This calculation added the prescription days' supply to the date the prescription was filled and then subtracting the date of death to obtain a number of overage days. Then the quantity dispensed is divided by the average number of days to find the daily quantity. The daily quantity and overage days are then multiplied to obtain the quantity wasted.

$$Overage\ Days = srvc\_dt\ +\ days\_suply\_num - bene\_death\_dt$$
$$Daily\ Quantity = qty\_dspnsd\_num/days\_suply\_num$$
$$Quantity\ wasted = Overage\ Days * Daily\ Quantity$$

Overage Days:	the number of days' supply left on a prescription after a patient's death.
bene_death_dt:	the date of death of the patient.
srvc_dt:	the date the prescription was filled.
days_supply_num:	the number of days' supply of medication dispensed by the pharmacy and will consist of the amount the pharmacy enters for the prescription.
Daily Quantity:	the quantity of a prescription taken per day.
qty_dspnsd_num:	the number of units, grams, milliliters, or other dispensed in the current prescription.
Quantity Wasted:	the quantity of prescription on hand at death.

Waste Threshold

This research recognizes that it is unrealistic for a prescription to always end exactly on a patient's date of death. This research also recognizes that shorter prescriptions could leave a patient without their medication or put an undue inconvenience on a patient who's already suffering. Therefore, this research developed a "waste thresh" variable using a calculated threshold that considered a reasonable amount of medication left on hand at time of death. To identify a reasonable waste threshold, information related to the 76,777 patients 204,952 prescriptions was analyzed in three main ways:

Analysis of all prescriptions – days' supply and quantity dispensed.

The histogram in Figure 1 shows the days' supply of all prescriptions. Most prescriptions were 30 days or less. The histogram in Figure 2 plotted the quantity dispensed of all prescriptions with most having a quantity of 20-40.

Analysis of left over medication after death - days' supply and quantity dispensed.

The histogram in Figure 3 displays the day supply of prescription medication wasted (on hand at time of death), which drops precipitately at 30 days. In Figure 4, the dispensed quantity wasted or the amount on hand drops off after 30-40 days.

Analysis of all prescriptions by prescription drug group.

In Table 3, all prescriptions were grouped by their Medi-Span GPI drug group with basic statistics on total prescriptions, average days' supply, average quantity dispensed, and wasted. Overall, the average prescription was 36.65 days long with 62.18 quantity dispensed. Examining the average days' supply from Figure 4 one can infer which categories of prescriptions are short-term (acute condition), long-term (maintenance) medications, or medications that have laws around the frequency. For example, antibiotics have an average day supply of 16.19 days and are typically used short-term for an acute condition, whereas pain management medications (24.01 average day supply) tend to have state laws and regulations their prescribing. On the other hand, the category of Hyperlipidemic medications (which averaged 48.47 days' supply) are generally used long-term for the maintenance of a condition.

Given this analysis the outcome measure "waste thresh" was set to 1-Yes where the days' supply was 30 days or greater and the dispensed quantity on hand at time of death was greater than 30. This definition is consistent with identifying long-term or maintenance medications (for conditions unrelated to the patient's terminal illness), which have 30, 60, 90-day supplies or greater. This definition also aligns with that of hospice and the 60- and 90-day benefit periods and recertifications [2]. Hospice care is given in benefit periods and at the start of each benefit period, the hospice doctor or a related provider must recertify a patient's life expectancy of six months or less. A patient

can get hospice care for two 90-day benefit periods followed by an unlimited number of 60-day benefit periods [3]. Given the frequency of a patient's evaluation and recertification, it is reasonable to assume the provider would consider aligning prescription durations with life expectancy to reduce waste.

Lastly, the unit of analysis in this research is the prescription events. Thus, there is the possibility of more than one event claim per patient. There is also the possibility a patient has one prescription that results in waste and another that does not.

Patient Characteristics

The models included patient sociodemographic characteristics such as age, reported race, sex, the original reason for Medicare enrollment (Aged or Disabled/End Stage Renal Disease (ESRD)), Medicaid and Medicare dual status, Part D low-income subsidy (LIS), and geographic residence. Patient clinical characteristics included prior hospice election, admitting hospice care setting, prior inpatient hospital admission, prior history of cancer, count of comorbidities (chronic obstructive pulmonary disease, heart failure, ischemic heart disease, diabetes mellitus, nervous system/neurological disease, renal failure, liver failure/disease, dementia, HIV, sepsis, hypertensive disease, and mood disorder), and number of predictors of death (health conditions) at time of hospice admission [31]. Predictors of death are defined by CMS in their coverage determination document "Hospice - Determining Terminal Status" [31]. They are defined with guidelines as a decline in clinical status predictive of a life expectancy of six months or

less and include: recurrent or intractable infections, progressive inanition - weight loss, dehydration or hypovolemia, dysphagia, cough, nausea/vomiting, dyspnea, diarrhea, pain, hypotension, ascites venous obstruction, edema pleural, cognitive impairment, change in consciousness, pressure ulcers stage 3-4, sepsis/septicemia, aspiration pneumonia, and upper urinary tract infection (pyelonephritis) [31]. Binary flags (1-Yes/0-No) were created for each condition and then summed to calculate the number of predictors of death. The comorbidities and health conditions were identified by examining the ICD-9 and ICD-10 diagnosis codes on the patient's claims for services that occurred the 6-months before and during the study period. All ICD codes were cross walked to Clinical Classifications Software (CCS) ICD-9-CM diagnoses codes, which groups the diagnosis codes into over 231 clinical categories [32].

Machine-learning Approaches and Prediction Performance Evaluation

Nearest Neighbor

Also known as K Nearest Neighbor (KNN), the basis of this method is feature similarity, with the idea that similar things exist in close proximity or distance [36]. The algorithm works by the researcher selecting the optimal number of neighbors "k" a data example must match to be classified [37]. The method begins with a training phase that consists only of storing the feature vectors and class labels of the training samples [38]. With a given "k" value boundaries for each class are determined. This optimal "k" is selected through training and validation analysis of the validation error curve and the error rate [39]. An optimal "k" should be big enough that noises won't affect the

prediction, but not too big that the lower variances have increased bias [38]. On the other hand, too small of a “k” could result in one factor dominating another [38]. Then the algorithm is applied to the test cases and the distance between the test cases and the training sample is calculated. These distances determine the nearest neighbor based on the “k” minimum distance and classify them based on the most frequent label [38] [39] [40]. KNN has a limited number of parameters for tuning; those being the “k” value and which distance function to use [38]. In comparison to more traditional statistical techniques such as linear regression, KNN has been found to be fairly accurate, more flexible in terms of data parameters, and better suited when the data has high signal to noise ratio [41] [42].

As KNN has become more popular, one of its biggest uses has been the development of Recommender Systems [37]. Due to its versatility KNN lends itself to many subject matters in research. With regards to the field of health services research, KNN has been used to develop mortality predictions [43], identify Medicare provider fraud [44], 30-day hospital readmission [45], and even create fall detection systems [46]. Specifically in the area of analyzing prescriptions and/or hospice patients, the method has been used to predict prescription opioid misuse in patients [47], predict diseases based on prescription [48], detection of medication list omissions [49].

LASSO Regression

Least Absolute Shrinkage and Selection Operator, also known as LASSO regression, using shrinkage the statistical model aims to identify the variables (or features) and corresponding regression coefficients that lead to a model that minimizes the prediction error [50]. LASSO regression performs L1 regularization, which adds a penalty equal to the absolute value of the magnitude (or weight) of coefficients. LASSO will start decreasing the coefficients of variables that are not so important, and potentially decrease some coefficients down to 0 effectively eliminating them from the model. This type of regularization is known as shrinkage and can result in sparse models with few coefficients. This regression coefficient 'shrinking' is done by forcing the sum of the absolute value of the regression coefficients to be less than a fixed value (λ) [51]. The choice of λ is often made by using an automated k-fold cross-validation approach. For this approach, the dataset is randomly partitioned into k sub-samples of equal size. While the k-1 sub-samples are used for developing a prediction model, the remaining sub-sample is used for validating this model. This procedure is carried out k times, with each one of the k sub-samples in turn being used for validation and the other ones for model development. An overall result is produced by combining the k separate validation results for a range of λ values and choosing the preferred λ, which is then used to determine the final model.

One of the reasons LASSO has become prevalent is it is well-suited for models showing high levels of multicollinearity or when you want to automate certain parts of

model selection, like variable selection/parameter elimination. Additionally, LASSO is a popular technique that can reduce overfitting without restricting a subset of the dataset to sole use for internal validation [50]. The method has been used widely in healthcare for a variety of studies, but some of those studies more relevant to this work include: predicting hospitalized cancer patients at risk for 30-day mortality based on admission criteria [52], patient prescription medication adherence [53], predicting opioid overdose among Medicare patients [54], predicting prescription filling among Medicare patients [55].

Random Forest

Random Forest (RF) is a supervised ensemble learning method that builds many decision trees and merges them together to predict the outcome of interest [56]. A decision tree is a series of yes/no questions asked about the data that eventually leads to a predicted class [57]. A decision tree is built by determining the splitting questions (called nodes), which are selected based on being the best feature of a random subset of features as opposed to overall the most important [58]. In essence, the decision tree tries to form nodes containing a high proportion of samples from a single class by finding values in the features that cleanly divide the data into classes [57]. RF tries to build multiple models with different samples and different initial variables repeating the process a specified number of times and then making a final prediction about each observation [59]. The final prediction is the function or mean of each observation's prediction.

One of the reasons RF has become a popular method is the lack of extensive tuning that is needed when there is a reasonably large number of trees constructed [56]. Additionally, other advantages of RF over traditional statistical techniques include running efficiently on large databases, ability to handle large quantities of input variables, providing an attribute importance output, and efficient estimates of the out of sample error [60] [61]. Given all the advantage of RF over traditional statistical method it's not surprising that research and studies have found it to be more accurate [62] [63] [64] [65] [66]. Due to the models being highly accurate it's no surprise that RF is utilized in health services research. Some of the research areas that have used this methodology include predicting disease risks [67], measuring pretreatment quality of care [68], chemotherapy-related predictive symptoms [69], and assessment of fetal maturation [70]. RF has been used in the research areas of hospice patients and/or prescriptions though studies that have examined risk feature assessment of readmission [71], improving palliative care [72], and predicting opioid overdose [73]. Given the flexibility and robustness of the RF method this research study would be a candidate as it will allow for a greater exploration of influencing attributes.

Gaussian Naïve Bayes

Naïve Bayes is a probabilistic algorithm that is based on Bayes theorem, with the additional assumption that the features (predictors) that go into the model are independent of one another (naïve) [74]. The basic idea of Bayes Theorem is the selected features experiences are used to predict the odds of the outcome [75]. This theory provides a way

of calculating the posterior probability, which is a revised probability of an event occurring after taking into consideration all existing evidence and background information [74] [76]. In summary the steps of this method include: 1) computing the prior probabilities for each of the outcome classes (usually from training data); 2) computing the probability of features, which Bayes refers to as the evidence; 3) compute the posterior probability, which is the product of all conditional probabilities of the features or the overall probability of the likelihood of evidence; and 4) the class with the highest posterior probability is the outcome of prediction [77] [78] [79].

The data used in this analysis consists of a categorical outcome variable and a mix of categorical and continuous covariates. Given the structure of the data the Gaussian Naïve Bayes (GNB) classifier is most appropriate. This method assumes that the continuous variables in the data follow a Gaussian (normal) distribution, and the categorical variables follow a multinomial distribution. However, it is important to note that the GNB classifier assumes independence between features, which may not hold true for attributes day supply and quantity supply, as well as others. However, this method is more appropriate than Bernoulli Naive Bayes, which assumes the data is binary, and Multinomial Naive Bayes, which assumes the data are multinomial.

The GNB classifier is easy to build and use because it has no parameter requirements. Thus, it is particularly useful with large data sets and data sets with many variables. While GNB is capable of outperforming traditional statistical methods, as well

as other advanced classification methods, it generally doesn't perform as well when collinearity exists in the data [41]. Due to their accuracy and simplicity GNB models have been used to make real time and multi class prediction systems like email spam filters and identifying positive and negative sentiments on social media. In the arena of health services research GNB has been used to examine stroke rates [80], predict hospital length of stay [81], predicting provider specialties to detect claim anomalies [82], and prediction of breast cancer anomalies [83]. GNB has been used in studies that have examined end-of-life pain outcomes [84], short-term mortality prediction [85], and predicting adverse drug events [86]. Using the GNB model for this research is appropriate as the algorithm can handle the large sample size and multidimensionality in the present study.

Data Analysis Approach

Descriptive statistics (means, standard deviations, proportions, etc.) were used to assess patient characteristics and describe Part D medications on hand at time of death. Part D prescriptions were plotted using histograms to determine the outcome waste threshold, which is defined as those prescriptions where the days' supply was 30 days or greater and the dispensed quantity on hand at time of death was greater than 30. Using the waste threshold parameters there were 49,286 or 24.1% of 204,952 prescriptions where the waste threshold equaled 1- "Yes" due to the medication on hand at death exceeding the threshold. In addition, this study examined the top ten medication types on hand at time of death using the GPI, which classifies medications based on their

therapeutic class. This is consistent with the source for this data and variables defined in the CMS research data support center ResDAC [87].

This study used four classifiers, GNB, KNN, RF, and LASSO regression to examine the influence of patient characteristics on prescriptions at time of death and to predict Part D prescriptions medications on hand at time of death based on the waste threshold. These classifiers were selected because of their ability to handle a variety of data and data types, the amount of data and variables, and their use in similar research [33] [34] [35]. Data was split 80% for training and 20% for testing, based on the Pareto Principle, which is a phenomenon that states that roughly 80% of outcomes come from 20% of causes [88]. Results from this analysis were captured in Table 6 with additional details for measuring performance captured in Table 7.

To assess discrimination performance (i.e., the extent to which patients predicted as having medication on hand at time of death as opposed to not), the area under the curve of the classifiers was compared (0.7 to 0.8: good; >0.8: very good). Additionally, this analysis also reviewed the following metrics of evaluation: (1) negative likelihood ratio, (2) negative predictive value, (3) positive likelihood ratio, (4) positive predictive value, (5) sensitivity, and (6) specificity (selectivity), to thoroughly assess the prediction ability. Figures 5-8 plot each model's sensitivity and specificity as well as precision and recall.

Area Under the Curve (AUC): AUC is a summary measure of the receiver operating characteristic (ROC) curve, which plots the true positive rate (TPR) against the false positive rate (FPR) at various decision thresholds. AUC represents the probability that a randomly selected positive instance will be ranked higher than a randomly selected negative instance by the classifier.

Accuracy: is a performance metric that measures the overall correctness of the classifier's predictions, expressed as the fraction of correct predictions among all predictions made by the classifier. Mathematically, accuracy can be defined as where true positives (TP) is the number of positive instances correctly classified as positive, true negatives (TN) is the number of negative instances correctly classified as negative, false positives (FP) is the number of negative instances incorrectly classified as positive, and false negatives (FN) is the number of positive instances incorrectly classified as negative.

Precision: Precision is the fraction of TP predictions among all positive predictions made by the classifier. Precision measures how accurate the positive predictions are, i.e., how many of the predicted positive instances are actually true positives.

Recall: Recall is the fraction of TP predictions among all positive instances in the dataset. Recall measures how complete the positive predictions are, i.e., how many of the actual positive instances are correctly identified by the classifier.

Sensitivity: Sensitivity is another name for recall, which is the fraction of TP predictions among all positive instances in the dataset.

Selectivity/Specificity: Selectivity or specificity is the fraction of TN predictions among all negative instances in the dataset. Selectivity measures how accurate the negative predictions are, i.e., how many of the predicted negative instances are actually true negatives.

F1-score: f1-score is the harmonic mean of precision and recall, which balances the importance of precision and recall in the overall performance of the classifier. F1-score ranges from 0 (worst) to 1 (best) and is high when both precision and recall are high.

Negative likelihood ratio (NLR): The NLR is the ratio of false negative predictions to true negative predictions, normalized by the prevalence of the positive class in the dataset. NLR measures how well the classifier can rule out the positive class, i.e., how many of the negative predictions are truly negative relative to the number of false negatives.

Negative predictive value (NPV): The NPV is the fraction of true negative predictions among all negative predictions made by the classifier. NPV measures how many of the predicted negative instances are actually true negatives.

Positive likelihood ratio (PLR)*:* The PLR is the ratio of true positive predictions to false positive predictions, normalized by the prevalence of the positive class in the dataset. PLR measures how well the classifier can predict the positive class, i.e., how many of the positive predictions are truly positive relative to the number of false positives.

Positive predictive value (PPV): The PPV is the fraction of true positive predictions among all positive predictions made by the classifier. PPV measures how many of the predicted positive instances are actually true positives.

As part of the analysis, a feature importance was run on LASSO and RF with the result presented in Figure 9. Feature importance was not run on GNB classifier as it uses a probabilistic approach to estimate the class probabilities and does not construct models that can be used to identify important features. Instead, they learn the parameters of the underlying probability distribution for each feature in the input data. Additionally, feature importance was not run on KNN as it is a non-parametric model that does not make any assumptions about the underlying probability distribution of the input features. Instead, it stores all the training instances in memory and classifies new instances based on the

majority class of their K nearest neighbors in the feature space. KNN does not explicitly model the feature importance or the relationship between the features and the target variable. Also, for KNN this study will test for the optimal K parameter as previously described [37]. Like other studies a greedy search algorithm will be used to identify the optimal parameter [43]. This will be done by first training the model using the training sample and setting all the model parameters to their default values, and then changing one parameter at a time and choosing the value that maximized AUC of the tuning sample [43]. AUC is the primary performance measure for all classifiers.

Following the feature selection and the identification of the most predictive covariates, additional model performance testing was done to assess the model's AUC with these features removed. Results from this analysis are captured in Figure 10. Lastly, for the top performing model, RF, additional testing of sociodemographic characteristics was conducted to determine if model bias existed for nine different populations with results presented in Figure 11.

RESULTS

Summary Statistics

Summary statistics for the sample of 76,777 patients are presented in Table 1. Compared to the non-cancer subset, the cancer cohort was younger (with 69.6% under the age of 85 vs non-cancer at 38.7%), has more Medicare/Medicaid non-dual eligible (65% vs 56%), has more Part D LIS patients (62% vs 54%), and has a much shorter

average length of stay in hospice (73.8 vs 111.4 days). Whereas the non-cancer cohort has more females (68.4% vs 55%) and tend to receive care in a care facility (52.8%) as opposed to in a private residence (44.0%) relative to the cancer cohort (private residence at 68.0%). Overall the cohorts that make up the sample are similar in that they are both predominately white (83.0%), has fewer patients located in the South and Midwest (as a result of the participating SEER regions), has a greater proportion of patients who've aged into Medicare (81%), have the same top four most common terminal hospice admitting diagnoses (cancer, dementia, chronic obstructive pulmonary disease, and congestive heart failure), and have not previously been admitted to hospice (94%). The distribution of the number and type of comorbidities and predictors of end-of-life health status are also similar between these cohorts.

The sample's 76,777 patients had a total of 204,952 Part D prescriptions dispensed following their admission to hospice. In Table 2, on average a patient's prescription was 36.7 days with an average of 62.2 quantity dispensed. For patients who had medication on hand at time of death the days' supply wasted averaged 20 days and a quantity of 34.2.

Identifying a Threshold for Medication on Hand at Time of Death

The histogram in Figure 1 (days' supply) shows that most prescriptions are 30 days or less followed by those at 90 days. The histogram in Figure 2 (quantity) presents most prescriptions having a quantity of 30, with additional rises between 80-100, and

180-200. Figures 3 and 4 and Table 3 display results related to the waste threshold and present the various waste patterns in this sample. In Figure 3, days' supply wasted drops precipitately at 30 days and similarly with quantity wasted between 30-40 in Figure 4. Additionally, using the average day supply from Figure 4 one can assume which categories of prescriptions are short-term (acute condition), long-term (maintenance) medications, or medications that have laws around the frequency. For example, antibiotics have an average days' supply of 16.19 days and are typically used short-term for an acute condition, whereas pain management medications (24.01 average days' supply) tend to have state laws and regulations their prescribing. On the other hand, the category of Hyperlipidemic medications (which averaged 48.47-days' supply) are generally used long-term for the maintenance of a condition. Given these findings and as previously stated, the outcome measure threshold was set where the days' supply was 30 days or greater and the amount on hand at time of death was greater than 30.

Table 4 presents a summary of those prescriptions that met the waste threshold for medication on hand at time of death. Of the sample's 76,777 patients, 30,895 (40.2%) had at least one prescription that met the waste threshold. These 30,895 patients attributed 49,286 prescriptions or 24.1% of the 204,952-prescription sample used in the classifier analysis. Of note is that the non-cancer cohort tended to have a higher quantity dispensed amount and leftover (waste) compared to the cancer cohort, whereas the reverse was seen for days' supply. Table 5 presents the top categories of medications

meeting the waste threshold definition. Over 80% of all prescriptions on hand at time of death are in categories of long-term maintenance medications in each group.

Classifiers

Table 6 presents the results for all four of the classifiers. Overall, the RF classifier performed the best with an AUC of 98.7% and an accuracy of 94.5%. However, it should be noted that the other three models had excellent to very good AUC's as well, KNN=96.3%, LASSO=88.6%, and GNB=84%. The data and analyses presented below were for a split of 80% for training and 20% for testing. Not presented are results from the scaling law (Appendix A), which found a split of 88% for training and 12% for testing was more appropriate for this data. This change, however, in the percentage distribution of the sample split did not result in any significant change for RF and the LASSO. For the GNB the results were worse, and the KNN was only slightly improved. The overall results are further discussed below within each classifier subsection.

K-Nearest Neighbor

Table 7A presents the results for the KNN classifier for which the k factor (number of nearest neighbors) was set to 10. KNN was the second-best performing model with an AUC of 96.3% and an accuracy of 90.7%. After tuning of the k parameter, it was found that k=10 produced the overall best score for both the training and testing data of the model as seen in Figure 5A.

In Table 7A for the negative classifier (not meeting the waste threshold), the KNN model correctly classified that a prescription will not meet the waste threshold 95% of the time for all instances in the dataset where a prescription indeed does not meet the waste threshold, as measured by recall, and 93% of the time for all negative predictions made by the KNN model, as measured by precision. For the positive classifier (meeting the waste threshold), the KNN model correctly classified that a prescription will meet the waste threshold 76% of the time for all instances in the dataset where a prescription indeed meets the waste threshold, as measured by recall, and 84% of the time for all positive predictions made by the KNN model, as measured by precision. The overall KNN model's precision and recall are plotted in Figure 5C.

From Table 6, the KNN model correctly classifies that 83.8% of prescriptions that are predicted to meet the waste threshold do meet the waste threshold. In terms of sensitivity, the KNN model correctly identifies 75.9% of prescriptions that met the waste threshold. Regarding specificity, the KNN model correctly identifies 92.6% of prescriptions that do not meet the waste threshold. Figure 5B plots the sensitivity and specificity of the KNN model. The PLR of 5.18 means that the odds of a prescription meeting the waste threshold are 5.18 times higher when the model predicts it to meet the threshold compared to when the model predicts it not to meet the threshold. An NLR of 0.08 means that the odds of a prescription meeting the waste threshold are 0.08 times lower when the KNN model predicts it to not meet the threshold compared to when the model predicts it to meet the threshold.

LASSO Regression

Table 7B presents the results for the LASSO classifier, where the max iterations were 1,000. Turning of the max iteration found that decreasing as low as 100 resulted in the model performing worse and increasing as high as 10,000, the model saw minimal improvement. LASSO was the third-best performing model with an AUC of 93.9% and an accuracy of 88.6%. The negative classifier (not meeting the waste threshold), the LASSO model had a recall of 98% and a precision of 88%. For the positive classifier (meeting the waste threshold), the LASSO model had a recall of 59% and a precision of 89%. The overall precision and recall for LASSO are plotted in Figure 6B.

As shown in Table 6, the sensitivity of LASSO was 59.3%, meaning that out of all the actual positive instances (met waste threshold of medication on hand at time of death) in the dataset, the model correctly identified 59.3% of them as positive. In other words, the model has a moderate ability to correctly identify positive instances. Figure 6A plots the overall sensitivity and specificity of the LASSO regression model. The PLR was 8.27 and the NLR was 0.13 (Table 6).

Gaussian Naïve Bayes

Table 7C presents the results for the GNB classifier, which is the lowest performing model with an AUC of 80.3% and an accuracy of 84%. The negative classifier (not meeting the waste threshold), of the GNB model had a recall of 92% and a precision of 87%. For the positive classifier (meeting the waste threshold), the LASSO

model had a recall of 58% and a precision of 70%. The overall precision and recall for the GNB are shown in Figure 7B.

As shown in Table 6, the sensitivity of the GNB model being 58% means that out of all the actual positive instances (met waste threshold of medication on hand at time of death) in the dataset, the model correctly identified 58% of them as positive. In other words, the model has only a moderate ability to correctly identify positive instances. Figure 7A plots the overall sensitivity and specificity of the GNB model. The PLR was 2.36 and the NLR was 0.14 (Table 6).

Random Forest

Table 7D presents the results for the RF classifier where the n estimator=100. Tuning the n estimator to 10 or 1,000 did not improve the model results. All other parameters for RF were left to the default status of either None, 0, or false. RF was the best performing model with an AUC of 98.7% and an accuracy of 94.5%. The negative classifier (not meeting the waste threshold) of the RF model had a recall of 96% and a precision of 96%. For the positive classifier (meeting the waste threshold), the LASSO model had a recall of 89% and a precision of 88%. The overall precision and recall for the RF regression are shown in Figure 8B.

The sensitivity of the RF model being 88.9% means that out of all the actual positive instances (met waste threshold of medication on hand at time of death) in the

dataset, the model correctly identified 88.9% of them as positive (Table 6). In other words, the model has a high ability to correctly identify positive instances. Figure 8A plots the overall sensitivity and specificity of the RF model. From Table 6, the PLR is 7.51 and the NLR is 0.36.

Feature Importance

The two models with the capability to conduct feature importance were LASSO regression and RF. The results for the feature importance are presented in Figure 9. In a LASSO regression, feature selection was integrated into the model training process by adding a L1 penalty term to the objective function. This resulted in a sparse model where some coefficients (features) were exactly zero, effectively removing those features from the model. Therefore, the magnitude of the coefficients can be used to identify the most important features. The feature importance for the LASSO regression is presented in Figure 9A with the most important features being GPI classified Dental and Vasodilator prescriptions followed by the diabetes comorbidity. In RF, feature importance can be measured based on the decrease in impurity or Gini index that each feature provides when used for splitting. The idea behind this is that the more a feature is used to split the dataset, the more important it is for the model. This importance score is calculated for each feature across all the trees in the forest and then averaged to get an overall importance score. The feature importance for the RF is presented in Figure 9B with the most important features being prescription quantity supply dispensed followed by day supply.

Notably, both models identified days' supply as an important feature with the RF identifying it as the second most important with quantity dispensed as the most important. Given that the RF was the best performing model, the sensitivity of the models was tested by first removing days' supply and quantity supply dispensed and then removing only quantity supply dispensed. Figure 10 presents the findings from this analysis. Figure 10A presents the original models which include both days' supply and quantity supply dispensed. We can see from Figure 10C that when both covariates were removed, all the models underperformed from the original in Figure 10A by 20-30%. RF which had an AUC of 98.8% in Figure 10A, in Figure 10C RF has an AUC of 73.5%. Figure 10B shows the results where only quantity supply dispensed was removed. It resulted in LASSO regression performing only 3% less in terms of AUC compared to that shown in Figure 10A, whereas RF decreased from 98.8% to 86.7%.

Sociodemographic Model Bias

RF was overall the best performing model across the metrics of evaluation (as defined in the Statistical Analysis section). Additionally, when model sensitivity testing was conducted by removing key features, i.e., days' supply and quantity supply dispensed, the RF model still performed the best achieving an AUC of 73.5%. With regards to the potential of model biases related to sociodemographic variables and the potential for the model to be biased in certain populations, the AUC of the covariates in the RF model were plotted to compare the classes within each covariate. Results from the

comparison are presented in Figure 11 where key sociodemographic variables of the model were examined such as cancer status, end-stage renal disease status, LIS status, age, Medicare enrollment status, patient's location of their hospice care, race, dual status, and gender.

DISCUSSION

Summary

The purpose of this study was to (1) examine the type and quantity of Medicare Part D medications on hand at time of death in hospice patients, and (2) explore the features (e.g., patient characteristics) that are predictive of prescription waste on hand at time of death in order to predict Part D prescriptions medications on hand at time of death based on an estimated prescription threshold using Medicare claims data and a machine learning approach. Findings for the first aim show that in this sample there is an even distribution across ages within the cancer population of medication on hand at time of death, unlike the non-cancer population where those 85 years and older made up 61% of the sample. Other sociodemographic characteristics were similar in representation between the two groups. Both groups top medication on hand at time of death were cardiovascular therapies which made up 30% medications. Overall, the top ten medications on hand at death and their distribution was similar between the populations. The mean prescription length was 36.65 days' supply with a mean of 62.18 quantity dispensed. Prescriptions resulting in medication on hand at time of death on average were

dispensed 72.69 days after a patient's admission to hospice and resulted in a mean of 20.02 days' supply and 34.18 quantity wasted.

The findings related to the second aim show that patient's sociodemographic characteristics, their health conditions, and prescription characteristics can successfully and accurately be used to predict medication on hand at time of death using a reasonable waste threshold such as this one identified in this sample. All four classifier models – KNN, GNB, LASSO, and RF – were able to accurately predict in this sample medication on hand at time of death using a threshold where the days' supply was 30 days or greater and the quantity (amount) on hand at time of death was greater than 30. This threshold was determined based on policy reviews of acute and long-term medications, a high-level review of participating SEER state prescribing regulations and federal government regulations [17] [18] [19], and an analysis of the data classified into the GPI therapeutic drug categories. Findings from this analysis show that long-term medications typically had prescription lengths of over 30 days and an analysis of the wasted medication (day supply and quantity dispensed) further supported the threshold selected. These findings are important for providers caring for hospice patients in that they signify the need of optimal prescription lengths that are in alignment with a patient's estimated time remaining. These findings show that prescription waste can be predicted in hospice patients accurately. Curbing the medication waste may require provider education about prescribing patterns. Policy reform and limiting maintenance medication prescription lengths to days remaining in the patient's current hospice benefit period can also play a

role in reducing waste. In addition, future research could explore a clinician support tool that can aid providers in prescribing the optimal prescription length based on a patient's sociodemographic, terminal illness, estimated life expectancy, and prescription characteristics.

While all four classifiers performed well, RF performed overall the best, when examining all the study's metrics of evaluation: (1) NLR, (2) NPV, (3) (PLR, (4) PPV, (5) sensitivity, and (6) specificity (selectivity). RF didn't have the best score in each of the metrics, but overall, it consistently performed the best. For example, LASSO regression had the lowest number of FP and the highest number of TN. However, the sensitivity of the LASSO regression model was 59.3% whereas RF was 88.9%. RF did have the lowest number of FN and the highest number of TP, the highest specificity, AUC, and accuracy. Additionally, as a few of the more predictive covariates were removed from the model RF still performed either the best or second best among the four models.

A feature analysis was conducted as part of the LASSO regression and the RF classifiers. The most predictive covariate in the RF model was the quantity dispensed. Quantity dispensed was not listed in the top 20 most predictive in the LASSO regression, which is why when that covariate was removed from the data, the AUC for the LASSO regression decreased only from 93.9% to 90.5%, whereas the RF was more impacted, decreasing from 98.8% to 86.7%. However, both models had days' supply as being in the

top 20 model predictors – ranked second for RF (importance score of 0.195) and thirteen for the LASSO regression (coefficient of 0.10). Interestingly, when both days' supply and quantity dispensed were removed, the AUC decreased less for RF (98.8% to 73.5%) than LASSO regression (93.9% to 68%).

Both classifiers, RF and LASSO regression uncovered several patient characteristics that were predictive of prescriptions on hand at time of death including, a patient's Medicare/Medicaid dual status, a patient's total time in hospice, the time between when the patient was admitted into hospice and when the prescription was filled, where the patient was receiving their hospice care, and if the wasted prescription was a cardiovascular GPI medication The LASSO regression, however, contained more features related to the different GPI prescription therapeutic categories and indicators of death, whereas the RF identified patient demographics and comorbidities as predictors of prescriptions on hand at time of death. Future research should be conducted to identify and understand the predictive features of medication type on hand at time of death.

As RF was the top performing model, an additional testing of sociodemographic characteristics was conducted to determine if model bias existed for certain populations. The key sociodemographic variables of the model that were examined included: cancer status, ESRD status, LIS status, age, Medicare enrollment status, patient's location of their hospice care, race, dual status, and gender. Almost all of the sociodemographic

variables had an accuracy over 80% indicating there may be little to no bias in this model for these variables.

Limited research exists exploring the type and quantity of medication on hand at time of death in hospice patients and no research exists that predicts which prescriptions will result in medication on hand at time of death. The two most relevant studies exploring this topic did so through retrospective case reviews of individual hospices and the medications related to the terminal diagnosis covered under the Medicare Part A hospice benefit with the majority of leftover medications being analgesics followed by anti-anxiety agents. [9] [10]. The studies found that patients had an average of 2.95 to 9.7 medications on hand at time of death, whereas this study found patients had on average 2.5 Part D medications on hand at time of death. These studies, however, differ from the present one in that they examined waste within hospice. The current study focused on the analysis of prescriptions unrelated to a patient's terminal illness and not provided by hospice providers. Similar to this study Zueger, et al. (2018, 2019) in two studies explored Medicare Part D prescriptions in hospice patients. The study from 2018 examined the 25 most dispensed medications between 2008 and 2013 in linked SEER Medicare data of hospice patients after their admission and found the most commonly dispensed were: Cardiovascular therapies (27.8%), Pain Management therapies (18.3%), and Gastrointestinal therapies (11.3%). These findings were similar to this study, which found GPI Cardiovascular therapies made up 30.6% of prescriptions and Gastrointestinal therapies 9.4% [14]. The biggest difference being GPI Pain Management therapies, which

comprised less than 3.7% of prescriptions in this population. This is due to Zueger, et al. (2018) using data between 2008 and 2013, prior to CMS implementing guardrails to prevent providers from prescribing and billing Part D medications related to a patient's terminal illness and covered under the Part A hospice benefit [89]. Zueger, et al. (2019) examined the predictive factors for continuing medication with limited benefit after hospice admission in linked SEER Medicare patients. This study was similar to Zueger, et al. (2019) finding that on average a patient had at least one Part D medication prescribed after their hospice admission and in terms of the population characteristics the distributions were relatively similar. Zueger, et al. (2019) found that hospice admission setting and duration in hospice were most predictive of the continuation of medication following admission. This study looked at factors predictive of medication on hand at time of death and found those two variables (setting and hospice duration) to be in the top 20 most important features but that days supply and quantity dispensed were the most predictive. A report from Visante (2013), more recently addressed the topic of Part D waste in hospice using secondary data. Specifically, the study examined prescription waste based on data from retail and mail order pharmacies on unused patient returned prescriptions. The study reviewed Medicare patient death data and cross compared it to prescription automatic refill data to estimate waste. They study found that over 50% of a prescription's medication was found to be on hand at time of death. This study had similar findings when looking at the average quantity dispensed and the average quantity wasted, finding 54.9% (Table 3: 34.18/62.18 days) of medication on hand at time of death.

The study of Part D prescription waste patterns in hospice patients is essential in allocating available resources, i.e., the prescriptions themselves and the Medicare program financials. Further understanding of Part D prescription potential waste patterns in hospice patients can bring about awareness for better prescribing patterns and improved care coordination between teams.

The use of techniques such as LASSO regression and RF in identifying patient characteristics that may influence Part D prescription medication on hand at death in hospice patients is novel. The study of prescription waste patterns in hospice patients has been previously conducted using individual hospice patient electronic health records (EHR) records [9] [10]. However, these prior studies have only been able to assess the amount of hospice Medicare Part A prescription waste, which has been estimated at about $2 million per year [90]. This study not only addresses the gap in research by using claims data, but it takes the research a step forward by building a model that is able to predict medication on hand at time of death, given a threshold, in this sample.

Limitations

This study has several limitations. Potential influential factors of the hospice and its providers such as the profit status, staffing levels, and age of the program were not considered in this study as they are unknown due to data privacy limitations. Additional measures that were not considered in this study include information surrounding the

physician prescribing the Part D medication, the Part D insurance plan, and the pharmacy where the prescription was filled. As noted in the assumptions, it is likely this research underestimates the amount of medication on hand at death as dispensing claims are imperfect for medication use and adherence. Additionally, the results of this study are limited to this sample of patients included in the linked SEER Medicare data and those from the 5% Medicare fee-for-service patients residing in the SEER areas. Because the scope of this study was to examine medication on hand at time of death based on an estimated threshold, the sample was limited to those patients (76,777) with prescriptions (204,952), excluding patients without prescriptions and those whose medications were prescribed by hospice providers. This study could be expanded in future research to include all Part D prescriptions (prescribed by hospice or non-hospice providers) dispensed after a patient's hospice admission in terms of predicting medication on hand at time of death.

Implications and Recommendations

This research has implications most importantly for CMS, but also for the patient, the provider, and Part D sponsors. State and government prescribing guidelines are needed to support changes in prescribing patterns to reduce unnecessary medication on hand at time of death in hospice patients due to over lengthy prescriptions. The findings of this study bring awareness to the prescribing behaviors of providers for patients who are in hospice. Policies and guidance for reducing waste are critical to the Medicare program while considering the challenges patients are facing at the end of their life.

APPENDICES A. SCALING LAW

Research evidence from Guyon in 1997 found that the Pareto Principle may not be the best method. Instead Guyon found the best training/testing split for a specific problem, preventing overtraining, was through scaling and setting the testing data to be "inversely proportional to the square root of the number of free adjustable parameters" [91]. In layman terms, the split is determined by how many unique features are in the dataset (not including the target) and not the number of observations.

Additional research into scaling law and splitting data found using the PowerTransform library in Python performed best. The scaling law is a mathematical relationship between two or more variables that describes how changes in one variable affect changes in the other. Power transforms are a type of data preprocessing technique used in statistics to transform data in a way that can improve the performance of certain statistical analyses, particularly those that assume normality or homoscedasticity.

In the context of scaling law, a power transform can be used to create a monotonic transformation of data using power functions. This means that the transformed data will be ordered in a consistent way, and that the transformation will be increasing or decreasing in a smooth, continuous manner. This can help to reduce the impact of outliers and improve the fit of statistical models to the data. Applying power transforms as part of preprocessing analyses can be especially useful when dealing with data that exhibits non-

normal distributions, such as data that is skewed or has heavy tails. By transforming the data using power functions, the distribution can be made more symmetric and closer to a normal distribution, which can improve the accuracy of statistical analyses.

The two most common methods of scaling are Box-Cox and Yeo-Johnson, with the later allowing for zero and negative values of y. This study tested using the Yeo-Johnson transformation method, which has two different ways to transform a continuous (numeric) variable so that the resulting variable is approximately normally distributed. Using the sklearn PowerTransform scaler set to the 'yeo-johnson' method, the data were transformed and then run through the train and test split function. Applying the scaling law (88.6%/11.4%) resulted in an 8.6% difference compared to the 80%/20% Pareto Principle. The methodology of scaling law is often used in feature engineering to reduce skew in the raw variables.

Overall, power transforms are an important tool in the statistical analysis of scaling laws, as they can help to address issues related to data distribution and improve the accuracy of statistical models.

APPENDICES B. TABLES AND FIGURES

Table 1. Characteristics of Patients (n=76,777)

Characteristics	Total		SEER Non-Cancer		SEER Cancer	
	n= 76,777	%	n= 15,857	%	n= 60,920	%
Age mean (std)	80.1 (10.1)		85.4 (9.7)		75.8 (9.7)	
≤69	11,707	15.2%	1,136	7.2%	10,571	17.4%
70-74	10,629	13.8%	990	6.2%	9,639	15.8%
75-79	12,429	16.2%	1,494	9.4%	10,935	17.9%
80-84	13,760	17.9%	2,520	15.9%	11,240	18.5%
85-89	13,751	17.9%	3,570	22.5%	10,181	16.7%
≥90	14,501	18.9%	6,147	38.8%	8,354	13.7%
Sex						
Male	32,436	42.2%	5,006	31.6%	27,430	45.0%
Female	44,341	57.8%	10,851	68.4%	33,490	55.0%
Race						
White	64,061	83.4%	13,566	85.6%	50,495	82.9%
Black	6,965	9.1%	1,190	7.5%	5,775	9.5%
Asian	2,082	2.7%	380	2.4%	1,702	2.8%
Hispanic	1,596	2.1%	390	2.5%	1,206	2.0%
Other/Unknown	2,073	2.7%	331	2.1%	1,742	2.9%
Geographic Region						
Northeast	26,398	34.4%	4,677	29.5%	21,721	35.7%
Southeast	17,141	22.3%	3,615	22.8%	13,526	22.2%
Midwest	6,885	9.0%	1,615	10.2%	5,270	8.7%
Southwest	1,821	2.4%	665	4.2%	1,156	1.9%
West	24,515	31.9%	5,282	33.3%	19,233	31.6%
Missing	17	0.0%	3	0.0%	14	0.0%
Entitlement Reason						
Old age and survivor's insurance (OASI)	62,556	81.5%	13,496	85.1%	49,060	80.5%
Disability insurance benefits (DIB)	14,006	18.2%	2,308	14.6%	11,698	19.2%
End-stage renal disease (ESRD)	215	0.3%	53	0.3%	162	0.3%
Medicaid Dual Eligible						
No	49,052	63.9%	9,016	56.9%	40,036	65.7%
Yes	27,725	36.1%	6,841	43.1%	20,884	34.3%
Part D Low-Income Subsidy						
No	46,685	60.8%	8,649	54.5%	38,036	62.4%
Yes	30,092	39.2%	7,208	45.5%	22,884	37.6%
Number of unique medications in year before admission, mean (std)	13.2 (15.5)		14.4 (16.5)		12.9 (15.2)	
Most Common Admitting Hospice Diagnosis						
Cancer	47,428	61.8%	1,321	8.3%	46,107	75.7%
Delerium/Dimentia	7,042	9.2%	4,143	26.1%	2,899	4.8%
COPD	3,902	5.1%	1,420	9.0%	2,482	4.1%
CHF	4,009	5.2%	2,037	12.8%	1,972	3.2%
Hospice length of stay, days mean (std)	81.6 (139.1)		111.4 (183.9)		73.8 (123.7)	
Hospice length of stay, median [interquartile range]	32 [11-87]		37 [11-126]		31 [12-81]	
≤7	13,497	17.6%	2,933	18.5%	10,564	17.3%
8-14	9,532	12.4%	1,849	11.7%	7,683	12.6%
15-30	14,593	19.0%	2,494	15.7%	12,099	19.9%
31-90	20,608	26.8%	3,614	22.8%	16,994	27.9%
91-180	9,438	12.3%	2,059	13.0%	7,379	12.1%
≥181	18,291	23.8%	12,090	76.2%	6,201	10.2%
Admitting Hospice Care Setting						
Private Residence	48,410	63.1%	6,983	44.0%	41,427	68.0%
Care Facility (Assisted Living or Nursing Facility)	25,344	33.0%	8,375	52.8%	16,969	27.9%
Hospice Facility	2,274	3.0%	374	2.4%	1,900	3.1%
Hospital, Inpatient Hospice Facility	749	1.0%	125	0.8%	624	1.0%

Prior Hospice Election						
No	72,210	94.1%	14,313	90.3%	57,897	95.0%
Yes	4,569	6.0%	1,546	9.7%	3,023	5.0%
Number of inpatient hospital admission in year before hospice, mean (std)	1.2 (2.2)		1.4 (2.6)		1.1 (2.1)	
0	44,699	58.2%	8,712	54.9%	35,987	59.1%
1	12,198	15.9%	2,302	14.5%	9,896	16.2%
2	8,007	10.4%	1,830	11.5%	6,177	10.1%
3	4,200	5.5%	966	6.1%	3,234	5.3%
4+	7,673	10.0%	2,047	12.9%	5,626	9.2%
Number of Comorbidities in 6 months before hospice mean (std)	3.1 (2.3)		3.4 (2.4)		3.0 (2.2)	
0	14,188	18.5%	2,777	17.5%	11,411	18.7%
1	6,912	9.0%	1,112	7.0%	5,800	9.5%
2	11,017	14.3%	1,944	12.3%	9,073	14.9%
3	12,486	16.3%	2,476	15.6%	10,010	16.4%
4+	32,174	41.9%	7,548	47.6%	24,626	40.4%
Comorbidities						
Chronic obstructive pulmonary disease	26,936	35.1%	4,503	28.4%	22,433	36.8%
Heart Failure	21,532	28.0%	5,691	35.9%	15,841	26.0%
Ischemic heart disease	28,614	37.3%	6,259	39.5%	22,355	36.7%
Diabetes mellitus	24,967	32.5%	4,954	31.2%	20,013	32.9%
Nervous System/ Neurological Disease	5,789	7.5%	1,673	10.6%	4,116	6.8%
Renal failure	17,202	22.4%	4,136	26.1%	13,066	21.4%
Liver Failure/Disease	9,122	11.9%	1,080	6.8%	8,042	13.2%
Dementia	21,722	28.3%	7,881	49.7%	13,841	22.7%
HIV	248	0.3%	39	0.2%	209	0.3%
Sepsis	12,625	16.4%	2,656	16.7%	9,969	16.4%
Hypertensive Disease	48,467	63.1%	10,101	63.7%	38,366	63.0%
Mood Disorder	19,228	25.0%	4,586	28.9%	14,642	24.0%
Number of Admitting Health Status Conditions mean (std)	1.9 (2.0)		2.0 (2.1)		1.9 (2.0)	
0	25,454	33.2%	5,330	33.6%	20,124	33.0%
1	14,200	18.5%	3,048	19.2%	11,152	18.3%
2	11,813	15.4%	2,401	15.1%	9,412	15.4%
3	9,186	12.0%	1,752	11.0%	7,434	12.2%
4+	16,124	21.0%	3,326	21.0%	12,798	21.0%
Health Status Conditions						
Recurrent or intractable infections	1,696	2.2%	439	2.8%	1,257	2.1%
Progressive inanition - weight loss	1	0.0%	0	0.0%	1	0.0%
Dehydration or hypovolemia	12,090	15.7%	2,364	14.9%	9,726	16.0%
Dysphagia	9,144	11.9%	2,697	17.0%	6,447	10.6%
Cough	7,747	10.1%	1,757	11.1%	5,990	9.8%
Nausea/ Vomiting	7,851	10.2%	1,010	6.4%	6,841	11.2%
Dyspnea	19,605	25.5%	3,626	22.9%	15,979	26.2%
Diarrhea	3,879	5.1%	706	4.5%	3,173	5.2%
Pain	12,374	16.1%	1,531	9.7%	10,843	17.8%
Hypotension	7,153	9.3%	1,524	9.6%	5,629	9.2%
Ascites Venous Obstruction	639	0.8%	35	0.2%	604	1.0%
Edema Pleural	15,789	20.6%	2,498	15.8%	13,291	21.8%
Cognitive Impairment	1,662	2.2%	489	3.1%	1,173	1.9%
Change in consciousness	1,411	1.8%	342	2.2%	1,069	1.8%
Pressure Ulcers Stage 3-4	7,999	10.4%	2,559	16.1%	5,440	8.9%
Sepsis/Septicemia	9,629	12.5%	2,142	13.5%	7,487	12.3%
Aspiration pneumonia	15,481	20.2%	3,020	19.0%	12,461	20.5%
Upper urinary tract infection (pyelonephritis)	15,059	19.6%	4,173	26.3%	10,886	17.9%

Table 2. All Part D prescriptions dispensed after hospice admission and on hand at time of death

	Total	SEER Non-Cancer	SEER Cancer
Any Amount (days supply)			
Patients	76,777	15,857	60,920
Prescriptions (n)	204,952	44,256	160,696
Days' supply dispensed mean (std)	36.7 (26.7)	33.4 (25.2)	36.7 (26.7)
Quantity supply dispensed mean (std)	62.2 (169.6)	59.3 (190.8)	62.9 (163.3)
Days supply leftover mean (std)	20.0 (19.8)	17.9 (18.0)	20.6 (20.3)
Quantity supply leftover mean (std)	34.2 (106.9)	32.3 (119.9)	34.7 (103.0)
Quantity supply leftover total	7,004,568	1,429,936	5,574,633

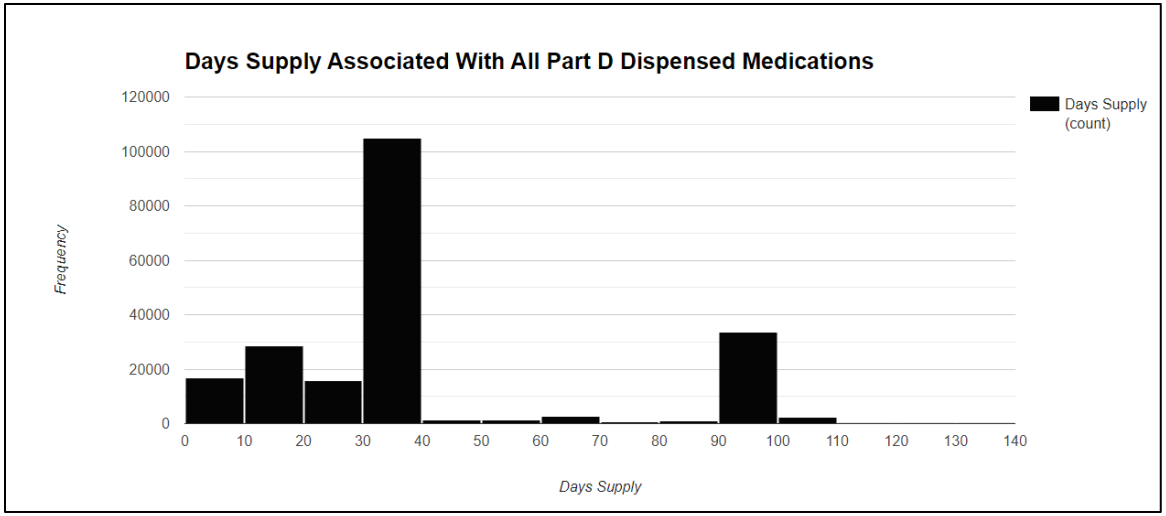


Figure 1. Histogram of Days' Supply of All Part D Prescriptions Dispensed

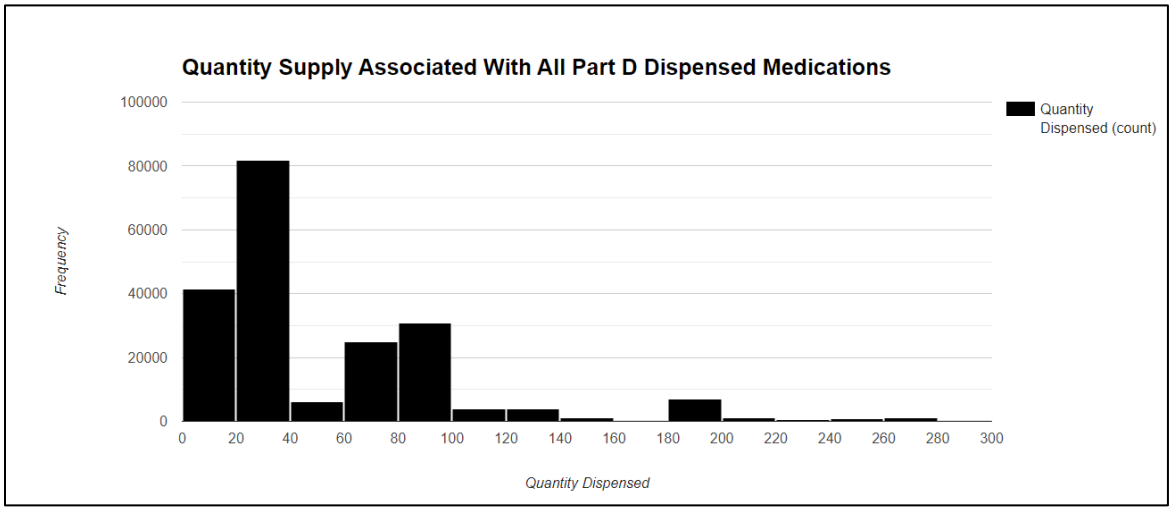


Figure 2. Histogram of Quantity Dispensed of All Part D Prescriptions

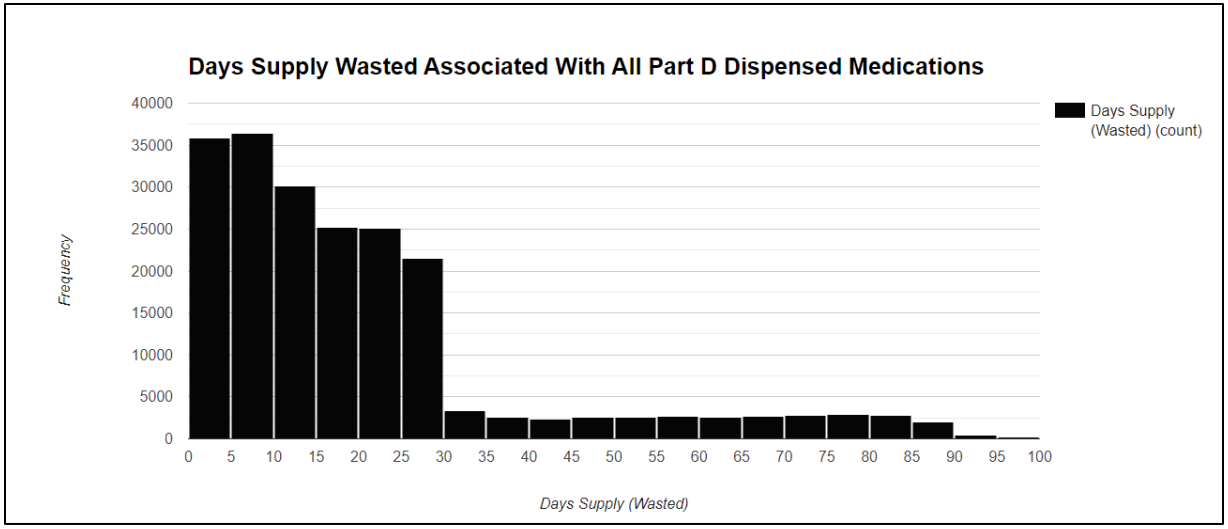


Figure 3. Histogram of Days' Supply Wasted of All Part D Prescriptions Dispensed

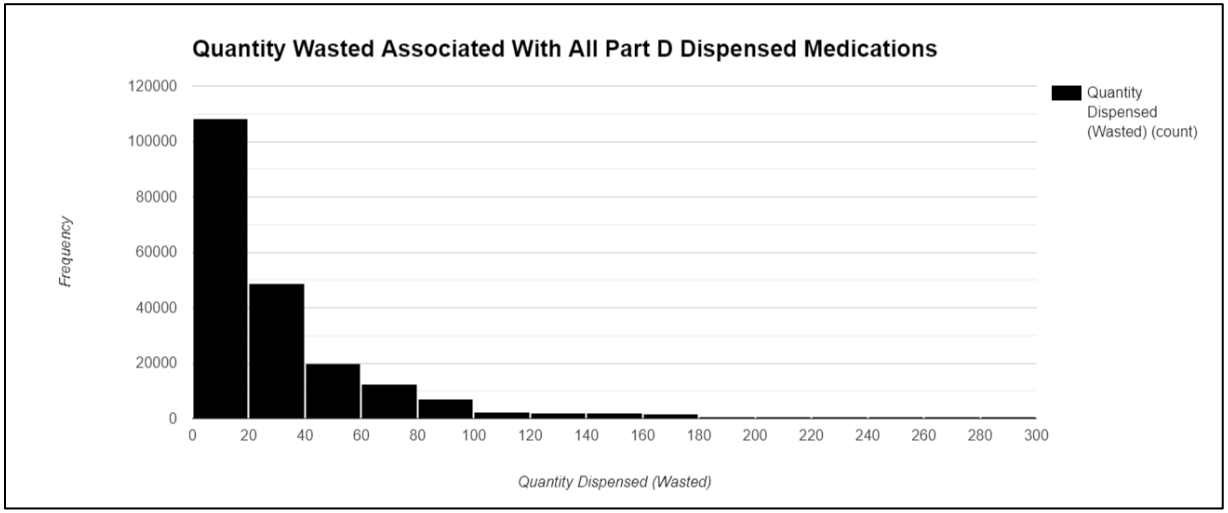


Figure 4. Histogram of Quantity Dispensed Wasted of All Part D Prescriptions

Table 3. Summary of all Part D dispensed prescription grouped by Medi-Span GPI therapeutic category (Drug Group)

Medi-Span GPI Therapeutic Category (Drug Group)	Total Prescriptions	Mean (sd) Days' Supply[1]	Mean (sd) Quantity Dispensed[2]	Mean (sd) Days' After Hospice Admission[3]	Mean (sd) Days' Supply Wasted[4]	Mean (sd) Quantity Wasted[5]
Antibiotics	4,598	16.19 (17.46)	46.74 (116.91)	63.54 (139.33)	8.61 (11.78)	24.76 (69.70)
Antineoplastics	1,947	36.43 (25.73)	130.90 (183.52)	68.66 (142.83)	19.89 (21.24)	70.32 (118.36)
Anti-Virals	659	27.10 (39.78)	41.59 (47.34)	71.19 (141.92)	14.34 (35.08)	21.18 (30.68)
Cardiovascular	51,147	41.97 (28.06)	55.79 (48.47)	75.72 (142.85)	22.95 (21.34)	30.53 (34.45)
Central Nervous System	40,408	33.07 (23.37)	61.48 (83.23)	78.88 (153.48)	17.87 (17.33)	33.57 (55.57)
Dental	778	16.40 (11.45)	274.87 (201.92)	41.97 (112.27)	9.04 (8.65)	151.66 (142.96)
Dermatology	3,341	20.31 (13.88)	75.38 (100.55)	64.67 (131.93)	11.06 (10.44)	41.03 (65.99)
Diabetes	10,281	42.25 (28.62)	47.57 (61.75)	75.01 (139.48)	23.54 (21.94)	25.98 (40.20)
Endocrine	16,422	40.22 (27.99)	46.77 (47.77)	83.20 (151.67)	21.68 (20.99)	25.31 (31.21)
Gastrointestinal	17,870	34.39 (24.61)	88.39 (201.97)	62.94 (131.67)	18.82 (18.26)	47.46 (113.39)
Genitourinary Agents	8,692	42.75 (28.54)	57.78 (198.89)	82.21 (143.40)	23.26 (21.54)	32.86 (150.77)
Hematology Agents	7,617	37.25 (26.48)	47.49 (40.25)	64.30 (124.22)	19.83 (19.61)	25.25 (28.08)
Hyperlipidemic Agents	7,552	48.47 (30.96)	51.42 (40.65)	69.29 (132.43)	26.59 (23.92)	28.28 (29.89)
Medical Devices/Supplies	1,811	49.31 (28.92)	126.14 (245.06)	67.73 (126.49)	27.58 (23.62)	66.92 (78.38)
Misc. Anti-Infectives	451	25.95 (23.39)	44.13 (65.72)	65.89 (150.05)	14.50 (16.59)	24.23 (37.57)
Misc. Therapeutic Classes	390	21.22 (20.00)	508.22 (1,714.01)	62.64 (131.38)	12.02 (14.66)	294.11 (848.81)
Nutritional Agents	4,064	34.98 (25.58)	194.20 (843.26)	76.39 (141.91)	19.04 (19.97)	112.05 (538.41)
Ophthalmic Agents	6,492	33.76 (25.57)	8.82 (15.32)	84.84 (153.47)	18.55 (18.45)	4.96 (9.84)
Pain Management	9,961	24.01 (20.56)	57.08 (77.37)	39.99 (114.90)	13.89 (15.04)	33.25 (56.54)
Passive Immunizing	1	28.00 (-)	1,200.00 (-)	179.00 (-)	16.00 (-)	685.71 (-)
Respiratory	10,344	32.87 (22.11)	46.58 (58.61)	65.70 (129.06)	18.03 (16.68)	26.37 (44.40)
Vaccines	1	30.00 (-)	0.65 (-)	77.00 (-)	23.00 (-)	0.50 (-)
Vasodilators	125	37.84 (23.42)	84.11 (74.59)	73.12 (121.74)	20.58 (20.04)	45.64 (52.54)
All Prescriptions	204,952	36.65 (26.70)	62.18 (169.61)	72.69 (141.93)	20.02 (19.83)	34.18 (106.90)

[1] *Average days' supply refers to the average length of all the prescriptions dispensed in the given therapeutic category.*
[2] *Average quantity dispensed refers to the average amount of a medication dispensed across all prescriptions in the given therapeutic category.*
[3] *Average days after hospice admission refers to on average how many days after a patient was in hospice were the prescriptions dispensed in the given therapeutic category.*
[4] *Average days' supply wasted refers to the average number of prescription days on hand following the patient's death.*
[5] *Average quantity wasted refers to the average quantity/unit of a prescription on hand following the patient's death.*

Table 4. Threshold Part D prescriptions dispensed after hospice admission and on hand at time of death

Threshold Amount (≥30 days' supply and >30 wasted quantity supply)			
Variables	**Total**	**SEER Non-Cancer**	**SEER Cancer**
	n= 76,777 Rx n= 204,952	**n= 15,857 Rx n= 44,256**	**n= 60,920 Rx n= 160,696**
Patients (n, %)	30,895 (40.2%)	5,440 (34.3%)	25,455 (41.8%)
Prescriptions (n, %)	49,286 (24.1%)	8,763 (19.8%)	40,523 (25.2%)
Days supply dispensed mean (sd)	63.4 (29.8)	61.1 (29.9)	64.0 (29.7)
Quantity supply dispensed mean (sd)	123.3 (176.5)	127.8 (200.5)	122.3 (170.9)
Days supply leftover mean (sd)	43.1 (24.1)	40.9 (23.6)	43.5 (24.2)
Quantity supply leftover mean (sd)	80.1 (108.3)	81.4 (125.0)	79.7 (104.4)
Quantity supply leftover total	3,950,216	713,608	3,236,608

Table 5. Top Medi-Span GPI therapeutic categories of Part D medications meeting waste threshold definition[1]

Variables	**Total**		**SEER Non-Cancer**		**SEER Cancer**	
	n= 49,286		**n= 8,763**		**n= 40,523**	
Top Categories of Part D Medications Meeting Waste Threshold						
Rank	**Medication**	**%**	**Medication**	**%**	**Medication**	**%**
1	Cardiovascular	30.6%	Cardiovascular	30.4%	Cardiovascular	30.6%
2	Central Nervous System	20.2%	Central Nervous System	25.5%	Central Nervous System	19.1%
3	Gastrointestinal	9.4%	Gastrointestinal	7.9%	Gastrointestinal	9.7%
4	Endocrine	7.4%	Endocrine	6.5%	Endocrine	7.6%
5	Diabetes	4.7%	Diabetes	4.2%	Diabetes	4.8%
6	Genitourinary Agents	4.3%	Genitourinary Agents	4.1%	Genitourinary Agents	4.4%
7	Hyperlipidemic Agents	4.2%	Hyperlipidemic Agents	3.8%	Hyperlipidemic Agents	4.3%
8	Hematology Agents	3.7%	Hematology Agents	3.3%	Pain Management	3.8%
9	Pain Management	3.7%	Pain Management	2.9%	Hematology Agents	3.8%
10	Respiratory	3.2%	Respiratory	2.9%	Respiratory	3.3%

[1]Waste threshold is defined as where the prescription's days' supply was 30 days or greater and the dispensed quantity on hand at time of death was greater than 30

Table 6. Assessment of model classifier performance by diagnostic testing

Classifier	False Positives	False Negatives	True Positives	True Negatives	Positive Predictive Value	Sensitivity	Specificity	LR+	LR-	AUC	Accuracy
K-Nearest Neighbor	1,438	2,366	7,446	29,707	83.8%	75.9%	92.6%	5.18	0.08	96.3%	90.7%
Gaussian Naïve Bayes	2,420	4,120	5,710	28,707	70.2%	58.1%	87.4%	2.36	0.14	80.3%	84.0%
LASSO regression	706	3,975	5,836	30,440	89.2%	59.3%	88.4%	8.27	0.13	93.9%	88.6%
Random Forest	1,168	1,090	8,767	29,932	88.2%	88.9%	96.5%	7.51	0.36	98.7%	94.5%

Positive likelihood ratio (LR+); Negative likelihood ratio (LR-); Area Under the Curve (AUC)

Table 7. Assessment of K-Nearest Neighbor, LASSO, Naïve Bayes Gaussian, and Random Forest model accuracy by waste threshold[1]

A.

K-Nearest Neighbor, k=10				
Waste Threshold Met	**N**	**Precision**	**Recall**	**f1-score**
No	31,145	93%	95%	94%
Yes	9,812	84%	76%	80%
Model AUC	96.3%			
Model Accuracy	90.7%			

B.

LASSO, n=1,000				
Waste Threshold Met	**N**	**Precision**	**Recall**	**f1-score**
No	31,146	88%	98%	93%
Yes	9,811	89%	59%	71%
Model AUC	93.9%			
Model Accuracy	88.6%			

C.

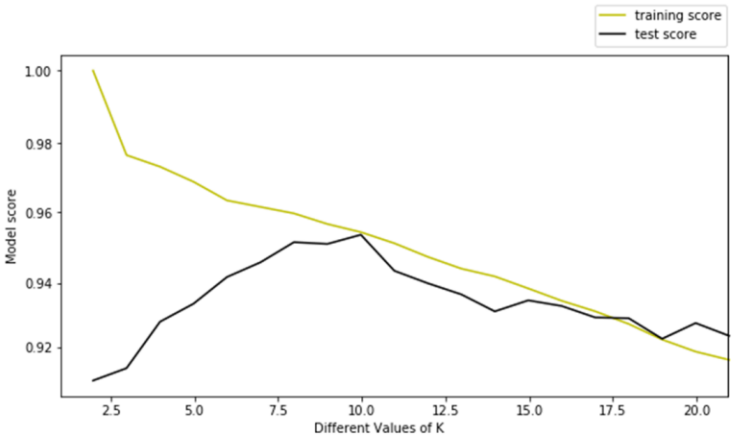
Gaussian Naïve Bayes				
Waste Threshold Met	**N**	**Precision**	**Recall**	**f1-score**
No	31,127	87%	92%	90%
Yes	9,830	70%	58%	64%
Model AUC	80.3%			
Model Accuracy	84.0%			

D.

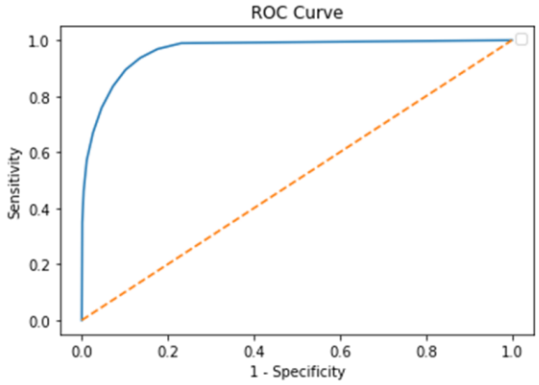
Random Forest, n=100				
Waste Threshold Met	**N**	**Precision**	**Recall**	**f1-score**
No	31,100	96%	96%	96%
Yes	9,857	88%	89%	88%
Model AUC	98.7%			
Model Accuracy	94.5%			

[1]Waste threshold is defined as where the prescription's days' supply was 30 days or greater and the dispensed quantity on hand at time of death was greater than 30
Area Under the Curve (AUC)

A. K-Nearest Neighbor model calibration of k



B. K-Nearest Neighbor sensitivity and selectivity



C. K-Nearest Neighbor precision-recall

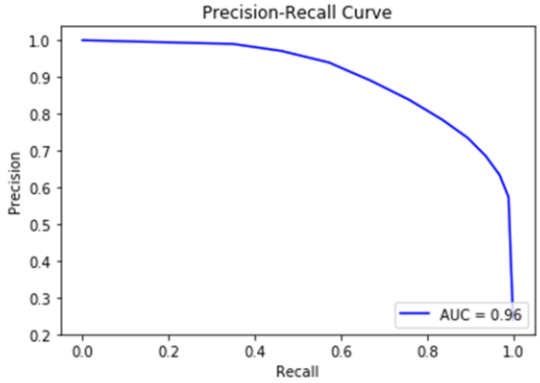


Figure 5A. Plots the different values of k (nearest neighbors) against the accuracy of the model for the model training and testing data. The results show that where k=10 is the optimal numbers of nearest neighbors for both datasets to obtain highly accurate score.

Figure 5B. Plots different the different classification thresholds of the model and its discriminatory power with the orange line indicating a random classifier. The optimal model performance is where sensitivity = 75.9% and specificity = 92.6%.

Figure 5C. Plots how the model performs across different classification thresholds while assessing the trade off between precision (likelihood of being correct on a positive instance) and recall (ability to successfully identify a large proportion of positive instances). The optimal model performance is where precision = 84% and recall = 76%.

Figure 5. K-Nearest Neighbor model evaluation by k-size, sensitivity-specificity and precision-recall

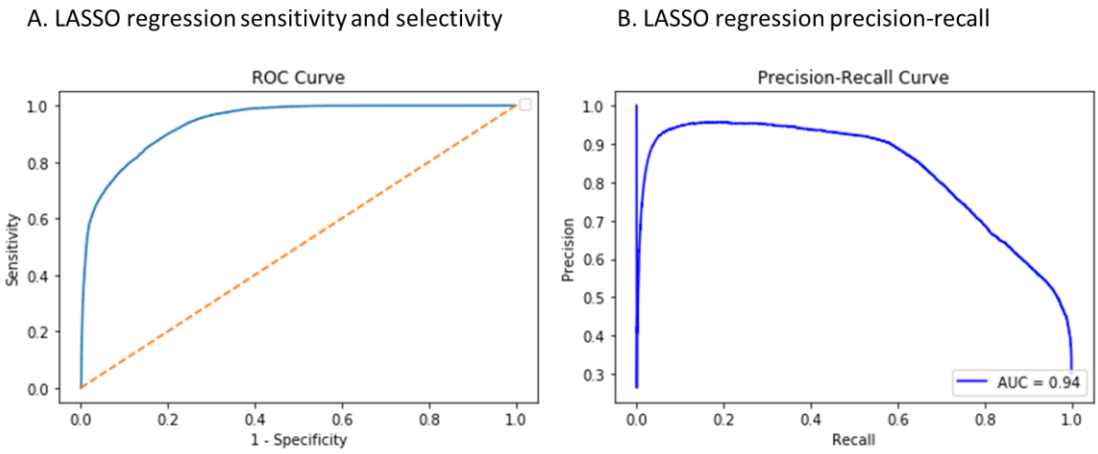


Figure 6A. Plots different the different classification thresholds of the model and its discriminatory power with the orange line indicating a random classifier. The optimal model performance is where sensitivity = 59.3% and specificity = 88.4%.

Figure 6B. Plots how the model performs across different classification thresholds while assessing the trade off between precision (likelihood of being correct on a positive instance) and recall (ability to successfully identify a large proportion of positive instances). The optimal model performance is where precision = 89% and recall = 59%.

Figure 6. LASSO regression model evaluation by sensitivity-specificity and precision-recall

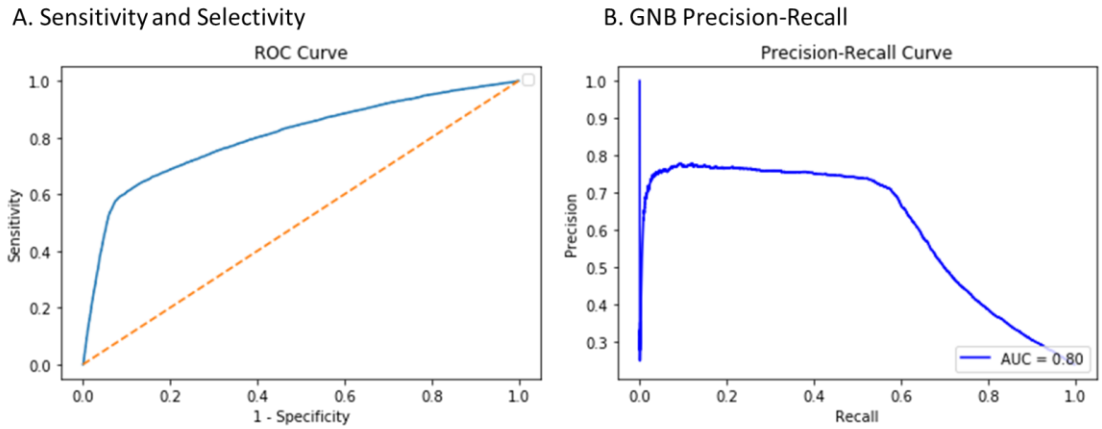


Figure 7A. Plots different the different classification thresholds of the model and its discriminatory power with the orange line indicating a random classifier. The optimal model performance is where sensitivity = 58.1% and specificity = 87.4%.

Figure 7B. Plots how the model performs across different classification thresholds while assessing the trade off between precision (likelihood of being correct on a positive instance) and recall (ability to successfully identify a large proportion of positive instances). The optimal model performance is where precision = 70% and recall = 58%.

Figure 7. Gaussian Naïve Bayes model evaluation by sensitivity-specificity and precision-recall

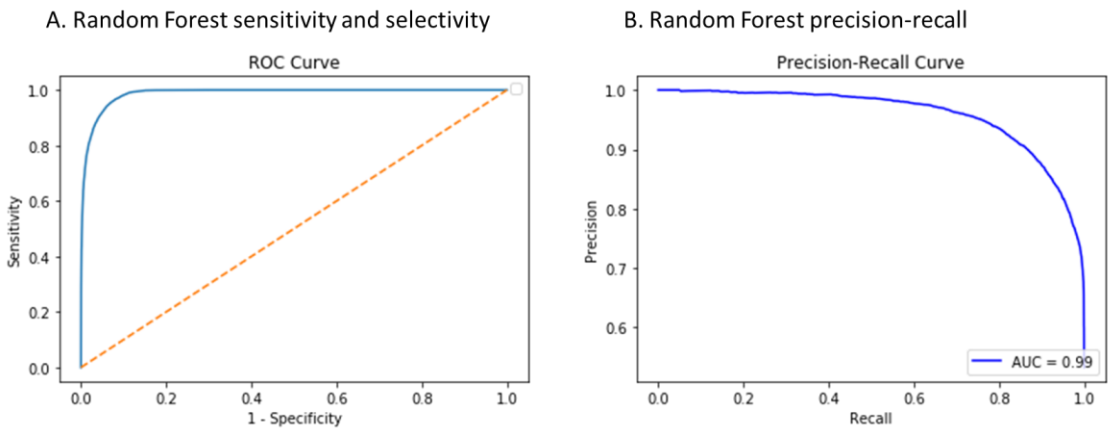


Figure 8A. Plots different the different classification thresholds of the model and its discriminatory power with the orange line indicating a random classifier. The optimal model performance is where sensitivity = 88.9% and specificity = 96.5%.

Figure 8B. Plots how the model performs across different classification thresholds while assessing the trade off between precision (likelihood of being correct on a positive instance) and recall (ability to successfully identify a large proportion of positive instances). The optimal model performance is where precision = 88% and recall = 89%.

Figure 8. Random Forest model evaluation by sensitivity-specificity and precision-recall

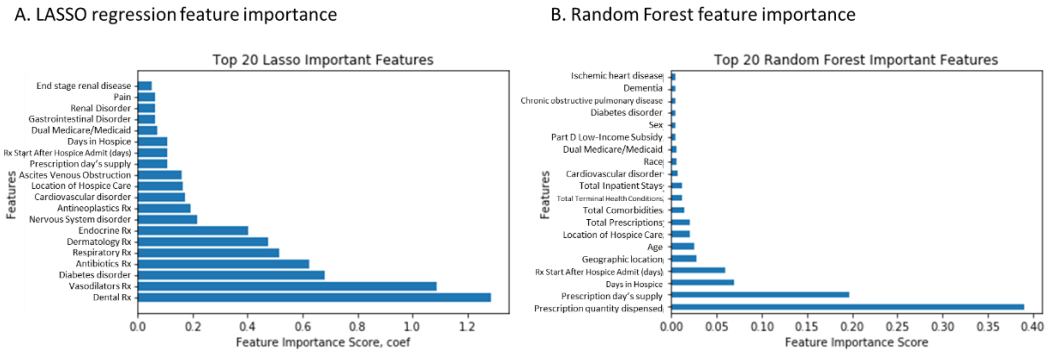
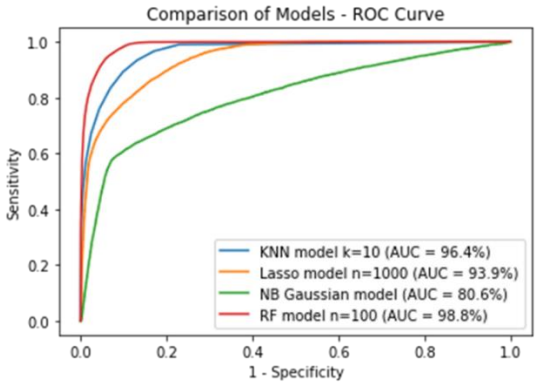
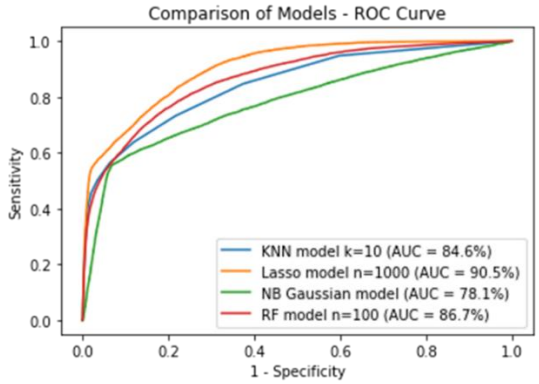


Figure 9. Feature importance comparison for predicting medication on hand at time of death between LASSO regression and Random Forest

A. Models Include Covariates Days Supply and Quantity Dispensed



B. Models Include Covariates Days Supply Removed Quantity Dispensed



C. Models Removed Covariates Days Supply Removed Quantity Dispensed

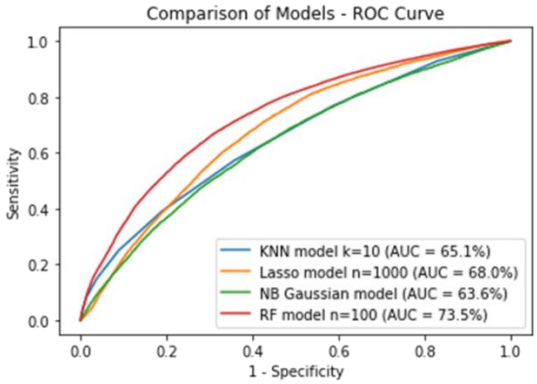


Figure 10. Model Comparison for Feature Sensitivity of K-Nearest Neighbor, LASSO regression, Gaussian Naïve Bayes, and Random Forest

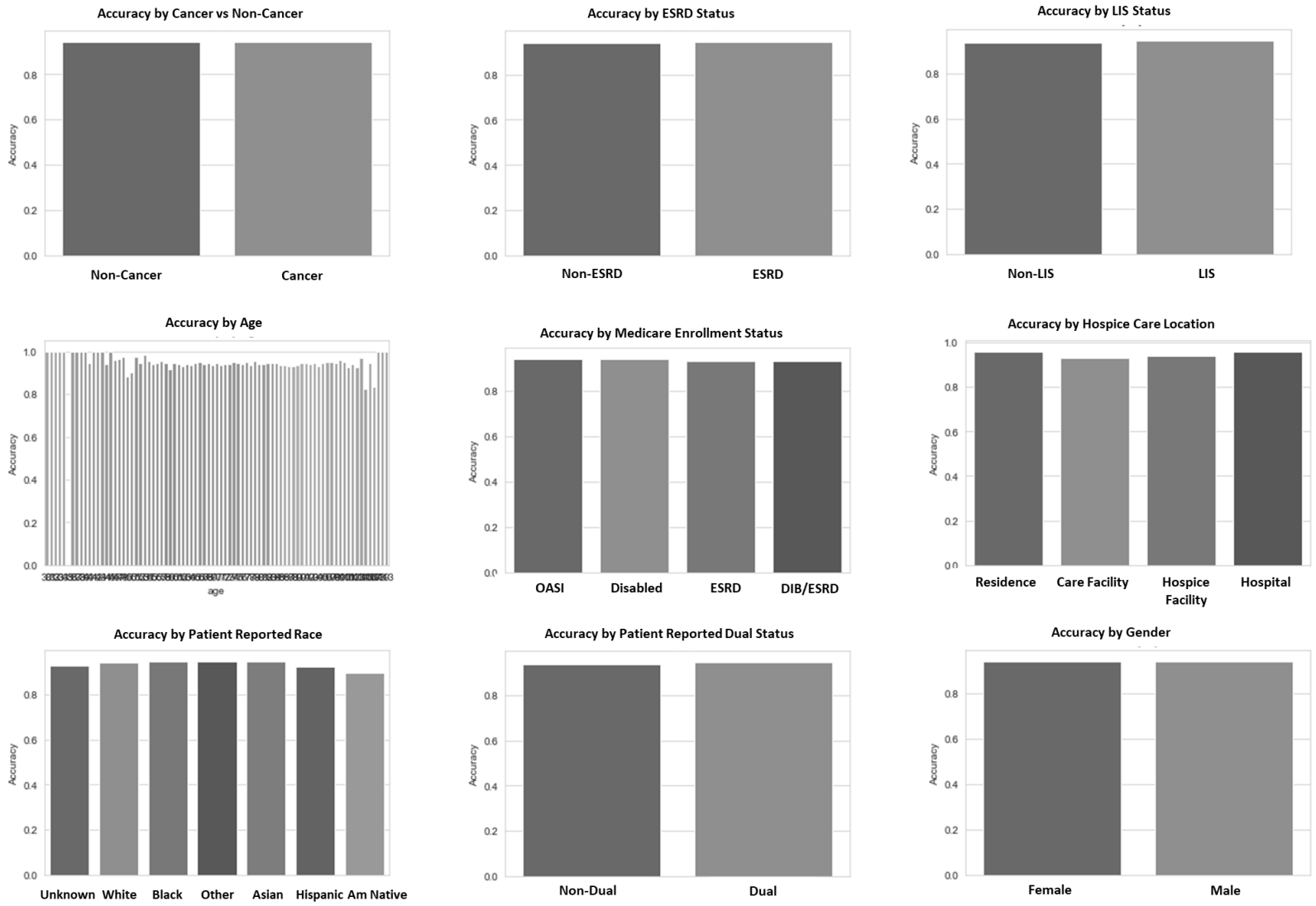


Figure 11. A review for sociodemographic bias of Random Forest model accuracy in predicting medication on hand at time of death

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MANUSCRIPT THREE: USING MACHINE LEARNING TO REDUCE PRESCRIPTION WASTE: A NEW METHODOLOGY FOR PRESCRIBING PART D PRESCRIPTIONS TO HOSPICE PATIENTS

ABSTRACT

In 2018, Medicare prescriptions made up an estimated $4.4 billion of waste across the Part A, B, and D benefits [1] [2] [3] [4]. One of the common causes of unused prescriptions is the death of a patient, with the waste being the amount of medication left on hand at death [2]. With over 55% of Medicare patients enrolled in hospice care at the time of their death [5], there should be a means of reducing some of this waste. One potential way to reduce Part D prescription waste in hospice patients is to determine prescription lengths based on a patient's life expectancy. However, there is a lack of research studies on estimating hospice patient's life expectancy based on their terminal diagnosis, as a way of informing Part D prescription durations and reducing waste. The purpose of this study was to develop and assess Part D rule-based prescription lengths that reduce medication on hand at the time of death among hospice patients, with a particular focus on individuals with a prognosis of 90 days or less. The aims of this study were to: (1) construct a rule-based prescription duration decision support tool leveraging patient survival days as a key determinant of appropriate lengths of Part D prescriptions for hospice patients to reduce medication on hand at the time of death, and (2) compare the change in the amount of medication on hand at time of death between traditional clinical prescription durations to rule-based prescription durations that have been assigned based on a patient's survival time (decision support tool generated from aim 1).

The first aim was achieved by refining the allocation of rule-based prescription lengths iteratively, which was informed by intervals of remaining survival days, literature reviews, and testing segmentation by survival days, quintiles, and time between prescription lengths, alongside calculating descriptive statistics of prescription durations and survival. The second aim was achieved by, first using Random Survival Forest (RSF) calibrated with median trapezoidal rule to simulate clinician estimated patient survival days, to which the rule-based prescription durations from aim 1 were applied to. Subsequently, medication on hand at time of death was then calculated for the rule-based prescriptions and compared to the amount caused by the clinician prescription durations. The comparison process included examining prescriptions where the: 1) rule-based resulted in the same overage as clinician prescriptions; 2) rule-based resulted in savings (less overage); and 3) rule-based resulted in losses (more overage). Two scenarios were considered that compared the overage for (1) all prescriptions regardless of when the clinician determined prescription ended and (2) prescriptions where a threshold excluded prescriptions where either the clinician or rule-based prescriptions ended more than 3 days before the death date. The intent being to address short-term or non-refilled clinician prescriptions and control for where the survival model under forecasted a patient's survival thus creating non-comparable scenarios. Result from the initial scenario found the rule-based prescriptions reduced overage in 28% of prescription events, leading to a decrease of 29.1% to 36.1% in the amount of prescription medication on hand at the time of death. The second scenario saw similar success with the rule-based prescriptions reducing overage in 32% of prescription events, leading to a decrease of 32% to 45.5% in

the amount of days' supply prescription waste. Overall, in this sample the rule-based initial and refill prescription durations resulted in reduced waste.

Keywords: hospice, prescription, Medicare, medication waste, SEER, deprescribing, end-of-life care, Cox Proportional Hazard, Random Survival Forest, Isotonic Regression, Trapezoidal Rule, and rule-based model.

INTRODUCTION

Hospice Benefit

The purpose of hospice is to relieve distressing symptoms in the dying while neither hastening death nor seeking to cure the terminal illness [6]. When a patient elects hospice care, it is covered under the Medicare Part A benefits, and includes services, care, medical equipment and supplies, and prescription drugs related to the palliative treatment of the terminal illness and the related conditions [25]. To be eligible to elect hospice care, a Medicare enrolled patient must be certified by a physician as terminally ill [8]. Terminally ill is defined as a disease where the medical prognosis is that the patient's life expectancy is 6 months or less if the illness runs its normal course [8]. Only upon the recommendation of the hospice's medical director in consultation with the patient's attending physician can a decision be made to admit a patient into hospice [8]. The medical director considers the following criteria: 1) the terminal diagnosis; 2) other related or unrelated health conditions; and 3) all clinical information supporting all diagnoses. Once a patient is admitted, the hospice care benefit consists of two 90-day benefit periods followed by an unlimited number of 60-day periods, with each benefit period requiring the recertification of the patient as being terminal [8]. These benefit periods are continuous unless the patient chooses to no longer receive hospice care or the physician discharges or does not recertify the individual [8].

Medicare Part D

As part of hospice care, medications a patient needs related to their terminal disease are covered and provided under their Part A hospice benefit. However, any other medications they are taking for unrelated conditions might not be covered by the hospice and need to continue to be filled through the patient's Part D benefit. As part of the Medicare Prescription Drug and Modernization Act of 2003, the legislation in 2006 established the Medicare Part D benefit. This benefit provided patients an optional election, whereby they pay a monthly premium to obtain coverage for their outpatient prescriptions, through CMS approved private insurance sponsors [9]. Medicare Part D covers prescription drugs in most cases, but there are circumstances where drugs are covered instead under either Medicare Part A or Part B [10]. As previously stated, hospice care covers only prescription drugs associated to the terminal illness and related conditions, medications unrelated may still be obtained through the Medicare Part D benefit [11]. These Part D medications are generally prescribed to treat chronic illnesses and maintain a stable medical condition [6]. Patients with terminal diagnoses do not wish to hasten their death just because they are terminal [6]. In fact, in some cases death may take months or even years to occur [6]. Only when a patient enters the very last stage, known as the active phase of dying, it is then appropriate to withdraw care of regular medications or unless the care plan dictates withdrawal sooner. Otherwise, removing the medications from a patient who is not at the end, is a form of hastening death or euthanasia [12].

Prescription Waste

In 2013, a report from Visante found that around 1% of all Part D prescriptions are wasted each year [2]. This equates to about 14 million prescriptions or about $1.68 billion [2] [4]. The report also found that death was one of the factors influencing waste, which, the study found to average about 50% of medication on hand at time of death for each prescription [2]. While the number of medications patients are prescribed as they approach the end of life has been shown to vary according to their terminal illness and associated disease trajectory, on average, they are prescribed more than 10 unique medications [13]. Several studies have addressed the disposal of prescription drugs [1] [14] [15]. Studies like that of Bain, et al. (2010) conducted a comprehensive review "on the public health issue of household pharmaceutical waste, describing its epidemiology, explaining its effects on aquatic and human life, estimating its cost burden, and discussing strategies for reducing environmental exposure to it" [1]. Additional studies like that of Fass, et al. (2011) discussed the importance of the existing Federal legislation and of the drug take-back programs [14]. Lastly studies like that of Haughey, et al. (2019) researched "the gaps in provider knowledge and devised a project to improve patient/caregiver knowledge of safe medication disposal" [15]. While research that has explored waste and the disposal of prescription drugs, little research has examined how to reduce this waste in the first place; specifically, in a population where we know the estimated survival to be less than 6 months.

Prescription Lengths

Federal and state laws that regulate time and dosage limits on the prescribing or dispensing of prescription medications have in place for some time [16]. These regulations are enforced by insurance companies through various mechanisms such as quantity-over-time limits, maximum daily doses, refill restrictions, and day supply limits [17]. Pharmacists leverage prescription management software to adhere to these laws in their prescribing activities. However, a 2016 report by the Centers for Disease Control and Prevention (CDC) highlighted the lack of substantial information on the efficacy of these statutes and regulations in curbing drug abuse, diversion, and waste [16]. While extensive literature exists on the prescription duration of opioids [18] [19] [20], scant attention has been given to exploring other types of prescriptions or prescription duration aimed at reducing waste among hospice patients.

Existing research on waste reduction through prescription duration primarily focuses on populations in England, where a universal healthcare system is in place. One notable study by Hawksworth et al. (1996) analyzed unused medicine returns to 30 community pharmacies over a month, revealing a positive correlation between longer prescription lengths and increased quantities and costs of returned drugs [21]. The study suggested that limiting prescription supplies to 28 days could potentially reduce wastage by a third [21]. More recently, Doble et al. (2017) conducted an analysis comparing short (<60 days) and long (≥60 days) prescriptions among patients with common chronic conditions. Their findings indicated a consistently larger proportion of days' supply

wasted with longer prescriptions, yet longer prescriptions were associated with lower total unnecessary costs when factoring in dispensing fees and prescriber time [22]. Similar conclusions have been drawn from studies in Europe [23] [24], while research in the United States, such as that by Taitel et al. (2012), has also shown increased medication waste with shorter prescription fills, albeit with decreased costs [25]. A secondary research article by Edlin (2013) corroborated these findings, emphasizing the cost-saving and waste-reducing benefits of shorter prescription fills [26]. A review of optimal prescription durations identified in a basic drug dispensing limit list from BlueCross BlueShield (2020), found the most common prescription dispensing limit was 30 days, with other common limits including 28, 90, 180, 270, and 365 days [27].

In the context of hospice care, literature exists on the most commonly prescribed medications [13] [28], the impact of polypharmacy [29], medication doses and routes of administration [30] [31], and the quantity of medication on hand at the time of death [32] [33]. Additionally, strategies to reduce waste among pharmacists have been explored, with evidence suggesting that patients receiving medications for more than 30 days are more likely to waste a portion of those medications [34]. However, research specifically addressing Part D prescription waste in hospice patients remains limited.

Long-term vs Short-term Medications

The duration of a prescription isn't just dependent on regulations or insurance dispensing limits, but also the type of type and severity of the medical condition being

treated, the specific medication being prescribed, the patient's response to treatment, and any potential side effects or risks associated with the medication. Long-term medications, sometimes referred to as maintenance drugs, are medications taken regularly to manage chronic conditions [35] [36]. These conditions may include high blood pressure, asthma, diabetes or high cholesterol [36], and typically have a 90-day supply or more [35]. On the other hand, short-term medications, or acute medicines, are intended for temporary use, with antibiotics being the most common [37]. Short-term medications are typically prescribed as a 1-month supply or less [38], with durations of 5, 7, 10, and 14 days also commonly prescribed [39] [40] [41]. Insurance companies often recommend that pharmacies dispense a maximum 30-day supply, or a fraction thereof, for first-time prescriptions of maintenance drugs [42]. Here, "fraction thereof" refers to any portion of a dose being administered over the recommended duration [43]. Despite this guidance, there is a lack of literature exploring the application of short-term medication durations (5, 7, 10, and 14-days), to maintenance drug for the hospice population.

Survival Time and Prescription Length

In this research survival time is defined as the time (days) between a patient's admission to hospice and their death [32] [33] [53]. As part of the hospice election process, clinicians assess the patient's estimated survival. This assessment helps determine the patient's eligibility for hospice care, as hospice services are typically provided to individuals with a prognosis of six months or less if the illness runs its normal course [8]. While the 6-month prognosis is a general guideline used to determine

eligibility for hospice care, clinicians do strive to provide as accurate an estimate as possible of the patient's survival. However, predicting an individual's exact lifespan can be challenging due to the uncertainty inherent in terminal illnesses [6]. Therefore, while the six-month estimate is a common threshold, clinicians aim to provide the most precise estimate based on the available information and medical expertise.

Prescription length refers to the duration of time for which a medication prescription is intended to be taken by a patient [42]. It indicates the period during which the prescribed medication should be taken as directed by a healthcare provider before a new prescription is required or a review of the treatment plan is necessary [27]. The prescription length can vary depending on factors such as the type of medication, the patient's condition, and the treatment goals [38].

Limited research exists on waste-reducing Part D prescription length based on the patient's survival time. However, studies do exist that explore various aspects of hospice length of stay prediction including: predicting length of stay before and after hospice enrollment [44], predicting survival in dementia patients [45], and using race and ethnicity in predicting length of hospice care [46]. Additionally, research exists examining prescription length with most focusing on the optimal length for opioids [18] [47] [48]. Other research in the arena of prescription length have assessed the optimal length of a patient's initial prescription [49], the associations of dialysis doses and session length with mortality risk [50], and optimal prescription length for medication adherence

[51]. The most relevant research to this study was a dissertation from Maurer, M.A. (2009) where an examination of predictors of length of survival in hospice care was conducted in order to inform optimal duration of end-of-life care for patients and families [52]. Researchers such as Hauser [32], Speer [33], and Zueger [53] who've examined medication waste in hospice patients have concluded that a creative means to reducing unnecessary prescriptions and waste are needed.

The purpose of this study was to develop and assess Part D rule-based prescription lengths that reduce medication on hand at the time of death among hospice patients, with a particular focus on individuals with a prognosis of 90 days or less. The aims of this study were to: (1) construct a rule-based prescription duration decision support tool leveraging patient survival days as a key determinant of appropriate lengths of Part D prescriptions for hospice patients to reduce medication on hand at the time of death, and (2) compare the change in the amount of medication on hand at time of death between traditional clinical prescription durations to rule-based prescription durations that have been assigned based on a patient's survival time (decision support tool generated from aim 1). The first aim was achieved by refining the allocation of rule-based prescription lengths iteratively, which was informed by intervals of remaining survival days, literature reviews, and testing segmentation by survival days, quintiles, and time between prescription lengths, alongside calculating descriptive statistics of prescription durations and survival. The achieve the second aim, first machine learning methods were assessed for their ability to simulate clinicians estimated patient survival

days at the time of the patient's hospice admission, with the estimated patient survival days from the best performing model selected. The prescriptions examined in this study were prescribed following the patient's hospice admission. To determine the appropriate rule-based prescription length to assign (generated in aim 1), the machine learning estimated patient survival days were modified downward to remove the time (days) between the hospice admission and when the prescription was filled, to ensure that the rule-based prescription lengths assigned were based on the patient's remaining survival time. To evaluate the change of using prescription lengths based on the patient's survival time (decision support tool generated from aim 1), the overage at the time of death was calculated and compared to that caused by clinician prescription durations. This comparison categorized outcomes into three groups: 1) instances where rule-based prescriptions resulted in the same overage as clinician prescriptions; 2) cases where rule-based prescriptions led to savings (reduced overage); and 3) scenarios where rule-based prescriptions resulted in losses (more overage). Two scenarios were conducted that compared the overage for (1) all prescriptions regardless of when the clinician determined prescription ended and (2) prescriptions where a threshold excluded prescriptions where either the clinician or rule-based prescriptions ended more than 3 days before the death date. The purpose was to address short-term or non-refilled clinician prescriptions and control for instances where the survival model under-forecasted a patient's survival, thus creating non-comparable scenarios.

METHODS

Data Source

This study uses secondary data sourced from the Surveillance, Epidemiology, and End Results (SEER) Program, in conjunction with the Medicare linked database, to identify patients admitted to hospice and their Part D prescriptions. This nationally representative, population-based database combines tumor registry data from the National Cancer Institute's SEER program with Medicare enrollment and billing records for Medicare patients and covers approximately 34.6% of the U.S. population [54]. Specifically, this data encompasses SEER regions in Connecticut, Iowa, New Mexico, Utah, Hawaii, Alaska Natives, Arizona Indians, Cherokee Nation, Georgia, California, Idaho, Kentucky, Louisiana, Massachusetts, New York, Wisconsin, and the cities of Chicago and Seattle-Puget [54]. Within the SEER-Medicare database, there were records for individuals with cancer as well as a randomly selected sample of Medicare patients without cancer. The "non-cancer" cohort is derived from a random 5% subset of Medicare fee-for-service patients residing in the SEER regions [54].

Study Sample

The process of selecting the sample involved two distinct steps. Firstly, during the initial phase of preprocessing, the study identified 221,451 patients who met specific criteria. These patients had passed away while under hospice care between January 1, 2015, and December 31, 2019, and they satisfied the Medicare entitlement eligibility requirements for this study. Patients were included if they had an active hospice benefit

election, meaning they were receiving care from a Medicare-certified hospice at the time of their death. Patients who were discharged from hospice before their passing were excluded from this selection. Additional preprocessing was done to the data to build episodes of hospice benefit elections for each patient, joining series of claims over the same overlapping date period, to identify the initial benefit period known in this study as the initial hospice start date. For patients with multiple hospice start dates (episodes), due to admitting and discharging from hospice, only the patient's most recent episode preceding death was used. To be included in the sample, these patients were required to maintain continuous enrollment in both Medicare Parts A and B during the six months leading up to their hospice admission and throughout their hospice care. These criteria were rigorously applied to ensure that our data comprehensively captured each patient's healthcare interactions through claims. Additionally, patients had to remain continuously enrolled in the Medicare Part D prescription benefit program for the six months preceding their hospice election, as well as throughout the duration of their hospice care. This meticulous approach ensured the inclusion of individuals whose prescription drug data would be integral to our study.

Secondly, the data were processed and limited to 188,263 patients who passed away within 90 days of being admitted to hospice (as shown in Table 1). This patient panel was used as part of the survival analysis to predict their survival time to simulate a clinical estimating life expectancy during the intake process. These 188,263 patients had a total of 214,571 prescriptions (Table 2), under the Part D benefit following their

hospice admission and filled prior to their death. Following the survival analysis, the resulting forecasted survival times from the test data were cross walked to this prescription dataset using Patient ID. By conducting analyses at the patient level, the study could predict their survival, determine rule-based prescription durations, and subsequently assess the reduction of medication on hand at the time of their passing.

The data did not contain missing values as enrollment data was used as the basis of building the eligible sample to pull claims and build the characteristics and demographics. If the enrollment record had been missing the beneficiary wouldn't have an entitlement record and therefore the patient wouldn't have been included in the study sample based on the continuous Part A/B/D enrollment requirements. In addition, as part of the sampling methodology hospice enrollment was identified using the claims data, therefore patients would've had to have had some claims record in the data. Furthermore, the characteristics, sociodemographic, and diagnoses are predictors pulled from the claims data and while there wouldn’t be missing values it is possible there is under coding as some codes may not be present in the claims.

The sample was divided into two categories: cancer (consisting of 154,649 patients with prior diagnoses of prostate, stomach, pancreas, lung, and breast cancer) and non-cancer (comprising 33,614 patients). This division allowed for an examination of any potential biases within the cancer dataset, which exclusively comprises individuals with cancer diagnoses, in contrast to the broader Medicare fee-for-service group (random

sample which may or may not have cancer). The study's sample encompassed both the cancer and non-cancer cohorts and drew upon their Medicare Enrollment data, Medicare Part A and B claims, as well as their Part D prescription claims provided by non-hospice healthcare providers.

Using cross-referencing, this study linked Part D prescription National Drug Codes (NDCs) for medications with the Medi-Span Generic Product Identifier (GPI) - Drug Group established by Wolters Kluwer. This GPI system is a recognized industry standard designed for organizing medications into therapeutic categories, facilitating the grouping of drugs by specific medical conditions [55]. The Wolters Kluwer's Medi-Span database employs a 14-character hierarchical classification system based on the primary therapeutic use of each medication. Within this 14-character structure, users can identify various attributes of a medication, including its drug group, class, sub-class, name, name extension, dosage, and strength [55]. The first six characters of the GPI denote the therapeutic class code, allocating two characters each for group, class, and sub-class, while the subsequent two pairs of characters specify the drug's name. The last four characters provide information about the medication's dosage and strength. These therapeutic classes are essentially groups of medications that share commonalities in terms of their mechanism of action (how they affect the body), physiological effects (how the body responds to them), and chemical structure (their composition). For this study, the focus was at the highest level of this hierarchical grouping system, known as the drug

group, which categorizes medications into one of 15 agents, products, or drug groups based on the specific medical condition or disease they are intended to treat or target.

The data were preprocessed in PostgreSQL and then imported into Jupyter Notebook for analysis with python.

Measures

Outcome Measures:

Rule-based prescription length (days' supply)

As part of the first aim and the construction of rule-based prescription durations, the prescription lengths used in the rules were based on common prescription durations of 7, 10, 14, 30, 60, and 90-days, as is standard of short-term (1-month supply or less) and intermediate prescription lengths (>30 days and <90 days) [27]. For example, a patient with a remaining survival of 12-days could be assigned a 14-day prescription length. Whereas a patient with a remaining survival of 40-days could be assigned a 30-day prescription with one 10-day refill. As previously stated, survival time is defined as the time (days) between a patient's admission to hospice and their death [32] [33] [53]. Whereas remaining survival days removes from survival time the days between the hospice admission and when a prescription was filled (described in more detail below (Total Survival Days)).

To determine the suitable intervals of survival days to prescription duration involved an iterative testing and refinement process. The process included literature reviews, segmentation by survival days, quintiles, and time between prescription lengths, and analysis of descriptive statistics (refer to Table 2 and Table 3). Additionally, the testing encompassed initial prescription durations and refills in cases where patients exhausted their medication before their passing.

Total Survival Days (90 days or less)

As part of the second aim, the research predicted survival days in patients who died within 90 days of their hospice benefit election as a means of simulating clinician survival estimates. This study only used the beneficiary's hospice benefit election period that immediately preceded their death. The cutoff of 90 days was selected for two reasons. Firstly, a patient's initial hospice election period is a 90-day benefit period. Secondly, a report from The National Hospice and Palliative Care Organization in December 2022 found the average length of stay in hospice for all Medicare patients was 97 days (18 days median) [56]. To compute survival days, this study creates a calculated field survival field that subtracts the patient's hospice start date from the death date.

$$\text{survival\_days} = \text{bene\_}death\_dt - clm\_hospc\_start\_dt\_id$$

bene_death_dt: the date of death of the patient.
clm_hospc_start_dt_id: the start date for admission into hospice.

Machine learning techniques were employed to construct models for predicting survival days, with calibration techniques subsequently integrated to mitigate

overconfidence in the model's predictions, as elaborated in the section on machine learning approaches. This process yields individual patient median calibrated survival days, which were meant to simulate the estimate a clinician would make during the hospice admission process. The prescriptions examined in this study were prescribed following the patient's hospice admission. To determine the appropriate rule-based prescription length to assign, the median calibrated survival days were modified downward, excluding the days between the patient's hospice admission and the prescription fill date, resulting in a field termed remaining survival days. The intent was to account for and remove the time (days) between the hospice admission and when the prescription was filled (from the calibrated survival days), to ensure that the prescription lengths were based on the patient's remaining survival time. On average, prescriptions were filled approximately 19.6 days (median 14 days) after a patient's admission to hospice (Table 2).

$$\text{remaining survival days} = \text{median calibrated survival days} - (\text{srvc\_dt} - clm\_hospc\_start\_dt\_id)$$

srvc_dt:	the date the prescription was filled.
clm_hospc_start_dt_id:	the start date for admission into hospice.
median calibrated survival days:	the calibrated survival days from the machine learning model.
remaining survival days:	the calibrated survival days from the machine learning model adjusted for time between the hospice admission and prescription fulfillment.

Survival Status (90 days or less)

A binary variable indicating whether the patient is dead (1) or still alive (0) was used in the analyses along with the Survival Days measure. The data used in this study were complete, not censored, as all patients included died during the data period.

Part D Prescription Medication on Hand at Time of Death

As part of the second aim, a comparison was done comparing the change in the amount of medication on hand at time of death (waste) between traditional clinical prescription durations to rule-based prescription durations (generated in aim 1). Waste refers to the overutilization of services or misallocation of resources, often stemming from carelessness, inefficiency, or lack of awareness, but it does not constitute a criminal offense [29]. Within Medicare Part D, each time a patient fills a prescription, the plan sponsor is required to submit a summary record, known as the prescription drug event, to CMS, forming the Part D claim files [30]. This study introduces calculated waste fields, employing conservative or "best-case" assumptions to determine the minimal amount of medication present at the time of death. These assumptions (limitations) include:

1. The patient filled the medication on the same day they received the prescription.
2. The patient initiated the medication immediately upon receiving it.
3. The patient did not discontinue the medication in the days leading up to death.
4. No alternative prescription was provided in place of the current one.
5. Dosage and frequency remained unchanged.

6. The prescription regimen did not include medications to be taken on an as-needed basis.

Medication on hand at time of death was identified by adding the prescription days' supply to the date the prescription was filled (service date) to obtain a prescription end date, taking into consideration where this prescription end date is greater than the date of death.

$$\text{bene}\_death\_dt < RX\ End\ Date = srvc\_dt\ +\ days\_suply\_num$$

bene_death_dt:	the date of death of the patient.
RX End Date:	the earliest date the prescription would be finished.
srvc_dt:	the date the prescription was filled.
days_supply_num:	the number of days' supply of medication dispensed by the pharmacy and will consist of the amount the pharmacy enters for the prescription.

A second calculated field was created to determine the amount of medication on hand at time of death. This calculation added the prescription days' supply to the date the prescription was filled and then subtracting the date of death to obtain a number of overage days.

$$Actual\ Overage\ Days = srvc\_dt\ +\ days\_suply\_num - bene\_death\_dt$$

$$Rule\ Based\ Overage\ Days = srvc\_dt + Rule\ Based\ Days\ Supply - bene\_death\_dt$$

Overage Days:	the number of days' supply left on a prescription after a patient's death.
bene_death_dt:	the date of death of the patient.
srvc_dt:	the date the prescription was filled.
days_supply_num:	the number of days' supply of medication dispensed by the pharmacy and will consist of the amount the pharmacy enters for the prescription.

Rule Based Days Supply	the number of day's supply of medication using day's supply prescription lengths allocated to intervals of remaining survival days.

This study examines the medication on hand at time of death, comparing the traditional clinical prescription duration surplus with the surplus produced by rule-based durations, aiming to ascertain whether rule-based durations can mitigate waste.

Outcome Measure Limitations

This study has several limitations, which through further analysis and the expansion of research efforts could improve the methodology. The primary limitation lies with the reliance of only claims data for predicting survival days. If this methodology were to be implement into a clinician support tool, it would leverage a patient's Electronic Health Record (EHR), which contains demographic details, medical and medication history, clinical notes, laboratory results, vital signs, procedures, treatments, and care plans. Additionally, the EHR encompasses qualitative data gathered from evaluation and assessment tools utilized by clinicians, that aid in decision-making. Tools such as these cover various domains, including pain management, symptom assessment, functional status, psychosocial care, caregiver evaluation, and quality of life [57]. The most commonly used tools in hospice are the Palliative Performance Scale (PPS) and Karnofsky Performance Score (KPS), which are utilized in predicting prognosis, mortality, or assessing functional ability in hospice patients [226]. The KPS, dates back to 1948, is an 11-point scale with scores ranging from 100 (indicating normal activity) to 0 (indicating death) [58]. While PPS, was developed in 1996 as a modified version of the

KPS and facilitates decision-making and communication in palliative care settings [59]. Similar to the KPS, the PPS also employs an 11-point scale, evaluating parameters such as ambulation, activity, extent of disease, self-care, oral intake, and level of consciousness. These assessment tools are typically administered by medical personnel upon a patient's admission to hospice and during the recertification process. Leveraging the additional information available in the EHR, results from evaluation tools, combined with claims data, are certain to enhance the accuracy of predicted survival days and the prescription rules, thereby improving overall accuracy.

An additional limitation of this study is the reliance on linked SEER Medicare data in addition to a 5% subset of Medicare fee-for-service patients living in the SEER regions. Consequently, over 82% of the sample comprises patients with cancer, potentially introducing unknown biases into both the predicted survivals and prescription rules. Moreover, the sample was restricted to individuals who passed away within 90 days of electing the hospice benefit, further constraining the representation of survival patients and the generalization of the results. Longer-term hospice patients may have different care needs and treatments, as well as patterns in their prescriptions, which could affect the accuracy of survival predictions and the development of prescription rules.

Another limitation of this study is in the approach to the rule-based prescriptions, which don't account for type or category of medication and diagnosis. Not accounting for the type or category of medications could be causing suboptimal or non-industry standard

prescription durations for certain groups of medications or diagnoses. Incorporating rules that are specific to medication and diagnosis combinations would allow for medications that serve multiple purposes to have different durations and address the needs of the patient and ensure they are receiving appropriate medications durations. Additionally, the rules could be further improved to incorporate more empirical reasoning including confidence intervals and statistical tests (e.g., ANOVA, Kruskal-Wallis test) to determine if there are significant differences in prescription durations between survival day groups, etc. The methodology could also be improved by the inclusion of feedback from clinical experts, including hospice physicians or pharmacists, to validate the findings and gather insights on Part D prescribing practices for patients in hospice.

Patient Characteristics

To support the first aim of developing rule-based prescription lengths based on patients' survival time, the research analyzed various factors including median and average prescription days' supply, survival days at the time of admission and prescription fulfillment, and their distributions across common prescription lengths. Additionally, the study examined the median and average number of days between admission and prescription fill dates. Furthermore, it assessed the total counts of prescriptions categorized by medication types following hospice admission, along with the median, average, and distribution of days' supply and medication on hand at the time of death, drawing from the findings of the second paper in this dissertation manuscript titled "A

Machine Learning Approach to Assessing Part D Prescription Medication Waste in Hospice Patients".

As part of the second aim and simulating clinician survival estimates, the machine learning survival model included patient sociodemographic and clinical characteristics-based findings from prior work detailed in the second paper of this dissertation manuscript, titled "A Machine Learning Approach to Assessing Part D Prescription Medication Waste in Hospice Patients". The included patient sociodemographic characteristics included: age, reported race, sex, the original reason for Medicare enrollment (Aged or Disabled/End Stage Renal Disease (ESRD)), Medicaid and Medicare dual status, Part D low-income subsidy (LIS), and geographic residence. Patient clinical characteristics included prior hospice election, admitting hospice care setting, prior inpatient hospital admission, prior history of cancer, count of comorbidities (chronic obstructive pulmonary disease, heart failure, ischemic heart disease, diabetes mellitus, nervous system/ neurological disease, renal failure, liver failure/disease, dementia, HIV, sepsis, hypertensive disease, and mood disorder), and number of predictors of death (health conditions) at time of hospice admission [60]. Patient medication characteristics were also incorporated by capturing information related to the filled Part D Prescriptions in the 12-months before a patient's admission to hospice.

Predictors of death are defined by CMS in their coverage determination document "Hospice - Determining Terminal Status" [60]. They are defined with guidelines as a

decline in clinical status predictive of a life expectancy of six months or less and include: recurrent or intractable infections, progressive inanition - weight loss, dehydration or hypovolemia, dysphagia, cough, nausea/vomiting, dyspnea, diarrhea, pain, hypotension, ascites venous obstruction, edema pleural, cognitive impairment, change in consciousness, pressure ulcers stage 3-4, sepsis/septicemia, aspiration pneumonia, and upper urinary tract infection (pyelonephritis) [60]. Binary flags (1-Yes/0-No) were created for each condition and then summed to calculate the number of predictors of death. The comorbidities and health conditions were identified by examining the ICD-9 and ICD-10 diagnosis codes on the patient's claims for services that occurred the 6-months before and during the study period. All ICD codes were cross walked to Clinical Classifications Software (CCS) ICD-9-CM diagnoses codes, which groups the diagnosis codes into over 231 clinical categories [61]. Binary flags (1-Yes/0-No) were created to capture the GPI classification of a medication a patient filled following their hopsice admission and included: Antibiotics, Antineoplastics, Anti-Virals, Cardiovascular, Central Nervous System, Dental, Dermatology, Diabetes, Endocrine, Gastrointestinal, Genitourinary Agents, Hematology Agents, Hyperlipidemic Agents, Medical Devices/Supplies, Misc. Anti-Infectives, Misc. Therapeutic Classes, Nutritional Agents, Ophthalmic Agents, Pain Management, Passive Immunizing, Respiratory, Vaccines, and Vasodilators.

Machine-learning approaches and prediction performance evaluation

This research needed estimated survival days for each patient as part of the second aim, which sought to compare and evaluate if rule-based prescription durations result in less medication (days' supply) on hand at the time of death. Although the limitations section has already outlined the shortcomings of using only claims data, this approach allowed for the simulation of clinician estimated survival days for the purpose of testing the overall research aims and methodology. To accomplish the goal of developing estimated survival days for each patient, the sample was first randomly divided with 80% of patients assigned to the training set and 20% to the testing set. The analysis then trained and tested two supervised machine-learning approaches used in survival analysis: Random Survival Forest (RSF) and Cox Proportional Hazards (Cox PH). These methods were selected based on their ability to handle the size, structure of the data, the ability of both in managing a high number of quantitative and categorical predictor variables, and their use in similar research [68] [77] [78] [71] [79]. And their widespread use in survival analysis literature and availability of packages in python contributed to their selection.

Cox Proportional Hazard

The CPH model is a common multivariable approach for analyzing survival time data in medical research [62]. CPH shares similarities with multiple regression models, which seek to understand how two or more predictor variables affect an outcome, with the exception that CHP focuses specifically on survival time analysis and the dependent variable is the hazard function at a given time [63]. CPH regresses the survival times, or

the “hazard function”, on the explanatory variable to try and find a mathematical relationship between them [63]. The hazard function can be defined as the probability that “an individual will experience an event, e.g., death, within a small-time interval given that the individual has survived up to the beginning of the interval” [63]. The regression coefficients (the covariates) represent the magnitude of the effect of explanatory variables (independent variables) on the hazard (the outcome), often expressed as hazard ratios [64]. Proportional hazard is the assumption of a constant relationship between the dependent variable and the explanatory variables over time; meaning the hazard function for any two individuals at any point in time are proportional [64].

CHP offers many advantages in survival analysis. Unlike parametric survival models, e.g., the Weibull regression model, where the equation is based on assumptions about how long individuals survive before experiencing the event, CPH is semi-parametric and does not require any assumptions concerning the hazard distribution [65]. CPH does make assumptions about the proportional hazards and the functional form of the covariates’ effects [65]. And similar to a logistic regression CHP requires minimal tuning of the model, however users may still need to regularize the model to detect and address multi-collinearity. A potential disadvantage of CHP is its ability to only capture linear patterns in the data and overfitting when the number of features exceed the number of observations [66]. However, in terms of the bias and variance, CHP achieves low variance by making distributional and functional form assumptions but when these

assumptions are incorrect the bias can be large, and the model will perform poorly [67]. Because of its versatility CHP lends itself to many different types of survival analyses subjects in healthcare, such as identifying market factors associated with the timing of hospice use [68], comparison of functional impairment tools in predicting survival [69], comparison of Part D drug discontinuation and switching rates upon reaching the spending gap [70], and hospital readmission in patients with heart failure [71].

Random Survival Forest

Random forests (RF) were developed by Leo Breiman in 2001 [72]. RF expanded the concepts of classic decision trees, which works by repeatedly splitting data according to input predictor variables, by partitioning the inputs recursively to form groups (nodes in the tree) of subjects which are similar according to the outcome [73]. Traditional RF methods are a supervised ensemble learning technique that build many decision trees and merges them together to predict the outcome of interest [74]. The final prediction is the function or mean of each observation's prediction. Breiman stated that "random forest uses an effective method called bootstrap aggregation, as well as the random subspace method to grow individual trees to achieve an extremely powerful aggregated predictor, capable of classification and regression, with better generalization error than an individual decision tree" [72]. The RF methodology has been extended to survival analysis to allow for censored data to be used optimally during the construction of trees in the forest. The approach "changes the dynamic of splitting rule selections during the tree and forest construction so that signaled variables can be emphasized more in the

refitted model" [75]. Censored data typically do not have any natural measure of within node homogeneity or "impurity," and this causes difficulty in inheriting the "impurity reduction" splitting rule [75].

In 2008, Ishwaran, et al. developed a RSF method based on the principles of Breiman [76]. Over the years, RSF has gained traction in healthcare research, particularly in predicting events like cardiovascular episodes [77], predicting patient survival in comorbidities like cancer [78], and impacts of patient behaviors, e.g. sleep patterns, on predicting mortality [79]. RSF allows researchers to explore how various factors influence survival outcomes over time by leveraging decision trees to predict survival probabilities. Instead of assuming a specific functional form for the hazard function (like CPH), RSF builds a model based on the data itself, making it non-parametric [76]. This means that RSF does not require any assumptions about the underlying distribution of survival times [76]. Additionally, RSF can handle many predictor variables and can handle outliers and multicollinearity in the data. One potential advantage of RSF over CPH is its ability to capture both linear and nonlinear relationships and interactions between predictors more effectively. And that is because RSF is based on decision trees, which recursively split the data based on the predictor variables, creating branches that represent different combinations of predictor values [80]. Additionally, when using RSF the researcher has the ability to control many of the parameters including: the number of trees constructed, number of candidate features to try at each split, minimum number of cases in a terminal node, the maximum depth of any tree, and most importantly the

splitting rule [80]. However, like CPH, RSF models may be prone to overfitting when the number of features exceeds the number of observations. In terms of how RSF converts the survival probabilities to survival days, the model uses the Kaplan-Meier estimator, which is a statistical method used to estimate the survival function (the probability of survival over time). Although the Kaplan-Meier estimator calculates survival probabilities at various time points throughout the observation period, this initial run selected the survival probability specifically at time 0 on the survival curve and extracted the corresponding survival time value. Further testing was done to try and improve the accuracy of the predicted survival days using the Inverse Probability Weighting (IPW) technique. Essentially this method applied a threshold to the probability curve for each record and selects the survival time at or below this probability threshold. A range of thresholds between 1 and 1.0 were tested, with 0.63 yielding the optimal performance based on evaluation parameters, although it was still outperformed by median trapezoidal rule (discussed below).

Model calibration

In survival analysis, calibration can aid in aligning predicted probabilities with actual outcome rates and accurately estimating survival days over the model's measurement period [81]. Various methods of calibrating exist for both CPH and RSF, including recalibration curves, Cox calibration, survival calibration forests, Platt scaling, isotonic regression, or median trapezoidal rule. Given the absence of an established readily available software package tailored specifically for survival calibration forests,

this study chose to explore the viability of alternative methods, i.e., isotonic regression and the median trapezoidal rule. Platt scaling was considered for RSF calibration but was ultimately not used due to requiring an additional training and test dataset and its limited ability to handle only linear relationships in the data. RSF and these calibration methods were selected based on preliminary modeling results indicating RSF's superior performance compared to CPH, a decision further elaborated upon in the Results section of this paper.

Isotonic regression was introduced by Frank Anscombe in 1952 and its application in machine learning for probability calibration was first proposed in 2002 by Bianca Zadrozny and Charles Elkan. Isotonic regression is a non-parametric approach that fits a piecewise-constant non-decreasing (step-like) function to the predicted probabilities with the goal of improving the prediction [82] [83]. Zadrozny and Elkan's work focused on addressing the issue of overconfident predictions generated by binary classifiers, where the predicted scores didn't accurately reflect probability estimates [82]. It is a popular methodology owing to its ability to manage both linear and nonlinear relationships between predicted probabilities, particularly when addressing overconfidence [84]. Isotonic regression works by identifying regions where the predicted probabilities are consistently higher or lower than the actual probabilities [85]. The probabilities are then adjusted by fitting a monotonic function to the predicted probabilities to reshape the curve while maintaining the probabilities order (likelihood of experiencing the event), addressing biases, and inconsistencies [85]. An interpolated

probability threshold is determined and is used to set a point at which the event (death) is experienced [85]. This knowledge learned from the training set is then applied to the test data probabilities. To translate the probabilities to survival days the probabilities are first normalized to add up to 1 (probability/sum of probabilities [85]. These normalized probabilities are then used as weights in a random selection process to determine the survival time. The randomness in the selection process comes from the probabilistic nature of the selection, where each time point has a chance of being selected based on its probability [85]. However, the probabilities themselves influence this randomness: time points with higher probabilities are more likely to be selected as the survival time, reflecting a higher confidence in survival at those time points [85]. As part of model evaluation, the interpolated probability threshold was tested at different values between 0 and 1.0 to identify the best performing isotonic calibrated model (where interpolated probability threshold = 0.35) based on the model evaluation criteria discussed below. Recent applications of RSF and isotonic calibration include: predicting readmission of death after discharge from the ICU [86], predicting heart transplant survival with LASSO and RSF and calibration [87], and predicting COVID-19 mortality in hospice [88].

The use of the trapezoidal rule can be traced as far back as 50 BCE where it was used by ancient Babylonian astronomers to calculate Jupiter's position from the area under a time-velocity graph [89]. In more recent times there isn't a specific researcher that can be attributed to the inclusion of this method into Machine Learning as its been extensively studied for decades (event centuries) [90] [91]. Recent work in survival

analysis includes: impacts of palliative care on patient functioning [92], heart failure patient's readmission of mortality prediction [93], predicting two-year survival with RSF after first heart attack [94], and predicting survival time for cancer patients [95]. For this study the RSF model predicts survival probabilities for each instance in the test data, following training, then the median calibrated predicted survival is calculated for each patient using the trapezoidal rule. After obtaining the median calibrated survival for each patient, the methodology converts these values into survival days by translating the probabilities into actual time intervals representing survival duration. The trapezoidal rule is a method for approximating the area under a curve and it works by dividing the survival probability curve into smaller trapezoidal segments (each formed with the x-axis) [96]. Then the area of each trapezoid is calculated and summed to the approximate total area under the curve [96]. The segment where the cumulative area first exceeds 0.5 (or the median) is identified for each record, and the corresponding survival time is determined [96].

Data Analysis Approach

Descriptive statistics

To understand the composition of the sample and discern any differences, the research employed descriptive statistics (means, standard deviations, medians, proportions, etc.) to assess patient demographic characteristics (Table 1) and survival time (Table 3). Additionally, summary statistics were also used to explain various aspects of patient's Part D prescriptions filled after admission to hospice. This included the

duration prescribed by the clinician, the categories of medications filled, the quantity of medications (days' supply) on hand at time of death, and time between hospice admission and prescription fulfillment (Tables 1-3). This data played a crucial role for the first aim in shaping the rule-based prescription durations and determining the appropriate prescription lengths corresponding to different ranges of remaining survival days. The data and fields presented in Table 1 provided the setup and input of patients for the survival machine learning methods, which were utilized as part of the second aim to simulate clinician estimated survival days.

Machine learning methods and calibration

This study evaluated two machine learning methods, CPH and RSF to estimate survival days as part of the second aim. The intention of the approach wasn't to try and develop a new method or improve estimating survival accuracy in hospice patients, but rather to simulate a clinician estimating a hospice patient's survival. The ultimate goal being to use the survival estimates to test the overall research goals and methodology of rule-based prescription durations to reduce medication on hand at time of death in this population. The data was split 80% for training and 20% for testing, based on the Pareto Principle, which is a phenomenon that states that roughly 80% of outcomes come from 20% of causes [88]. As discussed above calibration methods isotonic regression and the median trapezoidal rule were applied to RSF probabilities to improve model accuracy.

Prediction performance evaluation

To assess the performance of the models and calibrated iterations of their models the following metrics of evaluation were used: (1) Concordance Index (CI), (2) Time-dependent Area Under the Curve (AUC) – Receive Operating Characteristic (ROC), (3) Integrated Brier Score (IBS), (4), Mean Absolute Scaled Error (MASE) and (5) Kaplan-Meier survival curve. Results from this analysis were captured in Table 4 and in Figure 1.

To assess discrimination performance (i.e., the accuracy of the patient's predicted survival), the CI and time-dependent AUC of the models were compared and optimal performance as 0.7 to 0.8 as good and greater than 0.8 to be very good. The purpose of these measures is to inform if the model was able to effectively order/rank pairs of patients in terms of their risk of the event (death) over time. Additionally, this analysis also assessed model performance using IBS and MASE. The purpose of these metrics is to measure the overall accuracy of predicted survival probabilities and assess model performance. The optimal performance of these measures was values less than 1 and those closest to 0 being the best performing. The Kaplan-Meier survival curve is a graphical representation for visualizing the probability of survival over time comparing the predicted and the actual. Optimal performance is where there isn't significant separation between the predicted and the actual survival curves.

Concordance Index (c-index (CI)) is a measure of discriminatory ability for survival models [97]. The measure is equivalent to the traditional AUC ROC that evaluates binary classifiers. CI is calculated by comparing pairs of patients in the

dataset, whereby the model predicts which individual will experience the event sooner, and the actual outcomes are compared to the predictions [98]. If the predicted order aligns with the actual order of event occurrence (concordant pair), it contributes to the CI. The CI is essentially a measure of how well the model ranks individuals by their risk of experiencing the event over time. CI ranges from 0 to 1, where a CI close to 1 indicates the model has excellent discriminatory ability, i.e., higher risk patients are more likely to experience the event before lower risk patients, whereas a CI of 0.5 is a model that performs no better than random chance [98].

Time-dependent Area Under the Curve – Receive Operating Characteristic (AUC-ROC) is a metric used to evaluate the performance of time-to-event models, with values closer to 1 indicating excellent predictive performance. Traditional AUC-ROC analysis calculates the true positive rate (TP) against the false positive rate (FP) at various decision thresholds while the event status and outcome value for a record remain fixed in terms of time [99]. Patients' disease statuses are changing over time thus an AUC-ROC curve as a function of time, where AUC is calculated at multiple time points, thus it is more appropriate for survival analyses like RSF [99]. In survival analysis, the positive events are typically defined as events occurring after a certain time point, while negative events are defined as events occurring before that time point (censored) [99]. The data used in this study contained no censored data, with all patients included

dying during the performance period.

Integrated Brier Score (IBS) is a measure used to evaluate the overall model calibration and predictive accuracy in survival models and incorporates both the discrimination and calibration aspects [100], with values closer to zero indicating better predictive accuracy. IBS compares the predicted survival probabilities from the model to the actual outcomes and quantifies their agreement (e.g., whether an event occurred or not) for each time point in the model [101]. Specifically, the IBS for a time interval is the average of the squared differences between predicted probabilities and actual outcomes over that interval [101]. This process results in a curve that represents the model's performance across time intervals and ultimately a score that is as an overall average performance measure for the prediction model for all times [100].

Mean Absolute Scaled Error (MASE) is a measure that compares the difference between the predicted values and the actual values (errors) of the model to the errors of a sample naïve forecast or baseline [102]. The naive forecast is generally the previous value as the forecast for the next time point [103]. The MASE is then the average of the squared errors across all time points in the dataset, normalized by the mean absolute error of a naive baseline model [103].

Kaplan-Meier survival curve is a visual measure, a graphed plot, used to analyze the survival function and can be used to compare the actual to the predicted groups [104]. Time is represented by the x-axis and probability of survival is on the y-axis. At each point of time, the survival probability is estimated by dividing the number of individuals surviving beyond that time by the number of individuals who have not yet experienced the event (death) [105]. The calculation of survival probability is the dividing the number who have survived by the eligible population (at risk of the event cohort).

Rule-based prescription comparison

Table 5 presents the rule-based prescription lengths assigned to patients given their survival time at fulfillment as part of the first aim. The predicted survival days from the model were adjusted to subtract the time between admission to hospice and the prescription fill date (remaining survival days). The prescription lengths selected were based on the common prescription limits of 7, 10, 14, 30, 60, and 90-days as described in the rule-based prescription length (days' supply) methodology section of this paper. The rule-based prescription lengths were allocated based on intervals of remaining survival days through iterative testing and refinement. The testing process to determine the suitable prescription duration based on the range of survival days involved gathering and exploring information through literature reviews. It also included testing segmentation by survival days, quintiles, and time between prescription lengths, as well as calculating descriptive statistics of prescription durations and survival (refer to Table 2 and Table 3).

Additionally, the testing included initial prescription durations and refills in cases where patients exhausted their medication before their passing. Testing also included identifying a days' supply threshold for when hospice patient's prescription end before death and are not refilled. The testing process included testing refill lengths in addition to the initial prescription rules, where the initial prescription would've ended prior to the patient's passing potentially leaving them (unethically) without a needed medication. The three different refill iterations, which included:

1. 14-days' supply added to the rule-based prescription where the initial prescription end date was before death.
2. 30-days' supply added to the rule-based prescription where the initial prescription end date was before death.
3. 14-days' supply added and if need another 10-days' supply added to the rule-based prescription where the initial and follow-up prescription end date was before death.

As part of comparing tradition prescription durations to the rule-based prescription lengths the process involved comparing the number of prescriptions and days' supply on hand at death in Microsoft Excel between the actual and rule-based prescriptions in three categories: 1) rule-based resulted in the same overage; 2) rule-based resulted in savings (less overage); and 3) rule-based resulted in losses (more overage). Additionally, success was measured by the total days' supply and percent change where the rule-based prescriptions resulted in savings (less overage).

RESULTS

Summary Statistics

Summary statistics for the sample of 188,263 patients are presented in Table 1. The cancer cohort made up 82.2% (n=154,649) of the sample and the non-cancer made up the remaining 17.8% (n=33,614) of the sample. Both cohorts' races were predominantly white, constituting over 80% of the sample. Additionally, they had a similar geographic distribution, i.e., more than 50% of the sample was in the Northeast and Southeast (because of the participating SEER regions). Also, over 82% of the sample was enrolled in Medicare by aging into the program. The two groups have the same top four most common terminal hospice admitting diagnoses (cancer, dementia, chronic obstructive pulmonary disease, and congestive heart failure), albeit cancer makes up 78% of the admitting hospice diagnoses for the cancer cohort as opposed to 10% for the non-cancer. The average length of stay in hospice is the same for both groups at 31 days and both groups over 90% of the patient's had not had a prior hospice benefit election. There was nothing remarkable about the admitting health status conditions with both groups having similar distributions with prevalence no more than 4% for the various conditions. Lastly, the two groups had similar patterns, albeit slightly higher prevalence in the non-cancer cohort, in their Part D prescriptions filled following their hospice admission. Cardiovascular and central nervous system medication categories were the most prevalent in both groups.

Some of the differences between the two groups included the cancer cohort being on average 6.6 years younger (77.9 vs 84.5 years old) and having 74.6% under the age of 85 compared to the non-cancer at 42.3%. The cancer cohort saw a higher proportion of patients receive hospice care in their private residence (64.7%), compared to non-cancer (44%). The non-cancer cohort had a smaller proportion of patients with 2 or more inpatient admission in the year before hospice (22% vs 30%). As well as fewer comorbidities with only 37.4% having 4 or more compared to the non-cancer where 48% had 4 or more. The non-cancer cohort consisted of more females (65.4%), whereas the cancer cohort had a more even distribution of males (47.4%) and females (52.6%). The non-cancer cohort had a higher proportion of Medicaid dual eligible (10% higher) and Part D LIS patients (8.5% higher). On average the non-cancer group was taking more medications in the year before their hospice admission (16.1) compared to the cancer group (13.7). The non-cancer cohort saw over double the number of patients with dementia (44%) compared to the cancer group (18%).

Identifying rule-based prescription durations

To support the first aim of developing rule-based prescription lengths based on patients' survival time, the research analyzed various factors (i.e., mean, median, range, percent, distribution, etc.) of prescription days' supply, survival days, prescription lengths, days between admission and prescription fill dates, category of prescriptions, and medication on hand at the time of death. Table 2 presents results of these metrics regarding Part D prescriptions dispensed after hospice admission, which of the 188,263

patients in the sample only 56,266 (30%) patients had prescriptions that met this criterion. However, these 56,266 patients had over 214,571 prescriptions with a median days' supply of 30. In total 83% (179,682) of prescriptions were 10 days' supply or less. On average these prescriptions were filled 19.6 days after the patient's hospice admission and on average resulted in 22.5 days' supply on hand at time of death or 64% of the original prescription amount. The sample overall saw 2,683,125 days' supply of medication on hand at time of death, it's important to note overall quantity of medication could be higher. Like the overall sample, the cancer cohort made up a larger proportion of patients (76.7%) and Part D prescriptions dispensed (74.6%) after hospice admission. Some of the information from this table helped influence the rule-based prescription durations selected.

Empirical statistics were gathered from the data to better understand the samples survival times and distribution, as well as timing and distribution of when prescriptions were prescribed and how long they lived after fulfillment. Table 3 presents information pertaining to the sample's survival time in hospice and remaining survival time after prescription fulfillment. The median survival time of patients with prescriptions was 41 days, with 20-21% living 17 days or less. Additionally, 47-48% lived less than 17 days after filling their Part D prescription. Table 3 was instrumental in providing information that helped influence the rule-based prescription durations presented in Table 5.

Survival Model Results

After analyzing the sample's composition, the study proceeded to address the second aim by estimating survival days to simulate clinician-estimated durations. This allowed for the comparison of medication on hand at the time of death between traditional clinical prescription durations and rule-based prescription durations based on a patient's survival time (developed from aim 1). Table 4 and Figure 1 present the results for four machine learning methods that were tested. Although there were some slight variations between the cancer and non-cancer populations, in regard to the models and evaluation metrics, accuracy of predicted survival days, and the rule-based prescription comparison there were no major differences between the two groups (see Appendix A). Therefore, from this point forward the results section will focus on the sample as a whole and not the separate cohorts.

The identification of the optimal model was an iterative process that is discussed alongside the results. Initial survival modeling was done using CPH and RSF. CPH had a Cox partial likelihood score (measure of goodness of fit) of 0.02, which suggests that the model explains some of the variability in the survival data but may not be an excellent fit (scores closer to zero indicate poor performance, whereas scores closer to 1 indicate excellent performance). Looking at the Kaplan-Meier survival curve for CPH in conjunction with the IBS of 2.17 and a MASE of 1.16 (values less than 1 are good; values closer to 0 are excellent) it was determined that the CPH model was not the optimal compared to RSF. RSF had a CI of 0.79 and an AUC of 0.89. However, the

model resulted in unsatisfactory scores of 1.85 and 3.24 respectively for both IBS and MASE, which aligned with the performance of the model in the Kaplan-Meier plot and drastically over predicting survival. Further testing, albeit not presented, was done to try and improve the accuracy of the predicted survival days using the Inverse Probability Weighting technique. When the threshold to the probability curve was set to 0.63 the model evaluation metrics improved, i.e., CI=0.81, AUC=0.90, IBS=0.48, and MASE=0.44. The model is not presented or discussed further given its similarity in performance to the RSF model calibrated using median trapezoidal rule.

Calibration was then applied to the RSF model and the outputs for both the isotonic regression and median trapezoidal rule were compared. Isotonic regression resulted in a CI of 0.73 and a AUC of 0.80, both of which are reportedly lower than the non-calibrated RSF model. However, the IBS and MASE, respectively 0.26 and 0.54, indicated the model was more accurate in predicting survival days compared to the non-calibrated RSF. RSF calibrated with median trapezoidal rule emerged as the optimal model, boasting the best scores across all evaluation metrics, i.e., CI=0.82, AUC=0.90, IBS=0.11, and MASE=0.41. Additionally, the Kaplan-Meier survival curve had the closest graphically map representation between the actual and predicted survival functions. And although the models themselves don't provide individual survival time predictions, rather survival probabilities, Kaplan-Meier, Inverse Probability of Censoring Weights, Isotonic Regression, and Trapezoidal Rule were used to translate the survival probabilities to survival days for each individual patient.

Sociodemographic Model Bias

RSF using median trapezoidal rule was overall the best performing model across the metrics of evaluation (as defined in the Statistical Analysis section). To assess the potential of model biases related to sociodemographic variables and the potential for the model's predicted survival days to be biased in certain populations, the AUC of the covariates in the RSF model were plotted to compare the classes within each covariate. Results from the comparison are presented in Figure 2 where key sociodemographic variables of the model were examined such as cancer status, ESRD status, LIS status, age, Medicare enrollment status, patient's location of their hospice care, race, dual status, and gender.

There was no bias found between the non-cancer and cancer cohorts, which supports the decision to present finding and results at the combined level. There were slight variations between 0.01 and 0.06 in the AUC by gender and race, suggesting there is modest variation in predictive performance. The variation for both Dual and LIS status was the same, with those experiencing the status having an AUC of 0.68 compared to those not experiencing the status having an AUC of 0.78. Indicating a more notable variation in predictive performance based on Dual and LIS status. Some of this variation could be attributed to the status experiencing cohort making up a smaller proportion of the sample (30%). The largest differences in AUC between classes occurred between ESRD status, age, Medicare enrollment status, and primary location of hospice care indicating there could be potential bias. There is some overlap between the classes within

ESRD status and Medicare enrollment status, but the finding is similar in that the accuracy of predicting ESRD patients is higher (AUC=0.9) than other cohorts. Again, this could be attributed to smaller samples and less variation (<1% of sample). The biggest variation in AUC was within the classifiers of age. While the extremes (young and exceptionally old) achieved AUC=1.0 the ages in between varied between 0.6 and 0.8 in their AUC. The other predictor with the biggest variation across class was the location of where the patient was receiving their hospice care. Patients who received their care in home had an AUC of 0.63, whereas those who received hospice care in the hospital had an AUC of 0.96.

Rule Results

Table 5 contains the mapping of predicted survival time frames to the rule-based prescription durations, fulfilling the first aim of the paper. As a reminder the intention of the survival model, as part of the second aim, was to simulate the clinician's estimate of the patient's survival at admission. The predicted survival time is then adjusted to subtract the time between hospice admission and prescription fulfillment (remaining survival days). This can result in negative remaining survival days, particularly when the estimated survival is less than the actual survival.

> *Example: a patient is admitted to hospice on July 1, 2015, and survives 9 days before passing away on July 10, 2015; the survival model estimates their survival to be 4 days (July 5, 2015); the patient fills a prescription 5 days after their hospice admission (July 6, 2015); the patient's remaining survival days from the prescription fulfillment on July 6, 2015 would be minus one (-1=4-5).*

In those instances, patients with survival times less than zero were assigned a 7 days' supply. Similarly, patients with remaining survival times between 0-6.9 days were assigned 7 days' supply. Patients with remaining survival times between 7-17.9 days were assigned 14 days' supply, and so on. Less than 1% of patients had remaining survival days between 76-90 days at the time of filling their prescriptions, whereas 12.9% of the sample had a predicted survival time between 76-90 days at the time of admission (Table 3). It's worth noting that even though a 90 days' supply rule-based prescription existed no patients in this sample were assigned this duration.

After running the trained model on the test data, the forecasted survival times for the test data were cross walked to the prescription dataset using Patient ID. This resulted in 42,605 prescriptions from the test panel being used in the rule-based prescription evaluation. As described above in outcome measures, to determine the appropriate rule-based prescription length to assign, the forecasted survival days were modified downward, excluding the survival days between the patient's hospice admission and the prescription fill date, resulting in a field termed remaining survival days. Patients were then assigned an initial prescription duration based on the rules defined in Table 5 as part of aim one. Two additional fields were then created to determine the amount of medication on hand at time of death for both the clinician prescriptions and the rule-based prescriptions. This calculation added the prescription days' supply to the date the prescription was filled and then subtracted the date of death to obtain a number of overage days' supply. The two prescribing methodology's overages were then compared.

The comparison of medication on hand at time of death between actual and rule-based prescription lengths is presented in Table 6 and Table 7 as part of evaluating the success within the second aim. Table 6 displays where no adjustments were made for prescriptions that ended before the patient's death date, presenting four different iterations:

1. No Adjustments to prescriptions that end before the date of death.
2. 14-days' supply added to the rule-based prescription where the initial prescription end date was before death.
3. 30-days' supply added to the rule-based prescription where the initial prescription end date was before death.
4. 14-days' supply added and if need another 10-days' supply added to the rule-based prescription where the initial and follow-up prescription end date was before death.

The different iterations aimed to address scenarios where the rule-based prescription ended before the patient's death date, with the research focusing on mitigating concerns related to prematurely shortening or withdrawing care, as well as testing the ability of various refill prescription lengths to reduce waste.

Table 6 demonstrates that in 36-50% of cases the two different prescription methodologies resulted in the same amount of overage. However, in 22-28% of cases the rule-based prescriptions resulted in less overage and reduced the days' supply on hand at time of death to 304,016 to 320,505. Conversely, in 23-33% of cases the rule-based

prescriptions increased the amount of overage by 123,257 to 145,216 days' supply. Overall, the rule-based prescription duration led to a decrease of 29.1% to 36.1% in the amount of days' supply of prescription medication on hand at the time of death. days' supply of prescription medication on hand at the time of death. Although the initial prescription rules reduced overage, they resulted in 4,109 (9.6%) prescriptions ending before the patient passed, which raises concern around unethically withholding care. The refill prescription iterations were successful in reducing the number of prescriptions that potentially left a patient without necessary medication (unethically withholding care):

- 939 (2.2%) prescriptions with initial plus 14-days' supply refill that resulted in reduced overage but ended before the patient passed
- 120 (0.28%) prescriptions with initial plus 30-days' supply refill that resulted in reduced overage but ended before the patient passed
- 294 (0.69%) prescriptions with initial plus 14-days' supply refill and if needed a 10-days' supply refill that resulted in reduced overage but ended before the patient passed

Table 7 applied a threshold that excluded prescriptions where either the clinician or rule-based prescriptions ended more than days before the death date. This was done mainly to address instances where a short-term prescription was prescribed to a patient during their hospice stay, where the patient didn't seek a clinician refill for a medication that ended before death, or where the model underestimated a patient's survival. With this threshold applied, in all instances the two different prescription methodologies

resulted in the same amount of overage 32% of the time. The threshold did not impact the rule-based prescriptions in term of the amount of overage reduction and still decreased the days' supply on hand at time of death by 304,016 to 320,505. The threshold did result in the rule-based prescriptions causing less additional overages, 100,600 to 110,613, compared to Table 6. Overall, in simulation the rule-based prescription duration led to a decrease of 32% to 45.5% in the amount of days' supply of prescription medication on hand at the time of death.

DISCUSSION

Summary

The hospice benefit is designed to encompass all care and services related to the patient's terminal illness. Medicare Part A and B will continue to cover any health problems that are unrelated to a patient's terminal illness and related conditions. Similarly, hospice care extends to prescriptions and covers only prescription drugs associated to the terminal illness and related conditions. Unrelated medications may still be obtained through the Medicare Part D benefit. This study found 30% of cancer patients admitted to hospice, with a prognosis of 90 days of less, between 2015 and 2019 obtained at least one medication through their Part D benefit after being admitted to hospice. In 2013, a Visante report estimated that approximately 1% (~14 million prescriptions or ~$1.68 billion) of all Part D prescriptions are wasted annually [2] [4]; death was identified as a contributing factor and accounted for an average of 50% of medication on hand at the time of death for each prescription. This study found 56,266

patients had 214,571 prescriptions prescribed after their hospice admission and at their time of death the average prescription still had 64.3% days' supply remaining (~22.5 days').

Previous research exists that examines prescription durations, waste, and has described the challenges associated, e.g., dispensing fees and prescriber timing, finding a correlation between longer prescription lengths and increased quantities and costs of returned drugs and that limiting prescription supplies to 28 days could potentially reduce wastage by a third [21]. Research comparing the differences in short (<60 days) and long (≥60 days) prescriptions among patients with common chronic conditions, found a consistently larger proportion of days' supply wasted with longer prescriptions but overall lower total unnecessary costs when considering dispensing fees and prescriber time [22]. Retrospective case studies of hospice patient's charts were used in to two separate cases to examine the extent of waste and estimate associated costs and finding patient's had on average between 2.95 and 9.7 different medications on hand at time of death [32] [33]. Literature that explores waste-reducing strategies for pharmacists found "patients receiving medications for more than 30 days are more likely to waste a part of those medications" [34]. However, research specifically aimed at reducing Part D prescription waste in hospice patients remains unexplored.

The purpose of this study was to develop and assess Part D rule-based prescription lengths that reduce medication on hand at the time of death among hospice

patients, with a particular focus on individuals with a prognosis of 90 days or less. The aims of this study were to: (1) construct a rule-based prescription duration decision support tool leveraging patient survival days as a key determinant of appropriate lengths of Part D prescriptions for hospice patients to reduce medication on hand at the time of death, and (2) compare the change in the amount of medication on hand at time of death between traditional clinical prescription durations to rule-based prescription durations that have been assigned based on a patient's survival time (decision support tool generated from aim 1). To achieve the first aim a sample of 188,263 Medicare patients (Table 1) were selected. A review of literature and best practices in conjunction with various patient factors were analyzed to develop rule-based prescription lengths (Table 5) based on patients' survival time, including median and average prescription days' supply, survival days at the time of admission and prescription fulfillment, and their distributions across common prescription lengths (Tables 2-3). To achieve the second aim the aforementioned sample was divided into 80%/20%, into training and test datasets. Four survival methodologies, i.e., CPH, RSF, RSF calibrated with isotonic regression, and RSF calibrated with median trapezoidal rule, were evaluated to identify the most effective method capable of accurately predicting patient survival to simulate a clinician's estimation of a hospice patient's survival time.

Following iterative testing, tuning, and evaluation, RSF calibrated with median trapezoidal rule was determined to be the superior method as it performed the best across the chosen evaluation metrics, i.e., CI=0.82, AUC=0.90, IBS=0.11, and MASE=0.41

(Table 4). An examination of patient demographics and characteristics between the cancer and non-cancer cohorts found both were similar in terms of race, geographic location, their qualifier for Medicare, top terminal hospice admitting diagnoses, prior hospice election status, average length of stay in hospice, and similar patterns in their Part D prescriptions filled following their hospice admission. The cancer population cohort tended to be younger (77.9 vs 84.5 years old) and have fewer patients with four or more comorbidities (37.4% vs 48%). The analysis found there to be no significant difference observed between the cancer and non-cancer cohorts, concerning the models and evaluation metrics, accuracy of predicted survival days, and the rule-based prescriptions. While the model did identify sociodemographic model biases between age, Medicare enrollment status, and primary location of hospice care there was no difference between the non-cancer and cancer cohorts. Therefore, the results focused on the sample as a whole and not individual cohorts.

After the trained model was applied to the test data, the resulting forecasted survival times were cross walked to the prescription dataset using Patient IDs. This resulted in 42,605 prescriptions included in the comparison of the rule-based prescription durations (Table 5). The resulting mediation on hand at time of death was then calculated for the rule-based prescriptions and compared to the amount caused by the clinician prescription durations. The two methodologies of prescription durations, i.e., clinician determined and rule-based, were analyzed in two scenarios over four iterations each. The first scenario examined all prescriptions regardless of when the clinician determined

prescription ended and the second applied a threshold that excluded prescriptions where either the clinician or rule-based prescriptions ended more than three days before the death date. The intent being in the latter to 1) address short-term or non-refilled clinician prescriptions and 2) control for where the survival model under forecasted a patient's survival thus creating non-comparable scenarios. It should be noted that fewer rule-based prescriptions were excluded with this condition due to the refill rules in place. The four iterations were meant to test the initial prescription as well as the ability of various refill prescription lengths to mitigate concerns related to prematurely shortening or withdrawing care where the rule-based prescription ended before death. In the initial scenario, the rule-based prescriptions reduced overage in 28% of cases, leading to a decrease of 29.1% to 36.1% in the amount of prescription medication on hand at the time of death. The second scenario saw similar success with the rule-based prescriptions reducing overage in 32% of cases, leading to a decrease of 32% to 45.5% in the amount of prescription waste. Overall, in this sample the rule-based initial and refill prescription durations were able to reduce prescription waste.

Implications and Recommendations

Government entities, such as the CMS, have reported that EHR systems/software can improve patient care and reduce fraud, improper billing, and prevent waste [106] [107]. The Institute of Medicine has outlined eight fundamental functions of EHRs, including order entry/management (e.g., lab tests, prescription drugs, and radiology) and clinical decision support (e.g., alerts, reminders, assessments, care plan templates) [108]. Based on the results of this research, the incorporation of rule-based prescription

durations for hospice patients into a clinician EHR software or electronic prescriptions software could be beneficial in reducing medication waste in hospice patients requiring Part D prescriptions.

Ideally the incorporation of rule-based prescription durations for hospice patients would work best in situations where all providers in the patient's care plan have access to the patient's EHR through integrated electronic health systems (i.e., the hospice provider, the prescribing provider, etc.). And a robust system that includes templates for prognosis tools like PPS and KPS and it utilized by providers. In the ideal use case, a patient's doctor (i.e., the hospice provider, the prescribing provider, etc.) would complete a survival assessment tool within the EHR at either the time of the hospice admission or within the encounter where a Part D prescription is requested. The assessment would calculate the estimated survival days, or survival range, and make a recommendation for the prescription length using the rule-based durations. The prescribing physician would have access to more information in the EHR to make an informed decision on the rule-based prescription recommendation and if necessary, override the suggested amount. As a learning system the rules could be adapted overtime to adjust for changes in the population and errors in initial prescriptions and refills.

The rule-based prescription durations presented here were basic and simplistic in nature and could be designed to be more complex. The rules could be tailored to specific diagnoses, different medications, state-laws, and/or leverage additional information in the

patient's EHR. In cases where there isn't an EHR or coordination and collaboration of care, the prescribing provider can still use the rule-based prescription durations, they would just need to estimate (or obtain) the patient's predicted survival. In those cases, more basic rules could be beneficial as it could maintain simplicity of use decreasing complex rule tracing.

Challenges

Although the results from this research show there are benefits to Part D waste reduction in hospice patients using rule-based prescription durations, there are several challenges associated with this. Currently there exists guidelines for clinicians, from organizations like the American Society of Health-System Pharmacists and the National Hospice and Palliative Care Organization, suggesting steps and considerations for deciding prescription use and duration, as well as deprescribing medication in hospice patients [109] [110]. Additionally, clinician support tools have been developed, such as PPS and KPS, to aid in predicting prognosis, mortality, or assessing functional ability in hospice patients [226]. However, even with these resources and tools predicting a patient's prognosis at the end of life for patient's remains challenging, making the selection of a prescription length difficult. Clinicians could opt to prescribe minimal amounts of medication to avoid wasting medication, but this approach risks frequent refills, which will be inconvenient and a burden for patients and caregivers who are already experiencing a difficult situation and are potentially having trouble accepting the inevitable [33]. Conversely, prescribing liberal amounts of medication may alleviate

inconvenience but increases the likelihood of excess unused medication [33]. Furthermore, the multifaceted nature of end-of-life symptoms often necessitates the trial and error of various medications, contributing to the accumulation of unused medication [33]. This research supports the notion that rule-based prescriptions could be combined with EHRs and existing clinician support tools for predicting survival and provide a means of medication waste reduction (compared to clinician determined durations), while still considering the right balance of clinician-patient burden through clinical overrides.

Limitations

This study has several limitations primarily related to the data source, sample selected, and development of the rule-based durations. The findings of this study are limited to this sample of patients included in the linked SEER Medicare data and those from the 5% Medicare fee-for-service patients residing in the SEER areas. The scope also limited the data to those patients who died within 90 days of their hospice admission (n=188,263), thus excluding individuals with potentially longer and more complex hospice care episodes, which could influence post-hospice admission Part D prescription patterns differently. Additionally, due to lack of available data the study simulated clinician estimated survival times relying solely on claims data using RSF instead of real clinician projected times. This study could be further improved by using the estimated time of survival when the prescription was written as opposed to the survival time at the hospice admission. The rule-based durations used for this study are limited in their approach as they do not currently consider anything other than survival time. The rules

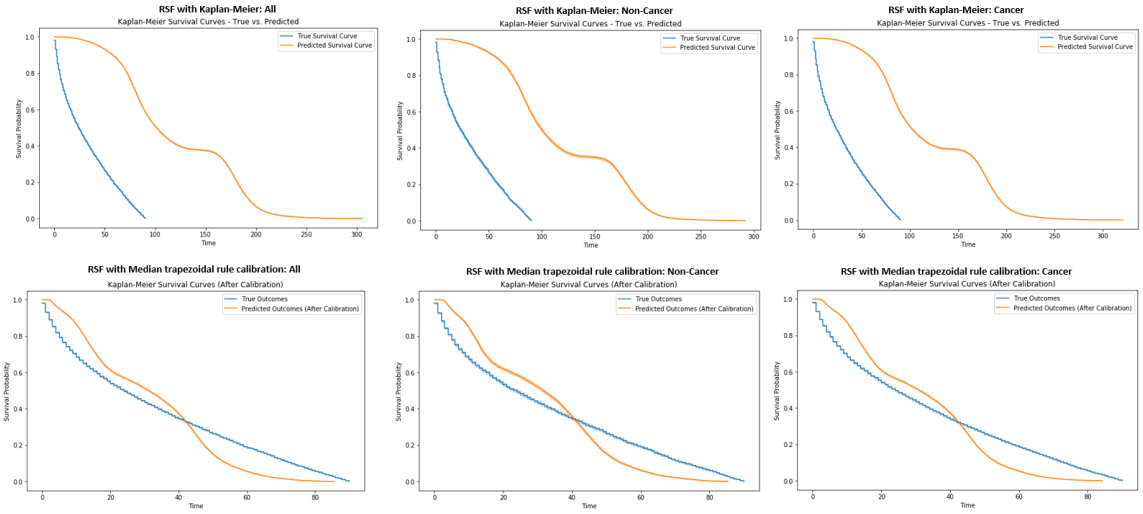
could be enhanced by considering the type or category of medication, diagnosis, and state laws and industry recommendations or guidance. The rules could be further improved with the inclusion of empirical reasoning, such as confidence intervals and statistical tests, and feedback from insurance plans and clinical experts. Lastly, there are limitations around the amount of medication on hand at time of death due to the following assumptions:

1. The patient filled the medication on the same day they received the prescription.
2. The patient initiated the medication immediately upon receiving it.
3. The patient did not discontinue the medication in the days leading up to death.
4. No alternative prescription was provided in place of the current one.
5. Dosage and frequency remained unchanged.
6. The prescription regimen did not include medications to be taken on an as-needed basis.

APPENDICES A. NON-CANCER AND CANCER COMPARISON

Presented below are results comparing outcomes for two different methods (RSF with Kaplan-Meier and RSF with trapezoidal rule) between the cancer and non-cancer cohorts.

Measure Evaluation	**RSF predicted survival days using the Kaplan-Meier estimator**				**RSF median calibrated predicted survival days using the trapezoidal rule**		
Population	**All**	**Non-Cancer**	**Cancer**		**All**	**Non-Cancer**	**Cancer**
C-index	0.79	0.82	0.79		0.82	0.82	0.81
Time-dependent AUC-ROC	0.89	0.91	0.88		0.9	0.91	0.89
Integrated Brier Score (IBS)	1.85	3.2	3.31		0.11	0.26	0.42
Mean Absolute Scaled Error (MASE)	3.24	4.4	3.01		0.41	0.39	0.53



APPENDICES B. TABLES AND FIGURES

Table 1. Patient Demographic and Characteristics in Hospice, Maximum of 90 days survival.

Characteristics	Total		SEER Non-Cancer		SEER Cancer	
	n= 76,777	%	n= 15,857	%	n= 60,920	%
Age mean (std)	80.1 (10.1)		85.4 (9.7)		75.8 (9.7)	
≤69	11,707	15.2%	1,136	7.2%	10,571	17.4%
70-74	10,629	13.8%	990	6.2%	9,639	15.8%
75-79	12,429	16.2%	1,494	9.4%	10,935	17.9%
80-84	13,760	17.9%	2,520	15.9%	11,240	18.5%
85-89	13,751	17.9%	3,570	22.5%	10,181	16.7%
≥90	14,501	18.9%	6,147	38.8%	8,354	13.7%
Sex						
Male	32,436	42.2%	5,006	31.6%	27,430	45.0%
Female	44,341	57.8%	10,851	68.4%	33,490	55.0%
Race						
White	64,061	83.4%	13,566	85.6%	50,495	82.9%
Black	6,965	9.1%	1,190	7.5%	5,775	9.5%
Asian	2,082	2.7%	380	2.4%	1,702	2.8%
Hispanic	1,596	2.1%	390	2.5%	1,206	2.0%
Other/Unknown	2,073	2.7%	331	2.1%	1,742	2.9%
Geographic Region						
Northeast	26,398	34.4%	4,677	29.5%	21,721	35.7%
Southeast	17,141	22.3%	3,615	22.8%	13,526	22.2%
Midwest	6,885	9.0%	1,615	10.2%	5,270	8.7%
Southwest	1,821	2.4%	665	4.2%	1,156	1.9%
West	24,515	31.9%	5,282	33.3%	19,233	31.6%
Missing	17	0.0%	3	0.0%	14	0.0%
Entitlement Reason						
Old age and survivor's insurance (OASI)	62,556	81.5%	13,496	85.1%	49,060	80.5%
Disability insurance benefits (DIB)	14,006	18.2%	2,308	14.6%	11,698	19.2%
End-stage renal disease (ESRD)	215	0.3%	53	0.3%	162	0.3%
Medicaid Dual Eligible						
No	49,052	63.9%	9,016	56.9%	40,036	65.7%
Yes	27,725	36.1%	6,841	43.1%	20,884	34.3%
Part D Low-Income Subsidy						
No	46,685	60.8%	8,649	54.5%	38,036	62.4%
Yes	30,092	39.2%	7,208	45.5%	22,884	37.6%
Number of unique medications in year before admission, mean (std)	13.2 (15.5)		14.4 (16.5)		12.9 (15.2)	
Most Common Admitting Hospice Diagnosis						
Cancer	47,428	61.8%	1,321	8.3%	46,107	75.7%
Delerium/Dimentia	7,042	9.2%	4,143	26.1%	2,899	4.8%
COPD	3,902	5.1%	1,420	9.0%	2,482	4.1%
CHF	4,009	5.2%	2,037	12.8%	1,972	3.2%
Hospice length of stay, days mean (std)	81.6 (139.1)		111.4 (183.9)		73.8 (123.7)	
Hospice length of stay, median [interquartile range]	32 [11-87]		37 [11-126]		31 [12-81]	
≤7	13,497	17.6%	2,933	18.5%	10,564	17.3%
8-14	9,532	12.4%	1,849	11.7%	7,683	12.6%
15-30	14,593	19.0%	2,494	15.7%	12,099	19.9%
31-90	20,608	26.8%	3,614	22.8%	16,994	27.9%
91-180	9,438	12.3%	2,059	13.0%	7,379	12.1%
≥181	18,291	23.8%	12,090	76.2%	6,201	10.2%
Admitting Hospice Care Setting						
Private Residence	48,410	63.1%	6,983	44.0%	41,427	68.0%
Care Facility (Assisted Living or Nursing Facility)	25,344	33.0%	8,375	52.8%	16,969	27.9%
Hospice Facility	2,274	3.0%	374	2.4%	1,900	3.1%
Hospital, Inpatient Hospice Facility	749	1.0%	125	0.8%	624	1.0%

Prior Hospice Election						
No	72,210	94.1%	14,313	90.3%	57,897	95.0%
Yes	4,569	6.0%	1,546	9.7%	3,023	5.0%
Number of inpatient hospital admission in year before hospice, mean (std)	1.2 (2.2)		1.4 (2.6)		1.1 (2.1)	
0	44,699	58.2%	8,712	54.9%	35,987	59.1%
1	12,198	15.9%	2,302	14.5%	9,896	16.2%
2	8,007	10.4%	1,830	11.5%	6,177	10.1%
3	4,200	5.5%	966	6.1%	3,234	5.3%
4+	7,673	10.0%	2,047	12.9%	5,626	9.2%
Number of Comorbidities in 6 months before hospice mean (std)	3.1 (2.3)		3.4 (2.4)		3.0 (2.2)	
0	14,188	18.5%	2,777	17.5%	11,411	18.7%
1	6,912	9.0%	1,112	7.0%	5,800	9.5%
2	11,017	14.3%	1,944	12.3%	9,073	14.9%
3	12,486	16.3%	2,476	15.6%	10,010	16.4%
4+	32,174	41.9%	7,548	47.6%	24,626	40.4%
Comorbidities						
Chronic obstructive pulmonary disease	26,936	35.1%	4,503	28.4%	22,433	36.8%
Heart Failure	21,532	28.0%	5,691	35.9%	15,841	26.0%
Ischemic heart disease	28,614	37.3%	6,259	39.5%	22,355	36.7%
Diabetes mellitus	24,967	32.5%	4,954	31.2%	20,013	32.9%
Nervous System/ Neurological Disease	5,789	7.5%	1,673	10.6%	4,116	6.8%
Renal failure	17,202	22.4%	4,136	26.1%	13,066	21.4%
Liver Failure/Disease	9,122	11.9%	1,080	6.8%	8,042	13.2%
Dementia	21,722	28.3%	7,881	49.7%	13,841	22.7%
HIV	248	0.3%	39	0.2%	209	0.3%
Sepsis	12,625	16.4%	2,656	16.7%	9,969	16.4%
Hypertensive Disease	48,467	63.1%	10,101	63.7%	38,366	63.0%
Mood Disorder	19,228	25.0%	4,586	28.9%	14,642	24.0%
Number of Admitting Health Status Conditions mean (std)	1.9 (2.0)		2.0 (2.1)		1.9 (2.0)	
0	25,454	33.2%	5,330	33.6%	20,124	33.0%
1	14,200	18.5%	3,048	19.2%	11,152	18.3%
2	11,813	15.4%	2,401	15.1%	9,412	15.4%
3	9,186	12.0%	1,752	11.0%	7,434	12.2%
4+	16,124	21.0%	3,326	21.0%	12,798	21.0%
Health Status Conditions						
Recurrent or intractable infections	1,696	2.2%	439	2.8%	1,257	2.1%
Progressive inanition - weight loss	1	0.0%	0	0.0%	1	0.0%
Dehydration or hypovolemia	12,090	15.7%	2,364	14.9%	9,726	16.0%
Dysphagia	9,144	11.9%	2,697	17.0%	6,447	10.6%
Cough	7,747	10.1%	1,757	11.1%	5,990	9.8%
Nausea/ Vomiting	7,851	10.2%	1,010	6.4%	6,841	11.2%
Dyspnea	19,605	25.5%	3,626	22.9%	15,979	26.2%
Diarrhea	3,879	5.1%	706	4.5%	3,173	5.2%
Pain	12,374	16.1%	1,531	9.7%	10,843	17.8%
Hypotension	7,153	9.3%	1,524	9.6%	5,629	9.2%
Ascites Venous Obstruction	639	0.8%	35	0.2%	604	1.0%
Edema Pleural	15,789	20.6%	2,498	15.8%	13,291	21.8%
Cognitive Impairment	1,662	2.2%	489	3.1%	1,173	1.9%
Change in consciousness	1,411	1.8%	342	2.2%	1,069	1.8%
Pressure Ulcers Stage 3-4	7,999	10.4%	2,559	16.1%	5,440	8.9%
Sepsis/Septicemia	9,629	12.5%	2,142	13.5%	7,487	12.3%
Aspiration pneumonia	15,481	20.2%	3,020	19.0%	12,461	20.5%
Upper urinary tract infection (pyelonephritis)	15,059	19.6%	4,173	26.3%	10,886	17.9%

Table 2. Actual Prescription Days' Supply Distribution.

Characteristics	Total	SEER Non-Cancer	SEER Cancer
Patients	56,266	13,098 (23.3%)	43,168 (76.7%)
Prescriptions (n)	214,571	54,551 (25.4%)	160,020 (74.6%)
Days' supply prescribed mean (std)	27.3 (21.8)	24.8 (19.5)	28.2 (22.4)
Days' supply prescribed median	30	29	30
Days after hospice admission prescription filled mean (std)	19.6 (18.4)	19.6 (18.5)	19.6 (18.4)
Days after hospice admission prescription filled median	14	14	14
Clinician Prescribed Durations			
≤7 days' supply	37,052 (17.3%)	11,083 (20.3%)	25,969 (16.2%)
8-10 days' supply	142,630 (66.5%)	35,534 (65.1%)	107,096 (66.9%)
11-30 days' supply	6,406 (3.0%)	1,994 (3.7%)	4,412 (2.8%)
31-60 days' supply	17,891 (8.3%)	3,220 (5.9%)	14,671 (9.2%)
61-90+ days' supply	10,592 (4.9%)	2,720 (5.0%)	7,872 (4.9%)
Prescriptions with days' supply on hand at death			
Prescriptions (n)	119,384	29,362 (24.6%)	90,022 (75.4%)
Days' supply leftover, total	2,683,125	579,607 (21.6%)	2,103,518 (78.4%)
Days' supply leftover, mean (std)	22.5 (35.4)	19.7 (19.5)	23.4 (29.2)
Proportion of days' supply leftover (%)	64.3%	62.9%	64.3%

Table 3. Actual Survival Days Distribution.

Characteristics	Total	SEER Non-Cancer	SEER Cancer
Prescriptions	214,571	54,551 (25.4%)	160,020 (74.6%)
Survival Days mean (std)	42.6 (25.1)	41.9 (25.5)	42.9 (24.9)
Survival Days median	41	40	41
Survival Days categorized			
0-6 days	13,243 (6.2%)	4,072 (7.5%)	9,171 (5.7%)
7-17 days	30,826 (14.4%)	8,144 (14.9%)	22,682 (14.2%)
18-45 days	74,495 (34.7%)	18,184 (33.3%)	56,311 (35.2%)
46-75 days	68,295 (31.8%)	16,988 (31.1%)	51,307 (32.1%)
76-90+ days	27,712 (12.9%)	7,163 (13.1%)	20,549 (12.8%)
Survival Days at time of prescription mean (std)	23.7 (18.4)	23.2 (18.5)	23.9 (18.3)
Survival Days at time of prescription median	19	19	18
Survival Days at time of prescription categorized			
0-6 days	40,587 (18.9%)	11,400 (20.9%)	29,187 (18.2%)
7-17 days	59,761 (27.9%)	15,130 (27.7%)	44,631 (27.9%)
18-45 days	82,338 (38.4%)	20,101 (36.8%)	62,237 (38.9%)
46-75 days	30,645 (14.3%)	7,592 (13.9%)	23,053 (14.4%)
76-90 days	1,240 (0.6%)	328 (0.6%)	912 (0.6%)

Table 4. Assessment of model performance by diagnostic testing.

Measure Evaluation	Cox Proportional Hazard	RSF predicted survival days using the Kaplan-Meier estimator	RSF interpolated calibrated predicted survival days using isotonic regression	RSF median calibrated predicted survival days using the trapezoidal rule*
CPH=Cox Partial Likelihood Score RSF=C-index	0.02	0.79	0.73	0.82
Time-dependent AUC-ROC	N/A	0.89	0.80	0.90
Integrated Brier Score (IBS)	2.17	1.85	0.26	0.11
Mean Absolute Scaled Error (MASE)	1.16	3.24	0.54	0.41

*Indicates model selected for this study, based on overall performance. The RSF model predicts survival probabilities for each instance in the test data, and the median calibrated predicted survival is calculated for each patient using the trapezoidal rule, which approximates the area under the survival probability curve. This method identifies the survival time intervals by determining the segment where the cumulative area first exceeds 0.5 (or the median), providing precise estimates of survival duration.

Table 5. Rule-based prescription lengths based on survival time at fulfillment.

Survival Days to Prescription Length		
Survival Start	**Survival End**	**Prescription Length**
<0	<0	7 days' supply
0	6.9	7 days' supply
7	17.9	14 days' supply
18	45.9	30 days' supply
46	75.9	60 days' supply
80	90	90 days' supply

Table 6. Comparison of medication on hand at time of death between actual and rule-based prescription lengths (no adjustments made for prescriptions that end before patient death date).

Medication on Hand at Time of Death
Predicted vs Actual
No Adjustments to prescriptions that end before the date of death
n= 42,605 prescriptions

Outcome of Rules	n	%		Actual Days' Supply at Death	Rule-based Days' Supply at Death	Difference	% Change Days' Supply at Death
Rule-based resulted in exact same overage	20,710	49%		109,233	109,233	0	
Ruled-Based resulted in savings (less overage)	11,962	28%		400,982	80,477	320,505	
Rule-based resulted in losses (more overage)	9,933	23%		35,938	159,195	-123,257	
Total	42,605			546,153	348,905	197,248	-36.10%

Medication on Hand at Time of Death
Predicted vs Actual
14-days' supply added to the rule-based prescription where the initial prescription end date was before death
n= 42,605 prescriptions

Outcome of Rules	n	%		Actual Days' Supply at Death	Rule-based Days' Supply at Death	Difference	% Change Days' Supply at Death
Rule-based resulted in exact same overage	17,865	42%		109,622	109,622	0	
Ruled-Based resulted in savings (less overage)	11,730	28%		400,121	94,562	305,559	
Rule-based resulted in losses (more overage)	13,010	31%		36,410	177,523	-141,113	
Total	42,605			546,153	381,707	164,446	-30.10%

Medication on Hand at Time of Death
Predicted vs Actual
30-days' supply added to the rule-based prescription where the initial prescription end date was before death
n= 42,605 prescriptions

Outcome of Rules	n	%		Actual Days' Supply at Death	Rule-based Days' Supply at Death	Difference	% Change Days' Supply at Death
Rule-based resulted in exact same overage	15,205	36%		109,622	109,622	0	
Ruled-Based resulted in savings (less overage)	9,462	22%		400,121	94,562	305,559	
Rule-based resulted in losses (more overage)	17,938	42%		36,410	177,523	-141,113	
Total	42,605			546,153	381,707	164,446	-30.10%

Medication on Hand at Time of Death
Predicted vs Actual
14-days' supply added and if need another 10-days' supply added to the rule-based prescription where the initial and follow-up prescription end date was before death
n= 42,605 prescriptions

Outcome of Rules	n	%		Actual Days' Supply at Death	Rule-based Days' Supply at Death	Difference	% Change Days' Supply at Death
Rule-based resulted in exact same overage	16,814	39%		109,625	109,625	0	
Ruled-Based resulted in savings (less overage)	11,559	27%		399,633	95,617	304,016	
Rule-based resulted in losses (more overage)	14,232	33%		36,895	182,111	-145,216	
Total	42,605			546,153	387,353	158,800	-29.10%

Table 7. Comparison of medication on hand at time of death between actual and rule-based prescription lengths (excluded prescriptions that ended more than 3 days before the date of death).

Medication on Hand at Time of Death
Predicted vs Actual
Adjustment made to exclude prescriptions that ended more than 3 days before the date of death
n= 24,878 prescriptions

Outcome of Rules	n	%		Actual Days' Supply at Death	Rule-based Days' Supply at Death	Difference	% Change Days' Supply at Death
Rule-based resulted in exact same overage	7,856	32%		109,233	109,233	0	
Ruled-Based resulted in savings (less overage)	11,962	48%		400,982	80,477	320,505	
Rule-based resulted in losses (more overage)	5,060	20%		35,938	108,150	-72,212	
Total	24,878			546,153	297,860	248,293	-45.50%

Medication on Hand at Time of Death
Predicted vs Actual
14-days' supply added to the rule-based prescription where the initial prescription end date was greater than 3 days before the date of death
n= 24,878 prescriptions

Outcome of Rules	n	%		Actual Days' Supply at Death	Rule-based Days' Supply at Death	Difference	% Change Days' Supply at Death
Rule-based resulted in exact same overage	7,875	32%		109,622	109,622	0	
Ruled-Based resulted in savings (less overage)	11,730	47%		400,121	94,562	305,559	
Rule-based resulted in losses (more overage)	5,273	21%		36,410	109,865	-73,455	
Total	24,878			546,153	314,049	232,104	-42.50%

Medication on Hand at Time of Death
Predicted vs Actual
30-days' supply added to the rule-based prescription where the initial prescription end date was greater than 3 days before the date of death
n= 24,878 prescriptions

Outcome of Rules	n	%		Actual Days' Supply at Death	Rule-based Days' Supply at Death	Difference	% Change Days' Supply at Death
Rule-based resulted in exact same overage	7,822	31%		110,600	110,600	0	
Ruled-Based resulted in savings (less overage)	9,462	38%		376,802	101,354	275,448	
Rule-based resulted in losses (more overage)	7,594	31%		58,751	159,351	-100,600	
Total	24,878			546,153	371,305	174,848	-32.00%

Medication on Hand at Time of Death
Predicted vs Actual
14-days' supply added to the rule-based prescription where the initial prescription end date was greater than 3 days before the date of death
n= 24,878 prescriptions

Outcome of Rules	n	%		Actual Days' Supply at Death	Rule-based Days' Supply at Death	Difference	% Change Days' Supply at Death
Rule-based resulted in exact same overage	7,855	32%		109,625	109,625	0	
Ruled-Based resulted in savings (less overage)	11,559	46%		399,633	95,617	304,016	
Rule-based resulted in losses (more overage)	5,464	22%		36,895	110,613	-73,718	
Total	24,878			546,153	315,855	230,298	-42.20%

Figure 1A. Cox Proportional Hazard

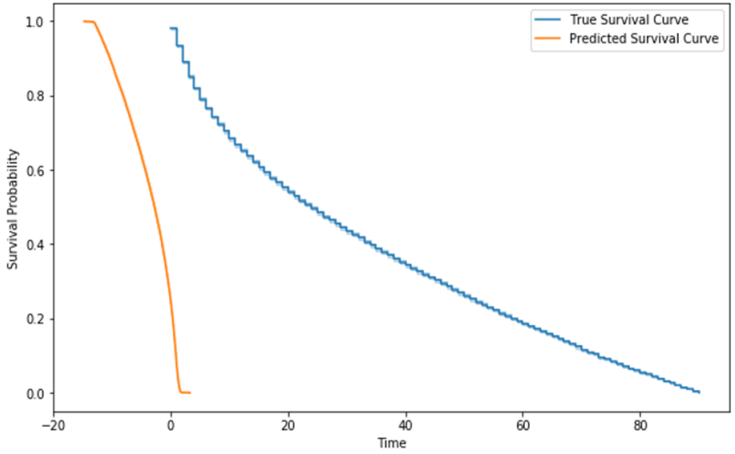


Figure 1B. Random Survival Forest (RSF)

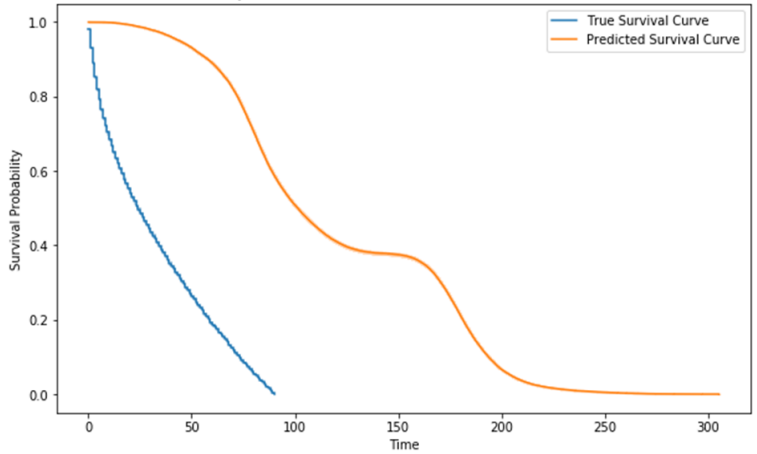
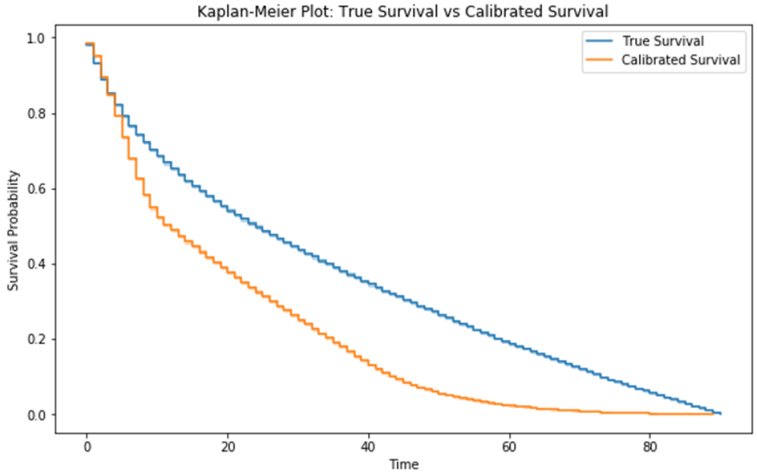


Figure 1C. RSF with Isotonic Regression Calibration



1D. RSF with Median Trapezoidal Rule Calibration

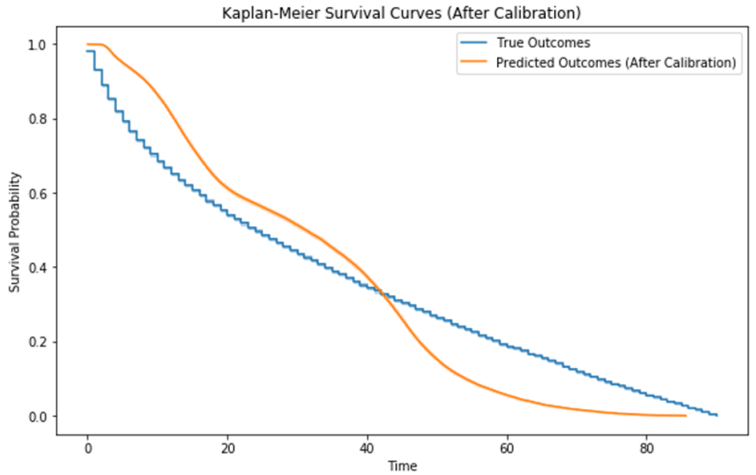


Figure 1. Kaplan-Meier Estimator plots by model performance for diagnostic testing.

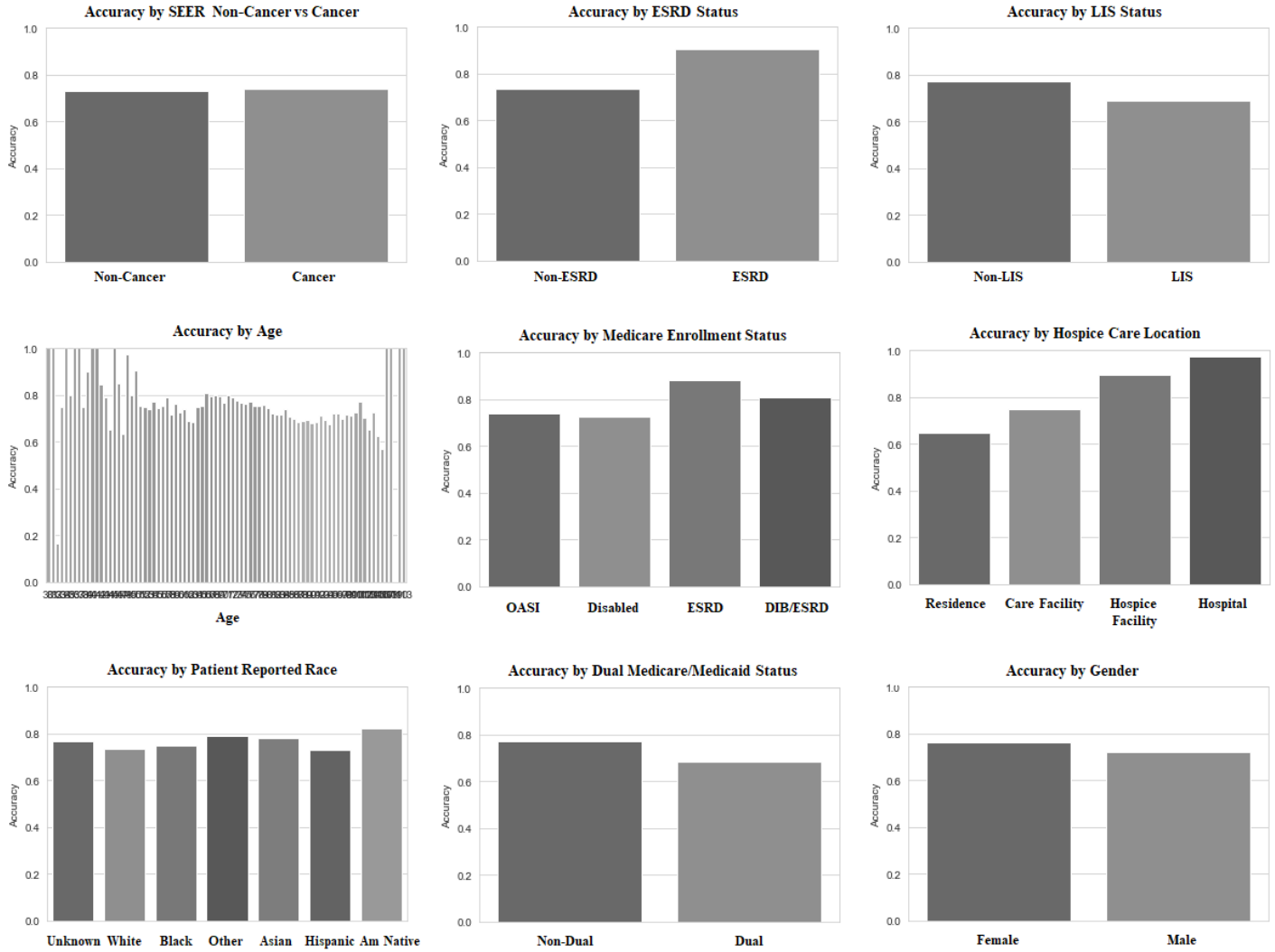


Figure 2. A review for sociodemographic bias of Random Survival Forest with median trapezoidal rule accuracy in predicting survival days.

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