

**Disparities in Healthcare Expenditure and Mortality by Neighborhood Income in
Chronic Myeloid Leukemia**

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THESIS

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This thesis is dedicated to all who have supported me during this long and arduous journey.

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LIST OF ABBREVIATIONS

ACA	Affordable Care Act
ABB	Abbreviation
BCR	Breakpoint Cluster Region
c-ABL	Abelson proto-oncogene
CI	Confidence interval
CML	Chronic myelogenous leukemia
DME	Durable medical equipment
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
HCT	Hematopoietic stem cell transplant
HLA	Human leukocyte antigen
ICD	International classification of disease
IPW	Inverse probability weighting
MCO	Managed care organization
mRNA	Messenger ribonucleic acid
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDC	National drug codes
OOP	Out-of-pocket
PCE	Personal Consumption Expenditure index
PDC	Proportion of days covered
PHC	Personal Health Care price index
PMPM	Per-member per-month
PPO	Preferred provider organization
PPPY	Per-patient per-year
RT-PCR	Reverse transcriptase polymerase chain reaction
SEER	Surveillance, Epidemiology, and End Results
SES	Socioeconomic status
TKIs	Tyrosine kinase inhibitors
US	United States

SUMMARY

Chronic myelogenous leukemia is a hematological malignancy commonly diagnosed among the elderly between 65 and 84 years of age. The primary treatment of chronic myelogenous leukemia (CML) is based on chronic oral therapy with tyrosine kinase inhibitors (TKIs). This class of targeted cancer therapy is associated with annual drug prices exceeding \$100,000. The price of cancer therapy is burdensome for the United States (US) healthcare system and especially to Medicare beneficiaries on a limited fixed income. Medicare beneficiaries whose treatment cost may exceed income may experience the financial toxicity of cancer treatment leading to impaired treatment access, suboptimal medication use, and an increased risk of mortality.

The objective of our research was to determine the impact of high cancer drug prices on Medicare patients with CML, identify if disparities in health outcomes exist, and estimate the cost associated with CML to inform economic and health policies affecting this population. We conducted three studies using the Surveillance, Epidemiology, and End Results (SEER) - Medicare database to measure the trend in TKI drug prices, and whether there was an association between income and TKI drug initiation, mortality, and non-cancer healthcare use.

Chapter I reviews the relevant epidemiologic and medical literature on CML including population characteristics, clinical presentation, and disease treatment. Chapters II and III review the economic burden of cancer therapy and the resulting financial toxicity it causes in cancer patients. The chapters highlight how out-of-pocket (OOP) TKI cost affect medication access and health outcomes and reviews the current evidence on the association between socioeconomic status (SES) and health outcomes specifically within the CML population. Chapter IV identifies the gaps in evidence found from our review of the economic burden of TKI therapy and the disparities experienced by CML patients due to the financial toxicity of cancer

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treatment. The chapter also discusses our specific aims and the theoretical framework from which the aims are based on.

In our first aim (Chapter V) we measured the annual trend in TKI utilization, Medicare gross payment, and patient OOP expenditure from 2007 through 2016. TKI utilization was measured as the proportion of cases with at least one TKI claim in each year. Average TKI gross payment and median per-member per-month OOP expenditure was calculated from claims data and plotted annually from 2007 through 2016. Year-to-year percent change in gross payment and OOP expenditure was compared to inflation indices. In a cohort of 3,189 CML cases with at least one TKI claim, the proportion of prevalent patients with a TKI fill in a year increased from 17.9% in 2007 to 52.8% in 2015. The average annual gross payment per 30-day supply of a TKI increased by an average of 12.8% throughout the period reaching values of \$9,000 to \$10,000 in 2016. There was no increasing trend in median OOP expenditure per 30-day supply, which varied between \$450 to \$600.

Our second aim (Chapter VI) measured the effect of neighborhood-income level (i.e., above/below the 50th percentile of census-tract median income) on the hazard of TKI initiation. Among TKI initiators, we measured the effect of neighborhood income on the hazard of all-cause and CML-specific mortality adjusted for time-varying TKI adherence. In a cohort of 503 CML cases, we found that neighborhood income was not associated with TKI-initiation. Among 354 CML cases who initiated a TKI, we found that neighborhood income was not associated with all-cause mortality, but low neighborhood income was associated with a significantly increased risk of CML-specific death.

In our third aim (Chapter VII), we measured the effect of neighborhood-income level (i.e., above/below the 50th percentile of census-tract median income) on non-cancer Medicare Part-B

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and Part-D 60-month cumulative expenditure among patients who started TKI therapy. We assumed that during the duration of TKI therapy, patients with low neighborhood income may be forgoing non-cancer care to finance cancer-related care. However, we found that neighborhood income was not associated with 60-month cumulative non-cancer Part-B and Part-D expenditure. Although we were not able to detect an association between income differences and non-cancer medical expenditures, it is possible that CML patients with low neighborhood income may be instead forgoing other consumer goods and services which we could not observe.

Finally, chapter VIII provides a conclusion of the dissertation. We discuss the results of our three studies and the implications for health economic policy and patient care. We also recommend future avenues of research.

I. CHRONIC MYELOGENOUS LEUKEMIA

1.1 Epidemiology

Chronic Myelogenous Leukemia (CML) is a hematological cancer arising from a subpopulation of hematopoietic stem cells that have developed a cytogenetic abnormality characterized by a translocation of the Abelson proto-oncogene (c-ABL) located on chromosome 9 at band 34 to the end of the breakpoint cluster region (BCR) on chromosome 22 at band 11.¹ Relative to common cancers such as female breast cancer and lung cancer, which account for 15.2% and 12.9% of new cancer cases in the US, respectively, CML is relatively rare and accounts for only 0.5% of new cancer cases.² Among blood cancers, leukemias account for 35% of new cases³, 15% of which are new CML cases.⁴ CML is primarily diagnosed in the elderly with a median diagnosis age of 65 years, and about 40% of new cases are diagnosed between the ages of 65 and 84 years. Men have a higher incidence of CML with a rate across all races of 2.4 per 100,000 compared to 1.4 per 100,000 in women. The risk of death is also higher among men across all races with 0.4 deaths per 100,000 compared to 0.2 deaths per 100,000 among women.

The age-adjusted incidence of CML across all races in males and females in the US gradually increased from 1.7 new cases per 100,000 in the year 2000 to 2.04 new cases per 100,000 in 2016.² In contrast, the number of deaths across all races in males and females decreased from 0.7 per 100,000 in the year 2000 to 0.3 per 100,000 in 2016. The current 5-year survival of CML based on patients diagnosed between 2009 to 2018 is 69.2%, which is a dramatic increase from 59% in 2005. The life expectancy of CML patients now approaches that of the general non-cancer population – a 65-year-old from the general non-cancer population would have a life expectancy of 20.1 years, and a CML patient of equivalent age would have a life expectancy of up to 18.9 years.⁵ This observation may be partly attributed to allogeneic stem

cell transplantation and targeted therapies, including tyrosine kinase inhibitors (TKIs). However, other factors such as changes in the prevalence of comorbidities, improvements in medical treatment, or other health policy changes that improve mortality across time may also explain the increased life expectancy of CML patients. The increase in incidence, combined with the decrease in the number of deaths, resulted in an increase in the prevalence of CML.⁶ There was an estimated CML prevalence of 54,226 cases in 2016², which is projected to increase to 144,000⁶ in 2030, 167,000 in 2040, and eventually plateau at about 181,000 in 2050.

Identified risk factors associated with the development of CML are lacking. Hereditary, familial, geographic, ethnic, and socioeconomic factors have not been associated with CML.¹ Observational studies found no associations between benzene exposure⁷ or cellular phone use⁸ and CML. However, there is limited evidence supporting an association between exposure to high-dose ionizing radiation and CML.^{9,10} There is very limited evidence based on case series studies that report the subsequent development of CML among men after receiving a platinum-based chemotherapy regimen with etoposide for treatment of germ cell tumor,¹¹ and among women after receiving adjuvant chemotherapy and/or adjuvant radiation therapy for treatment of breast cancer.¹² A large cohort-based study also found a significant increased risk of leukemia after chemotherapy for solid cancers, but only the development of acute myeloid leukemia was ascertained.¹³

1.2 Etiology and Pathogenesis

The cause of CML is a genetic abnormality involving a reciprocal translocation of genetic material between chromosome 9 and 22 in a single hematopoietic pluripotent stem cell.¹⁴ The c-ABL proto-oncogene breaks off the long arm of chromosome 9 and the simian sarcoma virus-transforming gene breaks off below the BCR gene of chromosome 22. The pieces then reciprocally translocate thus forming the BCR-ABL fusion gene on chromosome 22 (i.e., the

Philadelphia chromosome), which is a malignant transformation and the defining feature of CML. A normal c-ABL proto-oncogene is senescent but becomes transformed into an activated oncogene when fused to the BCR gene.¹ This BCR-ABL fusion gene encodes the p210 BCR-ABL tyrosine kinase protein, which is dysregulated and constitutively active.

Tyrosine kinases are a family of enzymes involved in intracellular signal transduction.¹⁵ In response to cellular signals, tyrosine kinase enzymes phosphorylate (i.e., activate) other cellular proteins which trigger a cascade of intracellular biochemical signals which result in the activation of genes related to cell growth and proliferation. As a result of the constitutive action of the p210 tyrosine kinase, the transformed hematopoietic stem cell is conferred a significant proliferative advantage over normal hematopoietic cells.¹ The stem cell gives rise to hematopoietic progenitor cells that have the capacity to excessively differentiate into all myeloid cell lines (i.e., thrombocytes, erythrocytes, granulocytes, and monocytes) in the bone marrow, liver, and spleen.¹⁶ Of the myeloid cell lines, granulocyte production dominates causing a high circulating number of basophils, eosinophils, neutrophils, and mast cells. Lymphoid progenitors that give rise to T-cells and B-cells may also be affected but to a lesser degree.

1.3 Clinical Presentation

The course of CML follows three phases that are defined based on symptoms, physical signs, and laboratory findings – chronic phase, accelerated phase, and blast crisis.¹ Ninety percent of patients with CML present in the chronic phase in which patients are asymptomatic or present with very minimal signs and symptoms.¹⁷ The diagnosis of CML is often incidental to routine care. The chronic phase is defined as having <10% blast cells (undifferentiated blood cells) in a peripheral blood sample or bone marrow sample.¹ Signs and symptoms of CML may be explained by increased proliferation of immature erythrocytes which may impair red blood cell production leading to manifestations of anemia and splenomegaly.¹⁷ Common findings in

patients who present with symptoms include fatigue and malaise secondary to anemia. The most common physical sign is splenomegaly, which may lead to early satiety, abdominal pain, and left upper quadrant abdominal pain. Hematologic signs may include leukocytosis, thrombocytosis, basophilia, eosinophilia, and left-shifted hematopoiesis (presence of immature neutrophils). The bone marrow appears hypercellular with myeloid hyperplasia due to increased myeloid proliferation. Lastly, identification of the Philadelphia chromosome with cytogenetic testing is confirmatory of CML.

Patients who progress to the accelerated phase exhibit 10% to 19% blast cells in a peripheral blood sample or bone marrow sample and a platelet count that is either $<100 \times 10^9$ cells/L or $>1,000 \times 10^9$ cells/L.¹ Additional supportive signs may include the presence of additional chromosomal abnormalities, progressive splenomegaly, worsening basophilia, and cellular proliferation outside of the bone marrow (i.e., extramedullary infiltrates). The third and terminal phase of CML is the blast crisis phase. Patients in this phase exhibit $>20\%$ blasts in a peripheral blood sample or bone marrow aspirate, large clusters of blasts on a bone marrow biopsy, and extramedullary infiltrates. Supporting signs may include fever, malaise, and splenomegaly.

1.4 Diagnosis

Initial work-up includes bone marrow aspiration and biopsy to evaluate marrow morphology and to evaluate chromosomal abnormalities in cells.¹⁸ If bone marrow aspiration and biopsy is contraindicated or infeasible, then fluorescent in situ hybridization using peripheral blood to detect chromosomal abnormalities may be conducted. Quantitative reverse transcriptase – polymerase chain reaction (RT-PCR) using peripheral blood is also included to establish the presence of the BCR-ABL gene products. The presence of the Philadelphia chromosome through cytogenetic evaluation of cells and quantifiable BCR-ABL messenger

ribonucleic acid (mRNA) transcripts through RT-PCR confirms the diagnosis of CML. Other components of initial evaluation for CML include patient history and physical (especially palpation of the spleen to detect splenomegaly), complete blood count with differential, blood chemistry, and a complete hepatitis panel.

In patients who are positive for the Philadelphia chromosome or have positive BCR-ABL transcripts, further evaluation may be needed based on the current phase of CML.¹⁸ Among patients who are diagnosed in the chronic phase, risk stratification using the Sokal score should be conducted to help guide treatment decisions. The Sokal risk score stratifies CML patients into three prognostic risk groups (low, intermediate, or high) based on age, spleen size, platelet count, and percent of blasts.¹⁹ Among patients on imatinib therapy, low risk patients have a better prognosis with a 6-year cumulative risk of death of 3% compared to 4% with medium risk and 8% with high risk.²⁰

Among patients who present in the accelerated or blast phase of CML, additional tests including flow cytometry to determine cell lineage and mutational analysis is recommended to guide treatment decisions.¹⁸ Major histocompatibility complex testing is also indicated in patients with advanced disease that are considering allogeneic hematopoietic stem cell transplantation (HCT). Among patients who are negative for the Philadelphia chromosome and BCR-ABL transcripts, other myeloproliferative cancers must be ruled out.

1.5 Management

1.5.1 Treatment Goals and Strategy

The treatment goals of CML management are to achieve treatment response and ultimately eliminate all leukemic cells from the bone marrow.¹ Response criteria are based on hematologic, cytogenetic, and molecular findings.¹⁸ Hematologic response is based on normalization of blood counts and includes a leukocyte count $<10 \times 10^9/L$, a platelet count

<4500 x 10⁹/L, a lack of immature cells (e.g., myelocytes and blasts), and a lack of signs and symptoms. Cytogenetic response is based on the presence of Philadelphia chromosome positive cells in a bone marrow biopsy. Complete cytogenetic response indicates no Philadelphia chromosome containing cells, major cytogenetic response indicates $\leq 35\%$ Philadelphia chromosome positive cells, and minor cytogenetic response indicates $> 35\%$ Philadelphia chromosome positive cells. Since BCR-ABL transcripts may be present even with complete cytogenetic response, detection of these transcripts via RT-PCR is a more sensitive measure of response.¹ Early molecular response is defined as $\leq 10\%$ transcripts at 3- and 6-months of treatment, major molecular response is defined as $\leq 0.1\%$ transcripts, and complete molecular response is the absence of transcripts, but is dependent on the assay's level of sensitivity.¹⁸ A relapse is indicated by reverting to a prior stage of response.

The primary modality of treatment is oral therapy with TKIs.¹⁸ Among patients in the chronic phase of disease, TKIs are 1st line therapy and the choice among TKIs is primarily dependent on patient specific factors such as comorbidities, Sokal risk score, and drug toxicities. Patients in the accelerated or blast phase may be treated with second- or third-generation TKIs as monotherapy or in combination with chemotherapy.¹⁷ A combination consisting of etoposide, cytarabine, and carboplatin is a commonly used regimen.¹ After the disease burden has been alleviated, patients should be evaluated for allogeneic HCT.¹⁷

1.5.2 Pharmaceutical Management

TKIs are the first-line treatment option for newly-diagnosed CML patients in the chronic phase.¹⁸ All TKIs indicated for CML are orally administered and taken daily, although doses may be varied based on tolerance and disease phase. The duration of treatment is indefinite, and patients will likely remain on life-long therapy. TKIs are a class of drugs that selectively inhibit the action of tyrosine kinases resulting in its inability to phosphorylate and activate other

downstream signaling pathways for cell growth and proliferation.²¹ TKIs developed for CML inhibit the BCR-ABL tyrosine kinase of Philadelphia chromosome positive leukemic cells, thereby inhibiting cell growth and proliferation. There are currently five Food and Drug Administration (FDA) - approved TKIs in the US, which includes the first-generation TKI Gleevec (imatinib); the second generation TKIs Sprycel® (dasatinib), Tasigna® (nilotinib), and Bosulif® (bosutinib); and third generation TKI Iclusig® (ponatinib). Imatinib is the only TKI currently available as a generic in the US. All TKIs are approved for 1st line therapy except for ponatinib, which is approved for patients with a specific TKI-resistant mutation.²² TKIs exhibit relatively high rates of complete cytogenetic response¹⁸ and major molecular response, with long-term survival on TKI treatment approaching that of the general non-cancer population.⁵

A meta-analysis of eight phase-III TKI clinical trials compared imatinib to new-generation TKIs (dasatinib, nilotinib, bosutinib, and ponatinib).²³ The study also included a new TKI, radotinib, that is currently not available in the US. There was a total of 2,974 newly diagnosed CML patients in the chronic phase with a median age of 41 to 58 years. Imatinib was less effective in achieving complete cytogenetic response relative to new-generation TKIs, but the reduction was not statistically significant (RR 0.70, 95% CI [0.70 to 1.14]). Imatinib was less effective in achieving major molecular response relative to new-generation TKIs (RR 0.63, 95% CI [0.46 to 0.87]). New generation TKIs achieved a greater reduction in progression to advanced-phase CML compared to imatinib (RR 0.37, 95% CI [0.20 to 0.67]). However, there were no significant differences in progression free survival (RR 0.48, 95% CI [0.21 to 1.10]) and overall survival (RR 0.80, 95% CI [0.33 to 1.91]). Lastly, patients who receive a transplant may receive maintenance treatment with TKIs. However, a landmark trial comparing survival in patients with CML who received a stem-cell transplant found no statistically significant

difference between maintenance TKI vs no maintenance TKI in leukemia-free survival (42% vs 44%, respectively, $p=0.65$) and overall survival (61% vs 57%, respectively, $p=0.61$).²⁴

Due to relatively similar rates of mortality, the selection of a TKI is primarily dependent on patient-specific factors including patient tolerability of adverse effects and drug-comorbidity interactions.¹⁸ However, second-generation TKIs may be considered over imatinib in patients who have an intermediate to high Sokal risk score due to the lower risk of disease progression relative to imatinib. Although TKIs selectively target tyrosine kinases, there is cross-reactivity with other tyrosine kinases in addition to the BCR-ABL kinase that leads to manifestation of common adverse effects (>10% incidence) such as rash, nausea, vomiting, diarrhea, and cytopenias.²² Imatinib is generally well tolerated, but musculoskeletal pain, arthralgia, myalgia, and cramps may substantially reduce quality of life. Dasatinib is associated with development of pleural effusion that may occur at any time during treatment, which can be managed by a diuretic, steroids, or dose interruption. If discontinued and restarted, pleural effusion may recur. Although rare, there is a risk of pulmonary hypertension that may be irreversible²² and requires permanent discontinuation of the drug.¹⁸ Due to these adverse effects, dasatinib should generally be avoided in patients with pulmonary comorbidities.¹⁸

Nilotinib is associated with serious cardiovascular adverse effects and must be avoided in patients with cardiovascular disease.^{18,22} There is a black box warning for QT interval prolongation and peripheral arterial occlusive disease that requires immediate discontinuation of therapy.¹⁸ Other serious and common cardiovascular adverse effects (>10% incidence) include arrhythmia, heart failure, and myocardial ischemia.²⁵ Nilotinib should also be avoided in patients with pancreatitis or hyperglycemia due to elevations in lipase and glucose.¹⁸ Bosutinib is associated with rare and serious pleural effusion, and patients who developed pleural effusions have a higher risk of recurrence if restarted on bosutinib. Abnormal liver function tests with

elevated liver enzymes are also common (>10% incidence), which may lead to drug discontinuation.¹⁸ Ponatinib is associated with serious cardiovascular and cerebrovascular events and should be avoided in patients with associated vascular comorbidities.²² Common vascular events (>10% incidence) include arrhythmia, heart failure, myocardial ischemia, peripheral arterial occlusive disease, and cerebral artery occlusion.²⁵

Omacetaxine is a last-line treatment option for patients in the chronic or accelerated phase of disease who have resistance and/or intolerance to at least two TKIs.²⁶ It is a protein synthesis inhibitor that binds to ribosomes and primarily reduces the production of proteins with short half-lives, which leads to apoptosis of primitive leukemic cells. Unlike TKIs, omacetaxine is administered subcutaneously and dosed based on body surface area. During the induction phase, one dose is administered twice daily for 14 consecutive days over a 28-day cycle until a hematological response is achieved. The maintenance phase then follows at a dosing schedule of one dose twice daily for 7 consecutive days over a 28-day cycle for as long as response is maintained. Omacetaxine was approved based on single-group phase-II trial data with a sample of 81 patients, which showed complete cytogenetic response in 13% of patients with two previous TKIs and 6% of patients with three previous TKIs.²⁷ Median overall survival was 33.9-months, and the most common adverse were thrombocytopenia, neutropenia, and anemia.

Since the development of TKIs, acute oral chemotherapy treatment with hydroxyurea or busulfan, and chronic parenteral treatment with interferon alfa have been relegated to last-line options or reserved for special circumstances.¹ Hydroxyurea may be used to quickly stabilize patients who present with hyperleukocytosis or as palliative therapy.²⁸ Hydroxyurea inhibits deoxyribonucleic acid (DNA) synthesis, which rapidly decreases the level of circulating white blood cells.¹ Once the white blood cell count falls near or below 10×10^9 cells/L, treatment may

be discontinued. Busulfan is rarely used for stabilization of hyperleukocytosis due to the risk of pulmonary fibrosis and a modest survival disadvantage when compared with hydroxyurea.²⁹

Interferon-alfa is primarily reserved for relapse after allogeneic HCT and is no longer preferred for maintenance treatment due to the higher survival rate and improved tolerability of TKIs.¹⁸ An open-label crossover clinical trial showed a higher 10-year survival rate with the first generation TKI Gleevec® (imatinib) compared to interferon-alfa plus cytarabine (83.3%, 95% confidence interval [CI] [80.1 to 86.6] vs 78.8%, 95% CI [75.0 to 82.5], respectively).³⁰ The acute and long-term adverse effect profile of interferon-alfa severely limits its utilization.¹ In a randomized clinical trial with crossover comparing imatinib with interferon-alfa plus cytarabine, 6.4% of patients discontinued interferon treatment due to adverse events compared to 2% in the imatinib group.³¹ Cross-over between trial arms were allowed in patients who failed or were intolerant to treatment. Among the 318 patients who crossed over from the interferon group to imatinib after randomization, which was a mutually exclusive group compared to those that discontinued, the most frequent reason was intolerance to interferon (43%). Lastly, patients who have an intolerance for TKIs or who have developed TKI-resistant mutations rendering multiple lines of TKI treatment ineffective may be candidates for Allogeneic HCT.³²

1.5.3 Treatment Monitoring

BCR-ABL transcripts are routinely monitored via quantitative PCR after therapy initiation at 3-months, 6-months, 12-months, and >15-months.¹⁸ Patients who maintain a BCR-ABL transcript level $\leq 1\%$ from 3-months to >15-months have TKI-sensitive disease and should continue therapy while adverse effects are monitored. Patients who do not achieve a BCR-ABL transcript level $\leq 1\%$ by 12-months or who maintain a transcript level $>10\%$ throughout therapy may have TKI-resistant disease. Sub-optimal adherence and drug interactions should be addressed or ruled out, and a mutational analysis should be conducted. Possible options

include continuation of the same TKI, switching to a different TKI, or escalating the dose of imatinib. Patients who are found to have a BCR-ABL gene mutation conferring TKI resistance should be switched to a TKI that is effective for the mutation type. Patients may consider allogeneic HCT if alternative TKIs are contraindicated or ineffective.

Due to the risk of cytopenias with TKI therapy, blood counts should be monitored for anemia, neutropenia, and thrombocytopenia.¹⁸ Cytopenias may be safely managed by dose modifications or treatment interruptions. Patients that display signs and symptoms of anemia may receive red blood cell transfusion and neutropenia may also be managed with myeloid growth factors.

1.6 Complications and Prognosis

The median survival time of CML patients on hydroxyurea, busulfan and interferon-alfa in the pre-TKI era was 3 to 7 years.¹⁷ Stratified by phase, the median survival was 47-months in the chronic phase, 12 to 24 months in the accelerated phase, and 3 to 6 months in blast crisis.¹ The annual mortality rate was 10% within the first 2 years, which rose to 15% to 20% after 2-years. In contrast, the annual mortality rate in patients on imatinib therapy decreased to 2% over a 16-year period. The 10-year all-cause survival rate is 85% and the 10-year CML-specific survival rate is 93% with TKI treatment. Patients with CML on a TKI may reasonably expect to have a life-expectancy similar to that of the general healthy population.⁵ However, improvement in survival is not equal across race/ethnicity in the US population – minority populations, particularly African-Americans, have lower relative survival rates compared to non-Hispanic whites and is most notable among those aged >55 years.^{33,34}

Patients can develop primary resistance, which may be defined by one of the following criteria: a lack of complete hematologic response at 6-months, a lack of any level of cytogenetic response at 6-months, failure to achieve major cytogenetic response at 12-months, or failure to

achieve complete cytogenetic response at 18-months.¹⁴ Primary hematologic resistance may occur in 2% to 4% of patients and cytogenetic resistance may occur in 15% to 25% of patients.³⁵ Secondary resistance occurs when a patient's response to therapy is lost. The most common mechanism leading to TKI resistance is mutation of the BCR-ABL tyrosine kinase which results in a structural change to the protein that reduces TKI binding affinity. Mutations of the BCR-ABL tyrosine kinase is associated with poor prognosis and a high risk of disease progression.¹⁸ In patients with suspected TKI resistance, a mutational analysis must be done to select the appropriate subsequent TKI along with consideration of drug toxicity.

Discontinuation of a TKI resulting in treatment-free remission is possible in a very narrowly defined population.¹⁸ Patients are required to be in the chronic phase, have no history of accelerated or blast-phase disease, be on TKI therapy for ≥ 3 years, have an age ≥ 18 years, have a documented history of quantifiable BCR-ABL transcript, and have a 4-log reduction in BCR-ABL transcripts from baseline with a level $\leq 0.01\%$ for ≥ 2 years on at least 4 tests taken 3-months apart. Patients on treatment-free remission are required to have very close routine follow-up visits with reliable access to RT-PCR for BCR-ABL quantification. A limited number of studies have shown long-term treatment-free remission rates from discontinuation of imatinib, dasatinib, or nilotinib, but not bosutinib or ponatinib. Median follow-up times range from 27-months to 77-months with treatment-free remission rates ranging from 33% to 61%.

II. THE ECONOMIC BURDEN OF CANCER THERAPY

2.1 Innovative Cancer Treatment and Cost Burden

Most chemotherapeutic agents for cancer are highly cytotoxic drugs that non-specifically target and kill rapidly dividing cells which lead to severe adverse effects.³⁶ Recent advances in the knowledge on the molecular and cellular biology of cancer has led to the development of novel cancer therapies, which transformed the treatment landscape of cancer from the use non-selective cytotoxic drugs to highly selective mechanism-based drugs including targeted therapies such as TKIs.³⁷ Although these novel therapies may provide patients additional treatment options and clinical benefits, they are associated with relatively exorbitant prices that impose a tremendous economic burden on patients. The average prices of FDA-approved novel cancer drugs across different types of cancers in the US within the last 10-years easily exceed \$100,000 annually.^{38,39} For example, all TKIs have annual treatment prices ranging from \$92,000 to \$138,000.⁴⁰ In 2012, two TKIs for CML were approved with annual treatment prices exceeding \$100,000 – ponatinib costs \$138,000 annually, and bosutinib costs \$118,000 annually.

These prices have raised concern among US oncologists that the price of CML drugs are excessively high, unsustainable, impair access, and harm the healthcare system.⁴⁰ In addition to approval of cancer drugs at high prices, there is an upward trajectory in price after launch with an inflation-adjusted median increase of 6% (range 10% to 44%) in ten patented intravenous cancer drugs approved between 1997 and 2012 across various cancers.⁴¹ In a study evaluating targeted oral cancer medications including TKIs between 2007 through 2012, the year-to-year increase in price averaged 12%, while the general prescription drug consumer price index increased 3% over the study period.⁴²

The provided rationale for exorbitant cancer therapy prices along with continual price increases is that the agents have novel mechanisms of action and/or improve patient outcomes relative to older or non-novel therapies. However, these variables weakly correlate with increases in price and may not justify the high price of a novel therapy.³⁸ Of 51 oncology drugs approved between January 2009 through December 2013, there were no significant differences in the median prices per year of 21 novel drugs (i.e., first-in-class) and 30 next-in-class drugs ((\$116,100 vs \$119,765, $p=0.42$). There was also no significant correlation between improvements in progression-free survival or overall survival and drug price. Lastly, pharmaceutical firms have been spending less in research and development relative to other research and development firms, but have profits up to 37 times higher, suggesting that research and development costs do not justify high drug prices.⁴³ The pricing of cancer drugs may be instead based on the maximum price the market is willing to pay. Current federal policies such as freedom from generic competition for 20-years, the right to extend drug patents, and the right to acquire exclusive rights of drugs developed through public research promote monopolistic or oligopolistic pricing of drugs by pharmaceutical firms.^{44,45} With a high barrier to entry in the drug market and limited patient choice, pharmaceutical firms can price drugs exorbitantly.

Regardless of the justification underlying the high price of cancer drugs, the cost of cancer treatment has become an economic burden for health systems, especially in the US which accounts for 46% of the global oncology drug market.³⁹ Of total spending on specialty medicines in the US, oncology accounts for the largest proportion of expenditures.⁴⁶ Healthcare sector expenditures on cancer drugs accounted for 7% (\$26.8 billion) of total US drug expenditures and grew to 9.4% (\$42.1 billion) of total

expenditures in 2016.⁴⁷ Of all cancer drugs in this period, the three drugs that exhibited the largest growth from launch were novel immunotherapies and targeted therapies: nivolumab and pembrolizumab (immunotherapies), and pertuzumab (targeted therapy). As of 2018, US cancer drug spending had reached \$57 billion and was projected to grow up to \$105 billion by 2023 primarily driven by adoption of new treatments.⁴⁸

Cancer treatment also places an enormous financial pressure on cancer patients. Between the years 2000 through 2014, the median monthly household income remained constant near \$4,000 while the median monthly cost of a new cancer drug grew to above \$10,000.³⁹ Based on nationwide data, cancer patients have an average annual healthcare expenditure of \$16,346 compared to \$4,484 in non-cancer patients, with pharmaceuticals accounting for 21% of patient expenditures.⁴⁹ Although commercial prescription insurance and Medicare Part-D plans cover a portion of the cancer cost, the cost-sharing requirements for patients are relatively substantial – oral cancer drugs such as TKIs are typically placed on “specialty tiers” with 25% to 33% co-insurance.⁵⁰ In Medicare Part-D plans, costs can increase to 45% to 50% co-insurance in the coverage gap phase once spending limits are exceeded. Additionally, increasing prices of branded drugs may be passed on to the patient through increasing coinsurance. Based on national commercial claims data, there is a moderate positive correlation between drug price and OOP cost ($r=0.38$; $P=0.001$).⁵¹ Among Medicare beneficiaries where cost sharing and coinsurance is based on drug price, increasing prices may result in increasing OOP costs.^{52,53} Among Medicare Part-D patients without a low-income subsidy, an inflation adjusted increase of 29% in drug price from 2014 to 2018 would result in a 48% and 10% increase in coinsurance requirements in the initial and catastrophic coverage phase, respectively.⁵²

The problem of cancer drug cost and value for patients and the health system has recently come to the forefront of issues facing the US government. The President's Cancer Panel, an independent panel established under the National Cancer Act of 1971 was charged with identifying high-priority issues in cancer care, submitted a report to the White House on March 2018 emphasizing the cost burden of cancer care and resulting financial toxicity to patients.⁵⁴ The report also includes recommendations promoting value-based drug pricing, stimulation of generic market competition, and protection of patients from excessive out-of-pocket (OOP) drug costs. It is unknown whether the current presidential administration has taken any action based on the recommendations of this report.

2.2 Financial Toxicity

The toxicity of cancer drugs is frequently associated with common adverse effects including nausea, vomiting, fatigue, hair loss, and anemia. Additionally, as mentioned, the financial burden of cancer therapy has become a common adverse effect of cancer therapy. The term "financial toxicity" can be conceptualized as the unintended objective financial burden on, and subjective financial distress experienced by patients with cancer as a consequence of treatment, particularly treatment with new cancer therapies and other related health services.⁵⁵ The objective financial burden on patients may be due to expensive OOP cost of drugs and medical procedures or non-medical costs such as lost-wages due to illness. Financial distress arises from the accumulation of drug and medical costs, depletion of financial resources, and the anxiety and discomfort caused by the disease. Factors at the time of diagnosis that may predispose patients to financial toxicity include socioeconomic status and related factors such as being low-income, unemployed, non-white race/ethnicity, and uninsured.⁵⁶ Use of expensive

cancer drugs also predispose patients to financial toxicity due to high OOP cost, even for individuals with insurance.

Financial toxicity can potentially lead to significant adverse patient outcomes including decreased treatment adherence or access, decreased quality of life, incurring significant debt, bankruptcy, and decreased survival.⁵⁷ In a cohort of cancer patients with solid tumors, patients who requested copayment assistance were more likely to miss refill prescriptions, partially fill prescriptions, or take less medications than prescribed relative to patients who did not require financial assistance.⁵⁸ Cancer survivors are also more likely to display a similar behavioral pattern of forgoing any prescription medications (i.e., cancer or non-cancer) relative to non-cancer patients, which may be indicative of the lasting financial toxicity beyond cancer.⁵⁹ In a cohort study of patients diagnosed with lung or colorectal cancer that evaluated the association of self-reported financial distress and quality of life based on the EuroQol-5D, a significant negative association was found (0.06 unit decrease in quality of life per increase in the level of financial difficulty from “not at all” to “impossible”).⁶⁰ In the same cohort of patients, increasing financial distress as measured by the amount of financial reserve (i.e., <3 months’, 3 to 6-months’, and 7 to 12-months’ worth of financial reserve) was significantly associated with increased pain, increased symptom burden, and decreased quality of life.⁶¹

The evidence of the impact of financial toxicity on survival is limited, but available research shows that financial burden is strongly associated with mortality. The 1996 Health and Retirement Study cohort showed that women who reported 3 or more financial hardships (e.g., insurance status, food insecurity, taking less medication) had a statistically significant 60% increased risk of mortality relative to women who did not report any financial hardships (HR 1.60 95% CI [1.05–2.46]).⁶² Similarly, men who reported at least 2 financial hardships had a significant 80% increased risk of mortality relative to men who did not report any financial

hardships (HR 1.80 95% CI [1.21–2.69]). A study linking the Western Washington State SEER registry to state bankruptcy records evaluated the association between bankruptcy among cancer patients and mortality.⁶³ The study found that there was a significant 79% increase in the risk of mortality in patients who filed for bankruptcy compared to those that did not.

Despite the apparent strong negative association between financial toxicity and mortality, it must be considered that all studies were observational and prone to selection bias and other weaknesses such as reverse causality and exposure misclassification.

2.3 Evidence on the Association Between Out-of-Pocket Cost of Tyrosine Kinase Inhibitors and Medication Access and Health Outcomes in CML and Other Cancers

The high cost of cancer treatment is not restricted to a class of cancer drugs nor is it limited to a type of cancer. However, attention has been drawn to TKIs, particularly for their use in CML, due to their relatively innovative and novel targeted mechanism, 1st-line treatment designation, ease of use (i.e., taken orally at home), exorbitant cost despite the presence of five competitor drugs, and the potential to achieve high rates of efficacy.⁴⁰ Therefore, CML can serve as a clinical situation in which to measure the impact of high cancer drug prices on medication access, health outcomes, and health disparities, which can be generalized to other cancers.

A literature review of cancer drug costs and utilization⁶⁴ showed that cancer patients' behaviors were consistent with the economic concept that demand is inversely proportional to cost sharing amount, meaning that consumers decrease demand of goods at high OOP cost (i.e., elastic demand).^{65,66} A study evaluating the association between the cost of Medicare Part-D specialty cancer drug OOP cost and the probability of using a specialty cancer drug measured a significant 5% decrease in the probability of using a specialty cancer drug in a year per \$100 increase in price.⁶⁷ Given the recent shift in cancer therapy to oral drugs such as TKIs

for CML or immunomodulators such as thalidomide for multiple myeloma, there has been increasing research on how OOP cost of oral cancer drugs affect utilization. Despite the convenience of oral drugs over parenteral chemotherapy, the likelihood of delaying oral therapy or discontinuing oral therapy increases per dollar increase in OOP cost.^{68,69}

In focusing on the effect of TKI OOP cost in the CML population, a handful of observational studies have shown consistent findings. Among Medicare patients, those who faced lower OOP costs by way of cost-sharing subsidies were significantly more likely to initiate TKI therapy relative to those who did not have subsidies and face higher OOP costs.⁷⁰ A subsequent study on Medicare patients found that patients who did not have low-income subsidies faced an average initial OOP TKI cost of \$2,600.⁵⁰ In comparing the probability of filling a TKI over a 180-day period between patients with and without subsidies, patients who did not have subsidies had a significantly lower probability of filling a TKI. A similar study in a population of younger, employed, and commercially insured patients found a lower median OOP cost of \$30.⁷¹ Despite a lower cost burden relative to the Medicare population, patients in the top quartile of OOP cost were significantly 70% more likely to discontinue TKI therapy and were more likely to be non-adherent with a proportion of days covered (PDC) <80%. However, another study in a similar population with commercial insurance found that OOP TKI cost was not significantly associated with the time to TKI initiation.⁷² A single study using the SEER registry linked to Medicare data found contrasting results – patients that were heavily subsidized, and therefore faced low OOP costs, were significantly less adherent (PDC <0.80) compared to patients that were not subsidized.⁷³ However, patients who were heavily subsidized were likely lower-income and therefore may have had fewer available resources, such as access to care and pharmacies, in addition to lower OOP costs.

Kinase inhibitors have also been developed for other cancers such as renal cell carcinoma and non-small cell lung cancer. Studies evaluating the effect of high kinase inhibitor cost on medication utilization in lung and renal cancer have shown consistent results with that of the CML population. Among Medicare patients with metastatic renal carcinoma, those without low-income subsidies were significantly less likely to initiate targeted oral cancer drugs.⁷⁴ In patients with metastatic non-small cell lung cancer, patients in the highest quartile of OOP cost had significantly lower adherence as measured by the medication possession ratio, significantly lower days of therapy, and a significantly increased risk of mortality.⁷⁵ Overall, the evidence suggests that TKI treatment OOP cost impairs access and medication adherence to TKIs.

III. DISPARITIES IN HEALTHCARE UTILIZATION AND MORTALITY BY SOCIOECONOMIC STATUS

3.1 The Association Between Socioeconomic Status and Health Outcomes

Healthy People, a US-based organization that provides science-based national objectives to improve the nation's health, defines a health disparity as a differential observation of a health outcome between groups of people due to a social, economic, and/or environmental disadvantage.⁷⁶ Due to the high financial burden of cancer care, disparities in health outcomes due to SES (i.e., the measure of combined economic and social status or standing attributed to education, income, and/or occupation)⁷⁷ is unavoidable in the US under the current healthcare system. Although SES may be measured by other proxy variables such as employment, education, race/ethnicity, or a combination of these variables, median income is the most relevant variable to define SES due to the deleterious financial effects of cancer. The behavior of patients may be influenced by the amount of financial resources, which may affect health outcomes. Regardless of how SES is defined, it is associated with adverse health outcomes across a multitude of illnesses.⁷⁸ Generally, health is a monotonic function of SES – decreasing the level of SES is associated with worse health outcomes – but the extent of disparity is often greater among racial and ethnic minority cancer patients.

The association between SES and health outcomes varies by cancer, but generally points to an increased risk of morbidity and mortality in patients with low SES relative to high SES. In a cross-sectional analysis of a sample of 3,135 counties in the US, low-SES counties with a median income of \$33,435 had significantly more cancer deaths relative to medium and high-income counties.⁷⁹ This observation is consistent among the most frequently diagnosed cancers (breast, lung/bronchus, prostate, and colorectal).^{80,81} In a systematic review evaluating the association between SES and survival in breast cancer patients, individuals with lower early-

life SES had a higher risk of death than did those with higher early-life SES.⁸² A long-term follow-up study of patients with breast cancer also found that education and neighborhood SES was significantly negatively associated with survival, and the association was moderated by race/ethnicity.⁸³ A meta-analysis of seventeen studies evaluating the association between SES and survival among lung cancer patients found that low-income patients had a significant 13% increase in the risk of death relative to high-income patients.⁸⁴ In a systematic review of patients with prostate cancer, the majority of studies found a significant association between low SES and an increased risk of death ranging from 2% to over 300%.⁸⁵ A systematic review in colorectal cancer spanning multiple countries found an increased mortality rate in low SES patients.⁸⁶

In the CML population, the association of SES and mortality has been inconsistent. In a prospective cohort study based in England, survival was significantly lower in areas of low SES as defined by a deprivation index.⁸⁷ However, in a Swedish study, there was no association between household income and mortality.⁸⁸

In addition to SES-related mortality disparities, there may also be disparities in healthcare utilization, which may link SES-related disparities to mortality. High OOP costs of cancer drugs has been significantly negatively associated with treatment initiation, adherence, and continuation, particularly with TKIs.^{50,70–75} Patients with low-SES may prioritize other basic needs of life such as food and shelter over treatment effectiveness and survival by forgoing cancer therapy or treatment for other health conditions.⁸⁹

IV. DISPARITIES IN HEALTHCARE UTILIZATION AND MORTALITY BY SOCIOECONOMIC STATUS IN CHRONIC MYELOGENOUS LEUKEMIA

4.1 Significance and Need

The treatment paradigm of cancer has shifted from use of non-selective chemotherapy to novel targeted therapies such as TKIs, or biologic-based immunotherapies. These therapies are exceedingly expensive upon release with prices $\geq \$100,000$ annually, which may not be based on novelty but on maximum willingness-to-pay. Prices continue to rise post-launch. The price of cancer treatment has become a financial burden to the US healthcare system and more concerning, to the patient whose treatment cost exceeds income. Cancer patients are experiencing the financial toxicity of treatment in addition to the disease burden, which may be leading to impaired treatment access, suboptimal medication use, decreased treatment effectiveness, and an increased risk of mortality with rising OOP treatment cost. The current cancer treatment paradigm, combined with the high cost and associated financial toxicity, may be leading to the marginalization or “pricing out” of a vulnerable population, such as Medicare patients, that cannot afford treatments leading to disparities in health outcomes by SES within this population. Therefore, the objective of this research is to determine the impact of high cancer drug prices on patients, estimate the costs associated with CML care to better inform policies affecting this population, and identify whether disparities exist in outcomes (**Figure 1**).

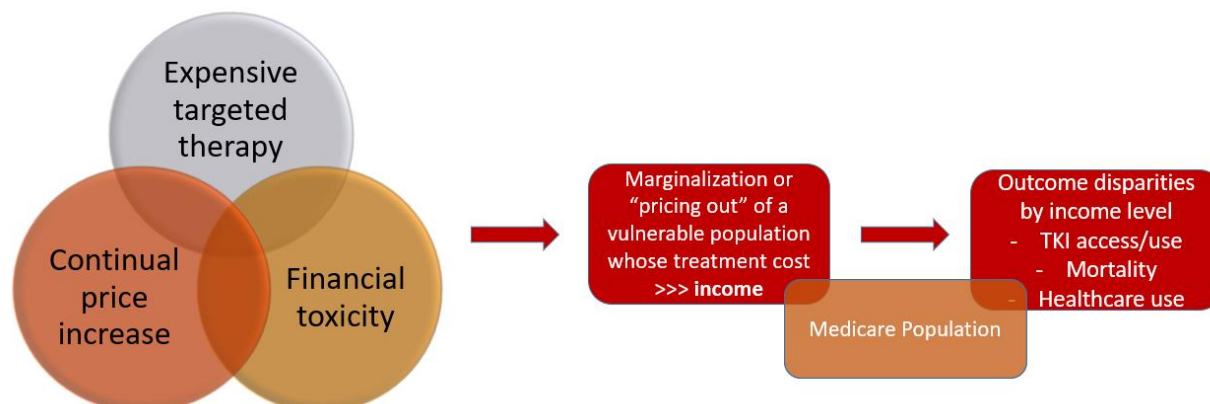


Figure 1. How cancer treatment may potentiate health outcome disparities by socioeconomic status.

4.2 Gaps in Evidence

Although there is a large body of evidence that supports the cost of cancer care is a significant economic burden and is deleterious to patient outcomes in various cancers, gaps in evidence exist specifically in the CML population. First, existing research on oral cancer medication pricing and OOP cost trends have a limited timeframe, do not focus exclusively on the CML population, do not capture currently available generic TKIs, and do not account for changing OOP cost across Medicare plan types. Research on the expected cost of TKI therapy for CML can serve as an invaluable resource for providers and patients to help inform treatment decision making. Second, to the best of our knowledge, there is no evidence on the association between SES and non-cancer healthcare utilization in the CML population. Specifically, it is unknown whether patients of differing SES differentially trade-off non-cancer healthcare in order to maintain financing of cancer care. Third, while there is a hypothesized impact of SES on mortality, there is limited and conflicting evidence from European countries where, unlike the

US, single-payer systems that provide universal healthcare may minimize the impact of high treatment costs for low SES patients.

4.3 Central Hypothesis and Specific Aims

Our central hypotheses are that patients with lower SES are less likely to use non-cancer healthcare resources and are at higher risk of mortality relative to patients with high SES. Our central hypothesis was tested by pursuing three specific aims in a Medicare sample:

- 1) To evaluate the trend in TKI drug price and patient OOP cost across time in CML patients on TKIs. We expected to see an increase in TKI drug price and patient OOP expenditure across time, exceeding general pharmaceutical and medical inflation. We qualitatively evaluated this trend by cross-sectionally plotting annual average drug price and OOP expenditure for each TKI (imatinib, bosutinib, nilotinib, dasatinib, and ponatinib) from 2007 through 2016 and compared the annual changes in price and OOP expenditure to medical inflation indices.
- 2) To evaluate the association between SES and treatment initiation and mortality in patients with newly diagnosed CML. We hypothesized that patients with low SES will have a longer time to TKI initiation and have a higher rate of mortality compared to high SES patients, which is affected by time-varying adherence level. We tested this hypothesis by constructing a Cox proportional hazards-model of the time to treatment initiation according to SES, the time to death, and the time to death adjusted for adherence level.
- 3) To evaluate the impact of SES on non-cancer healthcare expenditure in patients with newly diagnosed CML on TKI therapy. We hypothesized that patients with low SES will decrease non-cancer healthcare use in order to maintain TKI therapy resulting in lower non-cancer healthcare expenditure compared to high SES patients. We tested this

hypothesis by constructing an inverse probability weighted generalized linear model to evaluate the association between SES and non-cancer healthcare expenditure from TKI initiation until death.

4.4 **Theoretical Framework**

Patient decision-making in cancer is highly complex and requires weighing multiple factors of a decision in a state-of-mind that is likely not conducive for optimal decision making. In order to make a treatment decision, patients must weigh factors such as treatment effectiveness, toxicity, and tolerability. Furthermore, patients must also consider the financial effects of cancer and the burden of paying for treatment especially Medicare beneficiaries who are likely retired and on a fixed income. Despite the high cost of treatment, particularly TKIs for CML, patients tend to behave in a manner that is averse to a loss in life-expectancy and therefore, patients are likely to initiate TKI therapy.^{90,91} However, the behavior of patients on TKI therapy may differ based on SES (**Figure 2**). Patients face a heavy economic burden and may differentially make treatment decisions based on their income level. Even among patients with insurance, cancer drugs are typically placed on “specialty tiers” which require a 33% copay, which is a relatively substantial amount compared to lower-tiered medications.⁹² High SES patients with high income levels relative to treatment cost may prioritize survival, whereas low SES patients whose treatment cost may exceed income may prioritize cost minimization.⁸⁹ Consequently, low SES patients may delay or forgo TKI treatment, or if they choose to take TKI treatment, they may forgo other non-cancer healthcare resources (e.g., healthcare services and/or therapy for other chronic diseases such as hypertension) to maintain TKI therapy, which leads to a disparity in healthcare utilization for chronic diseases (top branch of Figure 2).

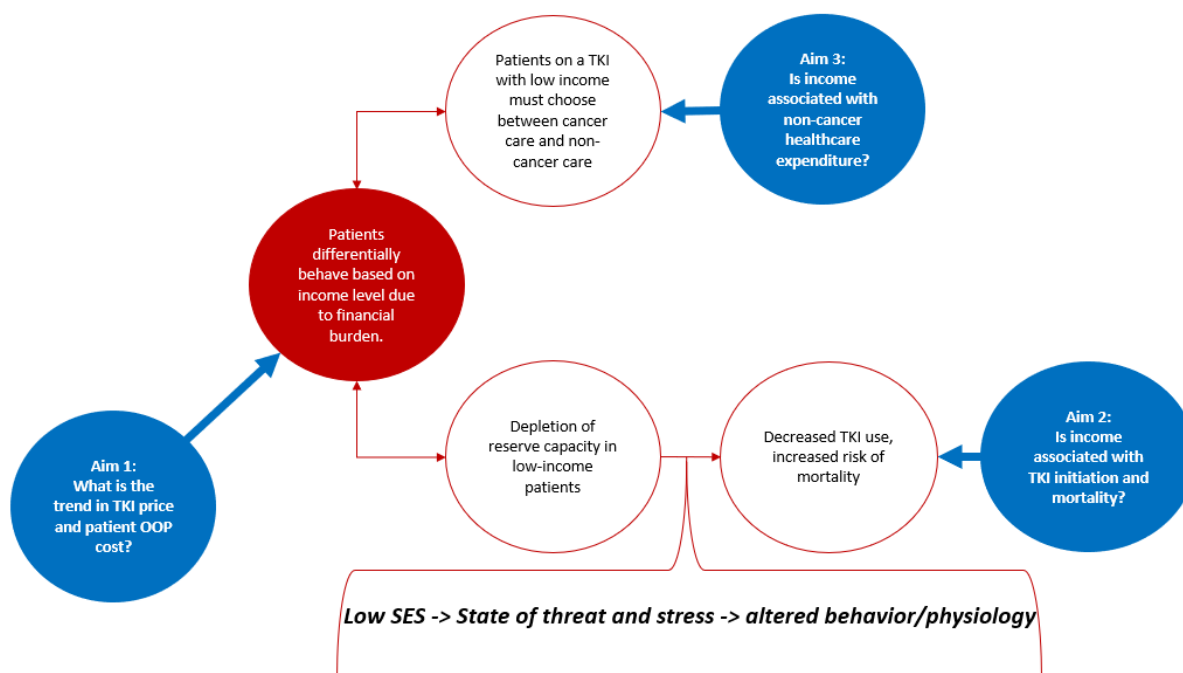


Figure 2. Theoretical framework.

Financial hardship may influence the risk of mortality^{55,62,63} as patients with low-SES may forgo or limit healthcare utilization⁵⁹ and other goods such as food and clothing⁵⁸ or deplete their psychological, social, and material resources (bottom branch of Figure 2).⁹³ The reserve capacity model links SES to adverse health outcomes and is explained in **Figure 3**.⁹³ Patients with low SES have reduced resources and/or reduced access to resources in addition to having a lower hierarchical position in society. When faced with a situation where demands, in this case financial demands related to food, shelter, and healthcare, exceed available resources, an individual experiences a state of threat or a physiological stress response. The stress then leads to increased negative emotion and cognition that may negatively affect numerous intermediate

paths. The intermediate paths may include behaviors that alleviate financial stress such as forgoing medical care in favor of more immediate needs such as food and shelter, and negative impacts in physiological response (e.g., the hypothalamic-pituitary-adrenal axis)^{94,95} to stress that lead to an increased risk of morbidity and mortality.

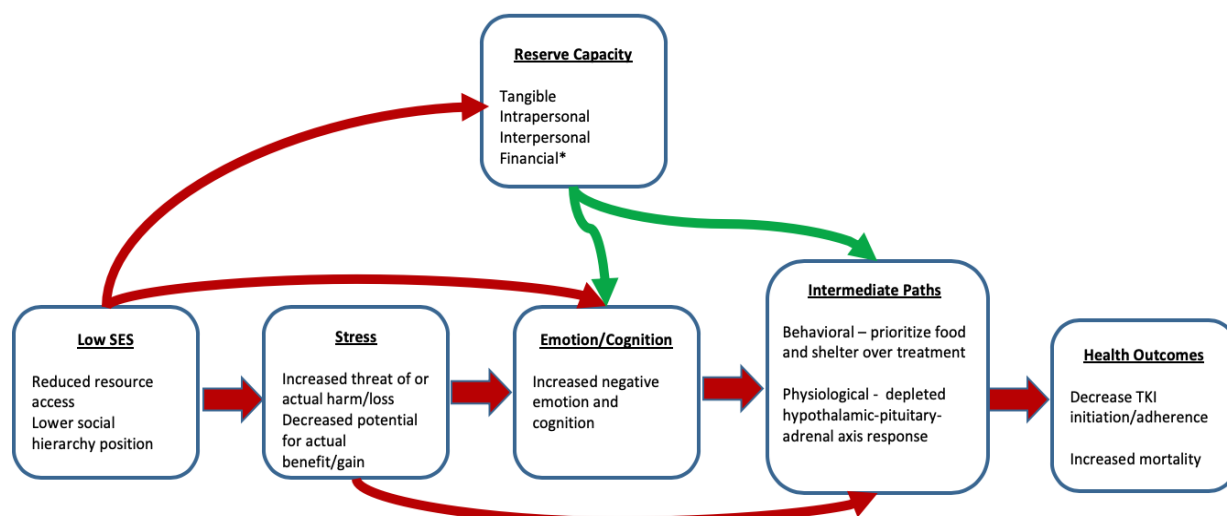


Figure 3. The reserve capacity model.

A patient's reserve capacity, or the amount of material, social (e.g., social support and integration), and psychological (e.g., perceived control, optimism, and self-esteem) resources of a patient, has the potential to mediate and attenuate the negative impacts of stress, emotion, and intermediate paths on health outcomes. Although not originally included, financial resources should also be included in the model. Patients with low SES may deplete their reserve capacity because of the financial and disease burden of cancer, thus predisposing them to an increased risk of morbidity and mortality relative to high SES patients. Simply put, the financial demands on individuals with low SES who need expensive cancer therapy exceeds their reserve capacity. Lastly, patients with low SES may not initiate therapy and have lower treatment adherence due to the high cost of TKI therapy relative to income, which may moderate the effect of SES on patient outcomes.

4.5 Research Implications

The expected outcome of our proposed research was to establish the trend in TKI drug price and OOP expenditure, which would indicate the financial burden of TKI treatment on patients and the healthcare system. Additionally, we helped address the gap in knowledge on the effect of SES on healthcare utilization and mortality in patients with CML, which would highlight the decision making of cancer patients under financial distress and identify disparities in cancer outcomes. Our research may have a positive impact on supporting policies such as those proposed by the President's Cancer Panel that mitigate increasing cancer drug prices and that promote access to optimal cancer care for vulnerable populations, and to encourage the incorporation of a patient's financial health as part of routine cancer care.

V. TREND IN TYROSINE KINASE INHIBITOR UTILIZATION, PRICE, AND OUT-OF-POCKET COST IN PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA

Originally published by the American Society of Clinical Oncology as “Trend in Tyrosine Kinase Inhibitor Utilization, Price, and Out-of-Pocket Costs in Patients With Chronic Myelogenous Leukemia. Brian Talon, Gregory S. Calip, Todd A. Lee, Lisa K. Sharp, Pritesh Patel, Daniel R. Touchette: J. Oncol. Pract Vol.17 (5), May 2021: 1-8]” ©ASCO. All Rights Reserved. Publication guidelines are described in the **Appendix**.

5.1 Preface

Our first manuscript, titled “Trend in Tyrosine Kinase Inhibitor Utilization, Price, and Out-Of-Pocket Expenditure in Patients with Chronic Myelogenous Leukemia”, explored whether TKI drug prices and OOP expenditures have increased across time. Results of this manuscript conveyed the financial burden of TKI therapy on patients and Medicare.

5.2 Introduction

CML is a hematological cancer characterized by the pathologic BCR-ABL tyrosine kinase protein.¹⁴ TKIs target the BCR-ABL tyrosine kinase and are indicated as first-line therapy for the treatment of chronic phase CML.¹⁸ There are currently five FDA - approved TKIs in the US – imatinib, dasatinib, nilotinib, bosutinib, and ponatinib.

Despite the benefits of TKIs, their high prices have drawn scrutiny due to possible deleterious effects on patients and the healthcare system.⁴⁰ The annual list prices of TKIs range from \$92,000 for imatinib to \$138,000 for ponatinib. While monthly median treatment prices are approximately >\$10,000, the median monthly household income of Americans has remained stagnant at \$4,000 over the last decade.³⁹ The price and associated OOP expenditures of TKIs may be financially burdening vulnerable patient groups, especially Medicare beneficiaries who are likely on a fixed income. Medicare drug prices for TKIs indicated for CML fall between

\$3,632 and \$8,429 per 30-day supply, and 40% of patients without low-income subsidies have an OOP expenditure over \$913 per 30-day supply.⁹⁶ Additionally, studies have shown that cancer drug prices continue to increase after launch,⁴¹ including TKIs indicated for CML.⁴²

The financial burden of cancer therapy, or “financial toxicity”, is associated with impaired medication access.⁵⁷ Among Medicare beneficiaries with CML, patients who face relatively high OOP expenditure without drug subsidies have a lower probability of initiating a TKI.^{50,70} In a commercially insured population, CML patients in the top quartile of OOP expenditure were more likely to be non-adherent and discontinue therapy.⁷¹ Thus, trends in drug pricing and OOP expenditure greatly affect Medicare beneficiaries. Existing research on price and OOP expenditure of cancer oral medications do not focus exclusively on the CML population and/or do not capture price and OOP expenditure trends across time. Additionally, research on the expected expenditure of TKI therapy for CML can serve as a resource for providers and patients to help inform treatment decisions. Therefore, the aim of our study is to describe the annual trend in TKI utilization, price as measured by Medicare payments, and patient OOP expenditure across time in CML patients from 2007 through 2016.

5.3 Methods

5.3.1 Data Source and Population

We used the SEER cancer registry linked to 2007 through 2016 Medicare claims data. The data contains information on patient demographics, cancer diagnosis, Medicare insurance status, and prescription claims.⁹⁷ We collected claim-level data on Medicare gross drug payment and patient cost-sharing and patient-level data on year of diagnosis, gender, race, insurance type, subsidy status, and SEER region. We also collected data on neighborhood poverty status by linking CML cases to the census tract file.

The population included prevalent CML cases (International Classification of Disease Code Oncology [ICD]-O-3 codes 9863 and 9875) between January 1st, 2007 through December 31st, 2016. We required that CML cases have Medicare Part-D enrollment and at least one TKI fill. The study period was restricted from 2007 through 2016 because the Medicare Part-D claims data was first available in 2007 and claims follow-up ended on December 31st, 2016.

5.3.2 Study Variables

The patient pay amount was used to measure OOP expenditure. It represents the amount not reimbursed by a third party (e.g., copays, coinsurance, and deductibles) and excludes other payments made on behalf of the beneficiary. Medicare Part-D gross drug payment was used to measure drug price, which is the sum of ingredient cost, dispensing fees, and sales tax. Gross drug payment does not reflect the negotiated amounts between insurers and manufacturers.

Median per-member per-month (PMPM) OOP expenditure was calculated by aggregating OOP expenditure and dividing by the aggregate total days' supply of all claims occurring throughout a calendar year at the patient level. The resulting expenditure per day was multiplied by 30-days to calculate PMPM OOP expenditure, which reflects expenditure for a 30-day supply each year. Patients with low-income subsidy status during the year were excluded due to minimal cost-sharing requirements. Average annual Part-D gross payment per claim of a 30-day supply was calculated by aggregating gross drug payment and dividing by the aggregate total days' supply of all claims occurring throughout the calendar year across all patients. The resulting amount was multiplied by 30-days to arrive at the gross drug payment for a 30-day supply.

5.3.3 Analysis

We identified prevalent CML cases from 2007 through 2016 and whether the patient received a TKI in each year to calculate the annual proportion of patients treated. Among patients treated each year, the average Part-D gross payment per 30-days across all TKIs and stratified by TKI was plotted across time from 2007 through 2016 to qualitatively evaluate trends. Similarly, median PMPM OOP expenditure across all TKIs and stratified by TKI was plotted across time from 2007 through 2016 among patients without low-income subsidies. OOP expenditure was further stratified according to the type of insurance drug plan the patient was in at the start of the year to evaluate trends across plan types (e.g., employer/managed care/regional preferred provider organization [PPO] and traditional Medicare Part-D). Year-to-year percent change in Part-D gross payment and OOP expenditure was calculated using the formula $(cost_{year+1} - cost_{year}) / (cost_{year})$ and qualitatively compared to changes in inflation rates derived from the Personal Healthcare (PHC) price index and Consumer Price Index (CPI) – Medical, respectively.⁹⁸ Annual OOP expenditure data for a TKI in which the number of patients was less than eleven were not reported per Medicare privacy restrictions.

5.4 Results

Of 73,705 leukemia cases, we identified 6,206 cases of CML. Among CML cases, 5,879 patients had Medicare Part-D, and 3,189 patients had at least one TKI fill. The mean age at the time of diagnosis was 67 years and the number of patients diagnosed was similar year-to-year (**Table I**). Most patients were male, white, and of non-Hispanic ethnicity. Most patients had a traditional Medicare Part-D plan or a managed care prescription plan at the time of diagnosis, and less than 3% of patients had a low-income subsidy at the time of diagnosis.

Table I. BASELINE CHARACTERISTICS OF TKI USERS AT THE TIME OF DIAGNOSIS

	TKI users (N=3,189)	
Age at diagnosis (SD)	67.3	(12.8)
Year of diagnosis (%)		
<2007	21	(0.7)
2007	277	(8.9)
2008	317	(10.2)
2009	343	(11.0)
2010	350	(11.2)
2011	365	(11.7)
2012	377	(12.1)
2013	380	(12.2)
2014	365	(11.7)
2015	318	(10.2)
Missing date of diagnosis	76	-
Sex (%)		
Male	1722	(54.0)
Race (%)		
White	2578	(80.8)
Black	340	(10.7)
American Indian/Alaskan	21	(0.7)
Asian/Pacific Islander	192	(6.0)
Unknown	58	(1.8)
Ethnicity (%)		
Hispanic	341	(10.7)
Non-Hispanic	2848	(89.3)
Part-D plan type at diagnosis (%)		
Employer or other	16	(0.52)
Managed Care	644	(20.8)
Medicare Part-D	1309	(42.3)
Regional PPO	47	(1.5)
Not enrolled or unknown	1076	(34.8)
Missing	97	-
Low-income subsidy at diagnosis (%)		
Subsidized	87	(2.81)
Eligible for low-income subsidy	605	(19.6)
Unsubsidized	1324	(42.8)
Not Medicare enrolled or unknown	1076	(34.8)
Missing	97	-

Table I (continued). BASELINE CHARACTERISTICS OF TKI USERS AT THE TIME OF DIAGNOSIS.

Urbanicity (%)	TKI users (N=3,189)	
Urban	2690	(84.4)
Rural	477	(15.0)
Unknown	22	(0.7)
Region (%)		
Northeast	513	(16.1)
Midwest	632	(19.8)
South	572	(17.9)
West	1472	(46.2)
Percent living below poverty threshold (%)		
Unknown or 0% to <5%	698	(21.9)
5% to <10%	770	(24.2)
10% to <20%	940	(29.5)
20% to 100%	781	(24.5)

The annual prevalence of CML increased annually and reached over 4,000 cases in 2015 (**Figure 4**). The proportion of prevalent patients with a TKI fill in the year increased from 17.9% in 2007 to 52.8% in 2015.

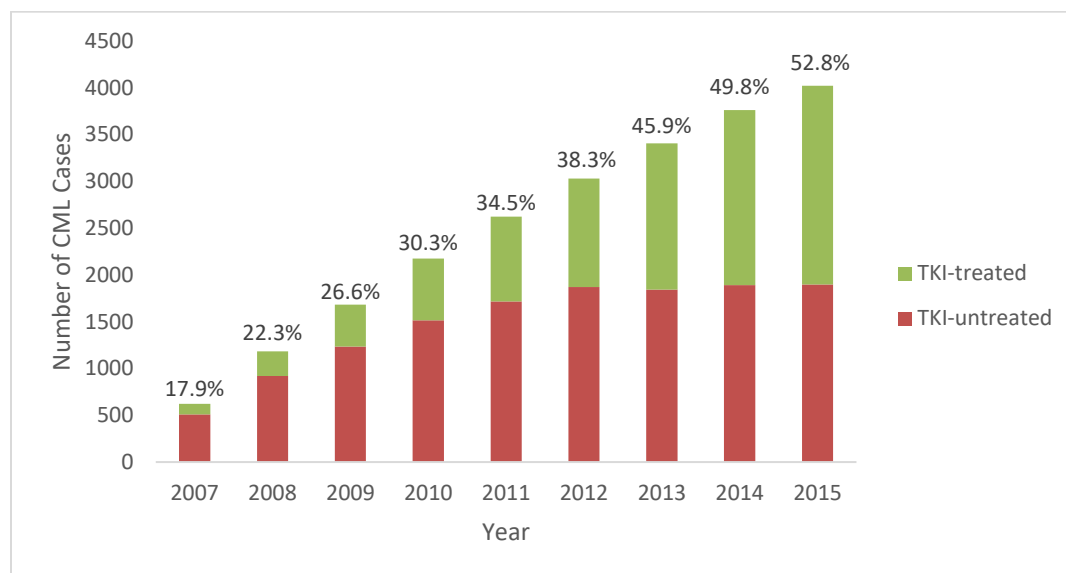


Figure 4. Annual proportion of prevalent CML patients treated with a TKI. The SEER data does not contain newly diagnosed CML patients in 2016 and data in this year was excluded.

Overall, the average annual Part-D gross payment per 30-day of each TKI increased from 2007 through 2016 (**Figure 5**). Imatinib, which was FDA approved prior to Medicare Part-D implementation, had a gross payment of approximately \$3,000 per 30-day supply in 2007, which increased to about \$9,000 in 2016. Dasatinib and nilotinib had initial annual gross payments per 30-day supply of about \$3,800 and \$6,200, respectively, which increased to over \$9,000 in 2016. Bosutinib had an initial annual gross payment per 30-day supply of about \$5,500 which then increased to about \$9,800 in 2016. Ponatinib had the highest initial annual gross payment per 30-day supply at about \$9,900 in 2013, which increased to about \$19,800 in 2016. Lastly, generic imatinib was released into the US market in 2016, and the initial annual gross payment per 30-day supply was about \$7,800.

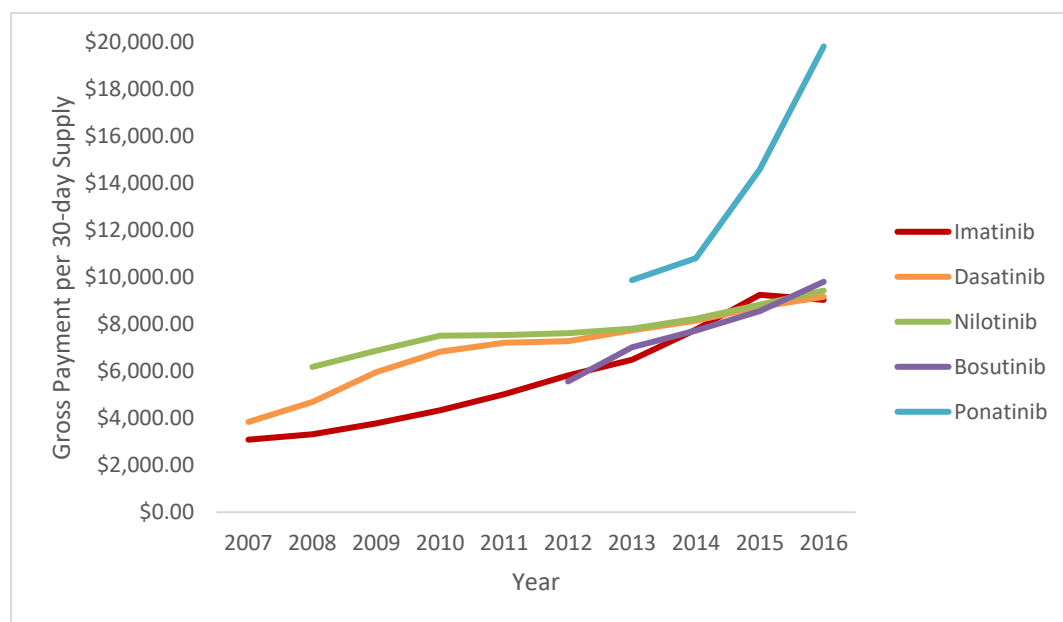


Figure 5. Trend in TKI Medicare gross payment per 30-day supply stratified by TKI. FDA approval year: imatinib (May 2003), dasatinib (June 2006), nilotinib (October 2007), bosutinib (September 2012), and ponatinib (December 2012). Dates were obtained from accessdata.fda.gov.

Across all TKIs and except for the years 2015 to 2016, the annual percent change was double-digits throughout the period (**Figure 6**). The average annual increase was 12.8%, which greatly exceeded the average 2% annual percent change in the PHC index. The period with greatest gross payment growth was from 2008 through 2011 when percent increase was sustained at about 18% year-to-year. The increase from 2015 to 2016 was the smallest change across the period at about 0.3%.

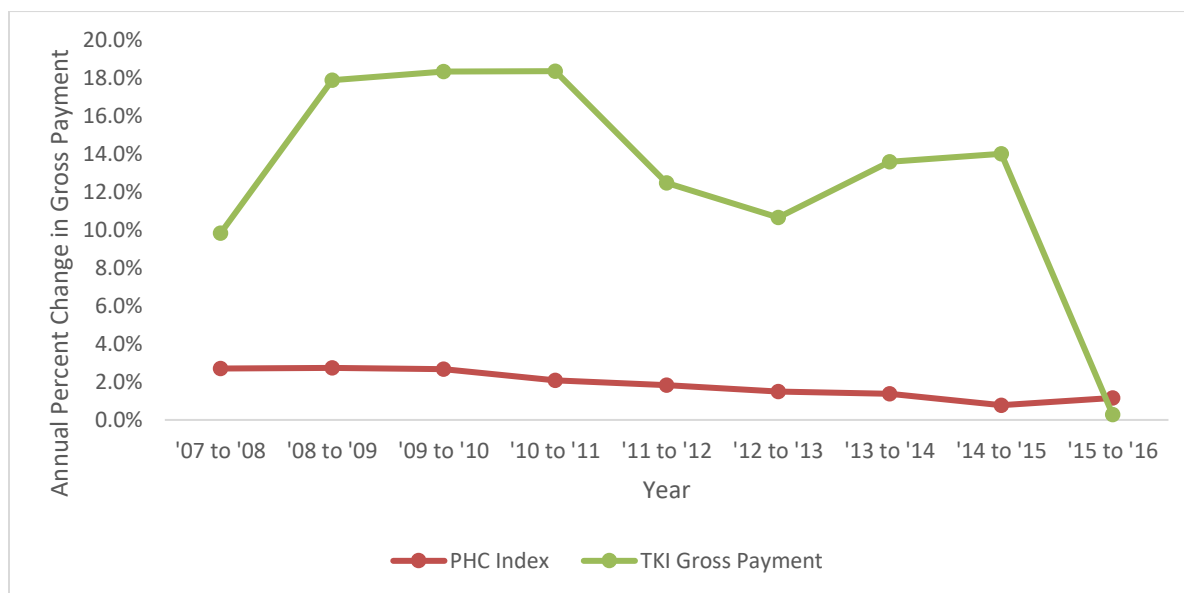


Figure 6. Annual percent change in gross payment per 30-day supply across all TKIs compared to annual percent change of the Personal Healthcare (PHC) index.

Median PMPM OOP expenditure across all TKIs among patients with no subsidies remained relatively constant between \$450 and \$600 throughout the period and was highly variable (**Table II**).

Table II. MEDIAN PER-MEMBER PER-MONTH OUT-OF-POCKET EXPENDITURE ACROSS ALL TKIS AMONG PATIENTS WITH NO SUBSIDIES.

Year	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
All TKIs	\$556	\$496	\$577	\$574	\$461	\$496	\$524	\$554	\$560	\$567
Quartile range	\$726	\$789	\$413	\$433	\$297	\$421	\$606	\$629	\$677	\$702

Stratified by TKI, imatinib, dasatinib, and nilotinib decreased in median PMPM OOP expenditure from 2010 to 2011 (**Figure 7**). However, PMPM OOP expenditure increased thereafter which was then followed by sharp decreases for nilotinib and imatinib from 2015 to 2016. In contrast, bosutinib and ponatinib both increased dramatically from 2013 to about \$660 and \$1,000 PMPM, respectively, in 2016. The median PMPM OOP expenditure for generic imatinib in 2016 was about \$600.

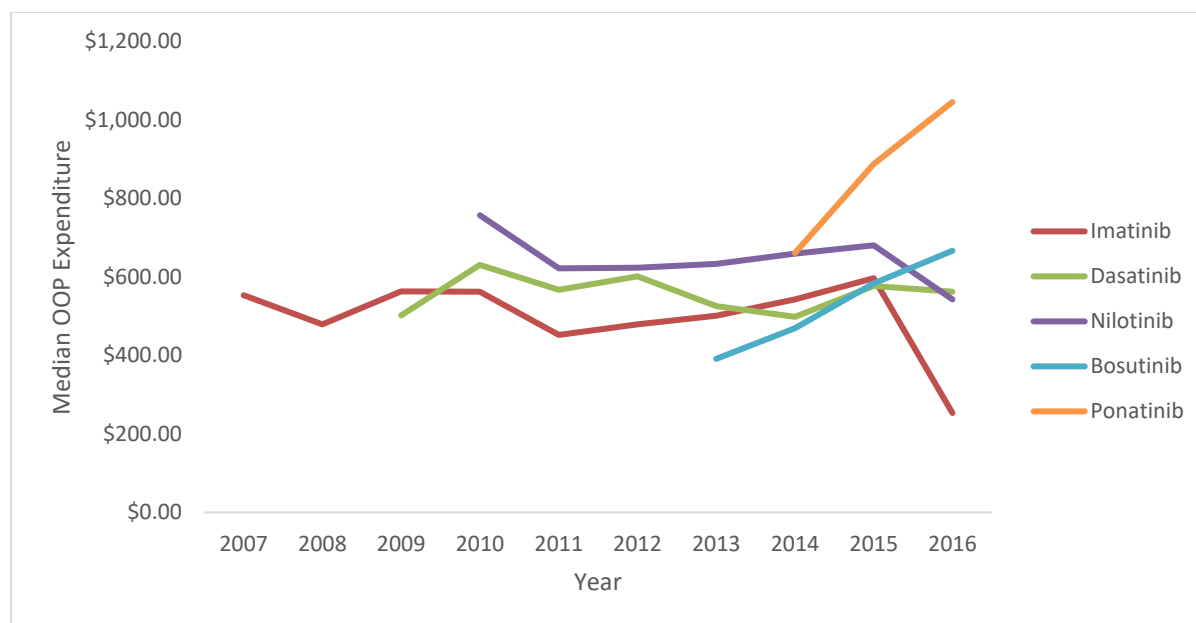


Figure 7. Median per-member per-month out-of-pocket expenditure among patients with no subsidies stratified by TKI.

FDA approval year: imatinib (May 2003), dasatinib (June 2006), nilotinib (October 2007), bosutinib (September 2012), and ponatinib (December 2012). Dates were obtained from accessdata.fda.gov.

Data points for Sprycel, Tasisign, Bosulif, and Iclusig containing less than 11 patients were excluded: dasatinib (2007,2008), nilotinib (2008, 2009), bosutinib (2012), and ponatinib (2013).

Across all TKIs, median PMPM OOP expenditure among patients with employer, managed care, or PPO drug plans was slightly lower relative to patients with traditional Medicare Part-D plans throughout the period (**Figure 8**).

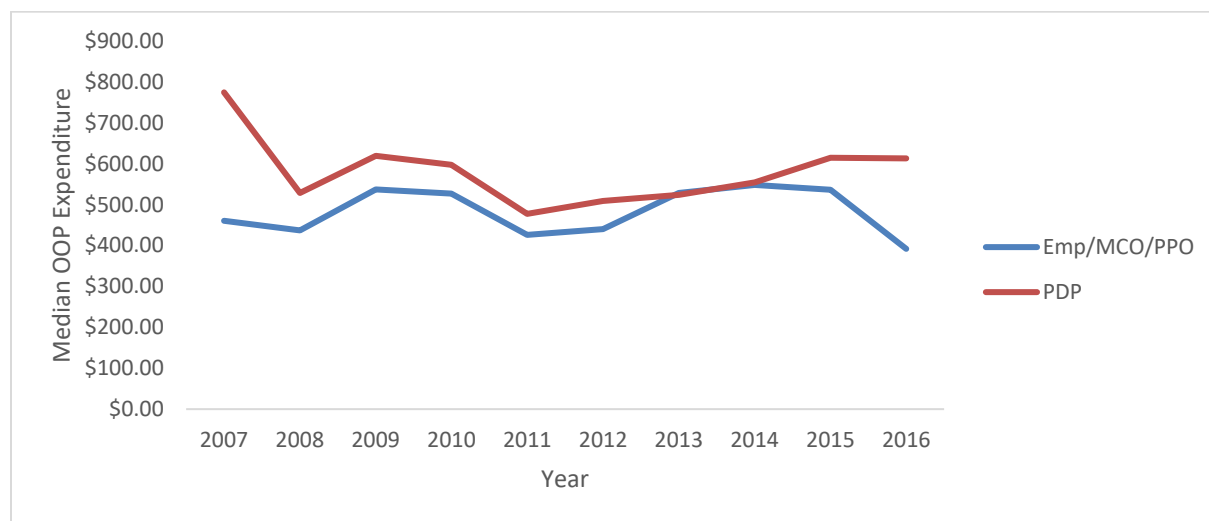


Figure 8. Median per-member per-month out-of-pocket expenditure across all TKIs among patients with no subsidies and stratified by prescription plan type.

The percent change in CPI-Medical remained relatively constant with an average 3% annual increase (**Figure 9**). In comparison, median PMPM OOP expenditure across all TKIs decreased from 2009 to 2011, with the greatest percent decrease at nearly 20% from 2010 to 2011. Median PMPM OOP expenditure increased about 5% to 8% year-to-year from 2011 to 2015 before a 5% decrease from 2015 to 2016.

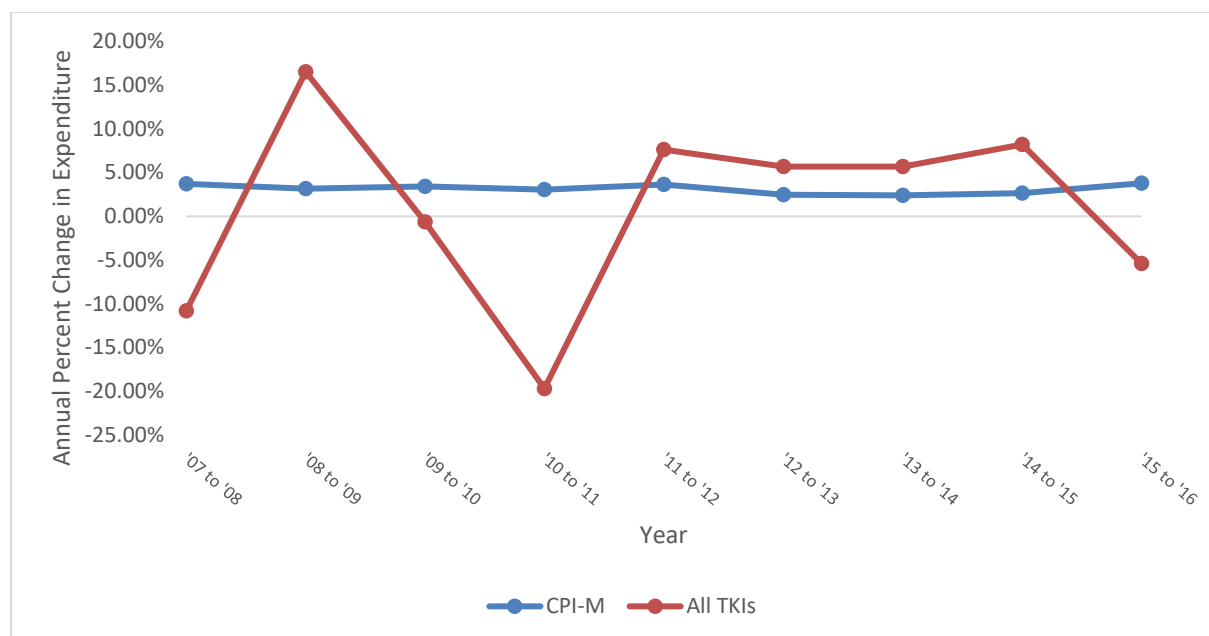


Figure 9. Annual percent change in median per-member per-month out-of-pocket expenditure across all TKIs compared to the annual percent change of the CPI-Medical (CPI-M) index.

5.5 Discussion and Conclusions

The treatment landscape for cancer therapy has shifted from the use of non-specific chemotherapeutic agents to targeted therapies such as TKIs.³⁷ We found an annual increase in the proportion of patients on a TKI. This likely reflects the increased use of TKIs due to its superior efficacy relative to non-TKI chemotherapy^{18,99} and improved survival.⁶ The TKI treatment rate of CML cases was 54% and may be considered low considering the benefits of therapy, but this finding is consistent with other studies using SEER-Medicare. Shen and colleagues reported a treatment rate of 16.5% (including patients with atypical CML, BCR-ABL negative CML, and myelomonocytic leukemia),⁷³ whereas Winn and colleagues reported a rate of 68.2%.⁷⁰

Although TKIs provide significant benefits, its high price must be considered. We found that the Part-D gross payment per 30-day supply of TKIs increased from 2007 through 2016 at an average of 12.8% year-to-year, exceeding that of medical inflation, which remained constant at about 3%. By 2016, gross payment per 30-day supply of a TKI reached about \$9,000.

Although there was a clear trend in increasing gross drug payment, the PMPM OOP expenditure generally fluctuated between \$450 to \$600. Generic imatinib was released into the US market in 2016 with a gross payment per 30-day supply of about \$7,800 and a median PMPM OOP expenditure of about \$600. Notably, gross payment increases across all branded TKIs was less than 1% from 2015 to 2016, presumably due to the market entry of generic imatinib.

Our finding of increasing drug price as measured by Medicare gross payment over time, exceeding medical inflation indices, is consistent with current evidence. Based on average sales prices of ten patented intravenous drugs approved between 1997 through 2012 indicated for various cancers, the inflation-adjusted median percent price increase was 6%.⁴¹ Shih and colleagues evaluated prices of oral cancer medications indicated for various cancers among Medicare beneficiaries and found an average 12% increase in price from 2007 to 2012, while the prescription drug consumer price index increased 3% annually.⁴² We found a similar 12.8% average increase in price from 2007 through 2016 among TKIs indicated for CML. The median price per-month in 2012 was found to be \$7,763 while we found the median price per-month of TKIs indicated for CML to be about \$6,630 in 2012.

With entry of generic imatinib in 2016, we observed gross payment increases for all TKIs except for imatinib, which decreased by 2.3%. The gross payment per 30-day supply of generic imatinib in 2016 was about \$7,800. When compared to the gross payment of branded TKIs (except ponatinib) that ranged from \$9,000 to \$10,000 in 2016, the gross payment of

generic imatinib reflects a 13% to 22% discount. Compared to typical price discounts of a single generic competitor ranging from 39% based on average manufacturer prices and 31% based on invoice prices, the gross payment for generic imatinib may be considered relatively expensive compared to its branded competitors.¹⁰⁰ Of all TKIs, ponatinib was the most expensive and exhibited the highest gross payment increase from about \$10,000 in 2013 to nearly \$20,000 in 2016.

With several branded TKI agents in the market indicated for 1st-line therapy with no differences in overall survival,¹⁸ the increase in gross payment is contradictory to a decrease that would be expected with inter-brand competition.¹⁰¹ Such was the case for the treatment of hepatitis C in which sofosbuvir had a launch price of \$84,000 in 2013, and the branded competitor glecaprivir/pibrentasvir subsequently launched at a lower price of \$26,400.¹⁰² The increase in price may be partly explained by the prohibition of Medicare Part-D by law to exclude cancer drugs from formularies, which limits its ability to pressure manufacturers for lower prices and diminishes the effect of competition. In the US, oncology accounts for the largest proportion of specialty medicine spending at \$39 billion in which protein kinase inhibitors were the biggest driver of growth.⁴⁶ In the context of increasing CML prevalence⁶ and TKI use, gross payment for TKIs will place a substantial financial burden on Medicare Part-D who face the majority of drug costs and who account for about 40% of national health expenditures.¹⁰³

In contrast to increasing gross payment, median PMPM OOP expenditure followed no clear trend and fluctuated between \$450 and \$600. Imatinib, dasatinib, and nilotinib OOP expenditure dropped nearly 20% in the period 2010 to 2011. This significant reduction in median PMPM OOP expenditure was also reported by Shih and colleagues across various targeted oral cancer drugs.⁴² During this period, the Affordable Care Act (ACA) began to close the coverage gap and provided a 50% discount to branded pharmaceuticals when beneficiaries reached the

coverage gap.¹⁰⁴ Although the discounted percentage of branded pharmaceuticals increased annually until complete closure of the coverage gap in 2020 per the ACA, median PMPM OOP expenditure increased 5% to 8% annually from 2011 to 2015. With gross payment annually increasing after 2011, ACA provisions may have minimized increases in OOP expenditure. Like the trend observed in TKI gross payment, median PMPM OOP expenditure decreased from 2015 to 2016 when generic imatinib entered the market.

Stratified by type of drug plan, median PMPM OOP expenditure was generally lower for patients enrolled in an employer, managed care, or regional PPO plan. In 2016, median PMPM OOP expenditure was about \$400 for a TKI with employer, managed care, or regional PPO plan, whereas median PMPM OOP expenditure was about \$600 in patients with traditional Part-D plans. This is consistent with the findings reported by Shen and colleagues who reported that 44% of patients with traditional Part-D paid >\$900 per 30-day supply compared to 36% of patients with managed care or regional PPO plans.⁹⁶ In stratifying by TKI across all plan types, there was a general trend towards a decrease in OOP expenditure for imatinib, dasatinib, and nilotinib, although there was an increasing trend in the OOP cost of bosutinib and ponatinib. The increase in OOP expenditure for these two TKIs may be due to the recent approval in 2012 and relatively small market share.

Despite no increasing trend in OOP expenditure, it is very likely that Medicare beneficiaries are financially burdened. A median PMPM expenditure of \$450 to \$600 may be burdensome for patients who are likely retired and who have a median annual per-capita income of \$26,200.¹⁰⁵ This burden is evident when compared to patients with commercial insurance in which the median OOP expenditure for the first 30-day supply for a TKI was \$42.⁷² High OOP expenditures have been associated with decreased TKI access in CML patients,^{50,70,71} and also across various cancers that are treated with specialty cancer drugs or

oral cancer therapies.^{67–69,74,75} High OOP expenditures will likely “price-out” patients whose treatment cost is a large proportion or exceeds income, thus leading to disparities in TKI access.

Given the continual increase in TKI gross drug payment and relatively high OOP patient expenditures, our findings reinforce the need to support legislation that limit increasing cancer drug prices.¹⁰⁶ Such legislation would penalize manufacturers who increase drug price at a greater rate than inflation by mandating a rebate to Medicare that would equal the difference between the actual price and inflation-adjusted price. The legislation would also allow Medicare to negotiate drug prices with manufacturers. If passed into law, these acts may protect Medicare Part-D insurers and its vulnerable population from the increasing price of cancer therapy.

Our study has several limitations. First, drug price was based on Medicare gross payment, which does not reflect the negotiated price between plans and manufacturers.¹⁰⁷ Therefore, our measured prices may not reflect the trend in negotiated prices. Based on limited data from Medicare, the rebate reflective of all branded drugs in 2014 was 17.5%.¹⁰⁸ With no further competition entering the TKI market for CML beyond 2012, it is likely that the rebate between 2012 through 2016 remained near 17.5%. Assuming the discount remained constant and observing an upward price trajectory through this period, the negotiated prices would be expected to follow an upward trend. Second, although we normalized patient OOP expenditure into a 30-day supply, the reported OOP expenditure reflects fills occurring through different Medicare coverage phases with varying cost-sharing requirements. Since the coverage phase is dependent on the cumulative amount of OOP expenditure the beneficiary has paid for all drugs, the OOP expenditure for a TKI will vary based on the starting month of TKI treatment and other prescription drugs. However, patients are likely to enter the catastrophic coverage phase within the first fill for a TKI.⁹⁶ Therefore, median PMPM OOP expenditure is weighted towards initial TKI fills in a year, which are the most expensive. Additionally, OOP expenditure was likely

reflective of maintaining therapy as prevalent patients accumulated across time. Third, Medicare beneficiaries may not pay the entire OOP expenditures if they qualify for charitable organizations or manufacturer patient assistance programs that cover the cost of TKIs. However, since we excluded patients with low-income subsidies who are likely to qualify for charities and Medicare beneficiaries are typically excluded from patient assistance programs, the population likely faced the full OOP expenditure. Lastly, the interpretation of the results is limited to Medicare beneficiaries.

In conclusion, we found an annual increase in TKI Medicare gross payment exceeding medical inflation but found no trend in OOP expenditure. Increasing gross payment and relatively high OOP expenditure may be burdensome to Medicare and its beneficiaries. Our findings support legislation which mitigate increasing drug prices to alleviate financial burden on Medicare and its beneficiaries.

VI. THE EFFECT OF NEIGHBORHOOD INCOME LEVEL ON TYROSINE KINASE INHIBITOR INITIATION AND MORTALITY IN PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA

6.1 Preface

Our second manuscript, titled “The Effect of Neighborhood Income Level on Tyrosine Kinase Inhibitor Initiation and Mortality in Patients with Chronic Myelogenous Leukemia”, evaluated whether patients with low neighborhood income had a lower rate of TKI initiation compared to patients with high neighborhood income. Among TKI initiators, we also evaluated whether patients with low neighborhood income had an increased rate of all-cause and CML-specific death. Results of our study highlighted disparities in survival among CML patients on TKI therapy, supported legislation which decrease the financial burden of TKI therapy, and emphasized the need to assess the financial health of CML patients on TKI therapy.

6.2 Introduction

Chronic myelogenous leukemia is a rare hematological cancer characterized by the expression of the pathologic BCR-ABL tyrosine kinase protein,¹⁴ and is commonly diagnosed in those aged >64 years.² First-line treatment of CML in the chronic phase, in which most patients are diagnosed,¹⁷ is with oral TKIs.¹⁰⁹ There are currently five marketed TKIs in the US – imatinib, dasatinib, nilotinib, bosutinib, and ponatinib. Patients with CML may now expect a lifespan that is comparable to that of the general non-cancer population – an effect partly attributed to TKI treatment.⁵

Despite the benefits of TKI therapy, the relatively high annual list prices of TKIs ranging between \$92,000 to \$138,000 may have negative financial effects on the healthcare system and patients.⁴⁰ Drug prices for a 30-day TKI supply paid by Medicare ranges from \$3,632 in the 10th percentile of price to \$8,429 in the 90th percentile of price.⁹⁶ The median OOP cost among

patients in a Medicare Part-D plan with no cost-sharing subsidies is \$828 per 30-day supply. The OOP cost to Medicare patients is relatively high when compared to CML patients with employer-based commercial insurance where the median is \$42 for the first 30-day supply of a TKI.⁷² The high OOP cost of TKIs have been associated with a lower risk of initiating a TKI among Medicare beneficiaries.^{50,70}

The term “financial toxicity” is defined as the unintended objective financial burden on, and the subjective financial distress experienced by patients with cancer as a consequence of treatment,⁵⁵ which may lead to adverse patient outcomes such as impaired medication access and decreased survival.⁵⁷ Financial toxicity may be especially onerous among Medicare beneficiaries who have a median annual per-capita income of \$26,200.¹⁰⁵ Medicare patients with CML and low SES, whose treatment cost is high relative to or even exceeds their income, may become “priced out” of treatment resulting in decreased TKI initiation and adherence. Additionally among TKI initiators, beneficiaries with low SES may experience a state of threat and stress when financial demands of TKI treatment exceed available resources (e.g., tangible, intrapersonal, and interpersonal resources), which can detrimentally affect intermediate behavioral and physiological pathways that lead to an increased risk of mortality.⁹³

Although studies have measured the impact of OOP cost on TKI access and adherence,^{50,70,71,73} the effect of SES on TKI access and CML outcomes is lacking. A study in the United Kingdom showed that high income-based measures of SES is associated with lower mortality while another study based in Sweden found no association,^{87,88} but European studies may not fully generalize to the US population. We sought to fill this evidence gap to support federal policies and legislation which allow Medicare to mitigate or lower cancer drug prices.

Our aim is to evaluate the effect of SES, as measured by census tract level median income (i.e., neighborhood income), on treatment initiation and mortality in patients with newly

diagnosed CML using the SEER – Medicare linked database. We hypothesize that compared to high neighborhood income patients, 1) patients with a low neighborhood income will have a lower rate of TKI initiation and 2) among TKI initiators, patients with a low neighborhood income will have a higher rate of mortality that is confounded or moderated by time-varying TKI adherence level.

6.3 Methods

6.3.1 Data Source and Population

The SEER-Medicare database is a linkage of two population-based data sources containing information about Medicare beneficiaries diagnosed with cancer and their Medicare claims.^{97,110} The SEER Program includes 18 cancer registries covering 28% of the US population. Data collected include patient demographics, cancer characteristics, dates of diagnosis and death, and ecologic measures such as census-tract level median household income based on the 2008-2012 American Community Survey. Medicare files include claims resulting from services provided from the inpatient setting, outpatient clinics, physicians and suppliers, and durable medical equipment from 2006 through 2016. Prescription drug claims through Medicare Part-D were available beginning in January 2007.

6.3.2 Study Design

We conducted a retrospective cohort study to evaluate the association between the independent variable neighborhood income level and dependent variables TKI initiation and mortality. To measure the effect of neighborhood income level on TKI initiation, we indexed patients based on their neighborhood income level at the date of CML diagnosis and followed them until the date of the first TKI prescription. Patients who died, lost Medicare Part-D coverage, or reached the end of the study period (December 31st, 2016) without initiating a TKI were right censored. To evaluate the effect of neighborhood income level on mortality with TKI

adherence as a time-varying covariate among TKI initiators, we indexed patients on the date of TKI initiation and followed them until the occurrence of death. Patients who were alive through the end of the study period were right-censored.

6.3.3 Cohort Selection Criteria

We included Medicare beneficiaries diagnosed with first primary CML (ICD-0-3 codes 9863 and 9875), which was diagnostically confirmed, between January 1st, 2007 through December 31st, 2015 (Figure 1). We further required that patients were aged >65 years, have Medicare as the primary payer at diagnosis, have Medicare Part-D at the time of diagnosis, have at least 12-months of continuous Medicare Parts-A and -B enrollment prior to diagnosis, and have no managed care enrollment within 12-months prior to diagnosis. Patients who started a TKI prior to diagnosis, were diagnosed at autopsy, were Medicare entitled through a disability or end-stage renal disease, had missing diagnosis dates, or had missing census tract median income were excluded.

6.3.4 Independent Variable

We defined SES as the census-tract (i.e., neighborhood-level) median household income at the time of diagnosis, which was dichotomized as low neighborhood income (<50th percentile) and high neighborhood income (≥50th percentile). The SEER tract-level data was based on the 2008 to 2012 American Community Survey, which is a nationwide survey that collects socioeconomic and demographic data.⁹⁷ Since SEER does not report the day of diagnosis, we assumed that all patients were diagnosed on the 15th of the month.

6.3.5 Dependent Variable

We evaluated two dependent variables - time to TKI initiation and survival time among TKI initiators. Time to TKI initiation was measured as the time in weeks from CML diagnosis to the first prescription for any TKI. Survival time was measured as the time in months from TKI

initiation to death. Since SEER does not report the date of death, we assumed that all patients who died had a date of death on the 15th of the month.

6.3.6 Covariates

Potential confounders were measured within a 1-year period before the date of CML diagnosis. Confounders were classified into categories. Patient demographics included age, gender, race, ethnicity, and marital status. Clinical characteristics included year of diagnosis, primary cancer sequence, claims-based frailty index,¹¹¹ National Cancer Institute [NCI] Charlson comorbidity index,¹¹² and total healthcare expenditures (sum of patient and insurer payments for inpatient, outpatient, and durable medical equipment claims). Insurance characteristics included Medicare plan type, Medicare prescription drug plan type, low-income subsidy status, and dual eligibility status. Lastly, geographic descriptors included urbanicity, SEER region, percent of neighborhood below the poverty threshold, and percent of neighborhood with only a high-school education.

Proportion of days covered, a measurement of medication adherence, was measured as time-varying 30-day cumulative adherence (e.g., total days' supply of all claims occurring in a 90-day interval divided by a 90-day interval) of all TKI claims occurring in the survival period.¹¹³ Time varying cumulative PDC reflects changes in adherence across the entire duration of indicated therapy. Among patients with two overlapping refills, fills were adjusted so that the second prescription was shifted forward in time to the end of the first prescription's days' supply.¹¹⁴ Patients with a PDC \geq 80% were defined as having high TKI adherence.¹¹⁵

6.3.7 Statistical Analysis

Baseline characteristics were compared between high and low neighborhood income levels using Chi-square or Fisher's exact test for categorical variables and pooled t-tests or Wilcoxon rank sums test for continuous variables.¹¹⁶ The probability of remaining TKI-naïve from

CML diagnosis was compared between neighborhood income levels using Kaplan-Meier curves with a log-rank test. A Cox proportional-hazards model adjusted for confounders was used to estimate the hazard of TKI initiation between income levels. Proportionality of hazards was met via log-log plots and Schoenfeld residuals. Model specification was varied by sequentially adding categories of covariates (demographics, clinical characteristics, insurance characteristics, and geographic descriptors) to the unadjusted model to evaluate changes in the coefficient of neighborhood income level.

Among TKI initiators, time-varying cumulative PDC was plotted across time in months from TKI initiation through death or censoring. Overall survival among TKI initiators was compared between neighborhood income levels using Kaplan-Meier curves with a log-rank test. A time-varying Cox model was used to evaluate the hazard of death by income level with PDC as a cumulative monthly time-varying confounder.^{117,118} Model specification was varied by sequentially adding categories of covariates to the model adjusted for time-varying adherence to evaluate changes in the coefficient of neighborhood income level. Lastly, income level and adherence status were interacted to determine whether the hazard of death differed between neighborhood income level among high- and low-adherers. The analysis was repeated to analyze the hazard of CML-specific death among TKI initiators by censoring patients who died of non-cancer causes.¹¹⁹

Lastly, E-values were calculated to estimate the potential impact of unobserved confounding on a significant association between neighborhood income and outcomes, if any.¹²⁰ The E-value represents the required minimum strength of association an unmeasured confounder(s) would need to have with both the independent and dependent variable to nullify an association conditional on observed confounders.

6.4 **Results**

A total of 5,134 cases of primary CML patients were identified (**Figure 10**). Among these, 503 patients met the inclusion criteria. The median neighborhood income of the cohort was \$55,763 and patients were classified as low neighborhood income ($< \$55,763$) and high neighborhood income ($\geq \$55,763$).

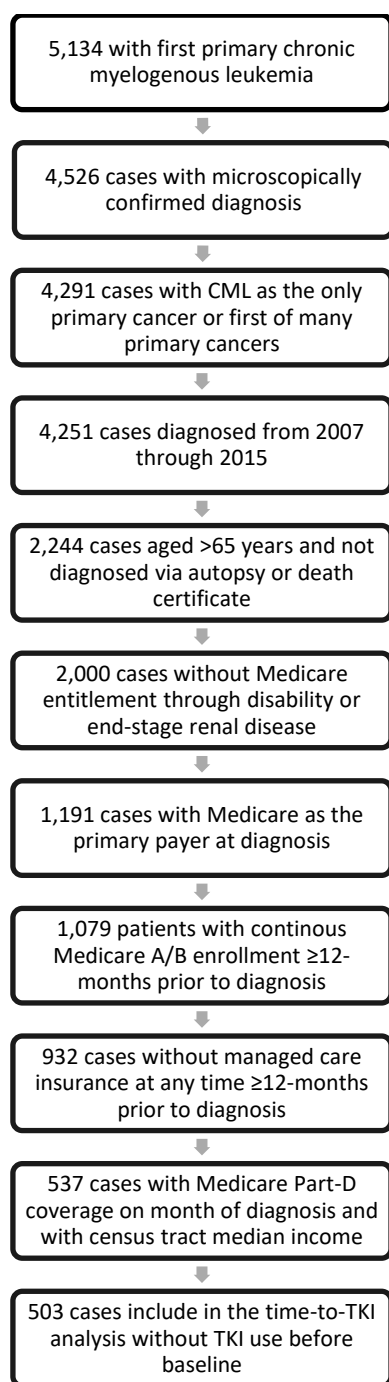


Figure 10. Patient selection criteria and attrition.

There were no significant differences between groups with respect to age, sex, ethnicity, and marital status, but a greater proportion of Blacks resided in low-income neighborhoods (**Table III**). There were no significant differences between groups in the year of diagnosis, cancer sequence, comorbidities, frailty, and healthcare utilization. A statistically significantly greater proportion of low neighborhood income patients were eligible for Medicare and Medicaid, whereas a significantly greater proportion of high neighborhood income patients had a Medicare supplement. Patients from low-income neighborhoods were significantly more likely to have a premium and copay subsidy. Lastly, patients in low-income neighborhoods were more likely to live in a rural area, live in a neighborhood with greater than 10% of the population falling below the federal poverty limit, and live in a neighborhood with a greater percentage of adults having high-school as the highest education level.

Table III. BASELINE CHARACTERISTICS OF CML PATIENTS BY NEIGHBORHOOD INCOME LEVEL.

Variable	Level	Low-income (<\$55,763) N=251	High-income (\$55,763) N=252	P-Value
Age at diagnosis Mean (SD)		76.57 (7.41)	77.54 (7.43)	0.12
Sex N (%)	Female	140 (55.78%)	135 (53.57%)	0.62
	Male	111 (44.22%)	117 (46.43%)	
Race N (%)	Asian/Indian/Other	14 (5.58%)	*	<.001
	Black	30 (11.95%)	*	
	White	207 (82.47%)	219 (86.90%)	
Ethnicity N (%)	Hispanic	21 (8.37%)	16 (6.35%)	0.39
	Non-Hispanic	230 (91.63%)	236 (93.65%)	
Marital status at diagnosis N (%)	Married or partnered	131 (52.19%)	136 (53.97%)	0.82
	Separated/divorced /widow/single	103 (41.04%)	102 (40.48%)	
	Unknown	17 (6.77%)	14 (5.56%)	
Year of diagnosis N (%)	2007	28 (11.16%)	15 (5.95%)	0.53
	2008	28 (11.16%)	22 (8.73%)	
	2009	14 (5.58%)	19 (7.54%)	
	2010	24 (9.56%)	23 (9.13%)	
	2011	30 (11.95%)	29 (11.51%)	
	2012	30 (11.95%)	29 (11.51%)	
	2013	32 (12.75%)	39 (15.48%)	
	2014	33 (13.15%)	37 (14.68%)	
	2015	32 (12.75%)	39 (15.48%)	
Cancer sequence N (%)	First and only	221 (88.05%)	226 (89.68%)	0.56
	First of many	30 (11.95%)	26 (10.32%)	
Frailty index Median (Q1, Q3)		0.17 (0.13, 0.22)	0.17 (0.13, 0.21)	0.77
NCI Charlson index Median (Q1, Q3)		1.34 (0, 2.66)	1.34 (0, 2.64)	0.81
Healthcare utilization (\$) Median (Q1, Q3)		4298.00 (1684.44, 11880.83)	5077.40 (2184.50, 13840.00)	0.05
Medicare plan at diagnosis N (%)	Medicare	85 (33.86%)	69 (27.38%)	0.045
	Medicare with Medicaid eligibility	41 (16.33%)	30 (11.90%)	
	Medicare with supplement	125 (49.80%)	153 (60.71%)	

Table III (continued). BASELINE CHARACTERISTICS OF CML PATIENTS BY NEIGHBORHOOD INCOME LEVEL.

Variable	Level	Low-income (<\$55,763) N=251	High-income (>=\$55,763) N=252	P-Value
Low-income subsidy plan at diagnosis N (%)	Eligible or with premium and copay subsidy	96 (38.25%)	57 (22.62%)	<.001
	No premium or copay subsidy	155 (61.75%)	195 (77.38%)	
Dual eligibility status at diagnosis N (%)	Not eligible	170 (67.73%)	204 (80.95%)	<.001
	Qualifies or with dual eligibility	81 (32.27%)	48 (19.05%)	
Urbanicity of area at diagnosis N (%)	Rural	61 (24.30%)	22 (8.73%)	<.001
	Urban	190 (75.70%)	230 (91.27%)	
SEER region at diagnosis N (%)	MW	80 (31.87%)	39 (15.48%)	<.001
	NE	22 (8.76%)	67 (26.59%)	
	South	68 (27.09%)	25 (9.92%)	
	West	81 (32.27%)	121 (48.02%)	
Neighborhood poverty at diagnosis N (%)	0% to <10% poverty	49 (19.52%)	205 (81.35%)	<.001
	10% to 100% poverty	202 (80.48%)	47 (18.65%)	
Neighborhood Highschool education level at diagnosis Mean (SD)		32.81 (9.47)	22.31 (10.11)	<.001

*Suppressed per Medicare privacy restrictions. Over 99% of patients had Traditional Medicare Part-D at the time of diagnosis and data on employer and managed care plan types were not reported due to cell sizes <11 per Medicare privacy restrictions.

By income level, patients residing in a low-income and high-income neighborhood both had a median time of remaining TKI-naïve of 7 weeks. Of the 503 CML patients, 354 initiated a TKI. The unadjusted difference in the probability of remaining TKI-naïve by neighborhood income level was not statistically significant (**Figure 11**).

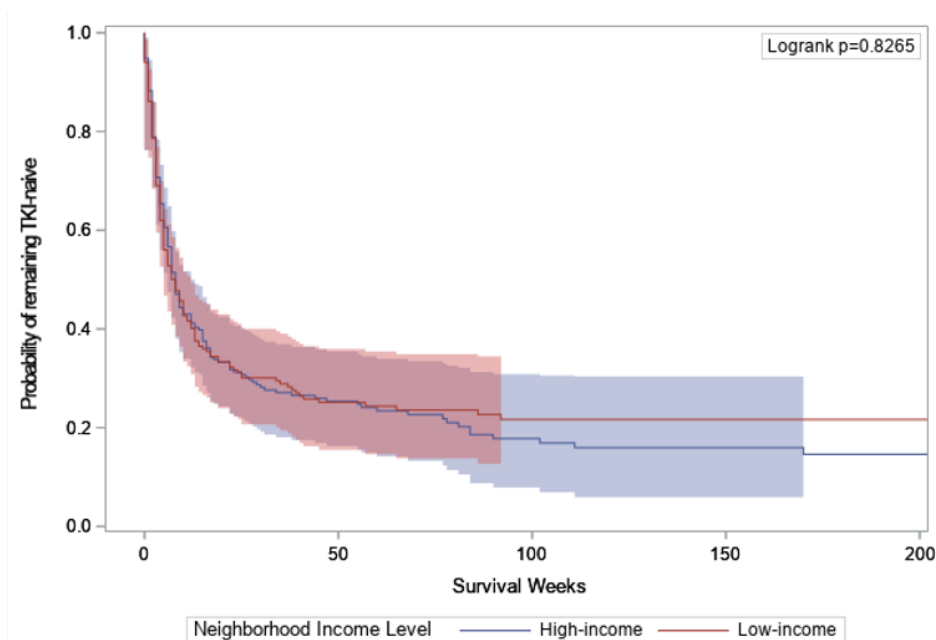


Figure 11. Probability of remaining TKI-naïve by neighborhood income level with 95% Hall-Wellner bands.

Of all CML patients, 354 patients initiated a TKI (185 patients with high neighborhood income and 169 patients with low neighborhood income).

In the unadjusted Cox model, neighborhood income did not have a significant effect on the hazard of TKI initiation (**Table IV**). The effect of neighborhood income on the hazard of TKI initiation remained insignificant when sequentially adjusting for patient demographics, clinical characteristics, insurance characteristics, and geographic descriptors.

Table IV. HAZARD OF TKI INITIATION IN PATIENTS WITH LOW VS. HIGH NEIGHBORHOOD INCOME.

	Hazard ^a	95% Wald CI	P-value
Crude model	0.98	0.79, 1.20	0.82
Model 1 ^b	0.95	0.77, 1.18	0.66
Model 2 ^c	1.01	0.81, 1.25	0.97
Model 3 ^d	0.99	0.80, 1.23	0.91
Model 4 ^e	1.12	0.82, 1.51	0.48

^aReference level is high-income patients and N = 503 CML cases for all models.

^bModel 1: Adjusted for age, sex, race, ethnicity, and marital status.

^cModel 2: Model 1 + year of diagnosis, cancer sequence, frailty index, NCI Charlson comorbidity index, healthcare expenditure.

^dModel 3: Model 2 + Part-D plan type, Medicare plan type, low-income subsidy status, dual-eligibility status.

^eModel 4: Model 3 + % of population living in an urban area, SEER region, % of neighborhood below the poverty threshold, % of neighborhood with only a high-school education.

Among the TKI initiators, the trend in monthly cumulative adherence was relatively similar between high and low neighborhood income groups (**Figure 12**).

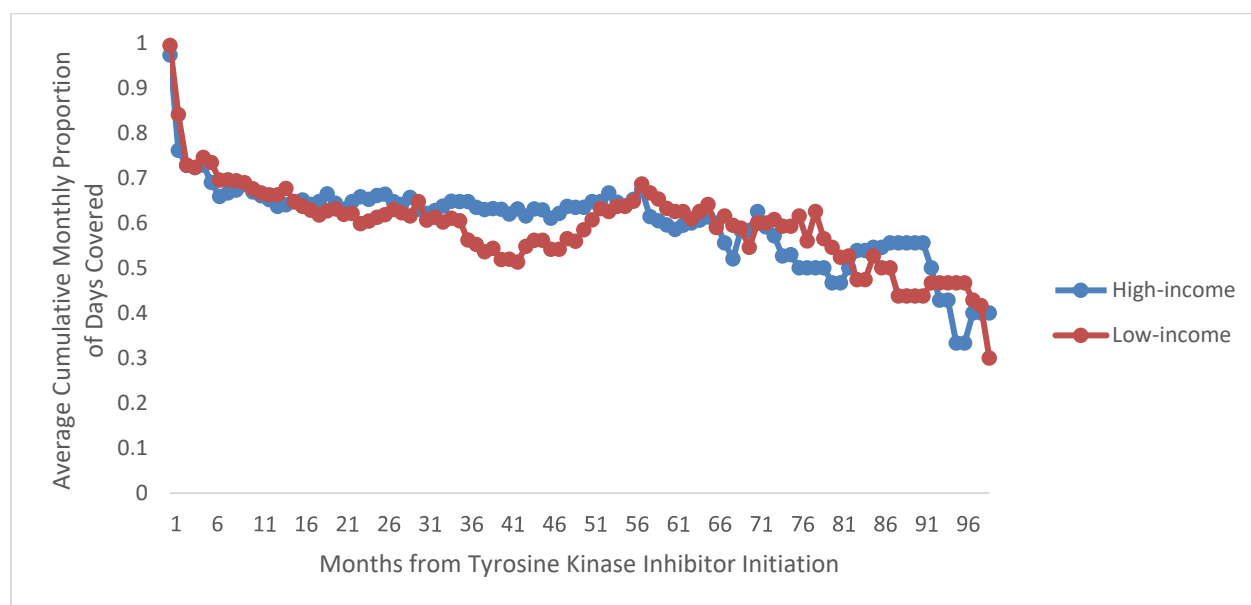


Figure 12. Average cumulative monthly proportion of days covered from TKI initiation through 100 months after TKI initiation by neighborhood income level.

Sample size attrition: low neighborhood income month after TKI initiation (sample size) – 1 (167), 25 (111), 50 (68), 75 (27).

High neighborhood income month after TKI initiation (sample size) - 1 (182), 25 (115), 50 (52), 75 (19). Sample sizes beyond 75 weeks were suppressed per Medicare privacy restrictions.

The median survival time from TKI initiation was 75 months. By income level, low neighborhood income patients had a median overall survival time of 81 months and high neighborhood income patients had a median overall survival time of 73 months. Of the 354 TKI initiators, 125 died within the study period. The unadjusted difference in the probability of survival by neighborhood income level was not statistically significant (**Figure 13**).

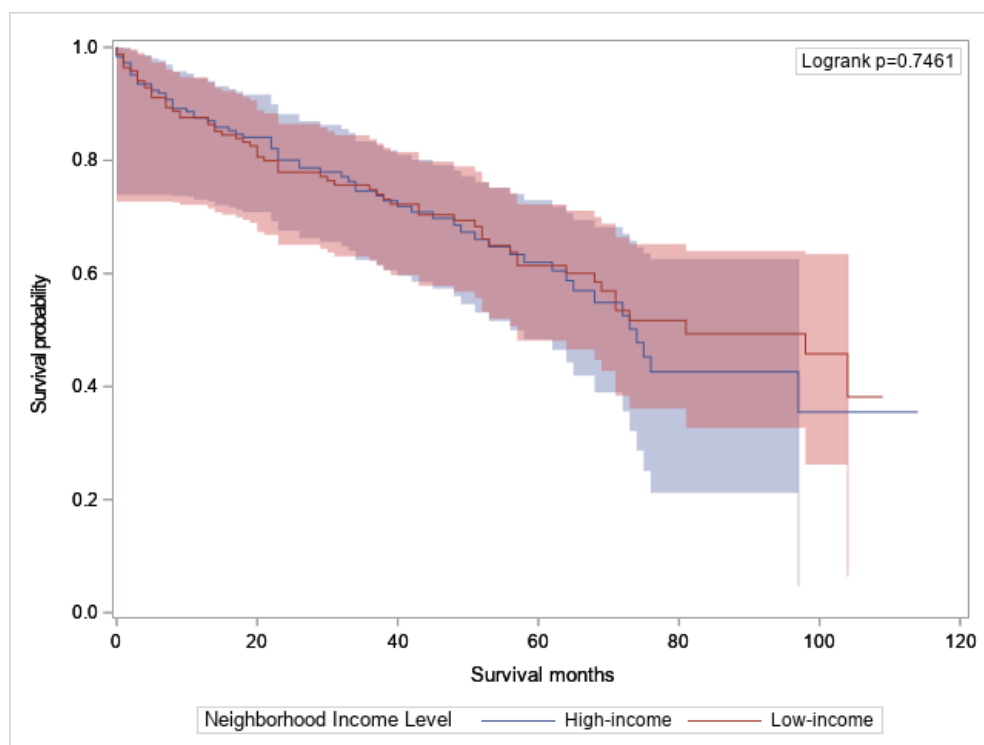


Figure 13. Overall survival probability from TKI initiation by neighborhood income level with 95% Hall-Wellner Bands.

Among TKI initiators, 125 patients died (63 patients with high neighborhood income and 62 patients with low neighborhood income).

In the unadjusted Cox model, neighborhood income did not have a significant effect on the hazard of all-cause death (**Table V**). In the adjusted models including time-varying cumulative adherence, neighborhood income did not have a significant effect on the hazard of all-cause death. In patients with a PDC level above 80%, the hazard of all-cause death decreased by 51% to 62% and remained strongly significant with addition of covariates. The interaction between neighborhood income level and adherence was not significant.

Table V. HAZARD OF ALL-CAUSE DEATH IN PATIENTS WITH LOW VS HIGH NEIGHBORHOOD INCOME.

	Hazard (95% Wald CI) ^a	P-value	Hazard of time-varying adherence (95% Wald CI) ^b	P-value	Hazard of interaction (95% Wald CI)	P-value
Non-time varying crude model (N = 354)	0.94 (0.66, 1.34)	0.75	-	-	-	-
Time varying adherence models						
Model 1 ^c	0.95 (0.67, 1.37)	0.80	0.38 (0.26, 0.55)	<.0001	-	-
Model 2 ^d	1.15 (0.78, 1.68)	0.48	0.45 (0.31, 0.66)	<.0001	-	-
Model 3 ^e	1.22 (0.82, 1.83)	0.32	0.49 (0.33, 0.73)	0.0004	-	-
Model 4 ^f	1.16 (0.77, 1.76)	0.48	0.48 (0.32, 0.72)	0.0004	-	-
Model 5 ^g	0.86 (0.48, 1.52)	0.60	0.48 (0.32, 0.71)	0.0003	-	-
Model 6 ^h	-	-	-	-	0.82 (0.40, 1.66)	0.83

^aReference level is high-income patients.

^bReference level is patients with low adherence (PDC <80%).

^cModel 1: Income level adjusted for time-varying PDC.

^dModel 2: Model 1 + age, sex, race, ethnicity, and marital status.

^eModel 3: Model 2 + year of diagnosis, cancer sequence, frailty index, NCI Charlson comorbidity index, and healthcare expenditures.

^fModel 4: Model 3 + Medicare Part-D plan type, Medicare plan type, low-income subsidy status, dual-eligibility status.

^gModel 5: Model 4 + % of population living in an urban area, SEER region, % of neighborhood below the poverty threshold, % of neighborhood with only a high-school education.

^hModel 6: Model 5 + low-income*high adherence.

Of the 125 deaths observed among TKI initiators, 32 patients died of CML and 93 died of other causes. The unadjusted difference in the probability of CML-specific survival by neighborhood income level was significantly lower in patients with low neighborhood income (Figure 14).

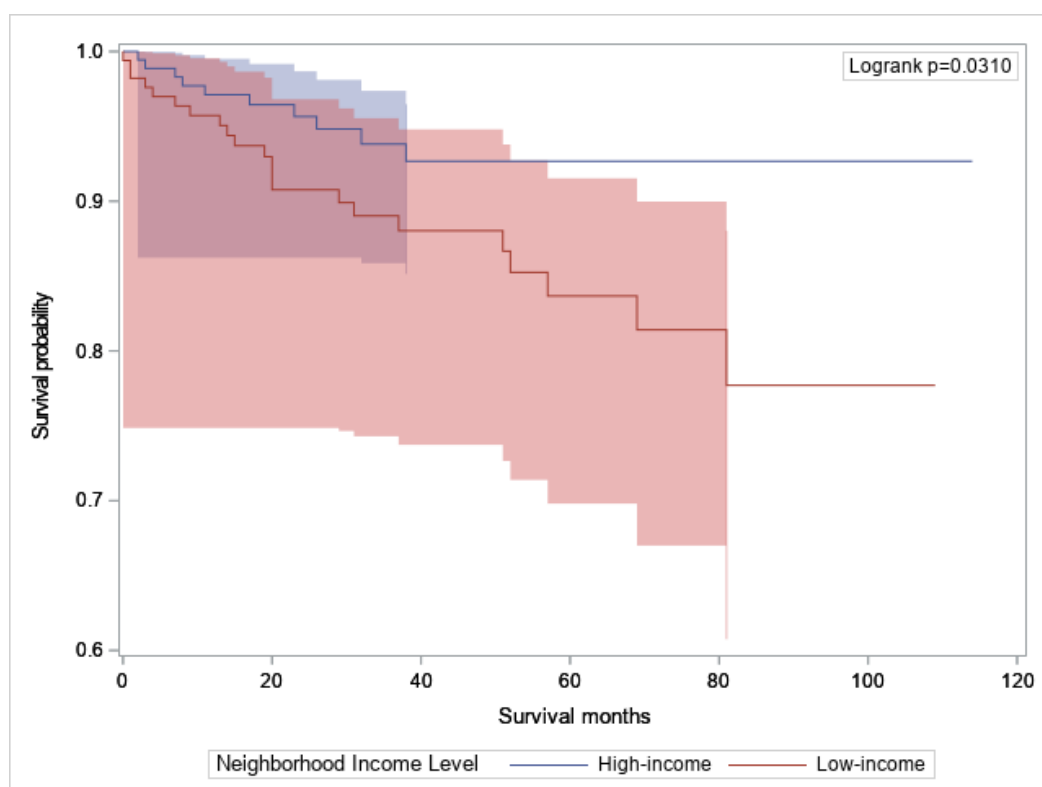


Figure 14. CML-specific survival probability from TKI initiation by neighborhood income level with 95% Hall-Wellner bands.

Thirty-two patients died of CML (deaths by neighborhood income level were suppressed per Medicare privacy restrictions).

Ninety-three patients died of other causes (40 patients with low neighborhood income 53 patients with high neighborhood income).

In the unadjusted model, low neighborhood income patients had a significant 2.2 times higher hazard of CML-specific death compared to high neighborhood income patients (**Table VI**). In the time-varying models adjusted for cumulative monthly PDC, low neighborhood income patients had a significant 2.8- to 3.6-times higher hazard of CML-specific death compared to high neighborhood income patients when sequentially adjusted for covariates. Among patients with high TKI adherence, the hazard of death was about 75% lower compared to patients with low adherence, and the significance of the effect remained consistent when adjusted for various covariates. The interaction between neighborhood income and adherence was not significant.

Table VI. HAZARD OF CML-SPECIFIC DEATH IN PATIENTS WITH LOW VS HIGH NEIGHBORHOOD INCOME.

	Hazard of income status (95% Wald CI) ^a	P-value	Hazard of time-varying adherence (95% Wald CI) ^b	P-value	Hazard of interaction (95% Wald CI)	P-value
Non-time varying crude model (N = 354)	2.23 (1.04, 4.71)	0.04	-	-	-	-
Time varying adherence models						
Model 1 ^c	2.13 (1.00 4.52)	0.05	0.24 (0.11 0.53)	0.0004	-	-
Model 2 ^d	2.83 (1.29 6.21)	0.009	0.25 (0.11 0.55)	0.0006	-	-
Model 3 ^e	3.61 (1.57 8.32)	0.003	0.26 (0.11 0.59)	0.0013	-	-
Model 4 ^f	3.37 (1.40 8.12)	0.007	0.26 (0.11 0.60)	0.0015	-	-
Model 5 ^g	3.24 (1.05 9.99)	0.041	0.26 (0.11 0.61)	0.0022	-	-
Model 6 ^h	-	-	-	-	2.62 (0.58 11.90)	0.68

^aReference level is high-income patients.

^bReference level is patients with low adherence (PDC <80%).

^cModel 1: Income level adjusted for time-varying PDC.

^dModel 2: Model 1 + age, sex, race, ethnicity, and marital status.

^eModel 3: Model 2 + year of diagnosis, cancer sequence, frailty index, NCI Charlson comorbidity index, and healthcare expenditures.

^fModel 4: Model 3 + Medicare Part-D plan type, Medicare plan type, low-income subsidy status, dual-eligibility status.

^gModel 5: Model 4 + % of population living in an urban area, SEER region, % of neighborhood below the poverty threshold, % of neighborhood with only a high-school education.

^hModel 6: Model 5 + low-income*high adherence.

To nullify the significant association between neighborhood income and CML-specific death, an unmeasured confounder would need a relative risk of at least 5.93 with both neighborhood income and CML-specific mortality to nullify the increased hazard of death conditional on observed confounders (**Figure 15**). Additionally, an unmeasured confounder would need a relative risk of at least 1.28 with both neighborhood income and CML-specific mortality to nullify the lower limit of the confidence interval.

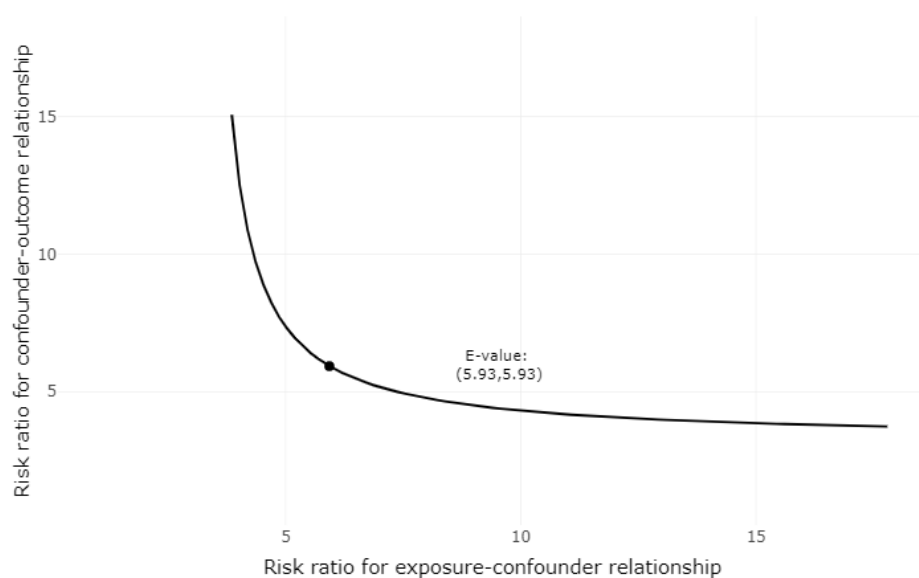


Figure 15. Plot of relative risk needed between a confounder(s) and both neighborhood income and CML-specific mortality to nullify the increased hazard of CML-specific death.

6.5 Discussion and Conclusion

We found that neighborhood income did not appear to play an important role in the hazard of TKI initiation nor in the hazard of all-cause mortality, but it was associated with an increased hazard of CML-specific mortality in patients residing in low-income neighborhoods. In patients who had high cumulative TKI adherence, the hazard of all-cause and CML-specific mortality was significantly lowered compared to patients with a low cumulative adherence.

In our study, we found that 70% of CML patients initiated a TKI, and the hazard of TKI initiation did not differ by neighborhood income level. Our results are consistent with Winn and colleagues and Seymour and colleagues who found a similar 68% and 70% rate of TKI initiation in the CML population, respectively.^{70,121} Winn and colleagues also found that the hazard of TKI initiation was not different between patients residing in areas where 20% to 100% of the population was living below poverty compared to patients living in areas where <20% of the population was living below poverty.⁷⁰ However, they did identify a significant 35% increase in the hazard of TKI initiation in low-income patients with cost-sharing subsidies. A possible explanation for the lack of difference in the hazard of TKI initiation among patients from low income neighborhoods is that patients frame a CML diagnosis as a loss to their predicted life expectancy.⁹⁰ Therefore, cancer patients are highly averse to a loss in life expectancy at the time of cancer diagnosis, and they are willing to take on great financial risk in initiating a TKI regardless of neighborhood income level.

Our 5-year overall survival probability of 61% among Medicare patients aged >65-years is similar to the observed 5-year overall survival of CML patients in SEER, which ranges from 40% to 71%.^{121–123} The literature has consistently shown that having low SES, as defined by variables such as income or education, is associated with a higher risk of all-cause and cancer-specific death among adults with solid cancers.^{79,80,82–86,124,125} However, contrary to our

hypothesis, we found that there was no significant effect of neighborhood income on the hazard of all-cause mortality among TKI initiators. In a similar study using the SEER database conducted by Perry and colleagues, the hazard of all-cause death was not associated with Medicaid, a proxy variable for low-income,¹²⁶ as compared to other forms of insurance among elderly Medicare patients.¹²³ The authors also found no difference in the hazard of all-cause mortality in Medicare patients above the county-level median household income compared to those below it.

In evaluating the effect of neighborhood income on CML-specific death, we found a significantly different 5-year CML-specific survival probability of 84% and 93% in patients with low- and high-neighborhood income, respectively, which reflects the 7-16% cumulative incidence of CML-specific death in this population.¹²² We also found a statistically significant 3-times increase in the hazard of death due to CML. A possible explanation is that CML patients on TKI therapy who reside in low-income neighborhoods may be experiencing the stresses of financial toxicity, which primarily affects CML prognosis. Clinical and epidemiologic studies show that psychological stress promotes physiological pathways which are conducive to progression of cancer and increase the risk of cancer-specific death.^{127,128} Patients with cervical cancer who were exposed to psychological stress related to cancer diagnosis or treatment around the time of diagnosis had a significant 33% increase in the hazard of cancer-specific mortality compared to patients without psychological stress.¹²⁹ The majority of such studies are based on solid tumors, and further research is needed to determine the mechanisms through which SES may affect the rate of cancer-specific death in hematological malignancies.

We found that high medication adherence (PDC >80%) was highly protective of all-cause and CML-specific death with hazard reductions of nearly 50% to 75%, respectively. Compared to the unadjusted hazard of all-cause death and CML-specific death (0.94 and 2.30,

respectively), adjustment for time-varying adherence did not meaningfully change the hazard ratios (0.95 and 2.13, respectively), which indicates that time-varying cumulative adherence was not a significant confounder of the association between neighborhood income level and all-cause or CML-specific mortality. However, TKI adherence is likely correlated with unmeasured variables such as adherence to other medications, seeking preventative health services, and partaking in healthy behaviors that may bias the association between adherence and death.¹³⁰

Our study has important clinical and policy implications. Low neighborhood income is associated with an increased rate of CML-specific death, and the effect may be mediated through mechanisms of financial toxicity of cancer treatment. This finding reinforces the need to support legislation that can potentially decrease drug cost for Medicare and its beneficiaries. Such legislation include those that penalize drug manufacturers who increase drug prices to a level exceeding that of inflation and others that allow Medicare to negotiate prices with drug manufacturers.¹⁰⁶ The results also underscore the importance of assessing the financial health of cancer patients not only upon diagnosis, but also prior to diagnosis, to proactively address financial toxicity.¹³¹ Patients with low neighborhood income may experience chronic stress associated with SES prior to diagnosis, which is additive on the financial stress associated with cancer.¹³² Health systems can employ patient navigators who can conduct a psychosocial assessment and screen for any financial stressors and barriers.¹³³

A major limitation of our study is that we assumed everyone living within a neighborhood had an income equal to the census tract median household income, which may not be true for every individual. However, census tracts are small subdivisions that average about 4,000 individuals and boundaries rarely change with time, which ensures a more homogenous population compared to a wider geographic area like a county-level income measure.^{134,135} Neighborhood income may not capture other valuable financial assets that individuals

accumulate over time. Additionally, neighborhood income overestimated the true income of Medicare patients, which may be differential or non-differential between high- and low-income neighborhoods. Medicare beneficiaries are reported to have a median annual per-capita income of \$26,200,¹⁰⁵ whereas we measured a median neighborhood income of \$55,763. We did not have data on disease phase and severity, both of which are likely confounders. If low neighborhood income patients are more likely to present with advanced phase, severe disease, or receive low-quality care, all of which may increase the risk of CML-specific death, then the hazard is likely biased upwards. Based on the E-value, both variables would need to be associated with neighborhood income and CML-specific death by a relative risk of 5.9 to nullify the association.

A potentially significant unmeasured confounder is the use of private- or manufacturer-based charitable organizations that subsidize TKI treatment at a near zero or zero OOP cost. Low neighborhood income patients are more likely to qualify for such programs, which may bias the hazard of TKI initiation in low neighborhood income patients upwards. We assumed that PDC was a valid measure of medication adherence among patients who initiated a TKI but is not reflective of actual medication administration and medication-taking behavior. We assumed censoring was non-informative, which may be incorrect if censoring was associated with our independent and dependent variables. Lastly, the generalizability of the results is restricted to the Medicare population with consistent Medicare and pharmacy coverage.

We found that neighborhood income level of CML patients does not appear to be significantly associated with initiating TKI therapy. Among TKI initiators, low neighborhood income was not associated with all-cause death, but was associated with a significantly higher rate of CML death. Our findings suggest that financial toxicity may be mediated through mechanisms that increase the rate of CML death, and further research is needed to elucidate

such mediating pathways. Our findings support legislation which decrease the financial burden of TKI therapy on CML patients and emphasize the need to assess the financial health of CML patients on TKI therapy.

VII. NEIGHBORHOOD INCOME AND NON-CANCER HEALTHCARE EXPENDITURES IN PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA ON TYROSINE KINASE INHIBITORS

7.1 Preface

Our third manuscript, titled “Neighborhood Income and Non-Cancer Healthcare Expenditures in Patients with Chronic Myelogenous Leukemia on Tyrosine Kinase Inhibitors”, evaluated whether patients with low neighborhood income had lower 60-month cumulative non-cancer health expenditures over a 60-month period. Results of our study may convey the financial burden of non-cancer healthcare expenditures and if patients with CML were willing to trade-off non-cancer care to maintain financing of TKI therapy and other cancer-related care.

7.2 Introduction

Chronic myelogenous leukemia is a hematological malignancy accounting for 0.5% of all new cancer cases and is commonly diagnosed in the elderly aged >64.¹³⁶ Chronic phase CML is primarily treated with TKIs which are chronic oral medications taken daily.¹⁸ Tyrosine-kinase inhibitors are associated with overall survival that approaches that of aged-matched controls,¹⁸ and patients with CML can expect to have a near-normal lifespan – an effect partly attributed to use of TKIs.⁵ However, the relatively high annual list prices of TKIs marketed in the US (imatinib, dasatinib, nilotinib, bosutinib, and ponatinib) range from \$92,000 to \$138,000 and may be detrimental to patient access and to the sustainability of the healthcare system.⁴⁰

Medicare prices for a 30-day TKI supply range between \$3,632 to \$8,429.⁹⁶ Medicare beneficiaries without a cost-sharing subsidy have a median out-of-pocket (OOP) expenditure of \$828 per 30-day supply. Relative to a median OOP expenditure per 30-day supply of \$42 with employer-based commercial insurance⁷², the OOP expenditure of Medicare patients, who have a median per-capita annual income of \$26,200, may be financially burdensome.¹⁰⁵ Among

Medicare beneficiaries, high OOP TKI expenditures have been associated with decreased treatment use.^{50,70}

Despite the high cost of treatment, patients with cancer are averse to a loss in life expectancy and are likely to initiate expensive cancer treatment with the risk of developing financial toxicity.⁹⁰ Financial toxicity is defined as the unintended objective financial burden on, and the subjective financial distress experienced by patients with cancer because of expensive treatment.⁵⁵ Financial toxicity of cancer treatment may adversely impact access to treatment, decrease quality of life, and increase the risk of mortality.⁵⁷ Cancer patients requiring copay assistance have reported decreasing adherence to prescription medications to alleviate financial stress and reducing consumer spending in an effort to afford cancer care.^{58,59} Patients with cancer who have low SES and whose cancer-related expenditure is high relative to, or even exceeds income, may prioritize decreasing OOP expenditures over treatment.⁸⁹ Specifically, they may be forgoing non-cancer healthcare to finance cancer-related care. To the best of our knowledge, there is no evidence on whether patients with CML of differing SES forgo non-cancer healthcare to maintain TKI and other cancer-related therapy. We sought to fill this evidence gap to better understand and quantify the financial burden of CML on patients and Medicare, and to also inform policies that may alleviate the financial burden.

Our aim was to evaluate the effect of SES, as measured by census-tract median income (i.e., neighborhood income), on non-cancer healthcare expenditure (i.e., sum of patient and Medicare expenditure) in patients with newly diagnosed CML on TKI therapy using the SEER – Medicare linked database. We hypothesized that beneficiaries with low neighborhood income would choose to forgo non-cancer medical services or products provided by Medicare Part-B and Medicare Part-D in favor of maintaining TKI therapy and cancer healthcare, resulting in lower 60-month cumulative non-cancer Medicare Part-B, Part-D, and durable medical

equipment (DME) expenditure compared to beneficiaries with high neighborhood income. We excluded Medicare Part-A services because patients may not have had a choice to avoid services or products provided in the hospital and in skilled nursing facilities.

7.3 Methods

7.3.1 Data

We used the SEER cancer registry linked to Medicare claims data from January 2007 through December 2016. The SEER registries are representative of 28% of the US population and include data related to patient demographics, cancer diagnosis, and ecological measures of SES derived from the 2008-2012 American Community Survey.⁹⁷ Medicare files included claims occurring in the hospital, outpatient clinic, and pharmacies. Claims data included dates of services, diagnosis codes, and amounts paid by Medicare and beneficiaries.

7.3.2 Study Design

We used a retrospective cohort design to evaluate the association between the independent variable neighborhood income and dependent variable non-cancer healthcare expenditure. Patients were indexed on the date of the first TKI prescription fill. Non-cancer healthcare expenditure was observed until death or censoring. Specifically, patients who lost Medicare Part -A/-B/-D coverage, started managed care enrollment, discontinued a TKI (i.e., ≥6-month gap without a prescription), or reached the end of the study period (December 31st, 2016) were censored. The observation period reflected the duration of TKI therapy and other cancer-related healthcare, and therefore a difference in cumulative non-cancer expenditure by neighborhood income level may have indicated that patients with low neighborhood income had more, or less, expenditure on non-cancer healthcare relative to patients with high neighborhood income. All TKIs were considered equivalent and switching between TKIs was considered as a continuation of therapy.

7.3.3 Inclusion Criteria

We included patients with diagnostically confirmed first-primary CML (ICD-0-3 codes 9863 and 9875) between January 2007 through December 2015 that were treated with a TKI. We required that patients be aged >65 years, have Medicare as the primary payer, and have Medicare Part-D at the time of diagnosis. We further required that patients have continuous Medicare coverage and no managed care coverage within a 1-year period prior to diagnosis. Patients who were diagnosed via autopsy or death certificate and who qualified for Medicare through a disability or renal disease were excluded.

7.3.4 Variables

The independent variable SES was defined as the census-tract (i.e., neighborhood-level) median household income at the time of CML diagnosis. Neighborhood income was dichotomized with low neighborhood income defined as <50th percentile. The dependent variable healthcare expenditure was measured as the sum of patient and Medicare payments for non-cancer Medicare Part-B services (i.e., physician and outpatient services), Medicare Part-D prescription drugs, and DME. Prescription claims associated with a national drug code for a TKI, and service or product claims associated with an ICD-9 or -10 code for myeloid leukemia were excluded from the analysis. Medicare expenditures were inflated to 2020 US dollars, first using the most appropriate Personal Health Care index to inflate to 2018, then using the using the Personal Consumption Expenditure index to 2020. Patient expenditures for Part-B and DME were initially inflated to 2018 US dollars using the Consumer Price index – Medical, and patient expenditures for prescriptions were inflated using the Consumer Price index – Prescription.⁹⁸ Healthcare expenditures were stratified as Part-B/DME, drug, and total (i.e., sum of Part-B, Part-D, and DME expenditures).

Baseline covariates were defined within a 1-year period before CML diagnosis and were classified into categories. Demographics included age, sex, race, ethnicity, and marital status. Clinical characteristics included year of diagnosis, primary cancer sequence, frailty index,¹¹¹ NCI Charlson comorbidity index,¹¹² and total inpatient and outpatient healthcare expenditure (sum of payer and patient payments). Insurance characteristics included Medicare plan type, Medicare Part-D plan type, low-income subsidy status, and dual-eligibility status. Lastly, geographic descriptors included urbanicity, region, percent of census-tract living below poverty, and percent of census-tract aged >25 with only a high-school education.

7.3.5 Statistical Analysis

Characteristics of low- and high-neighborhood income patients were compared using Chi-square or Fisher's exact test for categorical and pooled t-tests or Wilcoxon rank sums test for continuous variables. To account for censored expenditure data, we used inverse probability weighting (IPW) of expenditure.^{137–139} We divided the observation period into monthly intervals and limited the analysis to 60-months to maintain an interval sample size >50. Using a Kaplan-Meier estimator, we calculated the monthly probability of being uncensored in which the roles of censoring and death were reversed. Patients who were uncensored in the month had their monthly expenditure multiplied by the interval-specific IPW of being uncensored. Censored patients were assumed to be censored at the end of the month, such that they contributed a non-weighted expenditure in the month of censoring. Therefore, as the probability of remaining uncensored decreased with time, patients who remained uncensored had increasingly-weighted expenditures to represent expenditures of patients who were censored.¹⁴⁰

Unadjusted monthly average IPW expenditure was calculated as the total monthly expenditure across all patients divided by the sample size at the start of the observation period by neighborhood income level.^{137–139} Unadjusted average cumulative IPW expenditure was

similarly calculated by adding total monthly IPW expenditure, adding to the prior months' total expenditure, and dividing by the sample size at the start of the observation period over the 60-month period. To evaluate the association of neighborhood income level with cumulative non-cancer healthcare expenditure over 60-months adjusted for covariates, each monthly IPW expenditure was fit to an ordinary least squares model adjusted for demographic, clinical, insurance, and geographic characteristics. The coefficient of neighborhood income level was summed across the 60 monthly intervals to calculate the cumulative difference in non-cancer healthcare expenditure between low- and high-neighborhood income across 60-months. Standard errors were calculated using bootstrapped samples with replacement from the original cohort, and the process of fitting a separate regression for each monthly expenditure and summing the coefficient of neighborhood income across 60-months was repeated 1,000 times.

Lastly, to evaluate the impact of influential observations with very high expenditures, we repeated the analysis with asymmetrically Winsorized IPW Part-B/DME, drug, and total expenditures.¹⁴¹ Within each interval, expenditures above the 95th percentile were capped at the 95th percentile.

7.4 **Results**

Of 5,134 cases of first primary CML, 503 met inclusion criterion, and 354 initiated a TKI (**Figure 16**). The median neighborhood income of TKI initiators was \$57,224 and patients below the median were classified as low-income. There were no significant differences between neighborhood income levels with respect to patient demographic or clinical characteristics with the exception of Black patients who were more likely to reside in low-income neighborhoods (**Table VII**).

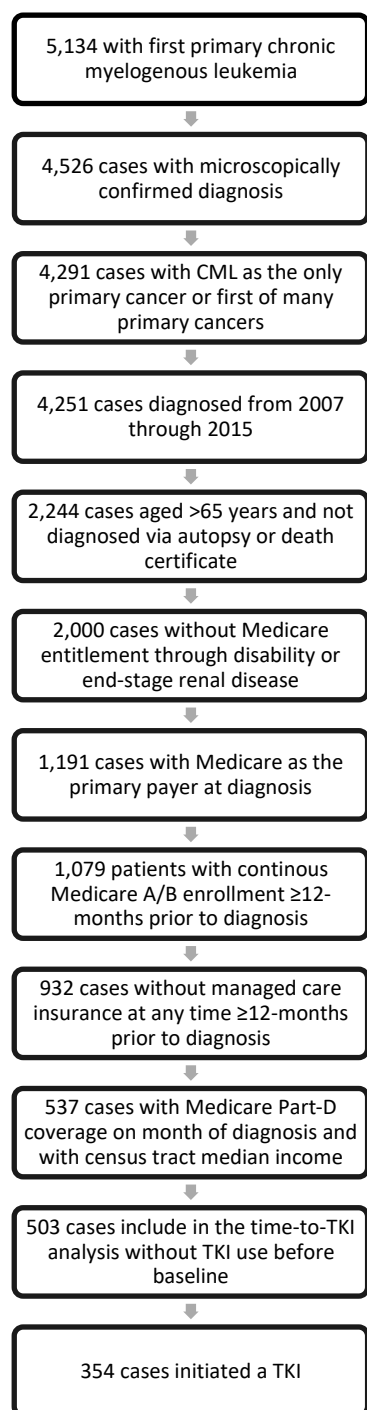


Figure 16. Sample selection criteria.

Table VII. BASELINE CHARACTERISTICS OF CML PATIENTS BY NEIGHBORHOOD INCOME LEVEL.

Variable	Level	Low-income (<\$57,224) N=177	High-income (\$≥57,224) N=177	P-Value
Age at diagnosis Mean (SD)		74.99 (6.58)	76.05 (6.92)	0.152
Sex N (%)	Female	107 (60.45%)	94 (53.11%)	0.163
	Male	70 (39.55%)	83 (46.89%)	
Race N (%)	Asian/Indian/Other	*	*	0.004
	Black	*	*	
	White	148 (83.62%)	153 (86.44%)	
Ethnicity N (%)	Hispanic	16 (9.04%)	12 (6.78%)	0.431
	Non-Hispanic	161 (90.96%)	165 (93.22%)	
Marital status at diagnosis N (%)	Married or Partnered	97 (54.80%)	102 (57.63%)	0.772
	Separated/divorced/ widow/single	66 (37.29%)	64 (36.16%)	
	Unknown	14 (7.91%)	11 (6.21%)	
Year of diagnosis N (%)	2007	16 (9.04%)	*	0.210
	2008	*	*	
	2009	*	14 (7.91%)	
	2010	13 (7.34%)	16 (9.04%)	
	2011	26 (14.69%)	19 (10.73%)	
	2012	23 (12.99%)	25 (14.12%)	
	2013	28 (15.82%)	28 (15.82%)	
	2014	26 (14.69%)	26 (14.69%)	
	2015	19 (10.73%)	31 (17.51%)	
Cancer sequence N (%)	First and only	154 (87.01%)	156 (88.14%)	0.747
	First of many	23 (12.99%)	21 (11.86%)	
Frailty index Median (Q1, Q3)		0.16 (0.13, 0.21)	0.16 (0.13, 0.19)	0.339
NCI Charlson index Median (Q1, Q3)		1.3 (0, 2.16)	1.32 (0, 2.09)	0.917
Healthcare utilization (\$) Median (Q1, Q3)		3423.81 (1683.77, 8563.01)	4501.41 (2005.98, 12183.68)	0.130
Medicare plan at diagnosis N (%)	Medicare	60 (33.90%)	46 (25.99%)	0.010
	Medicare with Medicaid eligibility	29 (16.38%)	16 (9.04%)	
	Medicare with supplement	88 (49.72%)	115 (64.97%)	

Table VII (continued). BASELINE CHARACTERISTICS OF CML PATIENTS BY NEIGHBORHOOD INCOME LEVEL.

Variable	Level	Low-income (<\$57,224) N=177	High-income (>=\$57,224) N=177	P-Value
Low-income subsidy plan at diagnosis N (%)	Eligible or with premium and copay subsidy	67 (37.85%)	31 (17.51%)	<.001
	No premium or copay subsidy	110 (62.15%)	146 (82.49%)	
Dual eligibility status at diagnosis N (%)	Not eligible	119 (67.23%)	148 (83.62%)	<.001
	Qualifies or with dual eligibility	58 (32.77%)	29 (16.38%)	
Urbanicity of area at diagnosis N (%)	Rural	41 (23.16%)	13 (7.34%)	<.001
	Urban	136 (76.84%)	164 (92.66%)	
SEER region at diagnosis N (%)	MW	55 (31.07%)	31 (17.51%)	<.001
	NE	14 (7.91%)	44 (24.86%)	
	South	48 (27.12%)	17 (9.60%)	
	West	60 (33.90%)	85 (48.02%)	
Percent of neighborhood living below poverty N (%)	0% to <10% poverty	36 (20.34%)	149 (84.18%)	<.001
	10% to 100% poverty	141 (79.66%)	28 (15.82%)	
Percent of neighborhood aged >25 with only a high- school education Mean (SD)		32.13 (9.63)	21.58 (10.20)	<.001

*Suppressed per Medicare privacy restrictions.

Patients residing in low-income neighborhoods were more likely to have Medicare with Medicaid eligibility, whereas high-neighborhood income patients were more likely to have a Medicare supplement plan. Patients with low neighborhood income were more likely to have a premium and copay subsidy. Low-neighborhood income patients were also more likely to live in a rural area, live in the Midwest or South, live in a neighborhood in which 10% to 100% of the residents lived below the poverty threshold, and live in a neighborhood in which a greater proportion of the neighborhood had a high-school education as the highest degree.

The median follow-up time was 23 and 24 months in low- and high-neighborhood income patients, respectively. The probability of remaining uncensored was not significantly different by income level (**Figure 17**). Unadjusted monthly average IPW non-cancer total expenditure (**Figure 18**), non-cancer Part-D expenditure (**Figure 19**), and non-cancer Part-B/DME expenditure (**Figure 20**) were relatively similar between neighborhood income levels throughout the observation period, until about 40-months after TKI start at which total expenditure and Part-D expenditure was higher in patients with high neighborhood income.

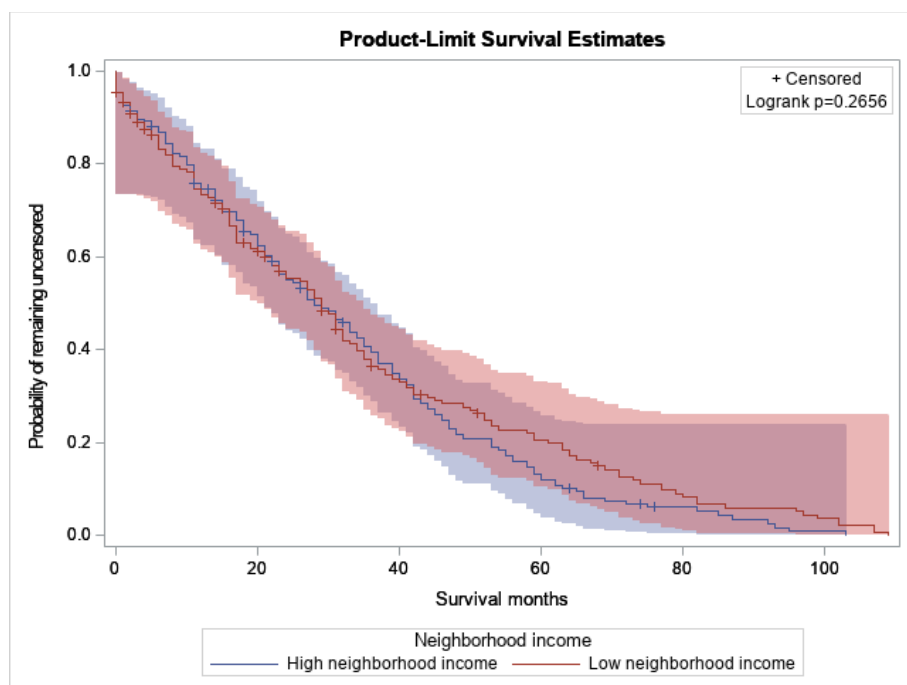


Figure 17. Probability of remaining uncensored by neighborhood income level.

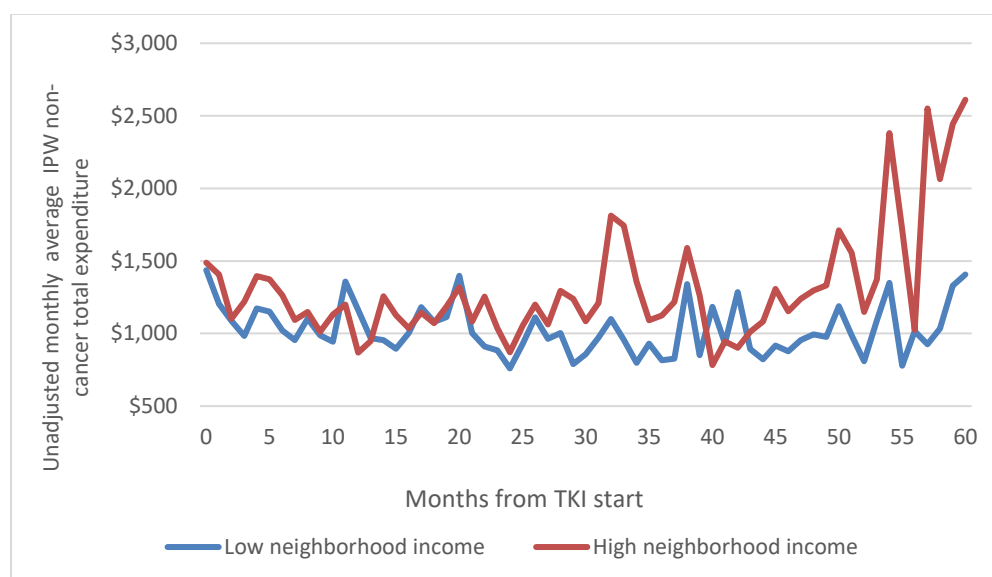


Figure 18. Unadjusted monthly average IPW non-cancer total expenditure by neighborhood income.

Interval (n) low income: 0 (177), 5 (146), 10 (131), 15 (118), 20 (100), 25 (86), 30 (74), 35 (60), 40 (50), 45 (43), 50 (40), 55 (32), 60 (29).

Interval (n) high income: 0 (177), 5 (154), 10 (140), 15 (120), 20 (107), 25 (89), 30 (78), 35 (67), 40 (55), 45 (43), 50 (33), 55 (29), 60 (21).

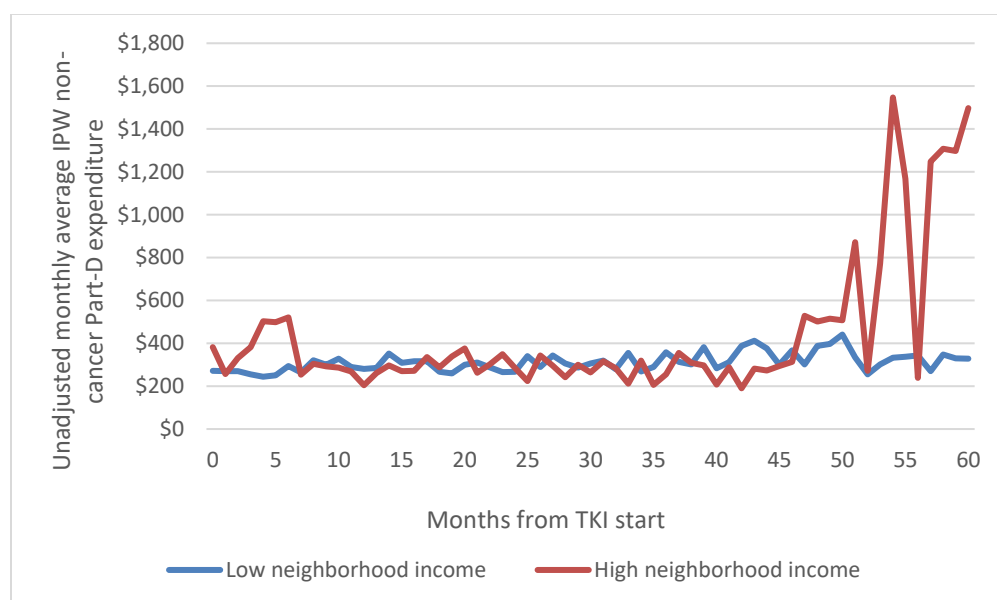


Figure 19. Unadjusted monthly average IPW non-cancer Part-D expenditure.

Interval (n) low income: 0 (177), 5 (146), 10 (131), 15 (118), 20 (100), 25 (86), 30 (74), 35 (60), 40 (50), 45 (43), 50 (40), 55 (32), 60 (29).

Interval (n) high income: 0 (177), 5 (154), 10 (140), 15 (120), 20 (107), 25 (89), 30 (78), 35 (67), 40 (55), 45 (43), 50 (33), 55 (29), 60 (21).

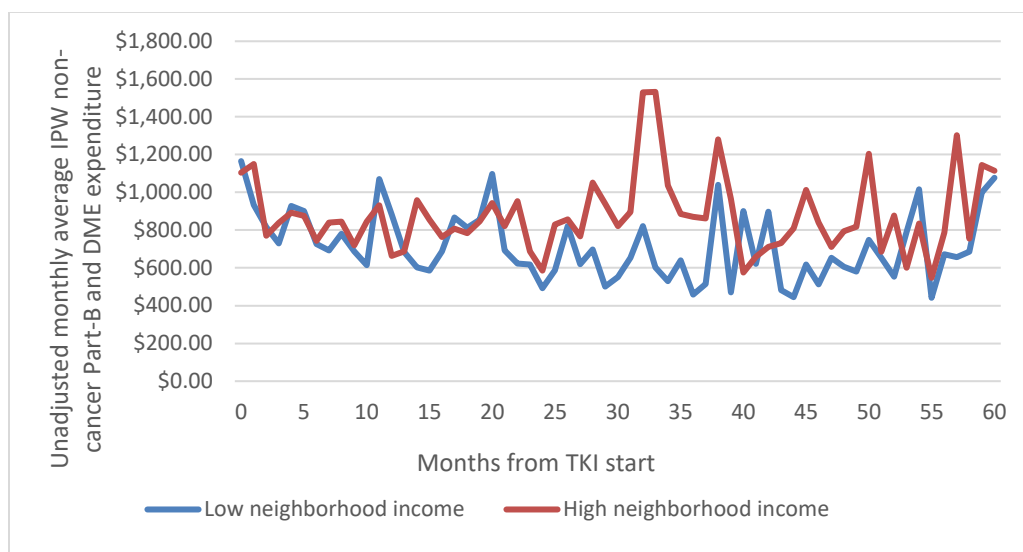


Figure 20. Unadjusted monthly average IPW non-cancer Part-B and DME expenditure. Interval (n) low income: 0 (177), 5 (146), 10 (131), 15 (118), 20 (100), 25 (86), 30 (74), 35 (60), 40 (50), 45 (43), 50 (40), 55 (32), 60 (29). Interval (n) high income: 0 (177), 5 (154), 10 (140), 15 (120), 20 (107), 25 (89), 30 (78), 35 (67), 40 (55), 45 (43), 50 (33), 55 (29), 60 (21).

Unadjusted average cumulative IPW total non-cancer expenditure was relatively similar between income groups until 30-months after TKI start at which average cumulative total expenditure of patients with high-neighborhood income outpaced that of patients with low neighborhood income (**Figure 21**). Stratified by expenditure type, average cumulative IPW non-cancer Part-B/DME and Part-D expenditures was higher in patients with high neighborhood income beginning at 25-months and 50-months, respectively.

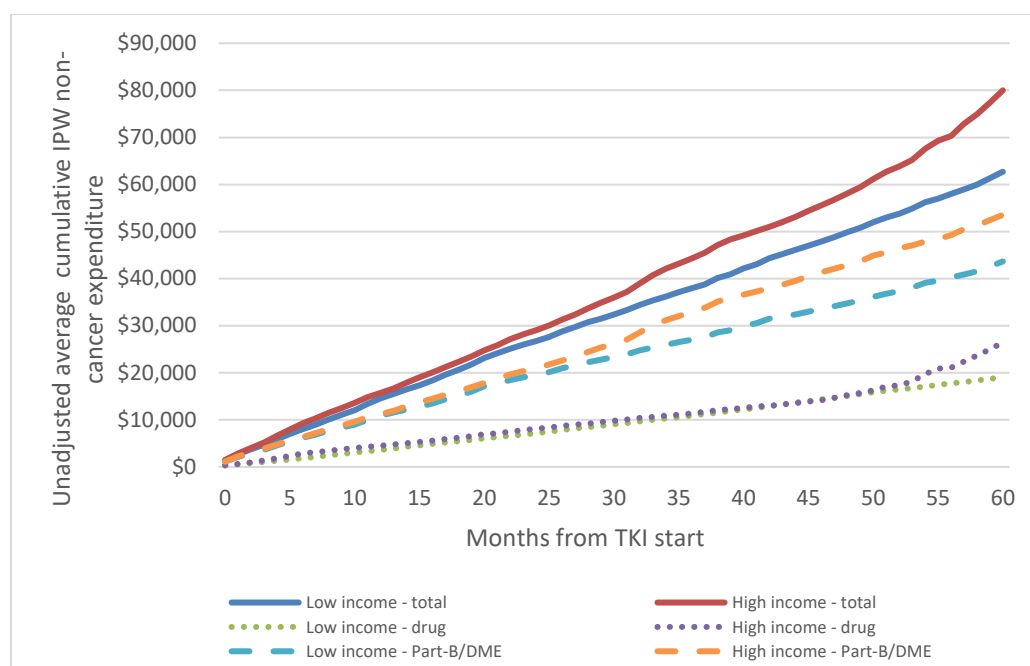


Figure 21. Unadjusted average cumulative IPW non-cancer total expenditure and stratified by expenditure type.

Interval (n) low income: 0 (177), 5 (146), 10 (131), 15 (118), 20 (100), 25 (86), 30 (74), 35 (60), 40 (50), 45 (43), 50 (40), 55 (32), 60 (29).

Interval (n) high income: 0 (177), 5 (154), 10 (140), 15 (120), 20 (107), 25 (89), 30 (78), 35 (67), 40 (55), 45 (43), 50 (33), 55 (29), 60 (21).

When adjusted for covariates, the trend in cumulative IPW incremental non-cancer total expenditure was similar by income level until 30-months after TKI start when incremental total expenditure of patients with low neighborhood income was slightly negative relative to patients with high neighborhood income (**Figure 22**). Non-cancer total expenditure in patients with low neighborhood income began to sharply decrease beginning at 50-months after TKI start, but the overall trend was not significant.

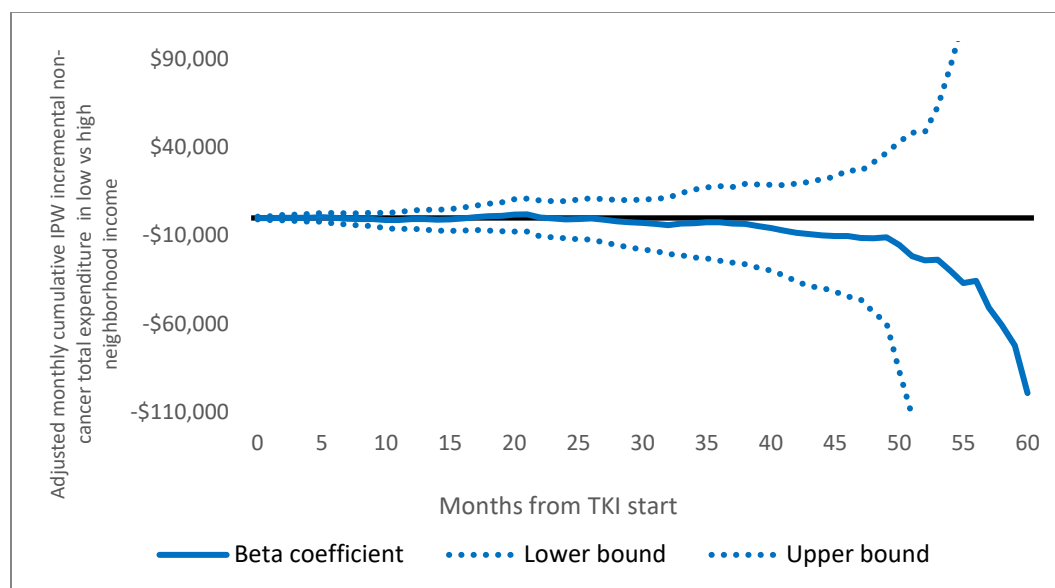


Figure 22. Adjusted 60-month cumulative IPW incremental non-cancer total expenditure with 95% confidence intervals.

Solid black line denotes \$0 or no difference in expenditure. Models were adjusted for all patient demographics, clinical characteristics, insurance characteristics, and geographic descriptors.

Interval (n) low income: 0 (177), 5 (146), 10 (131), 15 (118), 20 (100), 25 (86), 30 (74), 35 (60), 40 (50), 45 (43), 50 (40), 55 (32), 60 (29).

Interval (n) high income: 0 (177), 5 (154), 10 (140), 15 (120), 20 (107), 25 (89), 30 (78), 35 (67), 40 (55), 45 (43), 50 (33), 55 (29), 60 (21).

Stratified by expenditure type, non-cancer IPW Part-B/DME expenditure of patients with low-neighborhood income was negative relative to patients with high neighborhood income beginning at 25-months through 50-months after TKI start (**Figure 23**). The difference in non-cancer Part-B/DME expenditure between income groups began to decrease through 60-months after TKI start, however, the overall trend was insignificant.

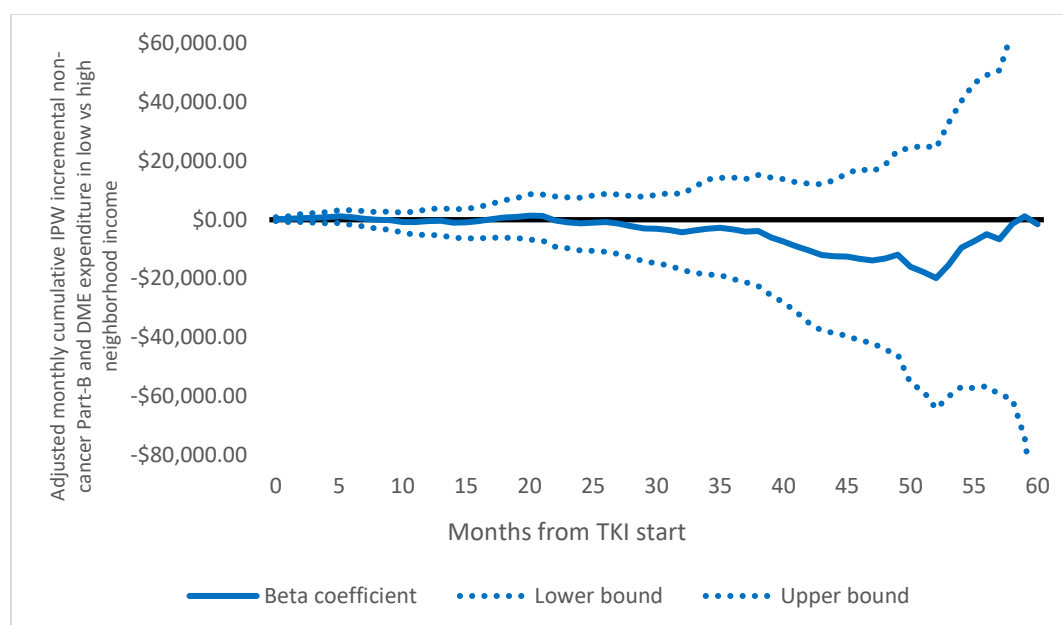


Figure 23. Adjusted 60-month cumulative IPW incremental Part-B and DME expenditure with 95% confidence intervals. Solid black line denotes \$0 or no difference in expenditure. Models were adjusted for all patient demographics, clinical characteristics, insurance characteristics, and geographic descriptors. Interval (n) low income: 0 (177), 5 (146), 10 (131), 15 (118), 20 (100), 25 (86), 30 (74), 35 (60), 40 (50), 45 (43), 50 (40), 55 (32), 60 (29). Interval (n) high income: 0 (177), 5 (154), 10 (140), 15 (120), 20 (107), 25 (89), 30 (78), 35 (67), 40 (55), 45 (43), 50 (33), 55 (29), 60 (21).

Part-D IPW expenditure was relatively equal throughout much of the observation period between neighborhood income levels. Beginning at 50-months after TKI start, non-cancer Part-D expenditures was negative in patients with low neighborhood income relative to patients with high neighborhood income and the difference increased in magnitude through 60-months, but the overall trend was insignificant (**Figure 24**).

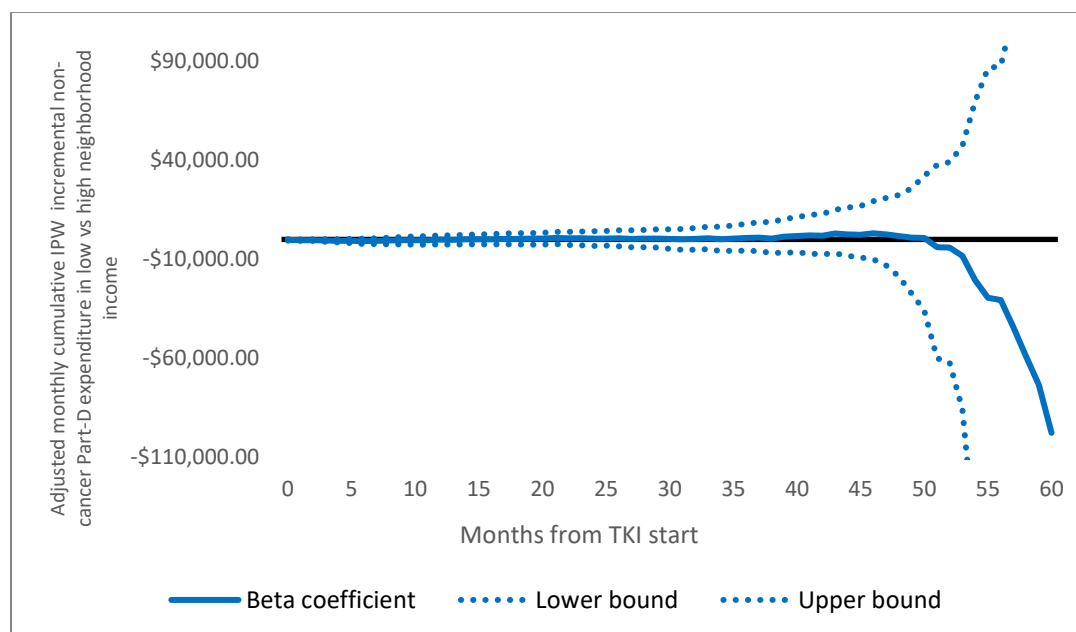


Figure 24. Adjusted 60-month cumulative IPW incremental non-cancer Part-D expenditure with 95% confidence intervals.

Solid black line denotes \$0 or no difference in expenditure. Models were adjusted for all patient demographics, clinical characteristics, insurance characteristics, and geographic descriptors.

Interval (n) low income: 0 (177), 5 (146), 10 (131), 15 (118), 20 (100), 25 (86), 30 (74), 35 (60), 40 (50), 45 (43), 50 (40), 55 (32), 60 (29).

Interval (n) high income: 0 (177), 5 (154), 10 (140), 15 (120), 20 (107), 25 (89), 30 (78), 35 (67), 40 (55), 45 (43), 50 (33), 55 (29), 60 (21).

Over the 60-month observation period, patients with low neighborhood income had an unadjusted cumulative IPW non-cancer total expenditure that was \$17,289 less compared to patients with high neighborhood income (**Table VIII**). Stratified by expenditure type, patients with low neighborhood income had an unadjusted 60-month cumulative IPW non-cancer Part-D expenditure that was \$7,405 less compared to high neighborhood income patients. Similarly, patients with low neighborhood income had a 60-month cumulative IPW non-cancer Part-B and DME expenditure that was \$9,884 less. Adjusted for covariates, patients with low neighborhood

income had a 60-month cumulative IPW non-cancer total expenditure that was \$99,110 (95% CI [-\$659,485 to \$275,113]) less than patients with high neighborhood income, but the difference was not significant. Stratified by expenditure type, the decrease in IPW non-cancer total expenditure in patients with low neighborhood income was primarily driven by a large \$97,565 (95% CI [-\$588,056 to \$210,251]) decrease in IPW non-cancer Part-D expenditure compared to a \$1,545 (95% CI [-\$107,179 to \$118,038]) decrease in IPW non-cancer Part-B/DME expenditure. However, the difference in 60-month cumulative IPW Part-D expenditure and Part-B/DME expenditure between neighborhood income levels were insignificant.

Table VIII. INCREMENTAL 60-MONTH CUMULATIVE IPW NON-CANCER TOTAL AND STRATIFIED EXPENDITURE IN PATIENTS WITH LOW NEIGHBORHOOD INCOME COMPARED TO HIGH NEIGHBORHOOD INCOME.

	Unadjusted difference	Adjusted difference	Bootstrapped 95% CI
Base Case			
Total	-\$17,289	-\$99,110	(-\$659,485 to \$275,113)
Part-D	-\$7,405	-\$97,565	(-\$588,056 to \$210,251)
Part-B/DME	-\$9,884	-\$1,545	(-\$107,179 to \$118,038)
Winsorized			
Total	-\$7,725	-\$4,305	(-\$115,911 to \$122,061)
Part-D	\$1,576	-\$1,145	(-\$42,012 to \$50,787)
Part-B/DME	-\$9,906	-\$5,261	(-\$78,692 to \$77,011)

The adjusted trend in Winsorized cumulative IPW incremental non-cancer total, Part-B/DME, and Part-D expenditure was similar throughout the observation period with the exception of large differences in expenditures near the end of follow-up being attenuated (Figure 25 - 27).

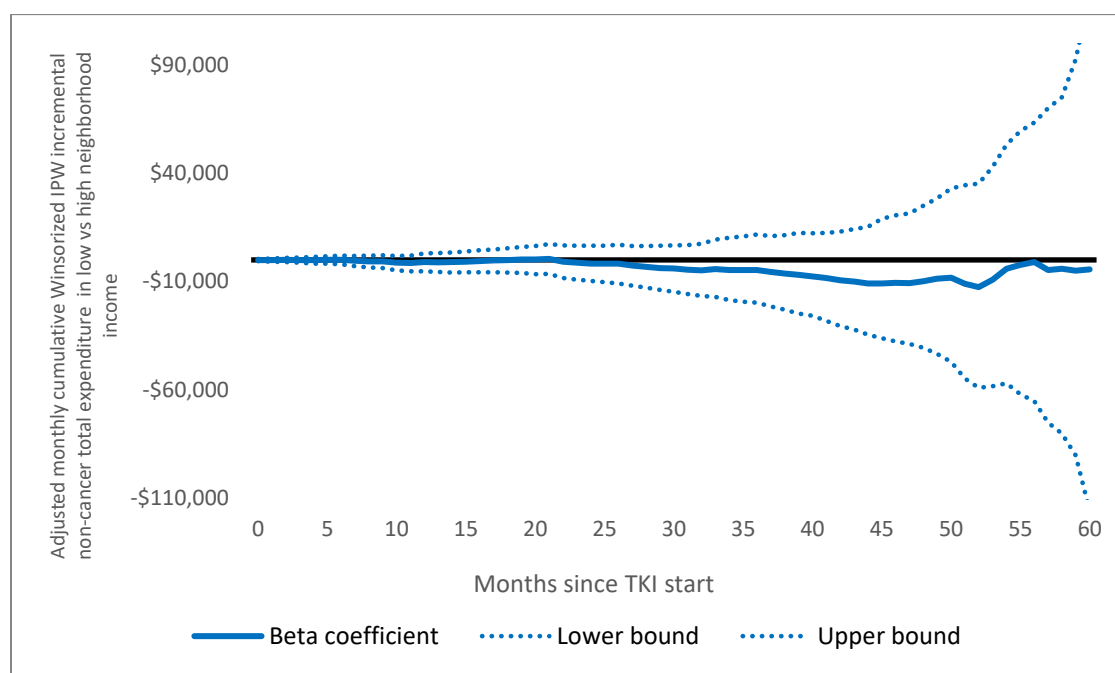


Figure 25. Adjusted 60-month cumulative Winsorized IPW incremental non-cancer total expenditure with 95% confidence intervals.

Solid black line denotes \$0 or no difference in expenditure. Models were adjusted for all patient demographics, clinical characteristics, insurance characteristics, and geographic descriptors.

Interval (n) low income: 0 (177), 5 (146), 10 (131), 15 (118), 20 (100), 25 (86), 30 (74), 35 (60), 40 (50), 45 (43), 50 (40), 55 (32), 60 (29).

Interval (n) high income: 0 (177), 5 (154), 10 (140), 15 (120), 20 (107), 25 (89), 30 (78), 35 (67), 40 (55), 45 (43), 50 (33), 55 (29), 60 (21).

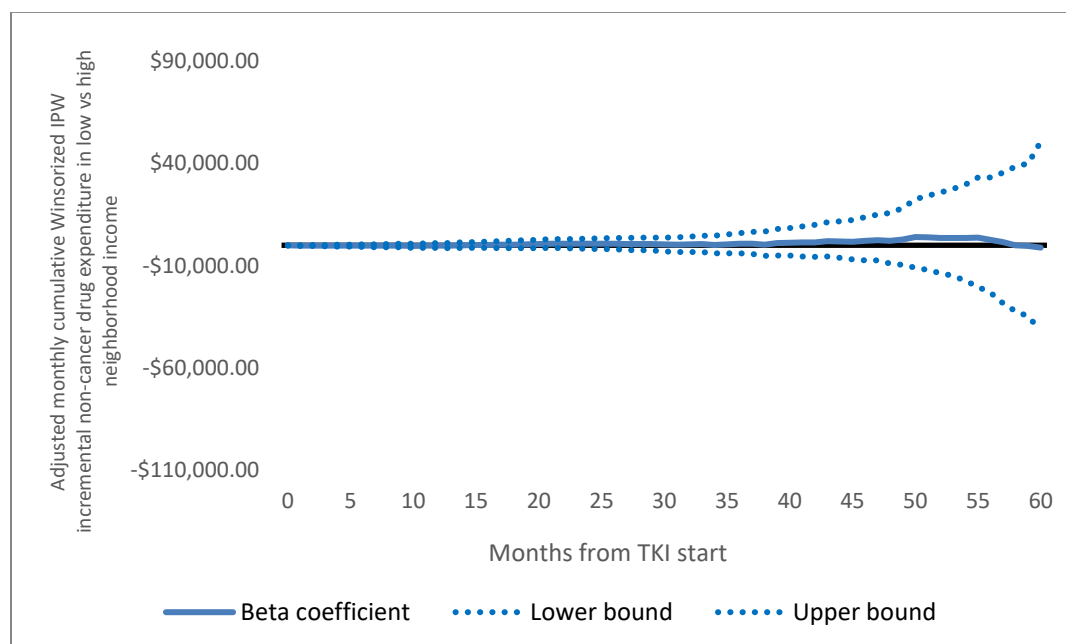


Figure 26. Adjusted 60-month cumulative Winsorized IPW incremental non-cancer Part-D expenditure with 95% confidence intervals.

Solid black line denotes \$0 or no difference in expenditure. Models were adjusted for all patient demographics, clinical characteristics, insurance characteristics, and geographic descriptors.

Interval (n) low income: 0 (177), 5 (146), 10 (131), 15 (118), 20 (100), 25 (86), 30 (74), 35 (60), 40 (50), 45 (43), 50 (40), 55 (32), 60 (29).

Interval (n) high income: 0 (177), 5 (154), 10 (140), 15 (120), 20 (107), 25 (89), 30 (78), 35 (67), 40 (55), 45 (43), 50 (33), 55 (29), 60 (21).

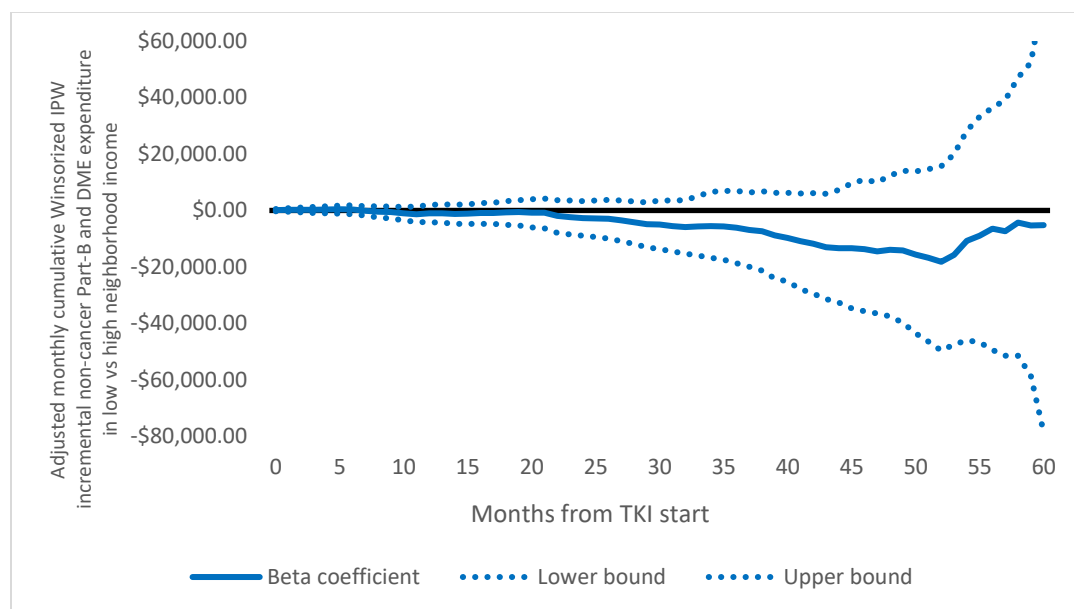


Figure 27. Adjusted 60-month cumulative Winsorized IPW incremental Part-B and DME expenditure with 95% confidence intervals.

Solid black line denotes \$0 or no difference in expenditure. Models were adjusted for all patient demographics, clinical characteristics, insurance characteristics, and geographic descriptors.

Interval (n) low income: 0 (177), 5 (146), 10 (131), 15 (118), 20 (100), 25 (86), 30 (74), 35 (60), 40 (50), 45 (43), 50 (40), 55 (32), 60 (29).

Interval (n) high income: 0 (177), 5 (154), 10 (140), 15 (120), 20 (107), 25 (89), 30 (78), 35 (67), 40 (55), 45 (43), 50 (33), 55 (29), 60 (21).

Sixty-month unadjusted cumulative Winsorized IPW non-cancer total and Part-B/DME expenditure remained lower in patients with low neighborhood income (-\$7,725 and -\$9,906, respectively), however, 60-month Winsorized Part-D expenditure was \$1,576 higher in patients with low neighborhood income (**Table VIII**). Adjusted Winsorized IPW non-cancer total, Part-B/DME, and Part-D expenditure remained lower in patients with low neighborhood income (-\$4,305, -\$1,145, and -\$5,261, respectively), but the differences remained insignificant.

7.5 **Discussion and Conclusion**

We found that during TKI therapy, CML patients with low neighborhood income do not appear to have less 60-month non-cancer cumulative expenditure compared to patients with high neighborhood income to finance TKIs and cancer-related healthcare. Additionally, our sensitivity analysis in which outlying high expenditures were Winsorized did not change the conclusions. We estimated a 70% TKI initiation rate (354 TKI initiators among 503 CML cases) which is consistent with other estimates based on the Medicare population.^{70,121} We would expect a higher TKI initiation rate given the high overall survival on TKI therapy,^{30,99} but the financial burden of TKI therapy and sensitivity of Medicare patients to cost may explain an initiation rate that is less than 90%.⁶⁷

A study evaluating cancer and non-cancer healthcare utilization (e.g., inpatient, outpatient, prescription, DME, and home health) in CML patients found that Medicare spending among patients on a TKI ranged from \$120,000 to \$143,000 annually and patient OOP responsibility ranged from \$9,000 to \$14,000 annually over a 5-year period.¹²² In focusing only on non-cancer Part-B, Part-D, and DME expenditure (payer and OOP expenditure), we measured a 5-year cumulative expenditure ranging from \$60,000 to \$80,000 in patients with low- and high-neighborhood income, respectively. Therefore, cancer related care accounts for the majority of health care utilization. Based on the results of our study, the burden of cancer care does not appear to affect non-cancer healthcare expenditure, for which patients have a choice of forgoing, between patients of differing neighborhood income levels within a short-term horizon. A possible explanation for this observation is that the patient responsibility of non-cancer Part-B, Part-D, and DME expenditure is marginal compared to cancer care, especially if patients receive financial support that we could not observe. Thus, patients are not sensitive to

this cost and it does not alter non-cancer healthcare use and expenditure. Additionally, patients may view non-cancer care as essential as cancer-related care.

We observed that the trend in average and cumulative expenditures for total, Part-B/DME, and Part-D was higher in patients with high neighborhood income, particularly near the end of the observation period. This trend remained consistent in the adjusted models. This may be partly explained by a select few patients with high neighborhood income with longer survival and who have very high expenditure near the end of life. This is consistent with evidence stating that the percentage of Medicare costs increases near the end of life and ranges between 13% to 25% of costs,¹⁴² and that patients with high SES have higher ambulatory care and drug expenditures in this period.¹⁴³ Upon Winsorizing patients with expenditures above the 95th percentile, the magnitude of the reduction in 60-month cumulative expenditure in patients with low neighborhood income were not as pronounced, which indicates that patients with high neighborhood income and high expenditures were very influential on results near the end of the observation period, particularly in Part-D expenditures. Despite these notable trends, we were unable to conclude that non-cancer expenditures were significantly different between income groups.

Treatment with TKIs is chronic and places a considerable burden on Medicare patients on a limited fixed-income. Given that the lifespan of CML patients approach that of the general non-cancer population, the prevalence of CML is continually increasing.⁶ Compounded by rising prices of TKIs and high OOP patient expenditure,^{42,96} the treatment of patients with CML will likely place considerable financial pressure on patients and Medicare. We found that CML patients do not have lower total Part-B/DME and Part-D expenditures, and therefore are not forgoing the cost of non-cancer care in favor of cancer-related care, which has implications on finances of patients and the Medicare system. First, patients may not be forgoing any medical

care, but instead forgoing other financial assets that we are unable to observe or receiving external financial assistance.¹⁴⁴ Second, maintaining non-cancer related care is beneficial for patients but is costly to Medicare as patients with CML have 13-times the Medicare expenditure of non-cancer patients.¹²²

Our study had several limitations. First, all patients residing in a census-tract may not have an actual income equal to that of the census tract. However, census tracts are neighborhoods of about 4,000 individuals and boundaries rarely change with time, which improves the homogeneity of the population relative to a larger county-level measure.¹³⁴ Second, neighborhood income does not capture all financial assets of patients, and our median income of \$57,224 overestimates a median annual per-capita income of \$26,200 for Medicare patients.¹⁰⁵ Third, we did not have data on phase of diagnosis nor disease severity. This may result in bias if patients with low-neighborhood income are more likely to present with advanced and severe CML disease, which would make expenditures higher in this group. Fourth, due to attrition of patients across time, our study was under-powered to detect cumulative differences in non-cancer expenditures at 60-months. Fifth, we did not measure quality of care received. This may bias the results if patients with low neighborhood income receive low-quality care, which may increase non-cancer expenditures if chronic conditions are not properly managed. Lastly, our dichotomization of neighborhood income level may have misclassified patients at the margin who may be low income but were defined as high income and vice versa.

There are also limitations in the assumptions on the services in which patients may forgo. We excluded Medicare Part-A claims, since patients likely do not have a choice in the bundled services nor in the ancillary services provided by hospitals and nursing facilities. However, patients can refuse certain inpatient treatments. Additionally, we may not have captured elective surgeries or procedures which may be conducted in the inpatient setting, such

as hip-replacement surgeries. Conversely, we assumed that patients have a choice in the products and services provided by Medicare Part-B, which may not necessarily be true if certain claims are absolutely medically necessary. There may also be misclassification in our definition of non-cancer related care in the outpatient setting because non-cancer services may have been associated with a CML-related diagnosis code. This may result in an underestimate of non-cancer expenditures which is non-differential between neighborhood income groups. Lastly, we were unable to observe if patients forgo non-medical services or products such as consumer goods and leisure activities.

In conclusion, we were unable to detect a difference in cumulative 60-month non-cancer Part-B/DME and Part-D expenditures between patients with high- and low-neighborhood income. Our findings suggest that CML patients may not alter the use of non-cancer related healthcare outside of the inpatient setting in response to the financial burden of cancer-related care. However, we did not observe other goods or services that patients may forgo. Further research is needed to understand and quantify the trade-offs patients make due to the financial toxicity of cancer treatment and clinicians should be aware of the financial health of CML patients.

VIII. OVERALL CONCLUSION

8.1 Summary

With the use of TKIs, CML has become a relatively treatable malignancy relative to other types of hematological cancers. Treatment with TKIs is associated with improved overall survival over non-TKI therapy, and patients can now reasonably expect to have a life-expectancy comparable to that of non-cancer patients. However, the cost of treatment is exorbitant for both health insurers, such as Medicare, and the vulnerable populations they serve. The high OOP cost of TKIs in addition to other CML-related care may be leading to financial toxicity, in which the financial burden and stress experienced by patients result in adverse health outcomes. Medicare patients with low neighborhood income, where treatment costs may exceed income, may experience decreased TKI initiation, increased mortality, and decreased non-cancer healthcare expenditure as compared to patients with a higher income level.

We identified that there is limited evidence on the cost burden of TKIs across time as measured by Medicare drug gross payment and patient OOP expenditure. Additionally, there are a lack of studies evaluating the association of income level with TKI initiation and mortality among TKI initiators. Lastly, there was no evidence on whether patients with low income forgo non-cancer healthcare services to maintain TKI and cancer therapy relative to patients with high income. We sought to fill these evidence gaps with three studies based on a cohort of Medicare patients with CML using the SEER-Medicare database in which income was defined at the aggregate neighborhood level.

Our framework depicted that TKI and cancer treatment is financially burdensome for patients and insurers. Aim 1 described this burden by describing the trends in Medicare drug prices and patient OOP expenditures. Due to the financial burden of treatment, patients

differentially behaved based on their neighborhood income level. Neighborhood income level can affect the decision of patients to initiate a TKI, and among TKI initiators, financial toxicity may increase the hazard of death among patients with low neighborhood income. Therefore, our second aim measured the association between neighborhood income level and TKI initiation and mortality among CML patients that initiated a TKI. Lastly, patients with low neighborhood income may choose to forgo non-cancer healthcare in order to prioritize TKIs and CML-related care. Our third aim measured whether neighborhood income level was associated with non-cancer healthcare expenditures.

The first aim found that drug price, as measured by Medicare gross payment per 30-day supply, increased year-to-year between 2007 through 2016. The average annual increase in Medicare gross payment per 30-day supply across all TKIs was about 13%, which greatly exceeded that of the PHC inflation index which remained relatively constant at 2%. Medicare gross payment for imatinib and dasatinib in 2007 to 2008 ranged between \$3,000 and \$4,000 per 30-day supply. By 2016, prices increased to nearly \$10,000 per 30-day supply for imatinib and dasatinib, and also for the new market entrants nilotinib and bosutinib. Contrary to the increasing trend in Medicare gross payment, there was no consistent increase in PMPM OOP expenditure, which ranged between \$450 to \$600 per 30-day supply. Notably, PMPM OOP expenditures decreased greatly by 20% between 2010 to 2011, which is likely due to start of the coverage gap closure as mandated by the ACA. However, OOP expenditures continued to increase marginally by 5% to 8% after 2011 but decreased by 5% from 2015 to 2016. This aim highlighted the continued excess increase of TKI drug price over inflation, which does not necessarily correlate with improved drug effectiveness. The results of this study emphasize the need to support federal policies which make drug pricing transparent, and which allow Medicare to negotiate drug prices. Although OOP expenditure remained relatively constant, an OOP

expenditure in excess of \$500 a month is likely burdensome for Medicare patients on a limited fixed-income, and monitoring of financial health should be made as important as physical health.

While the first aim described the cost burden of TKI therapy, aims two and aim three sought to identify outcome disparities resulting from financial toxicity by measuring the association between health outcomes by neighborhood income level. Our second aim found that the hazard of TKI initiation did not differ by neighborhood income level. The hazard of TKI initiation ranged from a 2% decrease to 12% increase in low vs high neighborhood income patients across varying covariate specifications, but the associations did not reach statistical significance. Among TKI initiators and adjusted for time-varying cumulative TKI adherence, the hazard of all-cause death varied from a 14% decrease to a 22% increase in low vs high neighborhood income patients across varying covariate specifications, but the associations also did not reach statistical significance. However, in evaluating CML-specific mortality, we found that the hazard of CML-specific death was about 3-times higher in patients with low neighborhood income as compared to patients with high neighborhood income, which remained consistent and statistically significant across varying covariate specifications. Our findings suggest that the association between neighborhood income and CML-specific death may be mediated through mechanisms of financial toxicity and more research is needed to elucidate the mediating factors. The results also emphasize the need for policy interventions to alleviate the financial burden of CML treatment since patients with low neighborhood income may be disproportionately affected by the disease and financial burden of CML.

Our third aim found that among CML patients who initiated a TKI, there was no difference in the 5-year cumulative non-cancer Medicare Part-B/DME and Part-D expenditures through the duration of TKI treatment. This finding may indicate that financing CML-related care

and TKI treatment does not seem to affect expenditure on non-cancer treatment for which patients have a choice in forgoing. Adjusted for covariates and outlier expenditures, total 5-year cumulative non-cancer expenditure was \$4,305 lower in patients with low neighborhood income, but this difference was statistically insignificant. Stratified by Part-B/DME and Part-D expenditure, the difference in cumulative expenditure by neighborhood income level was also insignificant. The results may indicate patients are not sensitive to the cost of non-cancer care and/or value it as highly as cancer-related care. It could also be the case that patients are forgoing non-medical consumer goods and services which we were unable to observe. Lastly, considering that CML patients are 13-times costlier than non-cancer patients¹²² and that CML patients maintain cancer and non-cancer care, Medicare will be financially burdened by the overall treatment costs.

In relating our results with our conceptual framework, we found that the increase in TKI drug price exceeds that of inflation. However, contrary to our hypothesis, OOP expenditures remained relatively constant between \$450 and \$600 per 30-supply. Considering that drug prices exceed \$100,000 annually with accompanying high OOP expenditures, and that Medicare patients have an annual per-capita income of \$26,000,¹⁰⁵ TKI therapy is likely financially burdensome for Medicare and financially toxic to its patients. We theorized that patients of differing income levels would respond differently to the financial toxicity of cancer treatment, resulting in outcome disparities in the rate of mortality and non-cancer healthcare expenditures. As hypothesized, we found that patients with low neighborhood income had a significantly higher rate of CML-specific mortality, but we did not detect an impact on all-cause mortality. Lastly, contrary to our hypothesis, non-cancer healthcare expenditures did not differ by neighborhood income level. Thus, we may conclude that there is a disparity in CML-specific mortality by neighborhood income level.

8.2 **Research Implications and Policy/Clinical Recommendations**

Our findings collectively have implications for both health policy and clinical practice. Given the increasing lifespan of CML patients⁶ who are 13-times costlier than non-cancer patients,¹²² our finding of a continual increase in TKI drug price, and the fact that the US spends \$42 billion (9.4% of total expenditures) on cancer drugs,⁴⁷ the financial burden of cancer treatment will likely worsen for Medicare. Although we did not detect an increasing trend in OOP cost, a continuing increase in TKI drug price may eventually result in increased Medicare cost-sharing requirements for TKIs.⁵¹ High OOP monthly expenditures for TKIs upwards of \$600 is likely financially toxic for Medicare patients on a fixed and limited income. Financial toxicity may contribute to an increased rate of CML-specific death in low-income patients. While we did not find a lower non-cancer healthcare expenditure in patients with low neighborhood income, this same patient group may be maintaining cancer and non-cancer healthcare at the expense of other financial assets. Low-income patients may be at higher risk of bankruptcy, which is associated with an increased mortality rate.^{63,144} Therefore, our findings collectively have implications for both health policy and clinical practice, and intervention at both levels is necessary and justified.

Policy interventions include legislation which limit drug price increases and give Medicare the ability to negotiate prices. The Elijah E. Cummings Lower Drug Costs Now Act (H.R. 3) contains several policy interventions that would address high prescription drug pricing and its negative impact on public health.¹⁴⁵ The bill would allow the Department of Health and Human Services to negotiate drug prices for brand-name drugs such as TKIs under the Medicare prescription drug benefit. Price negotiation provisions are estimated to result in a \$456 billion reduction in spending. The bill would also impose a penalty to manufacturers who increase drug price faster than the inflation rate by way of rebates to Medicare, and it would also

require manufacturers to report a qualifying price increase to the Department of Health and Human Services. The bill also contains policy interventions which would reduce the OOP spending threshold of Medicare Part-D beneficiaries and expand eligibility criteria to qualify for Medicare Part-D subsidies. The Prescription Drug Pricing Reduction Act of 2019 (S. 2543) contains similar policy interventions, but also requires pharmacy benefit managers to disclose drug discounts, rebates, and payments among insurers, manufacturers, and pharmacies.¹⁴⁶ Interventions provided H.R. 3, S. 254, and similar legislation are recommended and would likely put downward pressure on drug prices and alleviate the financial toxicity experienced by patients with CML as well as other cancers.

As discussed in section 2.1, increase in drug price among different categories of cancer drugs does not necessarily correlate with improved survival nor novelty in the mechanism of action.³⁸ In the case of TKIs indicated for CML, there was no difference in progression-free survival, overall survival,²³ mechanism of action, nor improvement in safety despite repeated price increases. Value-based pricing of TKIs offers an alternative method to pricing, in which the price of a drug is based on the additional benefit it offers (i.e., survival months) relative to its competitors.¹⁴⁷ However, the FDA can only approve cancer drugs based on efficacy and safety, not value. Value-based pricing can serve as another mechanism to attenuate the financial burden and toxicity of cancer treatment on Medicare and its beneficiaries, and it would also force manufacturers to compete on price and health outcomes.¹⁴⁸ Therefore, congressional action, such as those proposed by H.R. 3 and S. 254, to extend the FDA scope of approval to include value-based criteria is proposed by both acts.

Although the policy-level interventions discussed above such as price controls, limitations in OOP expenditure, and expansion of low-income subsidies would likely have the greatest and widest impact on patients, additional interventions at the point of care would result

in the most comprehensive mitigation of financial toxicity in CML and other cancers if financial toxicity has been identified. Patients with low neighborhood income, who we found to be at higher risk of CML-specific death and who may be forgoing non-medical goods or services, may be screened at diagnosis for a history and risk of financial toxicity. Screening may be conducted by social workers, clinicians, or even specialized personnel such as financial navigators. Screening tools that may be implemented during clinical evaluations include the National Comprehensive Cancer Network (NCCN) Distress Thermometer that can identify whether a recently diagnosed cancer patient currently has or had a history of insurance/financial problems,¹⁴⁹ or a more specific measure such as the Comprehensive Score for Financial Toxicity measure.¹⁵⁰ Despite the availability of such tools, the implementation of screening may not be routinely conducted in all health systems that treat cancer patients, particularly small health systems that may not have a resourceful cancer center.^{151,152} Additionally, financial toxicity may develop over time after a baseline assessment but such assessments may only be conducted once upon diagnosis. Therefore, we recommend that upon diagnosis of CML and throughout the course of treatment, patients should be screened routinely for financial toxicity using validated screening tools and at-risk individuals such patients residing in low-income neighborhoods must be identified. Assessments should not only focus on whether TKI and cancer treatment can be afforded, but whether patients forgo non-medical goods and services which can also impact health outcomes and quality of life.^{58,144}

If properly assessed, steps can be taken to proactively address financial problems that may arise upon initiation and throughout TKI therapy, particularly in patients who have been identified as having a low-income status. Examples of interventions include drug payment assistance programs, charity contributions, payment plans, finance counseling, and assistance with non-medical expenditures such as transportation and groceries.^{152,153} Interventions should

also target the health literacy of patients, since patients may not be familiar with information regarding treatment options and insurance coverage.¹⁴⁸ Similar to screening methods, the application of such interventions are not widespread nor comprehensive, and health systems may be limited with regard to time and personnel to provide the interventions.^{151,152} We recommend that health systems provide as much interventions that available resources would allow, but provide financial counseling to inform the patient at a minimum. A study which provided financial management and identification of grant funding found an improvement in physical and mental health scores of patients with a hematological malignancy as compared to baseline scores.¹⁵³

Lastly, an open conversation about treatment cost with regard to the risk-benefit of treatment is essential between the prescriber and patient.¹⁵⁴ Although knowledge of the insurance coverage details and exact OOP expenditure of each patient is not within the scope of a prescriber's practice, knowing the average patient cost of TKIs, discussing the cost, and considering the cost in clinical decision making is a step toward addressing financial toxicity.¹⁴⁸ This conversation should be routine practice and ongoing throughout the duration of treatment. Prescribers should also understand the treatment cost imposed on the health insurers since these costs may eventually be passed on to the insured patients by way of increased cost-sharing and premiums.¹⁴⁸ On the patient side, we recommend that patients be proactive in their decision making to undertake the financial risk of initiating TKI therapy by understanding their insurance coverage, actively discussing financing of care with their healthcare team, involving family members, and seeking financial assistance with the aid of financial navigators.

A comprehensive policy, clinical, and individual level application of the recommendations described above may reduce the financial burden of CML treatment for Medicare and attenuate the deleterious effects of financial toxicity in vulnerable groups such as patients with a low-

income level. These recommendations may be applied to other cancer patients who may also experience financial toxicity.

8.3 Strengths and Limitations

A strength of our study is that it is the one of very few studies to evaluate the association between neighborhood income level and outcomes in the context of financial toxicity in CML patients in the US. We used a framework to link three studies which described the financial burden of TKI therapy, and which attempted to identify disparities in mortality and non-cancer healthcare expenditure by neighborhood income level. We have extended the trend in TKI drug price and patient OOP expenditure beyond prior studies to the latest data available. We detected a disparity in CML-specific mortality which was robust to varying covariate model specifications. Although we did not detect a disparity in non-cancer healthcare expenditure, our study may point to other assets, goods, and services that patients may be forgone to maintain cancer care.

The results of our study must be interpreted in light of its weaknesses. In our study of trend in drug price, the price was based on Medicare gross payment amount, which does not capture negotiated prices between insurers and pharmaceutical manufacturers. Similarly, monthly OOP expenditure may not capture any external financial assistance patients may have received, such as charity grants. Additionally, monthly OOP expenditure reflected fills occurring throughout different Medicare coverage phases in which OOP amount varies. A major limitation of our studies is the assumption that all individuals within a neighborhood had an income equal to that of the census tract value, which introduces misclassification of income at the individual level. Additionally, neighborhood income does not capture all patient financial assets and was an overestimate of reported median per-capita income of Medicare beneficiaries.

Our measures of association between neighborhood income and outcomes may be biased by several unobserved variables. If patients with a low neighborhood income are associated with presenting with advanced-phase and/or severe CML, or are more likely to receive low-quality care, then mortality and expenditure may be biased upwards. A significant unmeasured confounder was the use of patient assistance programs or charitable grants which cover TKI OOP expenditures resulting in minimal or even zero OOP expenditure for a TKI prescription. Patients with low neighborhood income are more likely to qualify for such programs. This may reduce the effects of financial toxicity, and it may lower the rate of mortality and increase the use of TKIs and non-cancer healthcare in patients with low neighborhood income. In our analysis of non-cancer healthcare expenditures, we assumed that patients were unable to forgo services provide by Medicare Part-A but do have a choice in forgoing services billed through Medicare Part-B or -D, which may not be true for all services. We may also have misclassified non-cancer care if it was associated with a CML diagnosis code, and we were unable to make a conclusion regarding unobserved trade-offs a patient may make (e.g., consumer goods/services and leisure activities). Lastly, due to limitations in sample size, we were unable to use a finer stratification of neighborhood income level and we were underpowered to detect a difference in 60-month cumulative non-cancer expenditure between income groups.

8.4 Recommendations for Future Research

Future research on the financial burden of cancer and the resulting financial toxicity should continue to measure the trend in TKI drug price and OOP expenditure. Prices may continue to rise in excess of medical inflation, and although we did not observe a trend in OOP expenditure, rising prices may force OOP expenditures to increase in the near future. We recommend future research to focus on factors that mediate the association between

neighborhood income level and outcomes such as mortality and non-cancer healthcare utilization to inform research design. Identification of mediating factors may serve as a point of intervention to improve outcomes in patients who are financially burdened by cancer and treatment.

We also recommend qualitative research to further understand what cancer patients' value under financial toxicity and what medical or non-medical goods and services they may choose to forgo to alleviate financial pressure. Quantitative research on the trade-off cancer patients make should include use of non-medical goods and services which are not readily available in claims data and may necessitate the design of a prospective study that collects this type of data. Lastly, research on creating and validating financial toxicity screening tools to identify patients at risk of financial toxicity is needed. Once identified, financial toxicity interventions should be evaluated on the basis of non-surrogate outcomes such as overall survival and progression-free survival. Further research can also be done to identify a minimum set of standardized financial toxicity interventions that can be readily implemented alongside cancer care.

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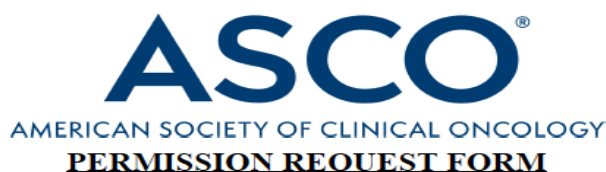
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XI. Vita

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Education

University of Illinois at Chicago College of Pharmacy

Ph.D. Candidate, Pharmacy Systems, Outcomes & Policy

Chicago, IL

Sept. 2016 – Graduating June 2021

- Concentration: Pharmacoeconomics and Outcomes Research

University of Illinois at Chicago College of Pharmacy

Pharm.D. with High Honors

Chicago, IL

Sept. 2012 – May 2016

Benedictine University

B.S. with Honors, Health Sciences

Lisle, IL

Sept. 2006 – May 2010

Research Experience

University of Illinois at Chicago College of Pharmacy

Dissertation Research | Advisors: Daniel Touchette, Pharm.D., M.A and Todd A. Lee, Pharm.D., Ph.D.

Chicago, IL

- Created a research agenda to evaluate the health outcomes of patients with chronic myelogenous leukemia using the Surveillance, Epidemiology, and End Results cancer registry linked to Medicare claims data.
- Evaluated trends in cancer drug pricing and measured the effect of financial toxicity on medication access, mortality, and healthcare utilization.
- Applied advanced statistical methods in analysis of survival data and censored cost data utilizing SAS.

June 2019 – Present

Institute for Clinical and Economic Review & UIC College of Pharmacy

Research Assistant | Supervisor: Daniel Touchette, Pharm.D., M.A.

Chicago, IL

- Conducted a health economic evaluation of esketamine indicated for treatment resistant depression.
- Co-led the conceptualization and design of the economic model.
- Managed a team to conduct systematic literature reviews to determine model parameters.
- Co-led the analysis of the economic model and reporting of results.
- Collaborated with the pharmaceutical manufacturers, insurance firms, and patient advocacy groups to inform model development and reporting of results.

July 2018 – May 2019

Takeda Pharmaceuticals

Outcomes Research Fellow | Supervisor: Robin Turpin, Ph.D.

Deerfield, IL

July 2017 - July
2018

- Supported the company's strategic plans aimed at demonstrating the value of biologic therapy for inflammatory bowel disease (IBD).
- Created study protocols and managed the execution of retrospective database and cost-effectiveness studies to evaluate the real-world effectiveness and value of biologic therapy for IBD.
- Managed the continual development of budget-impact models for insurance firms and health systems in accordance with the emergence of key competitors.
- Presented key health economic evidence to marketing, medical liaison, and health outcomes liaison teams to communicate the value of biologic IBD therapy to external stakeholders.
- Collaborated cross-functionally with U.S. Medical Affairs, Market-Access, and Regulatory Affairs to ensure proper conduct and effective communication of health outcomes data.

University of Illinois at Chicago College of Pharmacy

Outcomes Research Fellow | Supervisor: Daniel Touchette, Pharm.D., M.A.

Chicago, IL

July 2016 – July
2017

- Led and managed the cost-analysis of the Coordination of Health Care for Complex Kids (CHECK) program, a large care-coordination program for children with chronic conditions funded by the Centers for Medicare & Medicaid Services, to inform program development and insurer reimbursement.
- Conducted a systematic literature review on the economic evaluation of clinical pharmacy services to inform payer and healthcare systems regarding the cost-effectiveness of clinical pharmacy services to justify implementation and insurer reimbursement.

Takeda Pharmaceuticals

Clinical Science – General Medicine Intern | Ali Hariri, M.D., Ph.D.

Deerfield, IL

May 2014 – Aug.
2014

- Reviewed the epidemiological literature to identify celiac disease as an unmet need.
- Analyzed and evaluated the pathogenesis, histology, diagnosis, and treatment of celiac disease for application in clinical trial design.
- Assessed the current drug development landscape by analyzing phase I-II clinical trials of competitor pipeline drugs for celiac disease to inform clinical drug development.
- Designed a comprehensive clinical development plan for a celiac disease drug and evaluated patient reported outcomes as a primary endpoint.

Publications

- **Talon B**, Calip GS, Lee TA, et al. Trend in tyrosine kinase inhibitor utilization, price, and out-of-pocket cost in patients with chronic myelogenous leukemia. *J Oncol Pract*. Revision under review.
- **Talon B**, Gerges M, Perry-Bell K, et al. A work-sampling study of an innovative pediatric care coordination program aimed at children with chronic health conditions. *Prof Case Manag*. 2020;25(6):324-334. doi:10.1097/NCM.0000000000000430.
- Nabulsi NA, Alobaidi A, **Talon B**, et al. Self-reported health and survival in older patients diagnosed with multiple myeloma. *CCC*. 2020;31(7):641-650. doi:10.1007/s10552-020-01305-0.
- **Talon B**, Perez A, Yan C, et al. Economic evaluations of clinical pharmacy services in the United States: 2011-2017. *J Am Coll Clin Pharm*. December 2019. doi:10.1002/jac5.1199.
- Alobaidi A, Nabulsi NA, **Talon B**, et al. Depressive symptoms, mental health-related quality of life, and survival among older patients with multiple myeloma. *Support Care Cancer*. December 2019. doi:10.1007/s00520-019-05246-6.
- Touchette DR, Boyer N, **Talon B**, Schultz BG. Section 4. Long-Term Cost-Effectiveness. In: Institute for Clinical and Economic Review. Esketamine for the Treatment of Treatment-Resistant Depression: Effectiveness and Value. June 20, 2019. Available at <https://icer-review.org/material/trd-final-evidence-report-and-meeting-summary/>.
- Smith LA, Habib I, Shirkey S, **Talon B**, Milne A, Nadolski J. Sexual Dimorphism in the Effect of a Taurine Supplemented Diet on Life Span in Adult *Drosophila melanogaster*. *International J of Zoological Research*. 2011;7(1):34-48. doi:10.3923/ijzr.2011.34.48.

Presentations

- Touchette DR, Boyer N, Atlas SJ, Agboola F, **Talon B**, Schultz BG, Kumar VM, Rind D. Long-Term Cost-Effectiveness of Esketamine for the Treatment of Treatment-Resistant Depression. Poster presentation at the International Society for Pharmacoeconomics and Outcomes Research 2019 European Meeting; Copenhagen, Denmark, November 5th, 2019.
- **Talon B**, Perez A, Yan C, Alobaidi A, Zhang KH, Schultz BG, Suda KJ, Touchette DR. A Systematic Review of Economic Evaluations of Clinical Pharmacy Services in the United States: 2011 through 2017. Poster presentation at the 2019 American College of Clinical Pharmacy Annual Meeting; New York City, New York, October 28, 2019.
- Asfaw AA, **Talon B**, Nabulsi N, Alobaidi A, Zhou J, Sweiss K, Pritesh P, Chiu B, Calip GS. Depressive Symptoms and Risk of Cancer-Specific Mortality Among Patients with Non-Hodgkin Lymphoma: Analyses from the Surveillance, Epidemiology, and End Results (SEER) Medicare Health Outcomes Survey (MHOS). Poster presentation at the International Society for Pharmacoeconomics and Outcomes Research 2019 Annual Meeting; New Orleans, Louisiana, May 18th, 2019.
- Asfaw AA, **Talon B**, Wirth S, Sharp L, Touchette DR. Cost-Effectiveness of a Theoretical Breast Cancer Adherence Intervention. Oral presentation at the Midwest Social and Administrative Pharmacy Conference; University of Wisconsin, August 15-17, 2018.
- **Talon B**, Gerges M, Perry-Bell K, Caskey R, VanVoorhees B, Touchette DR. A Work-Sampling Study of an Innovative Pediatric Care-Coordination Program for Asthma, Diabetes, and Sickle-Cell Patients. Poster presentation at the International Society for Pharmacoeconomics and Outcomes Research 2018 Annual Meeting; Baltimore Convention Center, May 19-23, 2018.
- **Talon B**, Huang Z, Lissos T, Null KD. Infusion of Vedolizumab and Infliximab in the Physician Office and at Home was Less Costly Compared with Hospital Outpatient Settings. Poster presentation at the AMCP Managed Care & Specialty Pharmacy Annual Meeting; Boston Convention & Exhibition Center, April 2018.

- **Talon B**, Schumock GT, Caskey RN, Van Voorhees B, Touchette DR. Cost-Analysis of an Innovative Pediatric Care Coordination Program for Chronic Disease. Poster presentation at the UIC College of Pharmacy Research Day; University of Illinois at Chicago, February 10, 2017.

Teaching Experience

University of Illinois at Chicago College of Pharmacy

Teaching Assistant

- Pharmacoepidemiology and Biostatistical Reasoning Spring 2020 and 2021
- Pharmacoeconomics and Payment Fall 2019
- Contemporary Topics in Health Economics and Cost-Effectiveness Analysis Fall 2019
- Introduction to Economic Modeling for Pharmacy Students Fall 2019 – Spring 2019

Work Experience

United RX Long-Term Care Pharmacy

Hillside, IL

Pharmacy Technician

May 2015 – May 2016

- Accurately filled medications in a timely manner.

CVS Pharmacy

Hillside, IL

Pharmacy Intern

June 2011 – April 2015

- Served a culturally diverse patient population of differing socioeconomic statuses.
- Counseled patients on a variety of disease states and their indicated prescription medications.
- Recommended over-the-counter medications to patients according to their needs.

Leadership & Membership

Leadership

- **President**, International Society for Pharmacoeconomics and Outcomes Research, Student Chapter, University of Illinois at Chicago College of Pharmacy May 2018 – May 2019

Membership

- **Member**, Academy of Managed Care Pharmacy 2018 to Present
- **Member**, International Society for Pharmacoeconomics and Outcomes Research, Student Chapter, University of Illinois at Chicago College of Pharmacy 2016 to Present

Honors & Awards

- **Awardee**, Myron Goldsmith Memorial Scholarship February 2017
- **Awardee**, Rho Chi Academic Honor Society in Pharmacy May 2014

Licenses

State of Illinois Licensed Pharmacist	License#
	051299590