Exploration of HealthCoin: A Currency to Address US Private Payer Underfunding for Single or Limited Administration (SLA) Treatments with Long-Term Effectiveness

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Abstract

Exploration of HealthCoin: A Currency to Address US Private Payer Underfunding for Single or Limited Administration Treatments with Long-Term Effectiveness (SLA treatments)

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There may be a free-rider problem stemming from the distribution of future medical savings from single or limited administration (SLA) treatments with lifetime efficacy. Private commercial insurance through an employer is the biggest source of health insurance among the working age population in the United States. A commercial plan can only benefit from avoided future medical costs or additional QALYs gained for patients for paid treatments while a patient remains on their plan. Any benefit after the age of 65 is reaped by the Centers for Medicare and Medicaid Services (Medicare) from QALYs and avoided costs that are realized while patients are covered by Medicare. The free-rider problem is primarily due to a framework of decision-making that does not include any avoided medical costs or QALY gains after the age of 65 for plan members. This dissertation proposes the free rider incentives will impact the market through delayed or reduced access to cures and SLA therapies. We posit this will occur because SLA treatments will be valued less compared to treatments which are lower cost in the short-term and

generate benefit while the patient is being treated (i.e., chronic), given the same overall benefit from the treatments while the patient is on the plan.

This dissertation focuses on the misalignment in incentives that occurs because the payer for the patient changes at the age of 65, from private commercial payers to Medicare. The aim of this dissertation is to evaluate the need, feasibility, and potential values of HealthCoin in relevant markets. HealthCoin is a policy mechanism to correct underfunding of curative treatments in disease areas where they are available. We used three aims to achieve this goal. The first to demonstrate potential underfunding of SLA therapies in private plans and the second and third to demonstrate the feasibility and value distribution implications for HealthCoin in two markets where SLA therapies are developing.

Aim 1 examined if there is evidence that private payers are underfunding SLA therapies before patients enter Medicare. The results from Aim 1 were consistent with underfunding of SLA therapies in the private market. There was a discontinuous increase in the treatment rate where it was expected as patients entered Medicare, but not the chronic falsification study group where there is no underfunding expected. The research suggests there is a need to understand the impact of underfunding across the patient lifetime and in specific disease states with SLA therapies in development and currently used in treatment.

Aim 2 demonstrated HealthCoin could alleviate underfunding incentives through HealthCoin where cost-effectiveness thresholds for a QALY is $50,000. For lower cost-effectiveness thresholds, Medicare is not incentivized to provide HealthCoin because the net value to the health care sector is negative. At higher cost-effectiveness thresholds, private payers are incentivized to provide chimeric antigen receptor T-cell (CAR T) without the aid of Medicare

because the benefits realized will be positive, based on the model assumptions and list price of $475,000.

Aim 3 builds on aims 1 and 2 with a model for the potential value and feasibility of HealthCoin in the emerging hemophilia A and B gene therapy treatment markets. In the primary model of this aim, stakeholders are incentivized to participate in HealthCoin for a $250,000 gene therapy price, where the cost-effectiveness threshold is $100,000/QALY, providing a total population benefit of $92 million while patients are under the age of 65 and costing private payers $58 million. HealthCoin creates $11 million in benefit for the population while on Medicare, costing the public payer $26 million. In the hemophilia market, sensitivity analyses are vital because the gene therapies are still in development and there is uncertainty around their duration of efficacy and total target population. Sensitivity analyses in aim 3 revealed that HealthCoin may pass the market for lower thresholds or not at all, depending on price, approved ages of treatment, target population, and duration of efficacy.

Through the three Aims, we put forth evidence for the need and potential of a value-based financial tool (HealthCoin) to address the potential underfunding of SLA treatments. Our work indicates that further research is necessary to examine the magnitude for underfunding of SLA treatments in specific disease states. The second and third aims demonstrate that HealthCoin can increase net benefits for the health sector for specific diseases as more high cost SLA therapies are launched in the market. This dissertation suggests HealthCoin is a viable financial tool to redistribute the costs of SLA therapies in alignment with lifetime benefits realized for payers and patients, with opportunities for future research as markets develop.

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DEDICATION

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Chapter 1. INTRODUCTION

1.1 Background

In the United States health care environment, private employer-sponsored insurance is the largest source of payment for healthcare for people under the age of 65.[1] At the age of 65, most patients become eligible for Medicare, an insurance plan that is funded through the government agency, Centers for Medicaid and Medicare (Medicare).[2] The payer acts as one of the decision-makers for the patient by determining, within regulatory compliance, which procedures, providers, and treatments are available for payment in plans available to employers and private market purchasers. The relationship between the payer and patient in insurance has well-known misalignments of incentives, including profit or operating reserve maximization (payer) versus maximizing outcomes of the purchased protection from the insured potential event (patient).[3] There have been a number of federal and state regulations to protect consumers from the misalignment in incentives in this informationally complex market, including restrictions on medical loss ratios for payers and requirements of coverage for basic care.[4] This dissertation focuses on the misalignment in value-based incentives for patient treatment that occurs because the payer for the patient changes from private commercial payers to Medicare at the age of 65. In *Financing Cures in the United States,* Dr. Basu argues there is a free-rider problem that is created by the loss of all patients from the commercial market at age 65 that can lead to underinvestment in cures lasting over the lifetime of the patient.[5]

1.2 Free Rider Incentive for Underfunding

Fundamentally, the free-rider problem stems from future medical savings from a given treatment being distributed over all payers the patient will have while medical savings are incurred. Currently, 155 million patients in the United States are covered by private employer-

sponsored insurance.[6] A commercial plan can only realize the savings from avoided future medical costs and retain plan member QALY gains if a patient remains on their plan. If therapies that enter the market with lifetime cost savings and QALY gains, private payers only have the financial incentive to consider the cost savings and QALY gains until the patient reaches the age of 65 and exits the private market and enrolls in Medicare.

Additionally, patients have a 21% payer switch rate per year between insurers in the private market in the US.[7] Plan churn is more likely to impact free-rider incentives for smaller plans and rarer diseases because large plans can rely on reduced costs and improved quality of life for new plan patients who had been previously treated with greater certainty. As an example, if a small plan or self-insured employer pays to cure a young patient with twice relapsed acute lymphocytic leukemia and the patient switches payers, the plan loses the future medical savings. Where a large plan or high incidence means an average number of patients are entering and leaving the plan in various stages of treatment, future medical savings is shared between all private plans. Where the plan is small or the disease state is rare, plans cannot rely on average market averages, driving uncertainty of the potential benefits of using high cost cure or SLA therapies with lifetime efficacy, especially while there are few SLA therapies in the market. This could suggest HealthCoin has a function for small plans as new high cost SLA markets develop in rare diseases. Finally, patients can lose coverage entirely at certain times throughout their lifetime, or use another government sponsored insurance, such as Medicaid or VA care.

The free-rider problem is created because the inability to count on avoided medical costs and plan member QALY gains after the age of 65, reduced expected savings from turn over, and uncertainty around other plan behavior all reduce expected value of the treatment to the plan. This dissertation proposes the free rider incentives will impact the market through delayed or

reduced access to cures and SLA therapies. We posit this will occur because the value of treatments with lifetime benefit will be equal to the plan compared to treatments which are chronically administered, given equal gains from both treatments while the patient is on the plan. We also expect that the cost of the SLA treatment will be higher than the expected cost of the chronic treatment while the patient is on the plan if the expected QALY gains are the same, potentially leading to the private payer to have more financial incentive to invest in the chronic SLA treatment than the chronic treatment, with the expectation that all patients will leave the private market for Medicare at age 65.

This dissertation aims to empirically investigate if the free-rider problem is leading to measurable underinvestment in high cost products with single or limited administration. The three articles that comprise this dissertation build on work by Dr. Anirban Basu, which initially proposed HealthCoin, a financial instrument to address potential underfunding by commercial payers created by the free rider incentives for cures. The research aims to explore the evidence for underfunding driving a need for HealthCoin, and its potential impact in markets where SLA therapies are being developed.

1.3 Introduction to HealthCoin

HealthCoin is a currency that would be issued by Medicare to the commercial payer at the time the therapy is paid by the commercial payer. The HealthCoin currency is valued at a market value of the price per QALY for the improvement of SLA treatments compared to the current standard of care across markets where SLA treatments launch. When HealthCoin is issued, the number of HealthCoin depreciate over the expected lifetime of the patient and can be traded across payers until the patient hits Medicare enrollment age, when Medicare can repurchase the currency at the depreciated amount. The value of the HealthCoin will depend on

three primary components, the value of the gain in QALYs in the market, the number of QALYs that are gained for patients, and cost of treatment. Medicare will honor the purchase of HealthCoin for the remaining value of the patient's life when the patient hits age 65, as a matter of implementing the policy and mitigating the risk for payers of investing in the treatment.

There have been private company and government agency-initiated solutions around the different mechanisms to help incentivize and help private payers to fund these SLA treatments. While some small payers have managed to create new longer-term payment contracts around SLA treatments, none of these solutions (e.g., annuity payment, value-based contracts, individual patient-specific capitated payment contracts) have gained significant traction in the market to date.

One common strategy discussed in the space is simply to allow private plans to pay annuity-like payments to *manufacturers* (often proposed in combination with a pay-for-performance element). There are significant complications to implementing these contracts, primarily related to the time a patient remains with a plan and agreeing on the level of value-based risk to integrate into the payment amount for annuities. Because patients change insurers often in the United States, sometimes having gaps in insurance, the potential of losing the patient without reaping benefits and having to continue payments remains a risk concern for private payers.[8] Further, if a patient transfers to a new insurer, expecting to transfer the liability with the patient, without an upside to a new insurer, is unrealistic. Finally, even when the payer executes pay-for-performance, this is still done in a short term compared to the length of the expected efficacy of the treatments. Even for the longest example of 3-year contracts for cell therapies such as chimeric antigen receptor T-cell (CAR T) therapy, expected benefit over the lifetime of a patient treated and cured of twice relapsed or refractors acute lymphocytic leukemia (r/r ALL) in

their youth is a significantly longer period. The payments in those cases still do not reflect the period of value.

The advantage of the currency over the annuity payment is the allowable transfer of the value along the lifetime of the patient (rather than the transfer of a liability payment), and an ability to recover value for the patient at the age of 65 for the remaining lifetime.

This dissertation aims to examine the need and feasibility for HealthCoin through a series of three aims. Aim 1 measures the extent of underfunding in the market today, demonstrating the need for a tool such as HealthCoin to address the funding of treatments with long-term efficacy and single or limited administration in patients with private health insurance. Aims 2 and 3 model the feasibility and potential impact of HealthCoin in hemophilia A and B and twice refractory or relapsed ALL. The hemophilia A and B markets are characterized by lifetime burden of disease and high costs of care over many decades. Whereas CAR T therapies for r/r ALL are intended for patients under the age of 25 who previously had high mortality rates after treatment with the standard of care. These markets were selected because gene therapies in the late stages of development are emerging primarily for chronic orphan indications and acute orphan conditions with high mortality.[9]

1.4 Research Aims

The aim of this dissertation is to evaluate the need, feasibility, and potential values of HealthCoin in relevant markets. Aim 1 addresses the need for HealthCoin by examining the extent of underfunding of treatments with long-term efficacy and single or limited administration in the US. By testing if patients on private insurance are less likely to receive treatments with long-term efficacy and single or limited administration as they reach Medicare age (all citizens become eligible for Medicare no later than 65),[10] Aim 1 will examine if there is evidence that

private payers are underfunding SLA treatments and therefore, a need for HealthCoin. Aim 2 will use an assessment of CAR T therapies to demonstrate the potential feasibility of HealthCoin in a new curative market for patients with r/r ALL under the age of 25. Finally, Aim 3 builds on previous research to test the potential value and feasibility of HealthCoin in the emerging treatment markets of gene therapy for hemophilia A and B.

Aim 1: Examine the extent of underinvestment of treatments with long-term efficacy and single or limited administration for private payers. Aim 1 uses claims data to examine the extent that incentives to underinvest in SLA treatments impact private payer behavior. Regression discontinuity analysis evaluates the SLA treatment rate for patients prior to Medicare, to determine if payer expectation of return on investment in the long-term impacts access to such treatments where alternatives exist. Using a universe of indications that possess treatments with long-term efficacy and single or limited administration today (i.e., glaucoma, cataracts, and adhesive capsulitis of the shoulder), Aim 1 analyzes if patients are less likely to be prescribed and receive treatments with long-term efficacy and single or limited administration approaching eligibility to Medicare. Additional analysis includes a chronic falsification universe (i.e., rheumatoid arthritis, psoriatic arthritis, and psoriasis) to understand if the magnitude of change in prescribing at age 65 is significantly different than other similar disease states with different types of treatment options.

Aim 2: Build a model for testing the feasibility of HealthCoin in the double refractory ALL market to fund use of CAR T therapies. Basu et. al demonstrated that introducing HealthCoin into the diabetes market could create incentive for private payers to invest in a treatment with long-term efficacy and single or limited administration in a multi-payer environment.[11] CAR T cell therapies provide the opportunity to model the impact of HealthCoin for high cost single

administration products for a high mortality therapeutic area. Kymriah® (tisagenlecleucel), the first CAR T approved in the US demonstrated a 50% complete remission rate in patients under age 25 with refractory (2nd or more occurrence) acute lymphoblastic leukemia (ALL), a population with remission rates around 40% prior to this treatment.[12] Remission rates are connected to payments using an outcomes-based payment contract. Aim 2 uses survey, government, and clinical trial data to estimate the distribution of benefits and costs generated from the use of CAR T therapy over the lifetime of the patients among different stakeholders, exploring if HealthCoin can potentially improve access through redistribution of costs to reflect benefits over the lifetime of the patient.

Aim 3: Build a model for testing the feasibility of HealthCoin for gene therapy in patients with moderate and severe Hemophilia A and B. Aim 3 uses the Basu et. al HealthCoin framework to estimate potential value for the policy in an entire incident cohort of patients with moderate and severe hemophilia A and B. This aim uses claims, government, and clinical trial data to estimate the distribution of costs and benefits of gene therapy over the lifetime for patients in a high cost, but well managed market with low mortality, compared to aim 2. Understanding the conditions and implications for HealthCoin in the hemophilia A and B market will demonstrate the range of values HealthCoin would incentivize all stakeholders to participate for different conditions of an uncertain market.

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Chapter 2. THE UNDERFUNDING OF HIGH COST SINGLE/LIMITED ADMINISTRATION TREATMENTS IN COMMERCIAL HEALTH PLANS COMPARED TO MEDICARE

2.1 Introduction

Incentives of commercial payers for providing expensive curative therapies are becoming increasingly relevant as more high cost single or limited administration (SLA) products with lifetime effectiveness enter the market. Since the launch of direct acting antiviral agents for Hepatitis C in 2014, multiple SLA products have launched. The newer generation of products includes gene and cell therapies for oncology indications and retinal dystrophy, which require a shorter treatment process than the 8-24 weeks of the Hepatitis C product.[1,2,3] In 2017, the first cell therapy for twice relapsed or refractory acute lymphocytic leukemia (r/r ALL) launched, significantly reducing mortality for pediatric patients after a single administration of the treatment. The product continues to expand its approved oncology indications and faces competition on the market, but the price of the product is significantly higher than earlier line treatments and other approved treatments in the market. There are over 300 cell and gene therapies where single or limited administration to patients is common.[4]

There have been numerous innovative payment models proposed for payers to manage the lump sum cost of these new products which are expected to yield benefit over a patient lifetime.[5] The payment models have run into a number of operational concerns, including agreement on the relationship between outcomes payment amounts over time, as well as the feasible duration for a payment contract.[6] Switching of insurance types and plans happens throughout a patient's lifetime in the United States health insurance market. A study of patient turnover in the market in 2011 found that 21% of people with private insurance plans canceled

the plan in a single year, with 87% of those switching to a new plan.[7] In addition to switching private plans and payers within the private market, patients become eligible for Medicare, the Centers for Medicare and Medicaid Services (Medicare) sponsored health insurance for the elderly population. Outside of the private health insurance system, patients can spend time in their lifetime on other government insurance programs or have uninsured time.

The disaggregated nature of the payer system may result in underinvestment in high cost SLA therapies with long-term efficacy for the patient because each payer can only expect savings from treatment for the duration a patient remains in their insurance pool. Commercial payers primarily cover patients for some duration of their lives before age 65 and have primary payment responsibilities for none of the time after that age. Basu et. al describe how this potentially creates a free rider problem in the private market that leads to an underinvestment in SLA therapies, relative to a framework where patients have a single payer through their lifetime.[8,9]

One consequence of the predicted free rider behavior would be decreased incentive to invest in SLA therapy as patients age, where the realized benefit is lowest for a commercial payer right before the transition to Medicare. After the patient joins enrolls in Medicare, Medicare becomes the beneficiary of the future realized benefits. When the patient first enrolls, Medicare will realize the most benefit from treating patients, as the patient is likely to be covered by Medicare as a primary payer for the remainder of the patient's life. This suggests there will be a point in treatment where the rate of SLA therapy will be discontinuous, as patients reach the age of 65 and commercial payers will realize little benefit from treatment, and the beginning of a patient's time on Medicare.

This study aims to examine the impact of the free rider incentive on the treatment decisions and potential underfunding of SLA products in the private market where there is expected to be the greatest incentive for underfunding, just before patients become eligible for Medicare.

2.2 Methods

To test the potential underfunding of SLA therapies due to the free rider incentives of the market, we first define two groups of therapeutic indications (study groups) with properties aligned with the SLA therapies entering the market and in development today. We separate the SLA universes into surgeries with primarily quality of life implications and SLA therapies for disease indications that can significantly impact mortality if left untreated. The SLA therapies that exist on the market today for indications that are otherwise chronic in nature, are often surgical. Therefore, the study group that was development included pharmaceutical and surgical SLA therapies.

Data Source

- IBM/Watson Marketscan Databases Commercial Claims and Encounters Database from 2009-2015 was used to capture information on treatment decisions by the age of the patient. Demographic and clinical characteristics are used to determine if there is continuity and balance of the observations on either side of the cutoff (age 65). The Marketscan databases only include Medicare Supplemental database, which limits the generalizability for those who have supplemental Medicare coverage after exiting the commercial market. The Medicare supplemental population is covered on employer sponsored Medicare supplemental plans, in which CMS and the employer contribute to coverage, compared to standard public Medicare coverage which does not include employer contribution, whether fee-for-service, point-of-

service, or capitated plans. About 30% of Medicare enrollees receive employer-sponsored supplemental insurance (2016), or nearly 10 million beneficiaries. Those with employer sponsored Medicare have high incomes and education levels compared to typical beneficiaries.[10] The impact of enrolling in Medicare could be biased for patients with employer sponsored insurance compared to the general population because of greater access to care and other resources such as time, information, or money. Additional studies should consider the portion of patients who exit the private market to Medicare without the supplemental insurance. One tool we use to address this limitation is observing if a discontinuity exists in the commercial population in the decade prior to Medicare enrollment and in the non-SLA study group in the same sample age. Additionally, data was only included through September of 2015 to consistently sample using ICD-9 codes; ICD-10 diagnosis codes were implemented in the fourth quarter of 2015.

Study Group Selection (Therapeutic Indications)

We used the following steps to identify and define the study group that would be used to examine the potential underfunding of SLA therapies:

1. We initially identified broad therapeutic specialties where SLA therapies are common through physician expert consultation.
2. SLA treatments were efficacious in improving the quality of life (QoL) of the of the patients or had significant implications in mortality. Underfunding is expected for SLA treatments with mortality and QoL implications, but for this research we separate the different types of SLA treatments into separate study groups. We expect different magnitudes of discontinuities that result from the potential for greater perceived clinical

necessity of SLA therapies where there are higher mortality implications. We expect that the payer has greater autonomy in the treatment decision for SLA therapies where QoL is the primary consideration. In the scope of this research we aim to demonstrate evidence of underfunding, rather than the potential differences in ability to underfund based on clinical attributes of any specific indication.

3. After therapeutic specialties were identified, we performed literature searches using Google Scholar and PubMed for single and limited administration treatments within those therapeutic specialties. We identified the specific therapeutic indication where the SLA treatments are used on the market.
4. Therapeutic indications were included if:
    a. The prevalent treatment population includes patients aged 65, the Medicare qualifying age.
    b. The therapeutic indication would typically be chronic or long-term if left untreated. This criterion is necessary because the commercial payer needs an incentive for considering future benefits after the patient is expected to leave the plan. Therapeutic indications that are acute, such as infections, have SLA treatments, but the benefit is primarily realized for the patient at the time of the treatment.
    c. The list cost of the SLA treatment is a greater than the alternative treatment of similar effectiveness for the expected time a patient is on a private plan. Current SLA therapies identified from criteria (a) and (b) are not as expensive as the SLA therapies that have recently entered the market. Payer free rider incentive only exists if the cost of treatment is more expensive than the expected cost of an

alternative treatment. This inclusion criteria ensures the free rider incentive exists in the selected SLA therapy markets.

d. Treatments were used during the years 2009-2015. The data source used provides claims from 2009-2015, so the selected treatments must be available during that time.

Falsification Group

In addition to the study group, we created a falsification group with high cost chronic treatments where the discontinuity due to a free rider incentive is not expected around the age of 65.

The falsification group includes therapeutic indications where there are chronic treatments of differential cost and effectiveness. This falsification group does not have the free rider incentive that exists in the study group because payers are paying for averted medical costs as the patients is treated. The therapeutic indication selection process was as follows:

1. Therapeutic indications for chronic treatments were initially identified from a list of the highest cost chronic indications to treat today.[11] We searched the literature around these therapeutic indications to determine if these, or related indications, met the remaining inclusion criteria for the study group.
2. To remain consistent with the study group, we selected disease indications with implications for quality of life, but without significant implications for mortality.
3. Therapeutic indications were included if:
    a. The prevalent treatment population includes patients aged 65, the Medicare qualifying age.

b. The treatment is considered chronic and does not have an available SLA therapy that is significantly more effective that the current chronic standard of care.
c. The indication does not present a significant mortality burden. This inclusion criteria exists to target therapeutic indications where payers have greater ability to select a treatment based on value. Therapeutic indications where there are mortality differences in the treatment options are likely to compel payers to authorize more expensive treatments based on clinical guidelines or regulation.
d. Treatments were used during the years 2009-2015. The data source used provides claims from 2009-2015, so the selected treatments must be available during that time.

Analysis Design

We used a fuzzy regression discontinuity design (RD) model that examines the rate of SLA treatment in claims data around the age of 65 (the Medicare eligibility age). We examine the existence underfunding of SLA products as patients approach Medicare. RD was selected demonstrate underfunding at an instance where there is a discontinuity expected, the logical design in this case where no clear control sample exists to the insured market.

Data Analysis

For the primary study group in three identification steps.

1. We identified the first diagnosis of any indication from the study group in the Marketscan commercial and Medicare datasets in the years 2010-2015, where patients did not have a diagnosis in the previous year. It is a standard practice to require at least two outpatient claims with a given diagnosis code separated in time to minimize "rule-out diagnoses"

associated with outpatient services such as laboratory tests or radiology examinations when no diagnosis is found, in addition to minimizing coding errors.[12,13] For that reason, we only included patients that had at least one more diagnosis on a separate date within the year following the initial diagnosis.

2. Patient claims data was analyzed for the following year to determine if they were administered SLA treatment within one year. Observations were indicated as treated if they were diagnosed and then treated within a year, and not treated if there was no SLA treatment within a year of diagnosis. Observations were only included in the sample population for the first year after the recorded diagnosis, excluding patients with new diagnosis between the age of 64 and 65 to remove observations expected to have both insurance types in the same year. Patient enrollment was tracked in the dataset to ensure patients were continuously enrolled for the 2009-2015 period of the data.
3. The annual treatment rate in the year following diagnosis was calculated.

Statistical Model

We developed a patient-level linear fuzzy regression discontinuity model in STATA 15 where the dependent variable is the SLA or high cost chronic treatment status.[14] The independent variable is a score calculated as the distance from age 65, where patient age is identified at a year level. The fuzzy design uses the patient payer (i.e., commercial or Medicare) around the cutoff. [15] Patients are assigned their respective insurance indicator based on the insurance source at the time of the diagnosis. In the model, we include a control for seasonality and indication-specific treatment rates with covariates for quarter diagnosis and disease indication, respectively.

The model examines treatment behavior within four years of Medicare eligibility on either side of the cutoff and a linear estimation. However, because we excluded observations age 64 to avoid patients who switch payers in the year following diagnosis, we have three years of data before Medicare, and four years of data after Medicare. We used the default uniform kernel, which evenly weights the patients score, regardless of distance from the cutoff. [16] The data source is HIPAA compliant and the date of birth was not available, so the score is calculated discretely as years from age 65.

The analysis also includes cutoff falsification tests for a discontinuity on either side of Medicare eligibility (ages 63 and 66) in the study group and the chronic falsification group, to determine if the detected discontinuity also exists when patients are not changing insurance sources, where the free rider problem is expected to occur continuously and gradually from year to year of patient age for commercial insurance. We test either side of the cutoff because we expect a gradual decrease based on incentives in the commercial market prior to Medicare eligibility, and conversely, have no reason to expect underfunding from the public Medicare payer, and expect a smooth treatment rate after eligibility. Discontinuities on either side are intended to reveal if there are additional factors that may be driving discontinuities between the rates at different ages, or if the discontinuity is unique to patients switching from a private to public payer. We repeat the fuzzy regression discontinuity analyses with the same model specifications, using a cutoff at age 63 and 66 to examine the trends and discontinuities. In addition to falsifications in the primary dataset, we recreated the dataset in older adults not yet eligible for Medicare (ages 48 to 58) to create a second set of falsifications with no patients that are eligible for Medicare in the dataset. We test the discontinuities with four years of data on either side of the cutoff, where the cutoffs are ages 52, 52, 54, and 55.

Final Study Groups

The final therapeutic indications and treatment options used in the RD analysis are listed in **Table 2.1.** We included three indications in the QoL SLA study group, nine indications (seven oncology indications) in the mortality SLA study group, and three treatments in the chronic falsification group. Indications in the study groups all include surgical interventions which improve quality of life but not mortality significantly, to test for the discontinuity as a result of applying the inclusion criteria. SLA therapies are still rare and new in the pharmaceutical market.

It may be posited that differences detected at the discontinuity of age 65 are related to differences in patient cost-sharing for surgical compared to pharmaceutical treatments on private insurance instead of Medicare. In May 2016, the same claims dataset used in this analysis was used to demonstrate there was no significant difference in the use of outpatient surgical and imaging services (inclusive of all services, not only SLA treatments for otherwise chronically managed indications), although there was an out-of-pocket price reduction when patients entered Medicare.[17] Additionally, existing literature that proposes Medicare is more generous for patients eligible for nonurgent surgeries[18] is consistent with a benefit design that reflects underfunding of SLA therapies where clinical factors (i.e., mortality) are not important and financial incentives can drive decision-making. To more robustly examine if the surgical cost-sharing differences for patients are driving a detected discontinuity for the SLA therapies, we will ultimately include a falsification that includes recurring surgical therapies for chronic indications. We are unable to detect severity of disease in the dataset, so we identify patients through diagnosis code, expecting that changes in severity are continuous around the age of 65 in the model.

Table 2.1 – SLA Study Groups and Chronic Falsification Group Indications and Treatments

	Therapeutic Indication	Diagnosis Codes	Treatment Tested for Discontinuity
QoL SLA Study Group	Senile Glaucoma Adhesive Capsulitis of the Shoulder Cataracts	365.11, 365.10 726.0 366.1	Surgical Procedure
Mortality SLA Study Group	Gallstones Coronary Artery Disease *Cancer* Skin Lung Prostate Colon Rectal Breast Stomach	574 414.0 172, 173 162 185 153 154 174 151	Surgical Procedure
Chronic Falsification Group	Rheumatoid Arthritis Psoriasis Psoriatic Arthritis	714.0 696.1 696.0	Disease-Modifying Antirheumatic Biologics

QoL SLA Study Group Background

1. Senile Glaucoma

We included patients diagnosed with open-angle senile glaucoma (OAG) in the study group sample. OAG is characterized as a chronic, progressive disease that presents with optic nerve damage, retinal nerve fiber layer defects, and subsequent visual field loss. There are an estimated 2.22 million cases in the US, but at least half are undiagnosed. Patients do not usually experience symptoms until severe stages relating to restricted vision. OAG treatment generally begins with pharmacological intervention, before progressing to laser therapy and surgery. The pharmacological approach has been challenged as less effective than the other sequences of therapy, but guidelines note the clinician "must evaluate the possible impact of the treatment from a social, psychological, financial, and convenience standpoint." Surgery does lose

effectiveness over time, but, more than two sessions per individual eye is rarely indicated because repeat surgeries are not demonstrated to provide additional benefit. [19]

2. Cataracts

A cataract is defined as any opacity of the lens. The cataract must cause a significant reduction in visual acuity or a functional impairment to be considered clinically significant. Age-related cataracts are the most common. An estimated 28.5% of people ages 65-74 had lens opacities with associated vision decrease in an NHANES study. When vision loss affects the ability to perform activities of daily life, consideration should be given to cataract extraction. There are no alternatives with similar efficacy to extraction when providers determine treatment should be pursued.[20]

3. Frozen Shoulder

There are four stages of adhesive capsulitis, reflecting a continuum of pain, freezing, frozen, and thawing of the shoulder. Primary adhesive capsulitis is expected in 2% to 5.3% of the general population. Secondary adhesive capsulitis related to diabetes mellitus and thyroid disease is expected in between 4.3% and 38%. Both conservative and surgical treatment may result in equal outcome two to three years, but surgical treatment shortens the result to several weeks.[21,22]

Mortality SLA Study Group Background

1. Gallstones

Gallstones are usually cholesterol or bilirubin material that form in the gallbladder. When gallstones block the bile ducts of the biliary tract, it can cause pain, known as biliary colic.[23] About 15% of the population, or 20 million people, in the US have gallstones.[24] Surgical

treatment (laparoscopic or open cholecystectomy) is the most common for gallstone patients, but there are nonsurgical interventions that require chronic treatment for the return of gallstones.[25]

2. Coronary Artery Disease (CAD)

CAD is characterized by plaque growth within the walls of the coronary arteries, limiting blood flow to the heart. CAD may be chronic or acute, resulting from long-term narrowing of the coronary artery or a sudden rupture of a plaque and the formation of a thrombus.[26] Over 370,000 people in the United States die from coronary heart disease annually, resulting from CAD.[27] Treatment for CAD can be lifestyle or pharmaceutical management, or patients may be treated with the placement of a stent or a bypass surgery if there are multiple narrowing arteries.[28]

Cancer Indications: Cancer is a group of related diseases characterized by division of abnormal cells that spreads into surrounding tissues. As old or damaged cells survive that should have died, or new cells form that should not, the division of the extra cells creates tumors.[29]

3. Skin Cancer

Skin cancer is the most common form of cancer in the United States, with as many as an estimated 9,500 cases diagnosed per day.[30] There are about 4 million people with skin cancer annually, where about one quarter of patients have melanoma, the skin cancer with the highest risk of death.[31]

4. Lung Cancer

There are slightly fewer than 230,000 new cases of lung cancer in the United States annually, where 85% are non-small cell lung cancer and 15% are small cell lung cancer cases.[32,33] Both types of lung cancer can be treated with chemotherapy, radiation, or surgery to

remove tumors. There are other pharmaceutical treatments, especially in advanced stages, but surgery is used in early stages of severity for small cell and non-small cell lung cancer to target removal.[34]

5. Prostate Cancer

There are approximately 166 new cases of prostate cancer diagnosed per 100,000 men each year, making it the second highest incidence for cancers among men of all ages, after skin cancer.[35] Like lung cancer, prostate cancer that has not spread outside the prostate gland can be treated with surgery (radical prostatectomy). Early stages of prostate cancer may also be treated with radiation therapy, cryotherapy, hormone therapy, chemotherapy, or watchful waiting or active surveillance.[36]

6. Colon and Rectal Cancer (colorectal cancers)

Colorectal cancers commonly begin as growths on the inner lining of the colon or rectum known as polyps. The lifetime risk of developing colon and rectal cancer are 4.49% and 4.15%, respectively. There are over 100,000 new colon cancer cases and under 45,000 new rectal cancer cases expected in 2019.[37] Surgery is the primary treatment for earlier stages of colorectal cancer but is used in patients with all stages. Other treatments for colorectal cancer include radiation, chemotherapy, biologics, and interventional radiology.[38]

7. Breast Cancer

There are expected to be over 250,000 new cases of invasive breast cancer and over 40,000 deaths from breast cancer in a year.[39] Most breast cancers are ductal cancers, beginning in the milk carrying duct. Breast cancer may also be lobular (beginning in the milk gland) or

sarcomas and lymphomas (beginning in other breast tissues).[40] Like the other cancer indications we have selected, surgery is the primary mode of treatment, especially in earlier stages, where additional treatments such as radiation or chemotherapy are used in later stages of treatment.[41]

8. Stomach (gastric) Cancer

The stomach wall is made up of 5 tissue layers. The innermost layer to the outermost layer are: mucosa (where stomach cancer begins), submucosa, muscle, subseros, and serosa.[42] There are over 20,000 cases expected in 2019, with over 11,000 deaths.[43] Treatments are similar to the other cancer indications in the mortality SLA group, including surgery, chemotherapy, radiation, immunotherapy, and targeted treatments.[44]

Chronic Falsification Study Group Background

1. Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disease in which the body's immune system attacks the joints. This creates inflammation that causes the tissue that lines the inside of joints to thicken, resulting in swelling and pain in and around the joints. RA can damage cartilage, the elastic tissue that covers the ends of bones in a joint, as well as the bones themselves. Joint damage cannot be reversed, and because it can occur early, doctors recommend early diagnosis and aggressive treatment to control RA.

For naïve patients with early, symptomatic RA, guidelines recommend disease-modifying antirheumatic drugs (DMARD) therapy in patients with low disease activity. For patients with moderate or high disease activity despite DMARD therapy, guidelines recommend treatment with a combination of DMARDs or a TNFi or a non-TNF biologic, with or without methotrexate (MTX).[45,46]

2. Psoriasis

Psoriasis causes overproduction of new skin cells and, developing plaques (plaque psoriasis) in between 80% and 90% of people living with Psoriasis. Treatment with UVB or psoralen plus UVA phototherapy is recommended for patients with moderate to severe psoriasis as well as in those who have had minimal response to topical therapy. Methotrexate (MTX), cyclosporine, and acitretin are the most commonly prescribed systemic medications for severe psoriasis in the United States. Biologics are used when traditional DMARD and light therapies are not effective.[47]

3. Psoriatic Arthritis

Psoriatic arthritis is manifested by painful, stiff and swollen joints. Like psoriasis, psoriatic arthritis symptoms flare and subside, vary from person to person, and even change locations in the same person over time. Those with very mild arthritis may require treatment only when their joints are painful and may stop therapy when they feel better. Non-steroidal anti-inflammatory drugs such as ibuprofen (Motrin or Advil) or naproxen (Aleve) are used as initial treatment. If the arthritis does not respond, disease modifying anti-rheumatic drugs may be prescribed. Disease-modifying antirheumatic drugs (DMARDs) are a varied group of medications that suppress inflammation-causing chemicals to prevent joint damage and reduce symptoms. Technically a subset of DMARDs, biologics are complex drugs that stop inflammation at the cellular level. They are usually given by injection or infusion.[48]

2.3 Results

The most common diagnosis in the QoL SLA study group dataset is cataracts (89%), followed by glaucoma (14%), and adhesive capsulitis of the shoulder (5%). Overall, 21% of the

observations were treated with SLA treatments, where SLA rate of treatment is highest in cataracts, followed by glaucoma and finally, adhesive capsulitis of the shoulder. In the mortality SLA study group, the most common diagnoses is CAD (27%), followed by skin cancer (23%), gallstones (11%), breast cancer (10%), prostate cancer (6%), colorectal (2%), lung cancer (2%), and stomach cancer (<1%). In this study group, 24% of patients received the SLA treatment across indications. The highest treatment rates (>40%) are in breast cancer, skin cancer, and gallstones. All other indications in the mortality SLA Trudy group had <10% SLA treatment rates. In the chronic study group, the most common diagnosis is rheumatoid arthritis (59%), followed by psoriasis (38%), and psoriatic arthritis (9%). The highest rate of treatment with high cost chronic treatments is in psoriatic arthritis, followed by rheumatoid arthritis, and finally, psoriasis.

RD Model Results

Table 2.2 reports the treatment effect results from the RD model for both SLA study groups and the chronic falsification group. There is a significant discontinuous increase in the QoL SLA study group, but there is no discontinuous change in prescribing for the morality SLA study group or the chronic falsification study group. **Figure 2.3** is the RD plots with 95% confidence intervals of the treatment rates represented in each bin. The SLA study group demonstrates a decreasing trend prior to the age of 65 and a significant discontinuity of increased treatment after the patients enter Medicare. Both the mortality SLA study group and the chronic falsification group demonstrate a decreasing trend that continues after the age of Medicare enrollment.

Table 2.2 – SLA Study and Chronic Falsification Group Regression Discontinuity Model Results

	Coefficient	Standard Error	P-value	95% CI
QoL Study Group	.014	.002	.000	.010, .018
Mortality Study Group	-.005	.003	.102	-.011, .001
Chronic Falsification Group	.006	.005	.241	-.004, .015

Figure 2.1a – QoL SLA Study Group SLA Treatment Rate Scatterplots

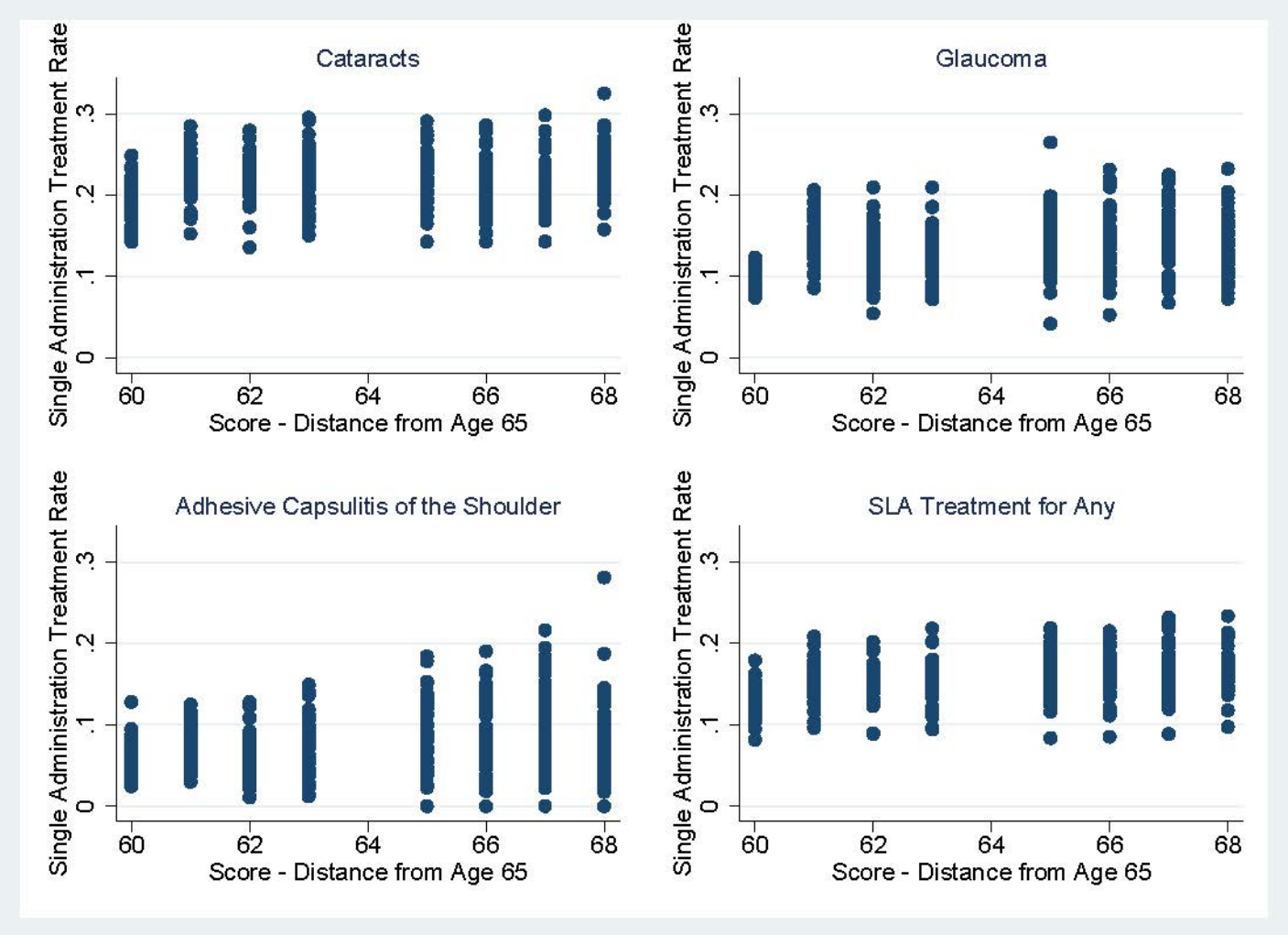
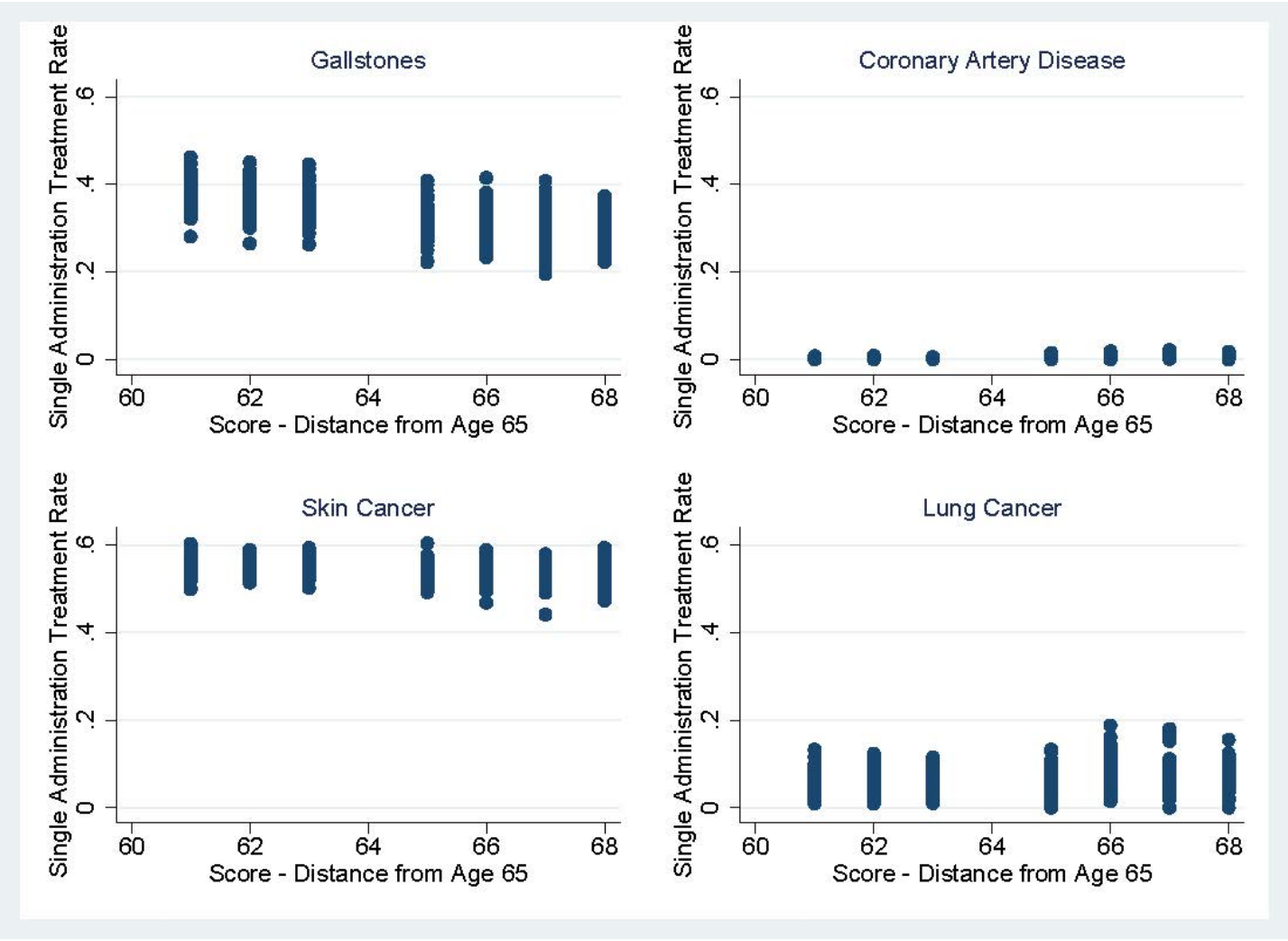
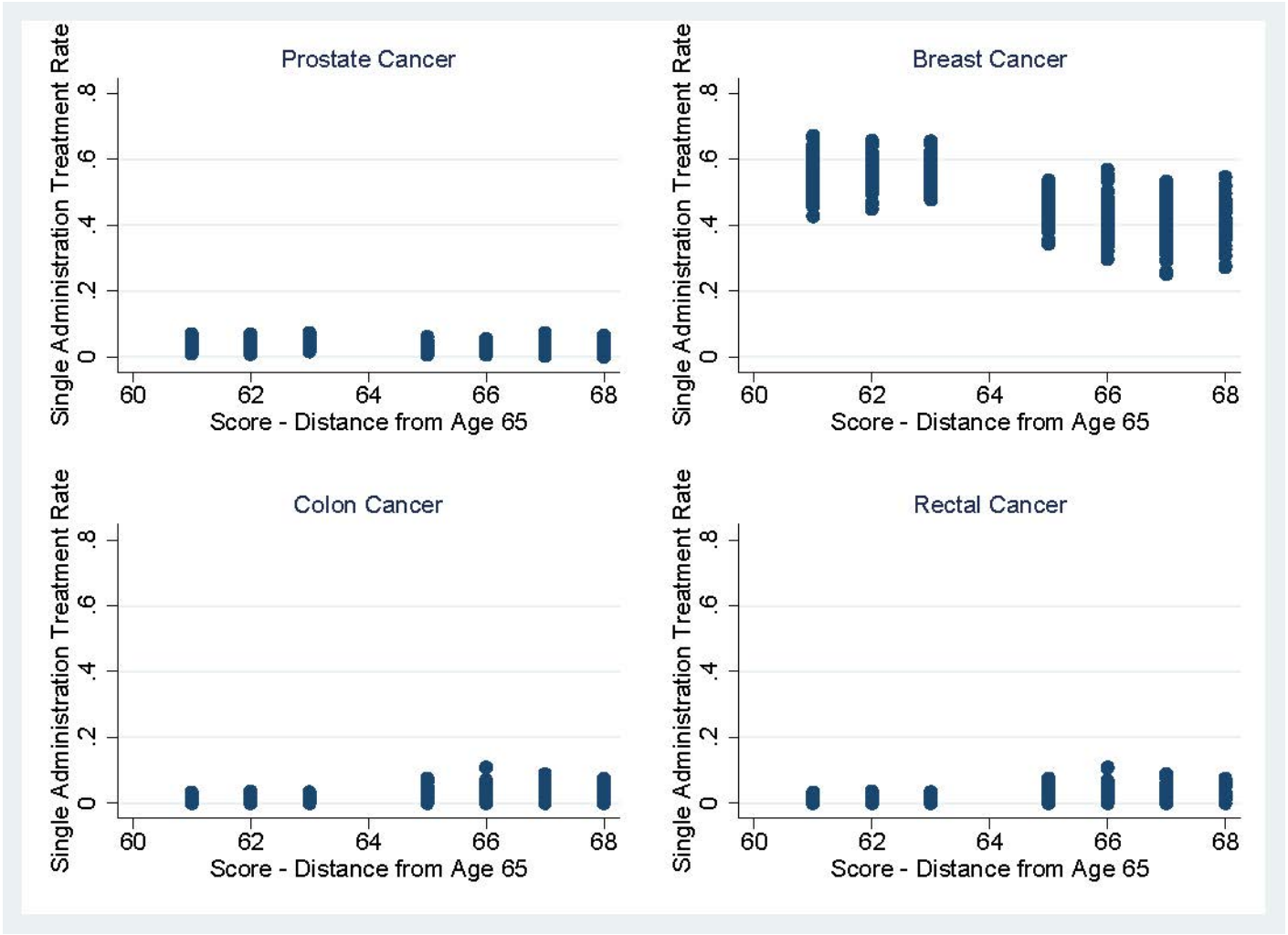


Figure 2.1a - Mortality SLA Study Group SLA Treatment Rate Scatterplots




Prostate Cancer
Breast Cancer
Colon Cancer
Rectal Cancer
Single Administration Treatment Rate
0
.2
.4
.6
.8
60
62
64
66
68
Score - Distance from Age 65

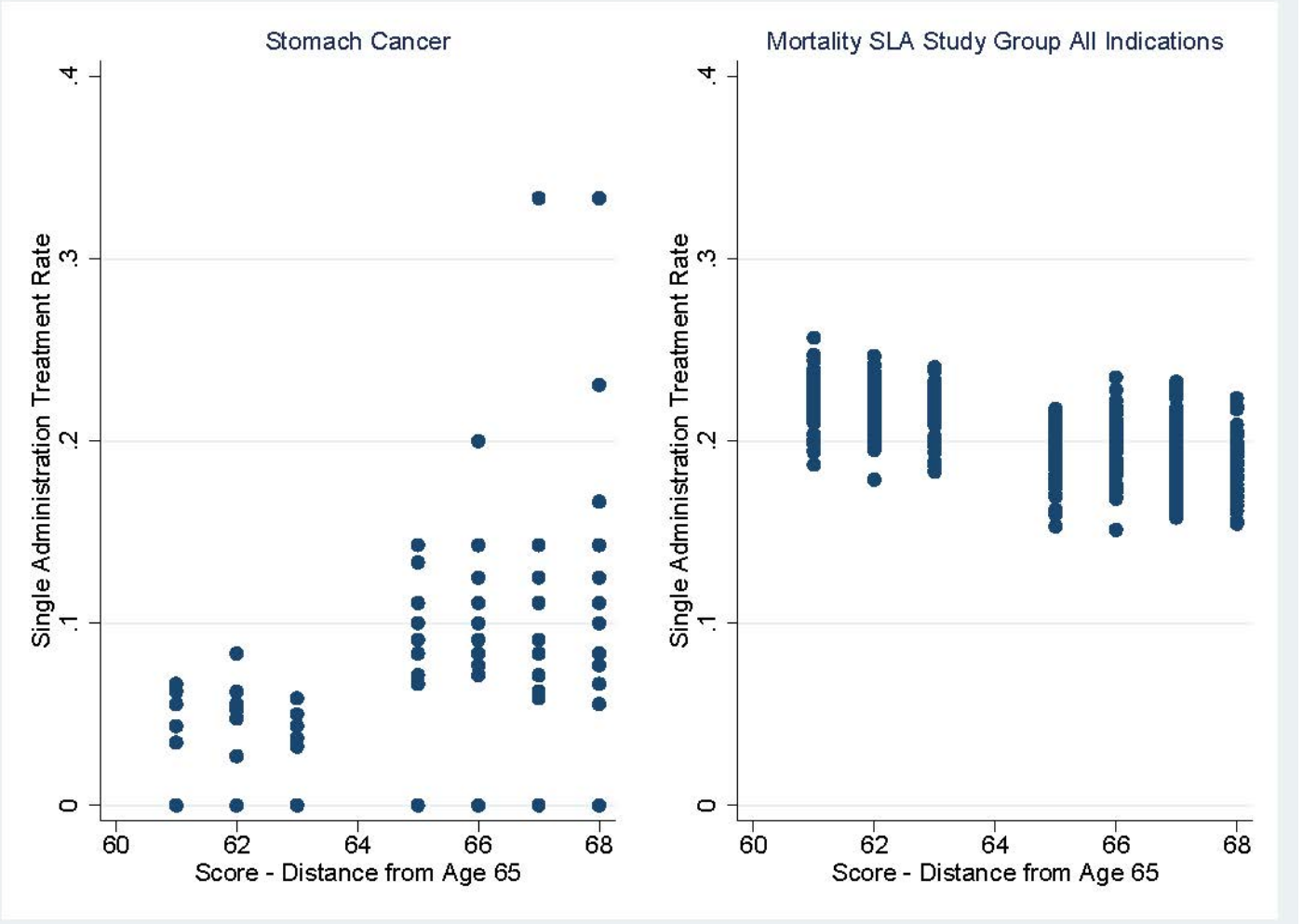

Stomach Cancer
Single Administration Treatment Rate
0
.1
.2
.3
.4
60
62
64
66
68
Score - Distance from Age 65
Mortality SLA Study Group All Indications
Single Administration Treatment Rate
0
.1
.2
.3
.4
60
62
64
66
68
Score - Distance from Age 65

Figure 2.2 – Chronic Falsification Group High Cost Treatment Rate Scatterplots

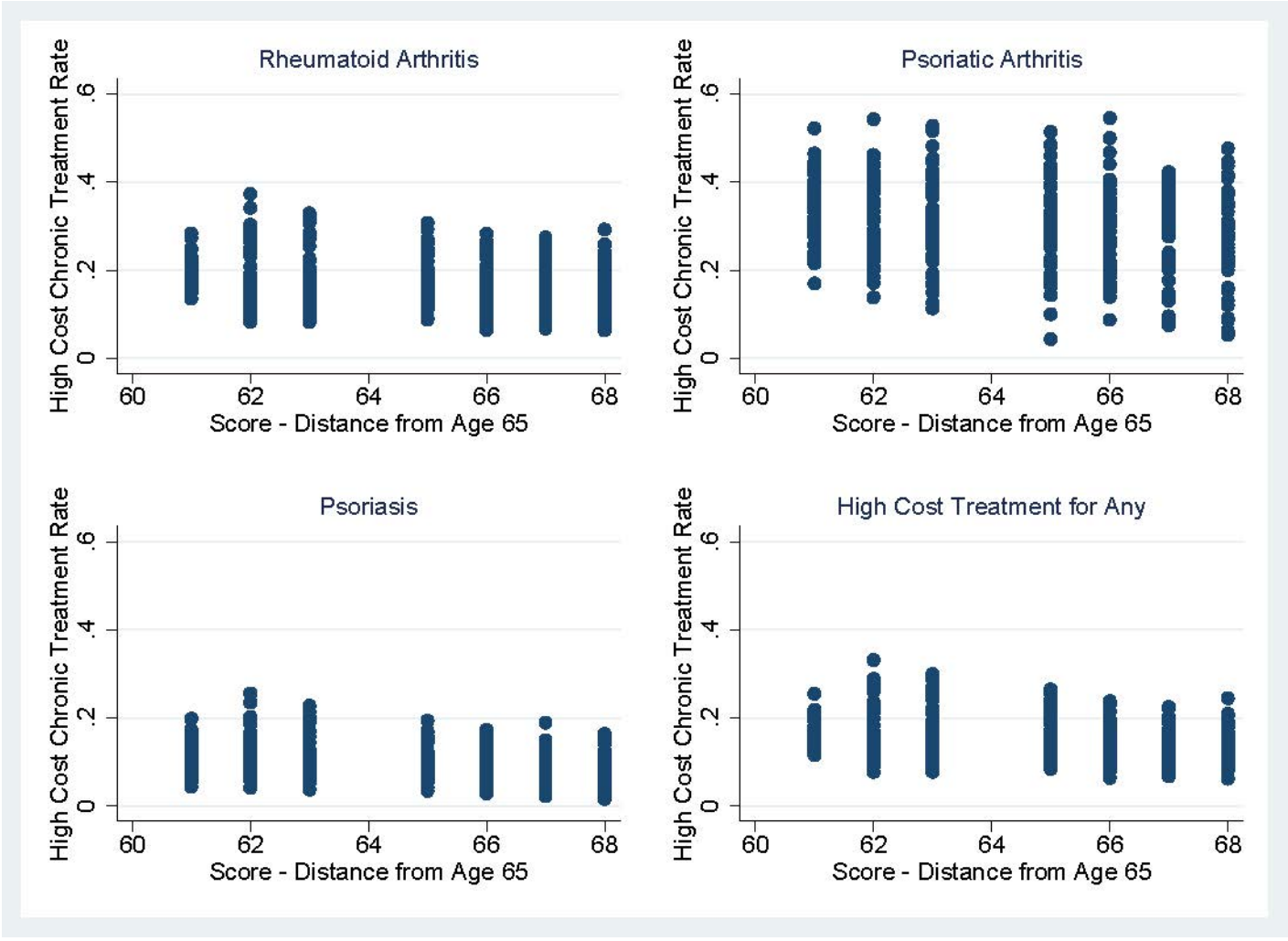
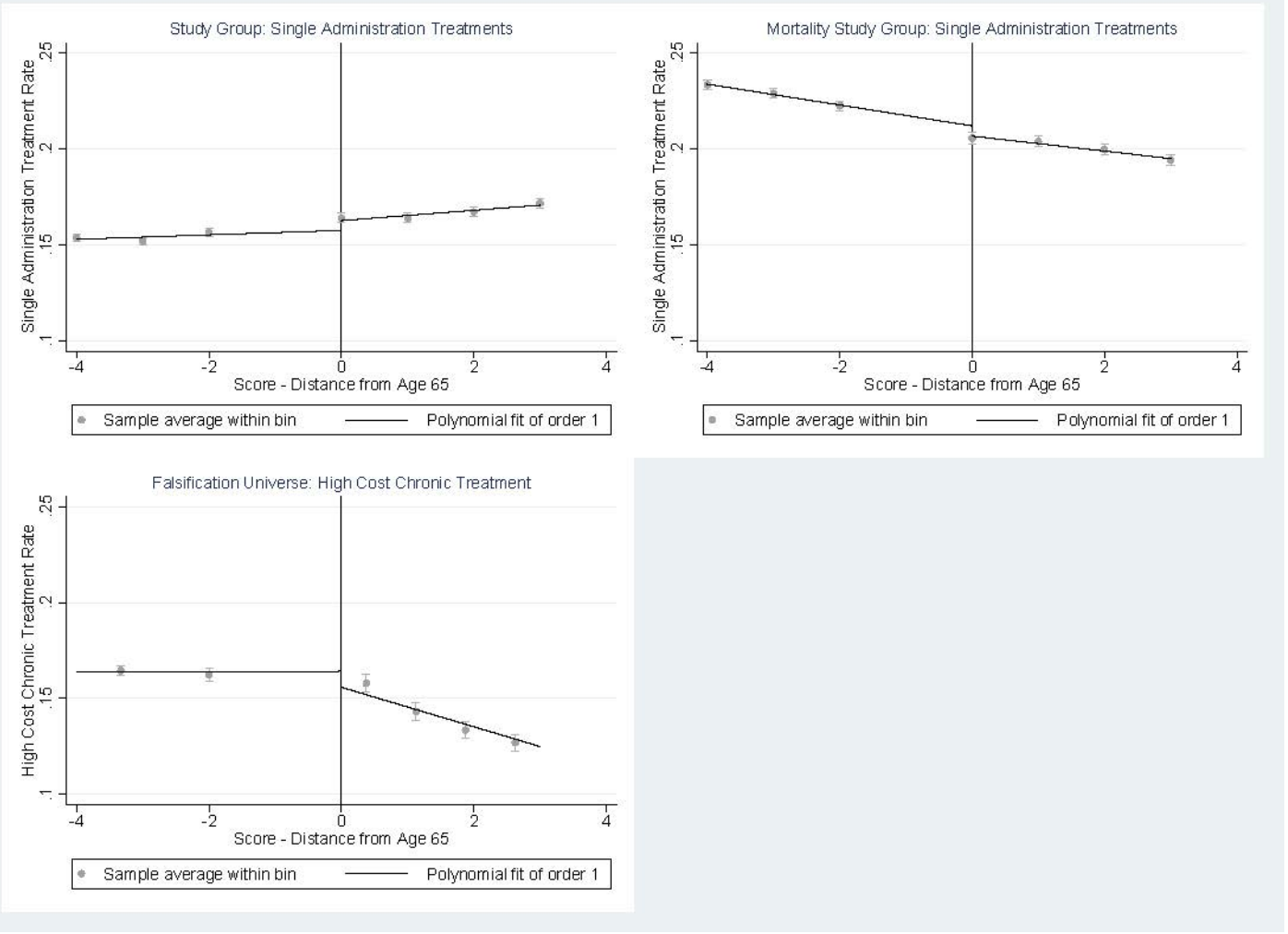


Figure 2.3 – QoL SLA, Mortality SLA, and Chronic Falsification Study Group Regression Discontinuity Results



Falsification Age

The age falsifications that tested for a discontinuity in both study groups and the chronic falsification study group at ages 52, 53, 54, 55, 63 and 66 are displayed in **Table 2.3**. In addition to falsifications around the age 65 with the dataset used for the primary RD analysis, we created a falsification dataset with older adults not yet eligible for Medicare or included in the primary dataset, including ages 48 to 58. We ran four falsification tests for discontinuities where we had four years of data on either side of the cutoff (ages 52 to 55). We included to age falsifications of the chronic group to consistently test differences between the SLA and chronic study groups. The falsifications around the age of 65 had a mix of significant and non-significant results, potentially due to proximity to the cutoff. Upon visual inspections of the data, there is a discontinuity at the age of 63 in the QoL which may be suggestive the discontinuity is not unique to the age of 65, or the difference after Medicare is influential enough in the model to remain significant two years from the cutoff in the primary analysis with the available ages to test in the data. The age falsifications in the chronic falsification study group both demonstrate the same decreasing trend, but there is a discontinuous decrease in the treatment rate at age 66.

In the dataset with claims for patients diagnosed between ages 48 and 58, there were no significant discontinuities at the p=.01 level for either the QoL SLA study group or the chronic falsification group, but there were significant discontinuities in the mortality SLA study group at the ages of 52 and 53. This is suggestive that the discontinuity found around the age of 65 is attributable to the age of Medicare enrollment in the QoL study group. The plot of the RD results for the falsifications are included in Appendix A **Figures 2.4 to 2.6**.

Table 2.3 – SLA Study Group Age Falsification Regression Discontinuity Model Results

	Coefficient	Standard Error	P-value	95% CI
QoL SLA Study Group *(original dataset)*				
Falsification Age 63	.146	.028	.000	.091, 202
Falsification Age 66	-.012	.001	.048	-.024, -.0001
QoL SLA Study Group *(ages 52 to 55)*				
Falsification Age 52	.007	.003	.036	.000, .142
Falsification Age 53	-.001	.003	.653	-.007, .005
Falsification Age 54	-.006	.002	.058	-.012, .000
Falsification Age 55	-.001	.003	.816	-.006, .004
Mortality SLA Study Group *(original dataset)*				
Falsification Age 63	-.003	.003	.309	-.009, .003
Falsification Age 66	.004	.002	.049	.000, .008
Mortality SLA Study Group *(ages 52 to 55)*				
Falsification Age 52	.008	.002	.001	.003, .013
Falsification Age 53	.005	.002	.002	.002, .009
Falsification Age 54	-.003	.002	.887	-.003, .003
Falsification Age 55	-.004	.002	.023	-.007, .000
Chronic Group *(original dataset)*				
Falsification Age 63	.177	.091	.052	-.001, .355
Falsification Age 66	-.040	.0126	.001	-.065, -.016
Chronic Group *(age 52 to 55)*				
Falsification Age 52	-.003	.003	.274	-.008, .002
Falsification Age 53	-.006	.003	.022	-.011, -.001
Falsification Age 54	-.001	.002	.703	-.001, .004
Falsification Age 55	.002	.002	.402	-.003, .007

2.4 Discussion

The discontinuity and trends in the treatment rate in the QoL study group are consistent with the hypothesized results for a group of indications where commercial plans are underfunding SLA therapies from the transference of future benefits to Medicare. The treatment trends around the cutoff are reasonably consistent with decreasing commercial investment. Basu notes that the free rider problem in the market will occur because commercial payers realize less benefit as the patient ages and is closer to exiting the market. [49] Alternatively, the lack of significant discontinuity in the mortality SLA study group suggests that payer incentives to underfund may not impact behavior in a measurable way when there are mortality consequences.

While we hypothesized that the discontinuity would be mitigated in high mortality indications because of the significant clinical implications of delaying or denying SLA treatment, the similarly decreasing trend on either side of the cutoff, with a nonsignificant decrease in the treatment rate does not provide evidence of underfunding for these indications. It is possible that the treatment window of a year is too long to detect a significant discontinuity because underfunding causes a shorter delay in treatment, or that payers do not act on the underfunding incentives because of the clinical implications, but this research suggests the difference in discontinuities and trends for the QoL and mortality study groups warrants further study for the overall potential impact of a HealthCoin currency.

The lack of a significant discontinuity in the chronic falsification group is consistent with an absence of a free rider problem where plans and patients are receiving benefits from treatments as they pay for them. The trend prior to the age of 65 was decreasing non-significantly and continues to decrease after patients become eligible for Medicare. Because the data are consistent with underfunding in the QoL SLA treatment group, the research is suggestive that future SLA treatments may face challenges in the market related to the high cost of the single administration of the product. With a greater number of SLA treatments entering the market for high disease and cost burden diseases such as oncology and hemophilia, it will be important to understand the implications of underfunding along the patient lifetime and for different disease indications. Additionally, it will be important to determine if there is measurable underfunding for SLA treatments with mortality implications in terms of delay for a shorter window than a year, or across the lifetime of patients.

The age falsifications around the ages of 63 and 66 have somewhat inconclusive results in supporting the hypothesis because the discontinuity exists at age 63 in the SLA study group.

This is indicative that further falsification tests with data from a younger cohort could fortify the robustness of the results. However, the lack of discontinuity in the QoL SLA treatment group in at the age of 66 is consistent with the hypothesis that the discontinuity is due to underfunding in the private market. Age falsifications for the chronic cost demonstrate the rate decreases discontinuously at age 66 and approaching discontinuity at age 63, but not the primary cutoff of age 65. This may suggest that the treatment rate is more consistent in the ages before and after patients enroll on Medicare than years around Medicare enrollment for the high cost chronic treatments. The second set of age falsifications in the younger group were consistent with the underfunding hypotheses because there were no significant discontinuities in either the QoL SLA study group or the chronic falsification group. There were some significant decreases in the mortality SLA group for the younger ages, which show a decrease in the treatment rate as patients age.

The evidence from the RD models is consistent with an environment where there is an underfunding of QoL SLA therapies by commercial payers as patients approach the age of 65 but not necessarily mortality SLA therapies. As previously mentioned, studies on use of all surgical and imaging services after Medicare enrollment, in studies with the same data and similar regression discontinuity methods, but not focusing on SLA therapies, showed no significant difference in the use of outpatient surgical and imaging services, despite out-of-pocket price reduction when patients entered Medicare.[50] Medicare has been shown to be more generous for patients eligible for nonurgent surgeries,[51] suggesting there is a need to do additional research to determine if this is driven by nonurgent surgeries with SLA characteristics such as the ones included in the study group. To further understand the differences between pharmaceutical and

surgical interventions we are developing an additionally study group of chronic surgical treatments for validation of the current results.

The results of this study are suggestive that further research is needed to confirm and generate evidence of the magnitude and impact of the underfunding in indications with developing SLA therapies over a patient's lifetime, and the policy potential for addressing this free rider problem for greater access to SLA therapies under the age of 65.

Limitations of the Study

The study group is limited because there are limited SLA therapies on the market today with chronic treatments of similar efficacy. The inclusion criteria of an alternative treatment with similar clinical efficacy was necessary to avoid therapeutic indications where payers are compelled by guidelines or regulations to provide one treatment over another. This limits the generalizability of the results but provided a better opportunity to understand the choice between treatments.

The SLA study group is additionally limited by the lack of pharmaceutical SLA products on the market during 2009-2015 with similar efficacy to other treatments. This study is intended to demonstrate the existence of the environment for underfunding because treatments with these properties, but a greater magnitude of cost different from the standard of care, are newly launched or in development.

The lack of a control group, requiring an RD design for this study limits the generalizability of the results for the potential underfunding that occurs in the private market at younger ages for different disease states and limits the conclusions that can be drawn in terms of causality. The results from the RD design suggest underfunding may exist in the environment,

but this study cannot determine what portion of the discontinuity is attributable to underfunding in commercial plans due to loss of future benefits for patients.

Finally, we are limited by a data source which does not include the entire Medicare population, but rather those for Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans. This database also contains predominantly fee-for-service plan data. As we noted in the methods section, this may bias have biased the results of the study because the Medicare population has greater average affluence than the remaining portion of patients covered on Medicare. [52] The falsification universes of other treatments and in ages where the Medicare switch is not expected provide evidence that the discontinuity found in the QoL SLA study group were not an artifact of the Medicare supplement population compared to including the entire population. Although we are still able to do a RD design based on the continuity of plan enrollment, we are limited in the generalizability. Additionally, we are unable to detect severity of disease through the claims database. Although we expect that differences in severity are continuous around the age of 65 and would not account for a discontinuity, selecting patients with severities of indicated treatments would increase the specificity and accuracy of the magnitude of the discontinuity around the age of 65. The Marketscan claims databases are also based on a large convenience sample; because the sample is not random, it may contain biases or fail to generalize well to other populations.

2.5 Conclusion

The evidence is consistent with underfunding of QoL SLA treatments by commercial payers before the cutoff age of 65, but the data and generalizability are limited and the data did not demonstrate an underfunding within a year of diagnosis for the mortality SLA study group. The falsification group demonstrated evidence that the discontinuity was not found in chronic

pharmaceutical treatments related to QoL, potentially suggesting underfunding of QoL SLA treatments for commercial payers relative to Medicare, but not the selected chronic treatments.

Based on the initial results in this study, there is a need to further test the robustness of the results of the RD model from the QoL SLA therapy study group result, especially as a greater number of high cost pharmaceutical SLA therapies enter the market. Additionally, this research captured a snapshot of the potential underfunding, but focusing on the impact of underfunding incentives over a patient lifetime will demonstrate the magnitude of the implications. Specifically, research should focus in developing SLA markets with high budget impact for payers because they pose a higher saliency risk and incentive for underfunding. Further, research should focus on the potential magnitude of underfunding in QoL SLA markets and whether there is any underfunding evidence at different ages or related to delay of treatment for mortality SLA therapies.

2.6 Appendix

APPENDIX A: Age Falsification Graphs

Figure 2.4 - All Age 63 and 66 Falsification Regression Discontinuity Results

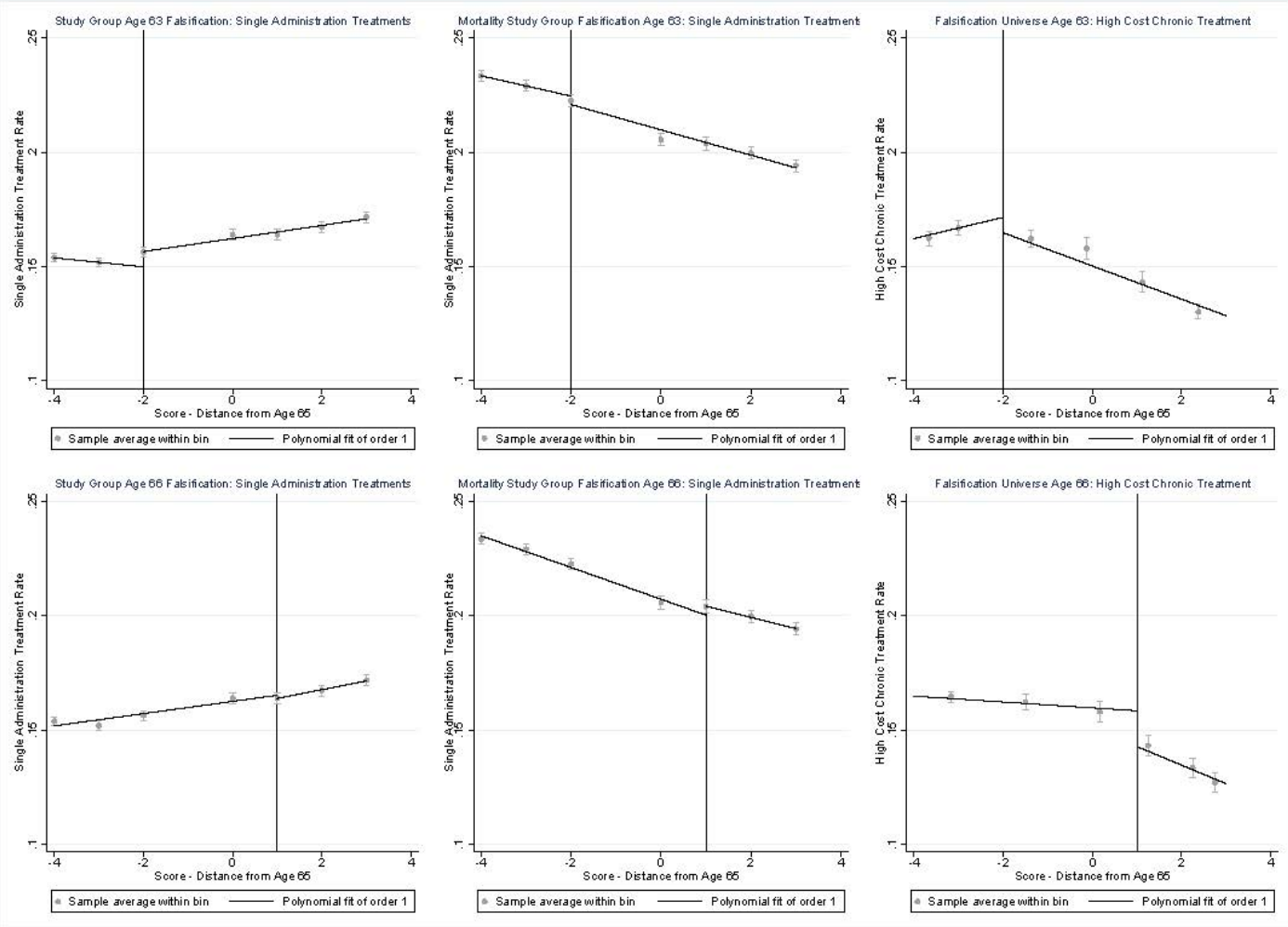


Figure 2.5a – QoL SLA Study Group Age Falsification Regression Discontinuity Results (Younger Cohort)

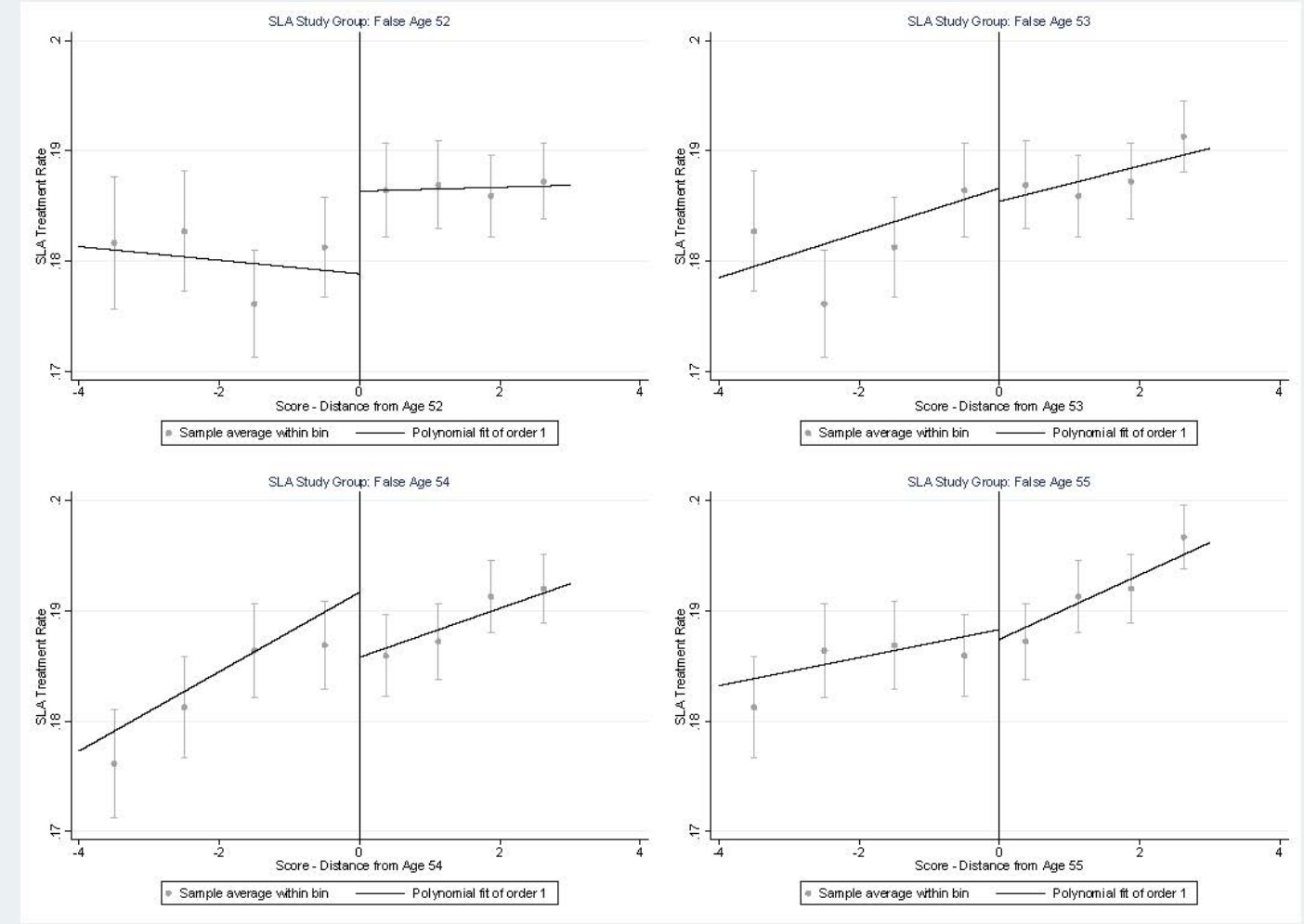


Figure 2.5b – Mortality SLA Study Group Age Falsification Regression Discontinuity Results (Younger Cohort)

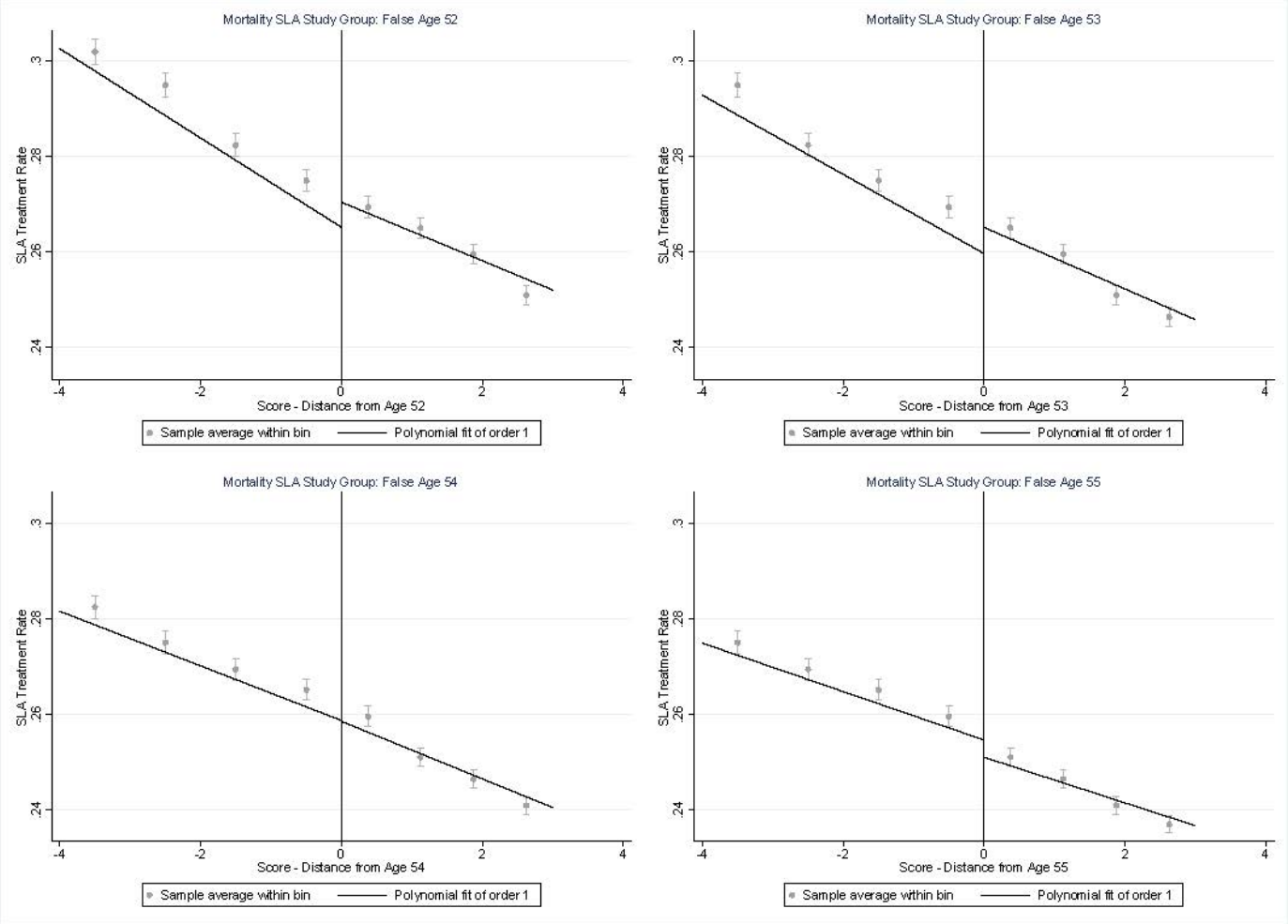
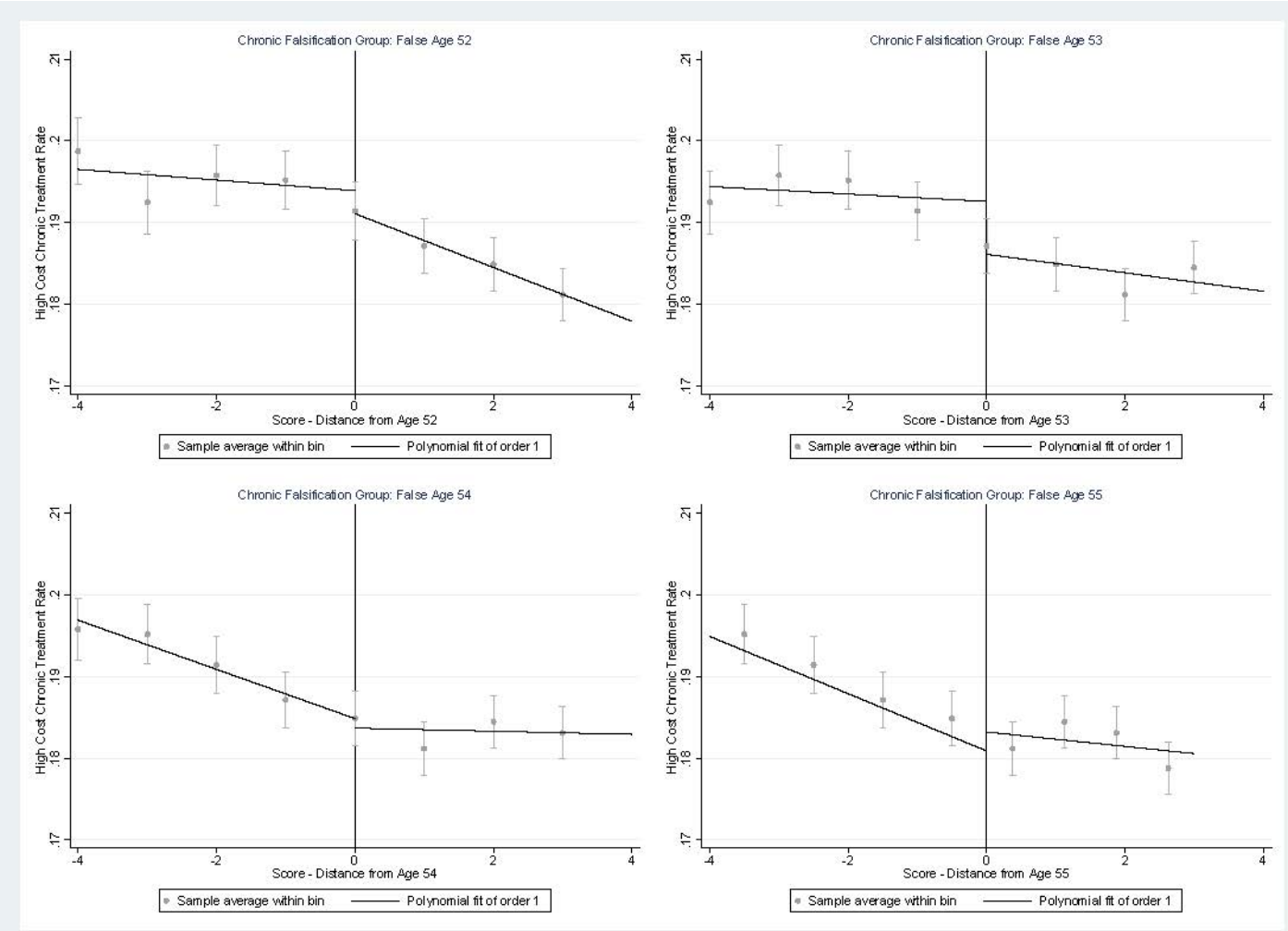


Figure 2.6 - Chronic Falsification Group Age Falsification Regression Discontinuity Results (Younger Cohort)



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Chapter 3. DISTRIBUTION OF COSTS AND BENEFITS OF CHIMERIC ANTIGEN RECEPTOR T-CELL (CAR T) THERAPIES FOR REFRACTORY AND RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA (r/r ALL) PEDIATRIC PATIENTS AND THE POTENTIAL ROLE FOR HEALTHCOIN

3.1 Introduction

Medical breakthroughs or single administration high efficacy treatments that can substantially alleviate the burden of a disease for patients are becoming a reality. In 2013, Gilead launched Sovaldi, a product with a response rate of 90% and had an initial list price of $1,000 per pill, or $84,000 for a 12-week course of therapy.[1] Similarly, in 2017, chimeric antigen receptor T-cell (CAR T) therapy from Novartis ($475,000 list price) was approved for twice relapsed or refractory acute lymphocytic leukemia (r/r ALL) in patients under 25 years old.[2] The treatment reengineers a patient's T-cells, infusing the reprogrammed cells into the patient.[3] There are numerous gene therapies in development that are aimed at providing cures or significant disease-modifying improvement in chronic and/or high mortality conditions such as hemophilia, heart failure, rare pediatric genetic diseases, and oncology.[4]

It is natural to expect that such innovations will continue to have high prices and pose affordability challenges. The role of access to credit markets for assisting in affordability has been discussed in the literature.[5,6] However, even with access to credit markets, the segmented US health insurance market poses an additional challenge in financing these innovations. Cures are applied quickly, but the benefits are realized over the lifetime of the patients, across many insurers. Consequently, a free-rider problem forms that may lead to underfunding of cures and therapies with high long-term efficacy in the private health insurance market.[7] We examine private payer incentives only because we assume public payers (e.g., Medicaid) will have similar

incentives to pay as the Medicare program (i.e., from an overall health sector perspective), with aligned incentives and purpose.

A potential solution to this free-rider problem is a new financial instrument called the "HealthCoin", a currency issued by Medicare to distribute treatment cost over the patient's lifetime, depreciating as the patient ages by the benefit realized since treatment. The purpose of this tradable instrument is to correct the underfunding in the market that occurs from lack of private payer exposure to the lifetime cost of the patient. Following the methods illustrated for developing such an instrument for a hypothetical cure for Type 2 diabetes,[8] this paper illustrates the first application of HealthCoin to a launched single administration and high efficacy therapy.

New CAR T treatments are potential candidates for a HealthCoin market, based on cost, administration, and efficacy. The first CAR T therapy has a 50% complete remission in patients under age 25 with twice r/r ALL at 12 months, previously with an overall survival rate of 38.8% after stem cell transplantation after one year.[9,10] Payers have created coverage policies for CAR T therapy, but initial uptake of the product is lower than was forecasted, despite a growing number of treatment centers.[11] Reports of innovative outcomes-based contracts, funding through reinsurance for some state Medicaid programs, and a missed forecast for CAR T therapy demonstrate a potential growing need to address underfunding.[12] As more gene and cell therapy products enter the market, payers will experience an increasing budget impact and a need to address free-rider problem stemming from the distribution of cost and benefits over the patient lifetime.

Twice r/r ALL

This analysis focuses on the feasibility and impact of using HealthCoin to finance CAR T therapy. The median age of diagnosis for ALL is 15.[13] ALL starts from lymphocytes in the bone marrow. Leukemia cells invade the blood and can spread to other organs. ALL is characterized by its origins in the blood cells, spreading to organs, rapid progression, and mortality within a few months if untreated.[14] CAR T therapy is indicated for B-cell precursor ALL, in which the cancer originates in the B lymphocyte subtype of the white blood cell, accounting to 80% to 85% of ALL cases in children.[15] In 2010, the cost of Leukemia was $5.44 billion for the US, the sixth highest among cancer types in the US,[16] with refractory patients accruing $15,507 greater costs from hospitalizations than those who are newly diagnosed in a year.[17] Additionally, long-term survival is 15.7% less than the general population on average.[18,19] Relapsed and refractory patients had 20.3% survival after 5 years before CAR T therapies launched.[20]

To evaluate the feasibility and impact of HealthCoin, we focus on an incident, single age, population patients that would potentially be eligible for CAR T therapy treatment. There were an estimated 5,970 new cases of ALL in 2017, with 56.1% of cases occurring before the age of 20 and an additional 10.1% before the age of 35.[21] For the purpose of illustration in this paper, we will develop our model for a cohort of patients at the median diagnosis age of 15 years. The FDA labeled indication for CAR T therapy is “refractory or in second or later relapse”, making the number of eligible patients somewhat uncertain. Estimates from the literature suggest 15% to 20% of children diagnosed with ALL will relapse or be refractory.[22,23,24,25] Finally, B-cell patients comprise 80% to 85% of patients with childhood ALL.[26] Based on these estimates, we will assume 140 incident cases of refractory or relapsed ALL in a year who will be CAR T therapy eligible and 20.1 that will be eligible for CAR T at age 15. [27]

3.2 Methods

Theoretical Setup

Unlike earlier work on evaluating HealthCoin for a potential diabetes cure (Basu et al, 2016), the ALL market is differentiated because patients are young. Beyond just the siloed perspective of Medicare or a private payer, an overall health sector perspective demonstrates the value of HealthCoin. It is assumed that this overall health sector decision maker aims to maximize the net monetary benefit (NMBs) in the population and is aware of her marginal willingness to pay for a year of quality-adjusted life year (denoted by λ). Net monetary benefits are given as QALYs* λ – Costs.

Let the total incremental net monetary benefits between using CAR T versus not using CAR T, *without considering the cost of CAR T therapy,* among the cohort of patients diagnosed with refractory or relapsed B-cell precursor ALL at age 15 be denoted by INMB. This total represents the net present value of the gains and losses in QALYs and healthcare costs (without the cost of CAR T therapy) that are distributed over the lifetime of the patients. Also, let the INMB be decomposed into two parts:

$$INMB = INMB_{PRIVATE} + INMB_{PUBLIC}$$

where $INMB_{PRIVATE}$ reflects the net present value of the portion of the discounted incremental costs and benefits that accrue through age 64 while they are covered under a private payer. Similarly, $INMB_{PUBLIC}$ reflects the net present value of the portion of the discounted incremental costs and benefits that accrue after age 64 while they will be covered under a public payer.

Medicare has no financial incentive to issue a HealthCoin because without the CAR T therapy applied earlier in life, it does not face any burden of treating ALL patient as these

patients would die before reaching the age of 64. However, from an overall health sector perspective, this is not an appropriate lens to value health. Failure to incentivize investment in earlier life may lead to opportunity losses in term of lives lost, that will remain unaccounted for if we take the narrow perspective of Medicare that only cares for beneficiaries who remain alive and enroll in Medicare at ager 65. Therefore, we refer to the post-65 INMB as that accruing to a public payer whose objective aligns with the overall health care sector.

For the healthcare sector perspective, investment in CAR T therapy is worth it if

$$P_{CAR\ T} \leq INMB \quad (1)$$

In the model, we assume that Medicare is taking a health sector perspective to evaluate the decision to engage in HealthCoin. Patients with r/r ALL that live to the age of 65 are not likely to be treated with CAR T by Medicare because patients who live to be 65 will be in remission from the cancer. However, Medicare is funded through the Hospital Insurance (HI) Trust Fund and Supplementary Medical Insurance (SMI) Trust Fund, which are funded through taxes, investments, and congressionally appropriated funds.[28] From the public agency perspective, a healthier society provides a more robust source for future agency funding. Additionally, Medicare is administered through CMS, a federal agency with the goal of improving the lives of their patients, which we interpret to include potential patients if they reach the age of 65. For these reasons, we consider that Medicare is also willing to invest in HealthCoin if the INMB is positive after the price of CAR T. For the private payer's perspective, it is worth investing in CAR T only if

$$P_{CAR\ T} \geq INMB_{PRIVATE} \quad (2)$$

An investment in CAR T is made by the private payer, the public payer enjoys value worth up to $INMB_{PUBLIC}$ without herself investing anything.

It is easy to see here that if condition in (2) is met, there is no need for a HealthCoin, as a private payer has the incentive to invest in CAR T itself. HealthCoin would be most useful when

$$INMB \geq P_{CAR\ T} \geq INMB_{PRIVATE} \quad (3)$$

That is, investing in CAR T is worthwhile from a healthcare sector perspective but not from a private payer perspective. This highlights the free-rider issue that arises due to the fragmented insurance system in the US. In fact, such a situation is most likely if manufacturers price their product based on INMB rather than $INMB_{PRIVATE}$.

The key insight for HealthCoin comes from the fact that the public payer can incentivize the private payer to invest in the CAR T therapy, even when condition (3) holds, by issuing a bond, a HealthCoin, that promises a certain sum of money to the private payer, should a patient remain alive and enter the public payer rolls at Age 65. The public payer can afford to issue this bond as they gain $INMB_{PUBLIC}$ with every investment in CAR T that the private payer makes. In the Basu et. al description of the HealthCoin conditions, the paper set up the condition that the public payer's will require HealthCoin to satisfy:[29]

$$HealthCoin \leq INMB_{PUBLIC}$$

In this model, we do not consider this condition to be necessary because Medicare will not have the opportunity to provide CAR T to patients at the age of 65 because those patients will be in remission. We assume that Medicare makes decisions based on the overall health sector perspective and does not need to consider the public INMB separately from the overall INMB. From the perspective of the private payer, however, since not all patients who have

received CAR T therapy would reach the age of 65, an adjustment needs to the acceptable value of a HealthCoin. Specifically, under condition (3), the private payer would invest in CAR T if

$$P_{CAR\ T} \leq INMB_{PRIVATE} + HealthCoin*S$$

Or

$$HealthCoin \geq (P_{CAR\ T} - INMB_{PRIVATE})/S$$

where S is the proportion of patients who would survive till age 65 after receiving CAR T therapy (Basu et al. 2016). Therefore, for a HealthCoin to exist, it must be valued such that:

$$INMB_{PUBLIC} \geq HealthCoin \geq (P_{CAR\ T} - INMB_{PRIVATE})/S \qquad (4)$$

We now try to estimate $INMB_{PUBLIC}$, $INMB_{PRIVATE}$, S and study conditions under which a HealthCoin would be feasible given the current price of CAR T. We also study the implication of having a HealthCoin versus not when condition (3) holds.

Empirical Analysis for Valuation of HealthCoin for CAR T

Like the Basu (2016) diabetes paper, the analysis for HealthCoin in the CAR T market consists of four steps with all calculations done using a 3% annual discount rate.

1. We develop a probabilistic model to estimate the health care costs and quality adjusted life-years associated with an incident of cohort of twice r/r ALL patients aged 15 years.
    - The CDC estimates 5,970 cases of ALL in 2017, 56.1% of which occur below the age of 20.[30] The rate of b-cell cases and subsequently rates for refractory and relapse rates were applied to a single year of incidence based on a linear incidence in the <20 age range from assumed from the CDC above. This gave an estimate of 20.1 cases per year of patients aged 15 eligible for the CAR T treatment.

- The MEPS (2011-2015) dataset was used to estimate annual age group-specific healthcare costs for the general population. Each age group included 10 years to ensure adequate sample of ALL patients. Additionally, a cohort of patients with unspecified cell leukemia from MEPS were used to estimate the annual cost of the 15-year-old cohort of incident patients. MEPS aggregates ICD codes with rare incidence to avoid identification of patients, and r/r ALL patients are included in this combined group. Four years of cost data were used to pool an adequate number of unspecified cell leukemia. Cost of the product is all in the first year of treatment, for $475,000 per patient.[31]
- Mortality for the treated incident population was estimated from the most recent CAR T data for r/r patients, demonstrating 50% event-free survival at one year of treatment. Patients with event free survival at 1 year were assumed not to relapse and pediatric ALL long-term survival mortality rates applied throughout their lifetime after treatment. The 50% of patients with events were assumed to have the same 5-year mortality as the non-CAR T treated incident control. Estimates from literature of long-term survival for pediatric ALL were used to estimate survival rates after 5 years.[32] Appendix A demonstrates the ALL cohort survival curves and Appendix B has greater detail on the creation of the survival curves.
- The product of the differences in life years are calculated for the treated and non-treated incident 15-year-old cohort and the age-specific QoL (3 age groups over the patient lifetime) are used to determine the difference in QALYs with and without CAR T treatment.[33]

- Cost-effectiveness thresholds are applied to the 3% discounted total of QALYs to determine the total benefit to the incident cohort over the 70 years. Alternatively, lifetime costs are calculated by summing the age-specific costs with a 3% discount over the 70 years.

2. We decompose the estimates from the cohort that accrue over the non-elderly years ($INMB_{PRIVATE}$) versus those that accrue in the elderly Medicare age (65+) ($INMB_{PUBLIC}$). We estimate the proportion of patients who would survive to Medicare age (S) if they are administered CAR T therapy. We compare the returns from the time on the private plan to the price to see if the private payer would have the incentive to pay for the CAR T therapy without the introduction of HealthCoin, and at which cost-effectiveness threshold per QALY.
3. We then estimated the potential range of values for HealthCoin that would clear the market between Medicare and private payers, incentivizing greater investment in the CAR T therapy.
4. Using the midpoint of each potential range, and the maximum of the current $475,000, we demonstrate consequences of the HealthCoin policy for Medicare, private payers, and the manufacturer for CAR T therapy in an existing medical breakthrough market.

3.3 Results

Table 3.1 displays the estimated net benefit for all stakeholders in providing CAR T for r/r ALL until the age of 85 for a single cohort of 15-year-old incident patients at different cost-effectiveness thresholds per QALY (ranging from $25K to $500K). Lifetime expected value differences driven by cost and QALY gained for patients range from $273,527 for $25,000/QALY valuation to $4,785,917 at a $500,000/QALY valuation. As the valuation of the QALY increases, CAR T therapy has a higher value over the patient lifetime because the value of gain in QALYs increase while price and cost remain consistent. CAR T has a positive net

monetary benefit at valuations of a QALY of across all valuations of QALY before price of the CAR T is considered.

Table 3.1 - Expected per patient returns from curing B-cell precursor relapsed or refractory ALL in the 15-year-old incident cohort in 2017 until the age of 85

No CAR T		CAR T		Difference (CAR T - No CAR T)	
E(QALY)	E(Cost)	E(QALY)	E(Cost)	Δ E(QALY)	Δ E(Cost)
4.36	$179,105	13.86	$143,072	9.50	-$36,032
			Threshold/QALY		Incremental NMB
			@$25,000		$273,527
			@$50,000		$511,021
			@$100,000		$986,009
			@$200,000		$1,935,986
			@$300,000		$2,885,963
			@$400,000		$3,835,940
			@$500,000		$4,785,917

Table 3.2 estimates the Medicare and private payer NMB for an average 15-year-old patient over their lifetime. Private payers are incentivized to purchase CAR T therapy in the for values of $100,000 or more per QALY without the presence of HealthCoin in the market. HealthCoin may be priced to incentivize private payers to invest in the CAR T therapy while the patient is in the private market where QALY gain is valued for $50,000 or less. An estimated 56.9% of CAR T therapy treated ALL patients would reach age 65 (S) with HealthCoin. Based on the assumptions made in the methods section, Medicare is willing to enter the market for a cost-effectiveness threshold of $50,000/QALY because the overall INMB is positive, despite a negative return expected for Medicare if the price of the CAR T is considered. At a valuation of $25,000 the overall lifetime net value of introducing CAR T is negative in the market for both private and public payer, implying the price of CAR T is too high for HealthCoin to work. Medicare cannot offer HealthCoin valued enough for private payers to accept because the overall market would not have a net benefit. Alternatively, private payers are not willing to accept a low

enough HealthCoin price for Medicare because the private return would remain negative, even after the introduction of HealthCoin to the market.

Table 3.2 - Returns to private and public payers in CAR T for pediatric B-cell precursor relapsed and refractory ALL among a 15-year-old incident cohort by a private payer until the age of 85

Per patient Returns during the entire period					
Difference: (CAR T - No CAR T)		Threshold/QALY	INMB (EINMB NE Lifetime)	Price	Net Value
Δ E(QALY)	Δ E(Cost)				
9.50	-$36,032	@$25,000	$273,527	$475,000	-$201,473
9.50	-$36,032	@$50,000	$511,021	$475,000	$36,021
9.50	-$36,032	@$100,000	$986,009	$475,000	$511,009
9.50	-$36,032	@$200,000	$1,935,986	$475,000	$1,460,986
9.50	-$36,032	@$300,000	$2,885,963	$475,000	$2,410,963
9.50	-$36,032	@$400,000	$3,835,940	$475,000	$3,360,940
9.50	-$36,032	@$500,000	$4,785,917	$475,000	$4,310,917
Per patient Returns during the non-elderly period (under age 65)					
Difference: (CAR T - No CAR T)		Threshold/QALY	INMB (EINMB NE Private)	Price	Net Value
Δ E(QALY)	Δ E(Cost)				
8.319	-$45,145	@$25,000	$253,113	$475,000	-$221,887
8.319	-$45,145	@$50,000	$461,081	$475,000	-$13,919
8.319	-$45,145	@$100,000	$877,018	$475,000	$402,018
8.319	-$45,145	@$200,000	$1,708,891	$475,000	$1,233,891
8.319	-$45,145	@$300,000	$2,540,764	$475,000	$2,065,764
8.319	-$45,145	@$400,000	$3,372,637	$475,000	$2,897,637
8.319	-$45,145	@$500,000	$4,204,510	$475,000	$3,729,510
Per patient Returns during the elderly period for those turning 65 (age 65 to 85)					
Difference: (CAR T - No CAR T)		Threshold/QALY	(INMB)	Price	Net Value
Δ E(QALY)	Δ E(Cost)				
1.18	$9,113	@$25,000	$20,413	$475,000	-$454,587
1.18	$9,113	@$50,000	$49,939	$475,000	-$425,061
1.18	$9,113	@$100,000	$108,991	$475,000	-$366,009
1.18	$9,113	@$200,000	$227,095	$475,000	-$247,905
1.18	$9,113	@$300,000	$345,199	$475,000	-$129,801
1.18	$9,113	@$400,000	$463,302	$475,000	-$11,698
1.18	$9,113	@$500,000	$581,406	$475,000	$106,406

The midpoint range of the HealthCoin was used to illustrate the impact of the proposed currency/bond on stakeholders in the market. For the list price of $475,000 and QALY valuation of $50,000, the midpoint is $249,731. Because the cost is constant and set for the treatment in this case, payers are willing to accept a lower HealthCoin price when the value per QALY higher, unlike the Basu (2016) model where the price of the cure was a function of value of QALYs gained. We use these midpoint estimates to demonstrate the private and public implications of HealthCoin at the $50,000 threshold for the $475,000 list price.

Table 3.3 - HealthCoin Valuation

Threshold/QALY	Price	(EINMB NE Private)	Price - (EINMB NE Private)/S	HealthCoin Low	HealthCoin High	Midrange Value for HealthCoin
@$25,000	$475,000	$253,113	$389,971			
@$50,000	$475,000	$461,081	$24,462	$24,462	$475,000	$249,731
@$100,000	$475,000	$877,018	-$706,556			
@$200,000	$475,000	$1,708,891	-$2,168,592			
@$300,000	$475,000	$2,540,764	-$3,630,628			
@$400,000	$475,000	$3,372,637	-$5,092,664			
@$500,000	$475,000	$4,204,510	-$6,554,699			

Note: S was estimated from the proportions of incident patients with b-cell precursor relapsed and refractory ALL who survive if they are treated with CAR T = .569.

Without CAR T therapy, 3.1 of the 20.1 average number of expected cases for incident 15-year-olds will live to 65. With CAR T therapy 11.4 patients are expected to live to 65. Because there are no 15-year-old patients on Medicare they will not fund the CAR T therapy prior to introducing HealthCoin, and private payers are not incentivized to pay for CAR T therapy when valuing a QALY at, or below, $50,000. When the valuation is above $50,000/QALY private payers pay to administer the CAR T treatment without the intervention of HealthCoin because the expected $INMB_{PRIVATE}$ is greater than the price, creating a net positive monetary benefit for private payers.

Table 3.4 - Population returns to different stakeholders with and without a HealthCoin at the threshold of $50,000/QALY

Without HealthCoin							
Incident cases (#)	CAR T applied at incidence	Private payer payment for CAR T	Total population return for private payer cure	No. of patients who reach age 65	Cure applied at age 65	Public payer cost	Total population return for public payer
20.1	0	$0	$0	3.1	0	$0	$0
With HealthCoin							
Incident cases (#)	CAR T applied at incidence	Private payer payment for CAR T	Total population return for private payer cure	No. of patients who reach age 65	Cure applied at age 65	Public payer cost	Total population return for public payer
20.1	20.1	$6,689,780	$9,265,442	11.4	0	$2,855,354	$493,788

When valuation of a QALY gained is $50,000 private payers are incentivized to pay for CAR T therapy because they expect to receive payment for HealthCoin they are issued when CAR T therapy is purchased upon the patients' entrance into Medicare. The investment in CAR T becomes net positive for the private payers with HealthCoin. Private payers pay $475,000 to the manufacturer, which is a total of $6.7 million for CAR T therapy after receipt of the HealthCoin. Total population benefit for the private payer is expected to be about $9.3 million. The total population will gain benefits from CAR T therapy of $0.5 million while insured by Medicare after the age of 65.

3.4 Discussion

HealthCoin will be preferable for any private payer who values QALY at $50,000 in the market. Private payers are adequately incentivized to pay for CAR T therapy if they value a QALY at $100,000 or more. Payers who value CAR T less than $50,000 will not invest because the return in investment will not be positive before the age of 65, even with HealthCoin. Because

the cure rate is high and patients are given CAR T at age 15, accruing benefits for 70 years when surviving, private payers have incentive to enter the market at reasonable cost per QALY values, compared to stated values of cost per QALY of orphan oncology indications in the literature.[34] Unlike the previous model for diabetes,[35] there is not a pareto improvement in this market because Medicare will incur an overall cost from implementing HealthCoin. However, taking the perspective that Medicare will benefit from a healthy and more robust population, and that CMS is interested in the overall health sector perspective, we assume that Medicare will still engage in HealthCoin for the overall health sector benefit. Medicare would not pay for the CAR T population because this population would be in remission by the time of reaching Medicare if they live to the age of 65, and the products are indicated for patients under the age of 65. Medicare is willing to engage in this market only if they take a health sector perspective. From a perspective where Medicare is only interested in an overall cost benefit and improving the life of patients currently enrolled, this market will not be feasible for HealthCoin because the expected INMB after the price of CAR T, for Medicare, is negative.

In small disease states, small plans or self-insured employers may have a member with r/r ALL eligible for CAR T therapy, and not expect to have another one, previously given CAR T therapy or otherwise, for an uncertain duration of time after that plan member leaves. This model assumes a single payer perspective for private payers under the age of 65. Without HealthCoin, small payers may make decisions for coverage based on the amount of time they expect the patient to be on their plan, which is significantly less time than the entire time the patient is in the market before Medicare. Coverage decisions will likely be made on a case by case basis more often. In this case, payers would have less incentive to enter the market before HealthCoin

because the expected impact to the plan has greater uncertainty. This potentially creates a need for HealthCoin for small private payers where larger payers may have the incentive to pay.

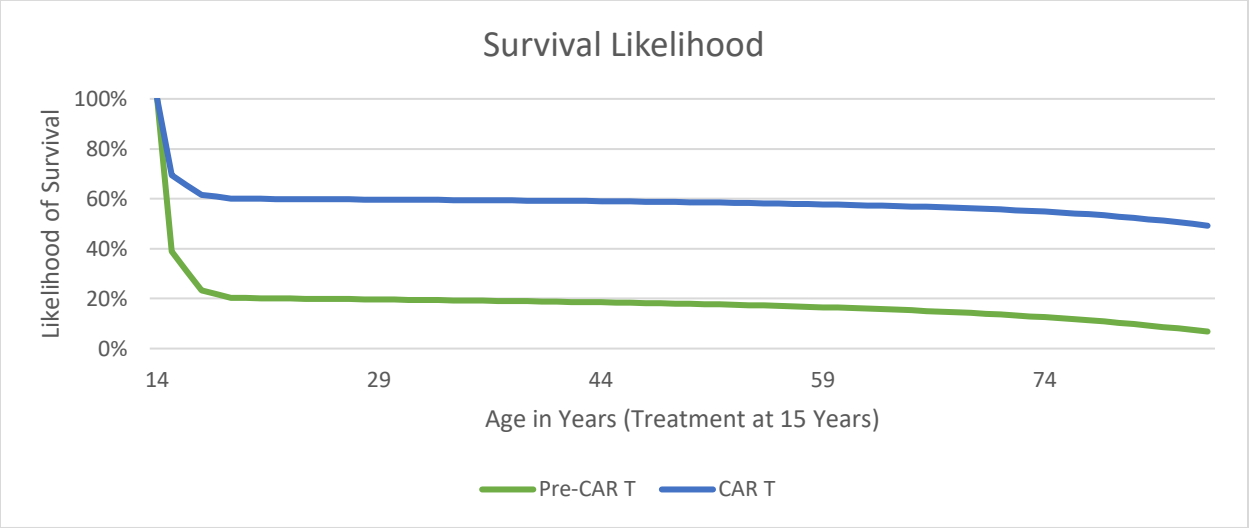
The primary limitation of the analyses is the limited survival data for CAR T, compared to that standard of care (i.e., clinical trial data and long-term survival for pediatric ALL patients). The MEPS does not directly identify r/r ALL patients or provide age of diagnosis for anonymity in rare indications.

3.5 Conclusion

HealthCoin will benefit the market if the valuation is $50,000/QALY, but this is a market where many private payers will be incentivized to purchase CAR T without the assistance of a HealthCoin of the cost-effectiveness threshold is higher than $50,000/QALY. Medicare is willing to engage in HealthCoin because it will benefit the health sector, despite an overall cost for Medicare and lack of pareto improvement across stakeholders. HealthCoin would benefit payers with a $50,000/QALY valuation or potentially payers with a greater valuation than $50,000 but believe there is high uncertainty around the number of treated patients that will be on the plan and length of time with the plan. Future research should explore the implications of HealthCoin under different plan assumptions and for upcoming cell and gene therapies with similar market characteristics to the CAR T treatments.

3.6 Appendix

Appendix A: Figure 3.1 - Survival Curve of r/r ALL Patients (Pre/Post-CAR T)



Appendix B: Cohort Size and Survival Estimates

General population: The overall survival of the general population was calculated using the life tables published in the. The age-specific population size estimates for 2017 from the U.S. Census 2010 provided the number of 15-year-olds in the general population for the base year in the model. Each subsequent year in the model, the population was reduced by the number of 15-year-olds expected to die. The life table age-specific probability of dying from the National Vital Statistics Report of 2014 was multiplied by the surviving number in the population from the previous year to calculate the reduction in population for each year of the model.

Pre-CAR T population: The CDC estimates 5,970 new cases of ALL in 2017, 56.1% of which occur below the age of 20. The model estimates 167.45 cases of ALL in the 15-year-old-cohort (5,970*56.1%/20). The rate of b-cell precursor (80%[36]) cases and subsequently rates for refractory and relapse rates (15%[37]) were applied for a final estimate of 20.095 cases eligible for CAR T among a single 15-year-old cohort. To estimate the survival of the eligible patients prior to CAR T, 1 (38%), 3 (23.2%), and 5 (20.3%) year survival for pediatric patients with r/r B-Cell ALL after stem cell transplantation were applied to the cohort of ~20.1 cases. The 2nd and 4th year survival rates were estimated as averages of the preceding and following years. The remaining 66 years in the model were calculated using the general survival life tables with a linearly distributed reduction of survival by 15.7% across all years, based on the long-term survival of pediatric acute lymphocytic leukemia patients.[38]

Post-CAR T population: The number of cases in the incident population of the model is the same for the pre/post-CAR T ALL populations. The ELIANA clinical trial demonstrated 12-month event free survival for 50% of patients. For the 50% of patients with an event in the first year, the model uses the same survival curve as the pre-CAR T population. The 50% of patients

without an event have the same survival as the general population with an additional 15.7% reduction in survival distributed across all years after treatment.

Appendix C: Cost Estimates in the Model

Cost Curves are estimated as 10-year means of total expenditures from the MEPS dataset. One ALL outlier from the 25 to 34 (annual average including the outlier: $124,219). The first two age groups were combined for the ALL group in the subsequent sensitivity analyses that required a younger cohort because of the small sample size in the MEPS data.

Table 3.5 - Cost Assumptions for r/r ALL and the General Population by Age

	ALL	General
15 to 24	$4,460	$1,645
25 to 35	$60,158	$2,361
35 to 44	$25,898	$2,816
45 to 54	$25,664	$4,339
55 to 64	$37,245	$6,766
65 to 74	$24,420	$8,460
75 +	$19,335	$10,807

Appendix D: Age Sensitivity Analysis Tables (5-year-old Cohort)

Table 3.6 - Expected per patient returns from curing B-cell precursor relapsed or refractory ALL in the 5-year-old incident cohort in 2017 until the age of 85					
No CAR T		CAR T		Difference (CAR T - No CAR T)	
E(QALY)	E(Cost)	E(QALY)	E(Cost)	Δ E(QALY)	Δ E(Cost)
4.60	$67,199	14.43	$67,832	9.84	$632
			Threshold/QALY		Incremental NMB
			@$25,000		$245,301
			@$50,000		$491,234
			@$100,000		$983,101
			@$200,000		$1,966,834
			@$300,000		$2,950,566
			@$400,000		$3,934,299
			@$500,000		$4,918,032

Appendix D: Age Sensitivity Analysis Tables (5-year-old Cohort)

Table 3.7 - Returns to private and public payers in CAR T for pediatric B-cell precursor relapsed and refractory ALL among a 5-year-old incident cohort by a private payer until the age of 85

Per patient Returns during the entire period					
Difference: (CAR T - No CAR T)		Threshold/QALY	INMB (EINMB NE Lifetime)	Price	Net Value
Δ E(QALY)	Δ E(Cost)				
9.84	$632	@$25,000	$245,301	$475,000	-$229,699
9.84	$632	@$50,000	$491,234	$475,000	$16,234
9.84	$632	@$100,000	$983,101	$475,000	$508,101
9.84	$632	@$200,000	$1,966,834	$475,000	$1,491,834
9.84	$632	@$300,000	$2,950,566	$475,000	$2,475,566
9.84	$632	@$400,000	$3,934,299	$475,000	$3,459,299
9.84	$632	@$500,000	$4,918,032	$475,000	$4,443,032
Per patient Returns during the non-elderly period (under age 65)					
Difference: (CAR T - No CAR T)		Threshold/QALY	INMB (EINMB NE Private)	Price	Net Value
Δ E(QALY)	Δ E(Cost)				
8.957	-$4,127	@$25,000	$228,062	$475,000	-$246,938
8.957	-$4,127	@$50,000	$451,997	$475,000	-$23,003
8.957	-$4,127	@$100,000	$899,868	$475,000	$424,868
8.957	-$4,127	@$200,000	$1,795,608	$475,000	$1,320,608
8.957	-$4,127	@$300,000	$2,691,348	$475,000	$2,216,348
8.957	-$4,127	@$400,000	$3,587,088	$475,000	$3,112,088
8.957	-$4,127	@$500,000	$4,482,829	$475,000	$4,007,829
Per patient Returns during the elderly period for those turning 65 (age 65 to 85)					
Difference: (CAR T - No CAR T)		Threshold/QALY	(INMB)	Price	Net Value
Δ E(QALY)	Δ E(Cost)				
0.88	$4,760	@$25,000	$17,239	$475,000	-$457,761
0.88	$4,760	@$50,000	$39,237	$475,000	-$435,763
0.88	$4,760	@$100,000	$83,233	$475,000	-$391,767
0.88	$4,760	@$200,000	$171,226	$475,000	-$303,774
0.88	$4,760	@$300,000	$259,218	$475,000	-$215,782
0.88	$4,760	@$400,000	$347,211	$475,000	-$127,789
0.88	$4,760	@$500,000	$435,204	$475,000	-$39,796

Appendix D: Age Sensitivity Analysis Tables (5-year-old Cohort)

Table 3.8 - HealthCoin Valuation

Threshold/QALY	Price	(EINMB NE Private)	Price - (EINMB NE Private)/S	HealthCoin Low	HealthCoin High	Midrange Value for HealthCoin
@$25,000	$475,000	$228,062	$434,411			
@$50,000	$475,000	$451,997	$40,466	$40,466	$475,000	$257,733
@$100,000	$475,000	$899,868	-$747,425			
@$200,000	$475,000	$1,795,608	-$2,323,207			
@$300,000	$475,000	$2,691,348	-$3,898,989			
@$400,000	$475,000	$3,587,088	-$5,474,771			
@$500,000	$475,000	$4,482,829	-$7,050,552			

Note: S was estimated from the proportions of incident patients with b-cell precursor relapsed and refractory ALL who survive if they are treated with CAR T = .5684.

Table 3.9 - Population returns to different stakeholders with and without a HealthCoin at the threshold of $50,000/QALY among a 5-year old cohort

Without HealthCoin							
Incident cases (#)	CAR T applied at incidence	Private payer payment for CAR T	Total population return for private payer cure	No. of patients who reach age 65	Cure applied at age 65	Public payer cost	Total population return for public payer
20.1	0	$0	$0	3.0	0	$0	$0
With HealthCoin							
Incident cases (#)	CAR T applied at incidence	Private payer payment for CAR T	Total population return for private payer cure	No. of patients who reach age 65	Cure applied at age 65	Public payer cost	Total population return for public payer
20.1	20.1	$6,601,090	$9,082,898	11.4	0	$2,944,045	$368,649

Appendix E: Age Sensitivity Analysis Tables (25-year-old Cohort)

Table 3.10 - Expected per patient returns from curing B-cell precursor relapsed or refractory ALL in the 25-year-old incident cohort in 2017 until the age of 85

No CAR T		CAR T		CAR T - No CAR T	
E(QALY)	E(Cost)	E(QALY)	E(Cost)	Δ E(QALY)	Δ E(Cost)
4.06	$253,839	13.09	$189,414	9.03	-$64,426
			Threshold/QALY		Incremental NMB
			@$25,000		$290,287
			@$50,000		$516,148
			@$100,000		$967,870
			@$200,000		$1,871,314
			@$300,000		$2,774,758
			@$400,000		$3,678,202
			@$500,000		$4,581,646

Appendix E: Age Sensitivity Analysis Tables (25-year-old Cohort)

Table 3.11 - Returns to private and public payers in CAR T for pediatric B-cell precursor relapsed and refractory ALL among a 25-year-old incident cohort by a private payer until the age of 85

Per patient Returns during the entire period					
Difference: (CAR T - No CAR T)		Threshold/QALY	INMB (EINMB NE Lifetime)	Price	Net Value
Δ E(QALY)	Δ E(Cost)				
9.03	-$64,426	@$25,000	$290,287	$475,000	-$184,713
9.03	-$64,426	@$50,000	$516,148	$475,000	$41,148
9.03	-$64,426	@$100,000	$967,870	$475,000	$492,870
9.03	-$64,426	@$200,000	$1,871,314	$475,000	$1,396,314
9.03	-$64,426	@$300,000	$2,774,758	$475,000	$2,299,758
9.03	-$64,426	@$400,000	$3,678,202	$475,000	$3,203,202
9.03	-$64,426	@$500,000	$4,581,646	$475,000	$4,106,646
Per patient Returns during the non-elderly period (under age 65)					
Difference: (CAR T - No CAR T)		Threshold/QALY	INMB (EINMB NE Private)	Price	Net Value
Δ E(QALY)	Δ E(Cost)				
7.451	-$76,524	@$25,000	$262,802	$475,000	-$212,198
7.451	-$76,524	@$50,000	$449,080	$475,000	-$25,920
7.451	-$76,524	@$100,000	$821,637	$475,000	$346,637
7.451	-$76,524	@$200,000	$1,566,750	$475,000	$1,091,750
7.451	-$76,524	@$300,000	$2,311,863	$475,000	$1,836,863
7.451	-$76,524	@$400,000	$3,056,976	$475,000	$2,581,976
7.451	-$76,524	@$500,000	$3,802,089	$475,000	$3,327,089
Per patient Returns during the elderly period for those turning 65 (age 65 to 85)					
Difference: (CAR T - No CAR T)		Threshold/QALY	(INMB)	Price	Net Value
Δ E(QALY)	Δ E(Cost)				
1.58	$12,098	@$25,000	$27,484	$475,000	-$447,516
1.58	$12,098	@$50,000	$67,067	$475,000	-$407,933
1.58	$12,098	@$100,000	$146,233	$475,000	-$328,767
1.58	$12,098	@$200,000	$304,564	$475,000	-$170,436
1.58	$12,098	@$300,000	$462,895	$475,000	-$12,105
1.58	$12,098	@$400,000	$621,226	$475,000	$146,226
1.58	$12,098	@$500,000	$779,557	$475,000	$304,557

Appendix E: Age Sensitivity Analysis Tables (25-year-old Cohort)

Table 3.12 - HealthCoin Valuation

Cost-Effectiveness Threshold	Price	(EINMB NE Private)	Price - (EINMB NE Private)/S	HealthCoin Low	HealthCoin High	Midrange Value for HealthCoin
@$25,000	$475,000	$262,802	$372,193			
@$50,000	$475,000	$449,080	$45,463	$45,463	$475,000	$260,231
@$100,000	$475,000	$821,637	-$607,998			
@$200,000	$475,000	$1,566,750	-$1,914,920			
@$300,000	$475,000	$2,311,863	-$3,221,841			
@$400,000	$475,000	$3,056,976	-$4,528,763			
@$500,000	$475,000	$3,802,089	-$5,835,684			

Note: S was estimated from the proportions of incident patients with b-cell precursor relapsed and refractory ALL who survive if they are treated with CAR T = .571.

Table 3.13 - Population returns to different stakeholders with and without a HealthCoin at the threshold of $50,000/QALY among an incident 25-year-old cohort

Without HealthCoin

Incident cases (#)	CAR T applied at incidence	Private payer payment for CAR T	Total population return for private payer cure	No. of patients who reach age 65	Cure applied at age 65	Public payer cost	Total population return for public payer
20.1	0	$0	$0	3.1	0	$0	$0

With HealthCoin

Incident cases (#)	CAR T applied at incidence	Private payer payment for CAR T	Total population return for private payer cure	No. of patients who reach age 65	Cure applied at age 65	Public payer cost	Total population return for public payer
20.1	20.1	$6,563,732	$9,024,281	11.5	0	$2,981,403	$659,478

3.7 References

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Chapter 4. THE DISTRIBUTION OF HEALTH CARE COSTS AND BENEFITS OF GENE THERAPIES IN DEVELOPMENT FOR AN ENTIRE INCIDENT COHORT OF PATIENTS DIAGNOSED WITH MODERATE AND SEVERE HEMOPHILIA A AND B OVER THEIR LIFETIMES AND THE POTENTIAL ROLE OF HEALTHCOIN

4.1 Introduction

The launch of high cost cell and gene therapies for oncological indications, gene associated retinal dystrophy, and spinal muscular atrophy since 2017 has generated private and public payer concern around the implications of single/limited administration (SLA) therapies with lifetime benefits.[1] As a greater number of SLA therapies enter the market, it will be increasingly important to understand the impact of payer incentives for these products. Basu et. al discuss the free rider incentives that drive potential underfunding of single administration cures.[2] The gene and cell therapies entering the market and in development often effectively behave as cures for a portion of patients, but uncertainty remains concerning rate and durability of efficacy for each newly developed treatment.

There are several gene therapies in development for patients with hemophilia A and hemophilia B that demonstrate about 90% efficacy, varying slightly by each trial and treatment, in reducing bleeds for hemophilia patients after administration.[3] BioMarin and Spark pharmaceuticals are testing gene therapies that increase Factor VIII production and treat hemophilia A, while Pfizer and UniQure are doing the same for gene therapies to increase Factor IX production and treat hemophilia B.[4] Clinical trials to date have been for severe or moderate/severe and severe adult patients, but there is uncertainty if the gene therapies will ultimately target a larger hemophilia population in the market. Factor activity is restored to normal or near normal levels in clinical trials to date, while annualized bleeds have been reduced

by 90% or more in the first two years after administration of the gene therapy.[5] The prospect of gene therapy for patients with Hemophilia has been met with excitement from the clinical community but concern over the potential price of products in early clinical development.[6,7]

Gene therapies for hemophilia are expected to have a high price because of their potential to increase quality of life, reduce future costs from hospitalizations and bleeds, and the shift in the treatment paradigm from chronic management to a single treatment.[8] Patients are typically diagnosed with hemophilia A or B in the first few years of life[9], and while current clinical trials are focused in adult patients, after a market for gene therapy matures, patients will likely be eligible in childhood, and conservatively in adolescence or early adulthood. In this case, private commercial payers will be subject to the underfunding incentives of SLA therapy markets, expecting to pay for a treatment that will benefit for other payers Medicare once the patient reaches the age of 65.

A potential solution to this free-rider problem is to develop a currency, "HealthCoin", issued by Medicare to distribute the cost of the cure over the lifetime in the patient. HealthCoin depreciates and distributes cost over all payers during a patient's lifetime, with a Medicare (i.e., government) guarantee to purchase HealthCoin from payers upon Medicare enrollment. The purpose of this tradable instrument is to correct any underfunding in the market that results from transfer of benefits realized when patients switch payers.

Hemophilia

Hemophilia A is the most common form of hemophilia, caused by deficiency of the clotting protein, Factor VIII (FVIII). Hemophilia B is a deficiency of the clotting protein Factor IX (FIX). There are about 400 Hemophilia A births and 100 Hemophilia B births per year.[10]

Hemophilia is primarily inherited from parents, carried through the X chromosome, but about one third of cases occur from spontaneous mutation of the gene.[11] Whereas normal FVIII and FIX range from 50% to 100%, levels below 50% are classified as hemophilia. Mild hemophilia A and B are classified as 6% to 49% of their respective factors, moderate cases have between 1% and 5% of the clinical threshold, and patients with severe cases have less than 1% of necessary factor proteins.[12]

Patients with hemophilia experience many symptoms related to their lack of clotting factor, including joint bleeds, cranial bleeds, external bleeds, bruising, and a historically higher rate of infections.[13] Today, patients manage hemophilia with prophylaxis or on-demand treatments. Prophylaxis, regular infusions of clotting factor concentrates to prevent bleeding, and treatment to stop bleeding (on demand) are the primary methods of management for hemophilia today.[14]

Hemophilia Gene Therapies

There are gene therapies for hemophilia in all stages of development, but this research uses the reported results of the four in the latest stage of development in the market to generate assumptions about the potential impact of hemophilia gene therapies.

Table 4.1 - Gene Therapies for Hemophilia A and B Currently in Late Stage Development by the First Quarter of 2019				
Manufacturer	**Product**	**Target Population**	**Status**	**Summary**
UniQure	AMT-061	Moderate/Severe and Severe Hemophilia B	Enrolling Phase III Pivotal Trial	Mean of 38% FIX after 12 and 16 weeks with one infusion No patient in the study has experienced a material loss of FIX activity, reported any bleeding events or required any infusions of FIX replacement therapy
Pfizer	Fidanacogene elaparvovec	Moderate/Severe and Severe Hemophilia B	Phase III	Based on individual participant history for the year prior to the study, the overall ABR for all 15 participants was reduced by 98% (calculated based on data after week four; 97% based on data after infusion)
BioMarin	valoctocogene roxaparvovec	Severe Hemophilia A	Phase III	6e13 vg/kg cohort: 97% mean ABR reduction, with no spontaneous bleeds and elimination of all bleeds in target joints in the second year; 96% reduction in mean FVIII usage through week 104 4e13 vg/kg cohort: 92% reduction in ABR, Mean Factor VIII usage decreased by 98% at a year
Spark	SPK-8011	Moderate/Severe and Severe Hemophilia A	Entering Phase III	The 12 participants had a 94% reduction in bleeds and a 95% reduction in FVIII infusions, beginning four weeks after vector infusion, across 9.7 years of cumulative follow up data

4.2 Methods

Theoretical Setup

The theoretical setup for the HealthCoin financial instrument was first explored for the diabetes market (Basu et al, 2016). The conceptualization of HealthCoin follows the structure of the Diabetes paper, demonstrating the potential market in an orphan chronic indication where patients are diagnosed in the first few years of life. In this framework, it is assumed that this overall health sector decision maker aims to decisions to maximize the net monetary benefit

(NMBs) in the population and is aware of its marginal willingness to pay for a year of quality-adjusted life year (denoted by λ). Net monetary benefits are given as quality adjusted life years (QALY)s* λ – Costs.

The total incremental net monetary benefits between using gene therapy versus not using gene therapy, *without considering the cost of gene therapy,* among the cohort of patient diagnosed with moderate/severe or severe hemophilia A or B is denoted by INMB. This total represents the net present value of the gains and losses in QALYs and healthcare costs (without the cost of gene therapy) that are distributed over the lifetime of the patients. INMB is decomposed into two parts:

$$INMB = INMB_{PRIVATE} + INMB_{PUBLIC}$$

where $INMB_{PRIVATE}$ reflects the net present value of the portion of the discounted incremental costs and benefits that accrue through age 64 while they are covered under a private payer. Similarly, $INMB_{PUBLIC}$ reflects the net present value of the portion of the discounted incremental costs and benefits that accrue after age 64 while they will be covered under a public payer.

Medicare has an incentive to provide gene therapy for patients when the patient reaches the age of 65 and enters public insurance for the rest of the patient's lifetime. However, failure to incentivize investment earlier in life will result in lost lives that remain unaccounted for if we take the narrow perspective of enrollees in Medicare. Therefore, we refer to the post-65 INMB as that accruing to a public payer whose objective *aligns with improvement in the overall health care sector*. Medicare is funded through the Hospital Insurance (HI) Trust Fund and Supplementary Medical Insurance (SMI) Trust Fund, which are funded through taxes, investments, and congressionally appropriated funds.[15] From the public agency perspective, a

healthier society provides a more robust source for future agency funding. Additionally, Medicare is administered through CMS, a federal agency with the goal of improving the lives of their patients, which we interpret to include potential patients if they reach the age of 65. For these reasons, we consider that Medicare is also willing to invest in HealthCoin if the INMB is positive after the price of gene therapy. For the healthcare sector perspective, investment in gene therapy is worth it if

$$P_{GeneTherapy} \leq INMB \quad (1)$$

For the private payer's perspective, it is worth investing in gene therapy only if

$$P_{GeneTherapy} \leq INMB_{PRIVATE} \quad (2)$$

An investment in gene therapy is made by the private payer, the public payer enjoys value worth up to $INMB_{PUBLIC}$ without financial investment.

It is easy to see here that if condition in (2) is met, there is no need for a HealthCoin, as a private payer itself the incentive to invest in gene therapy. HealthCoin would be most useful when

$$INMB \geq P_{GeneTherapy} \geq INMB_{PRIVATE} \quad (3)$$

That is investing in gene therapy is worthwhile from a healthcare sector perspective but not from a private payer perspective. This highlights the free-rider issue that arises due to the fragmented insurance system in the US. In fact, such a situation is most likely if manufacturers price their product based on INMB rather than $INMB_{PRIVATE}$. We discuss why this may be the case in the US in the discussion section.

The key insight for HealthCoin comes from the fact that the public payer can incentivize the private payer to invest in the gene therapy, even when condition (3) holds, by issuing a bond,

a HealthCoin, that promises a certain sum of money to the private payer, should a patient remain alive and enter Medicare at age 65. The public payer can afford to issue this bond as they gain $INMB_{PUBLIC}$ with every investment in gene therapy that the private payer makes. From the public payer's perspective, the value of this HealthCoin must satisfy:

$$HealthCoin \leq INMB_{PUBLIC}$$

We do not consider this condition to be strictly necessary because we expect that Medicare will take a health sector perspective and have interest in funding HealthCoin to improve population health. However, this condition is required for pareto improvement across the market. We assume that Medicare makes decisions based on the overall health sector perspective and does not need to consider the public INMB separately from the overall INMB. From the perspective of the private payer, however, since not all patients who have received gene therapy would reach the age of 65, an adjustment needs to the acceptable value of a HealthCoin. Specifically, under condition (3), the private payer would invest in gene therapy if

$$P_{GeneTherapy} \leq INMB_{PRIVATE} + HealthCoin*S$$

Or

$$HealthCoin \geq (P_{GeneTherapy} - INMB_{PRIVATE})/S$$

where S is the proportion of patients who would survive till age 65 after receiving gene therapy (Basu et al. 2016). Therefore, for a HealthCoin to exist, it must be valued such that:

$$INMB_{PUBLIC} \geq HealthCoin \geq (P_{GeneTherapy} - INMB_{PRIVATE})/S \quad (4)$$

We now try to estimate $INMB_{PUBLIC}$, $INMB_{PRIVATE}$, S and study conditions under which a HealthCoin would be feasible given the current price of gene therapy. We also study the implication of having a HealthCoin versus not when condition (3) holds.

Because gene therapies are in development for hemophilia and there is significant uncertainty around the durability and populations who can expect treatment in a mature market for the products, this study presents a probabilistic model with deterministic sensitivity analyses. To run a sensitivity analysis in the probabilistic model, we kept the primary model assumptions constant, except the variable of interest.

Table 4.2 –Sensitivity Variables and Cases for Analysis

Variable	Primary Model	Sensitivity
Treatment Age	After 18 years	Treatment at age 1 tested for earliest potential future treatments
Efficacy	90% cost reduction and QoL improvement relative to the general population	From 90% to 50% over the lifetime of the patient
Price	$250 thousand per patient	Additionally tested: $500 thousand, $1 million, and $1.5 million

Empirical Analysis for Valuation of HealthCoin for Hemophilia Gene Therapy

Like the Basu (2016) diabetes paper, the analysis for HealthCoin in the gene therapy market consists of four steps with all calculations done using a 3% annual discount rate. We develop a probabilistic model to estimate the health care costs and quality adjusted life-years associated with an incident of cohorts of hemophilia A and B patients from birth.

- The CDC estimates there will be 400 live birth cases of hemophilia A and 100 live birth cases of hemophilia B in a single year.[16] Of those 500 cases, 60% are considered severe and 15% are considered moderate. The additional 25% that are mild will not likely be treated in with the gene therapies in the latest stages of development today and are not in the treatable population. This meant that we began the model with a

birth cohort of 375 potentially treatable patients. Of the 375 patients, we model 300 as severe and 75 as moderate.

- The IBM/Watson Marketscan Commercial and Medicare Supplemental Databases 2009-2015 were used to estimate the age-specific cost for patients with hemophilia and the general population, absent any hemophilia incidence.[17] Patients with hemophilia were identified in each year of the Marketscan data using the ICD9 codes for hemophilia A (268.0) and hemophilia B (268.1).[18] Patients were included in the diagnosis group if they had any hemophilia in the duration of the dataset and had continuous enrollment in the dataset from 2009-2015, measured total number of member days in each year. All claims for identified patients were summed from the inpatient and outpatient files to estimate the mean costs per patient for each age, controlling for differences in time and adjusting the currency to 2017 for inflation. The cost estimates were repeated for the general population, after removing any patients with a hemophilia diagnosis. Although hemophilia gene therapy clinical trials exclude mild patients today, all patients with the ICD9 code in a respective year were included in the treatment group because there is no indicator of severity in the Marketscan claims data. This is likely to give conservative estimates for individual costs attributable to moderate/severe and severe patients because mild patients rarely experience major or impactful bleeds. We consider this further in the discussion.
- Mortality without gene therapy for the treated incident population was estimated from a study in the UK which looked at the lifetime survival of male hemophilia patients.[19] Quality of life was estimated from the literature for patients using prophylaxis and on demand management today for patients with hemophilia.[20] Improvements in ABR are

modeled linearly with improvements in mortality and improvements in quality of life in the model (e.g., 10% improvement in ABR leads to a 10% improvement in survival and QoL for patients with hemophilia, and a 10% reduction in expected annual costs at each age, relative to the general population). Age-specific survival for the general population is estimated from the National Vital Statistics Reports (NVSR) data.[21] Age-specific quality of life information was sourced from the EQ-5D estimates of the general population for the United States.[22] EQ-5D estimates were used for QoL because it is the primary tool used measure across patients with hemophilia and the health of a larger population.

- The product of the differences in life years calculated for the treated and non-treated incident birth cohort and the age-specific QoL are used to determine the difference in QALY with and without gene therapy for hemophilia.[23]
- Valuation threshold values were applied to the 3% discounted total of QALYs to determine the total benefit to the incident cohort over the 85 years.
- Price is set to $250,000 per patient for the primary model. Gene therapies for hemophilia are still in development and do not have list prices available. Analysts and market stakeholders have speculated a wide range of potential prices.[24,25,26] Because the price and exact target population are still uncertain for the gene therapies in development, we run the primary model with a $250 thousand price, assuming a gene therapy will be applied to all moderate and severe hemophilia A and B patients. Additionally, we run the model with prices of $500 thousand, $1 million, and $1.5 million in the sensitivity analyses for the primary model, and all three additional sensitivity scenario cases.

- Lifetime costs are calculated by summing the average age-specific costs per patient with a 3% discount over the 85 years.

5. We decompose the estimates from the cohort that accrue over the non-elderly years ($INMB_{PRIVATE}$) versus those that accrue in the elderly Medicare age (65+) ($INMB_{PUBLIC}$). We estimate the proportion of patients who would survive to Medicare age (S) if they are administered gene therapy. We compare the returns from the time on the private plan to the price to see if the private payer would have the incentive to pay for the gene therapy without the introduction of HealthCoin, and at which value thresholds for a life-year.
6. We then estimated the potential range of values for HealthCoin that would clear the market between Medicare and private payers, incentivizing greater investment in the gene therapy.
7. Using the midpoint of each potential range and the expected price, we estimate the consequences of the HealthCoin policy for Medicare, private payers, and the manufacturer for gene therapy in a developing medical breakthrough market.

4.3 Results

Primary Model

Table 4.3 displays the estimated incremental net benefit for all stakeholders in providing gene therapy for an incident cohort of all moderate and severe hemophilia A and B after age 18, until the age of 85 for a single cohort of incident patients at different cost-effectiveness threshold per QALY (ranging from $25K to $500K). Lifetime expected value differences driven by cost and QALY gained for patients range from $120,858 for $25,000 per year valuation of a life-year to $1,277,852 at a $500,000 per life year valuation. As the valuation of the QALY increases, the value of gene therapy increases because price and cost remain consistent. Gene therapy has a

positive net monetary benefit at valuations of a QALY of across all valuations of QALY before price of the gene therapy is considered.

Table 4.3 - Expected per patient returns from treating moderate and severe patients treated after age 18, incident cohort in 2017 until the age of 85

No Gene Therapy		Gene Therapy		Gene Therapy - No Gene Therapy	
E(QALY)	E(Cost)	E(QALY)	E(Cost)	Δ E(QALY)	Δ E(Cost)
20.78	$453,480	23.21	$393,517	2.44	-$59,964
			Incremental NMB		
			@$25,000/QALY		$120,858
			@$50,000/QALY		$181,753
			@$100,000/QALY		$303,541
			@$200,000/QALY		$547,119
			@$300,000/QALY		$790,697
			@$400,000/QALY		$1,034,274
			@$500,000/QALY		$1,277,852

Table 4.4 estimates the Medicare and private payer NMB for an average incident cohort from birth, if given gene therapy at age 18, over their lifetime. It demonstrates that the net value for the gene therapy is negative unless the cost-effectiveness threshold per QALY is $100,000 or higher. This means Medicare would only be interested in participating in HealthCoin if each QALY is valued for at least $100,000 because the impact to the overall health care sector would be negative for lower valuations of a QALY.

Net value for Medicare of treating a patient from 65 to 85 is negative at all cost-effectiveness thresholds/QALY except $500,000/QALY, suggesting Medicare would not pay for the treatment as the incident patients age into Medicare. Much of the cost and quality of life benefits are realized before the patient reaches Medicare age, including improved quality of life and reduced health care costs from reduced use of factor. Private payers would be incentivized to participate in the gene therapy market for all moderate and severe hemophilia A and B patients

after the age of 18 if their cost-effectiveness threshold is above $100,00. Payers who would value a QALY at $100,000 expect a net value of -$2,767 per patient, suggesting HealthCoin would facilitate greater willingness to treat at this cost-effectiveness threshold and price.

Table 4.4 - Returns to private and public payers in Gene Therapy for moderate and severe hemophilia A and B among a birth cohort by a private payer until the age of 85

Per patient Returns during the entire period					
With - Without Gene Therapy		Threshold	INMB	Price	Net Value
Δ E(QALY)	Δ E(Cost)				
2.44	-$59,964	@$25,000/QALY	$120,858	$250,000	-$129,142
2.44	-$59,964	@$50,000/QALY	$181,753	$250,000	-$68,247
2.44	-$59,964	@$100,000/QALY	$303,541	$250,000	$53,541
2.44	-$59,964	@$200,000/QALY	$547,119	$250,000	$297,119
2.44	-$59,964	@$300,000/QALY	$790,697	$250,000	$540,697
2.44	-$59,964	@$400,000/QALY	$1,034,274	$250,000	$784,274
2.44	-$59,964	@$500,000/QALY	$1,277,852	$250,000	$1,027,852
Per patient Returns during under the age of 65					
With - Without Gene Therapy		Threshold	INMB (EINMB NE Private)	Price	Net Value
Δ E(QALY)	Δ E(Cost)				
1.958	-$54,635	@$25,000/QALY	$102,785	$250,000	-$147,215
1.958	-$54,635	@$50,000/QALY	$150,934	$250,000	-$99,066
1.958	-$54,635	@$100,000/QALY	$247,233	$250,000	-$2,767
1.958	-$54,635	@$200,000/QALY	$439,830	$250,000	$189,830
1.958	-$54,635	@$300,000/QALY	$632,428	$250,000	$382,428
1.958	-$54,635	@$400,000/QALY	$825,025	$250,000	$575,025
1.958	-$54,635	@$500,000/QALY	$1,017,622	$250,000	$767,622
Per patient Returns during ages 65 to 85					
With - Without Gene Therapy		Threshold	(INMB)	Price	Net Value
Δ E(QALY)	Δ E(Cost)				
0.51	-$5,328	@$25,000/QALY	$18,074	$250,000	-$231,926
0.51	-$5,328	@$50,000/QALY	$30,819	$250,000	-$219,181
0.51	-$5,328	@$100,000/QALY	$56,309	$250,000	-$193,691
0.51	-$5,328	@$200,000/QALY	$107,289	$250,000	-$142,711
0.51	-$5,328	@$300,000/QALY	$158,269	$250,000	-$91,731
0.51	-$5,328	@$400,000/QALY	$209,249	$250,000	-$40,751
0.51	-$5,328	@$500,000/QALY	$260,230	$250,000	$10,230

Because the net value from HealthCoin is expected to be negative for cost-effectiveness thresholds below $100,000/QALY for the lifetime of the patient, we do not consider $50,000 and $25,000 per QALY as potential cost-effectiveness thresholds where there would be acceptable HealthCoin ranges, as Medicare would not engage in the market. HealthCoin may be priced to incentivize private payers to invest in the gene therapy while the patient is in the private market where QALY gain is valued for more than $100,000, leaving a cost-effectiveness threshold of $100,000 as the viable valuation for HealthCoin to clear the incentives of all stakeholders. An estimated 75.88% of patients with hemophilia treated with gene therapy would reach age 65 (S) if they were administered gene therapy after the age of 18.

The midpoint range of the HealthCoin for a cost effectiveness threshold of $100,000/QALY was used to illustrate the impact of the proposed currency/bond on stakeholders in the market. For the list price based on the valuation of the QALYs gained expected per person ($250 thousand) and QALY valuation of $100,000, the midpoint is $126,823. Private payers are willing to engage in HealthCoin for the cost-effectiveness thresholds of $25,000 to $100,000 as demonstrated in **Table 4.5**, but Medicare only has incentive to provide HealthCoin for overall health sector benefit at the highest valuation of the three.

Table 4.5 - HealthCoin Valuation

Threshold	Price	(EINMB NE Private)	Price - (EINMB NE Private)/S	HealthCoin Low	HealthCoin High	Midrange Value for HealthCoin
@$25,000/QALY	$250,000	$102,785	$194,017	$194,017	$250,000	$222,009
@$50,000/QALY	$250,000	$150,934	$130,560	$130,560	$250,000	$190,280
@$100,000/QALY	**$250,000**	**$247,233**	**$3,647**	**$3,647**	**$250,000**	**$126,823**
@$200,000/QALY	$250,000	$439,830	-$250,180			
@$300,000/QALY	$250,000	$632,428	-$504,007			
@$400,000/QALY	$250,000	$825,025	-$757,833			
@$500,000/QALY	$250,000	$1,017,622	-$1,011,660			

Note: S was estimated from the proportions of incident patients with moderate and severe hemophilia A and B who survive if they are treated with gene therapy is 75.88%.

Without gene therapy, 188 (50%) of expected cases for an incident cohort of moderate and severe hemophilia patients will live to 65. With gene therapy 285 (76%) patients are expected to live to 65. Because Medicare can expect a negative net value at a price of $250,000 at all valuations except $500,000/QALY, they will not fund the gene therapy prior to introducing HealthCoin for an incident population, and private payers are not incentivized to pay for gene therapy when valuing a QALY at $100,000 without HealthCoin.

When HealthCoin is introduced into the market, the private payers are now incentivized to pay for gene therapy because they expect to receive payment for the HealthCoin currency/bond they are issued when gene therapy is purchased upon the patients' entrance into Medicare. **Table 4.6** provides the impact of HealthCoin at the population level for the incident cohort of patients over their lifetime. Private payers will now pay the list price to the manufacturer, which will between $200 million after receipt of payment for the HealthCoin, for a population return of $309 million. The total population will gain benefits from gene therapy of $40 million after an investment of $175 million from Medicare.

Table 4.6 - Population returns to different stakeholders with and without a HealthCoin at the feasible cost-effectiveness thresholds

Without HealthCoin								
Cost-Effectiveness Threshold	Incident cases (#)	Gene Therapy applied at incidence	Private payer payment for Gene Therapy	Total population return for private payer cure	No. of patients who reach age 65	Cure applied at age 65	Public payer cost	Total population return for public payer
@$100,000/QALY	375	0	$0	$0	188	188	$46,968,750	$10,578,993
@$200,000/QALY	375	0	$0	$0	188	188	$46,968,750	$20,156,900
@$300,000/QALY	375	0	$0	$0	188	188	$46,968,750	$29,734,807
@$400,000/QALY	375	0	$0	$0	188	188	$46,968,750	$39,312,715
@$500,000/QALY	375	0	$0	$0	188	188	$46,968,750	$48,890,622
With HealthCoin								
Cost-Effectiveness Threshold	Incident cases (#)	Gene Therapy applied at incidence	Private payer payment for Gene Therapy	Total population return for private payer cure	No. of patients who reach age 65	Cure applied at age 65	Public payer cost	Total population return for public payer
@$100,000/QALY	375	375	$57,663,573	$92,712,295	285	0	$36,086,427	$10,739,618
@$200,000/QALY	375	375	$93,750,000	$164,936,309	285	0	$0	$20,317,525
@$300,000/QALY	375	375	$93,750,000	$237,160,323	285	0	$0	$29,984,905
@$400,000/QALY	375	375	$93,750,000	$309,384,337	285	0	$0	$39,652,285
@$500,000/QALY	375	375	$93,750,000	$381,608,351	285	0	$0	$49,319,666

Sensitivity Analyses

Tables 4.7 displays the feasible HealthCoin ranges for the sensitivity scenarios in **Table 4.1**. The full output from the sensitivity analyses can be found in the Appendix. The results are separated four cases, varying age of treatment and the duration of efficacy. Each case is tested over four price points ($250 thousand, $500 thousand, $1 million, $1.5 million). The Case numbers correspond to the sensitivity variables from **Table 4.1**, as follows:

1. **Case 1:** Treatment administered at age 18 with 90% duration over the lifetime of the patient.

2. **Case 2:** Treatment administered at age 18 with linearly depreciating efficacy from 90% to 50% over the lifetime of the patient.
3. **Case 3:** Treatment administered at age 1 with 90% duration over the lifetime of the patient.
4. **Case 4:** Treatment administered at age 1 with linearly depreciating efficacy from 90% to 50% over the lifetime of the patient.

Across the four cases and four price points tested, there were 9 total cost-effectiveness thresholds in the market where all stakeholders would be incentivized to participate in the HealthCoin market at different cost-effectiveness thresholds per QALY within each case. There are three prices where HealthCoin is viable in the first case ($250 thousand, $500 thousand, and $1 million), one price point in case 2 ($1 million), three price points in case 3 ($250 thousand, $1 million, and $1.5 million, and two price points in case 4 ($500 thousand and $1 million). Case 3 (treatment at age 1 with lasting duration) leads to 300 of the 375 incident patients surviving to age 65, up from 188 prior to HealthCoin.

Table 4.7 - Population returns to different stakeholders with and without a HealthCoin at the feasible cost-effectiveness threshold for a moderate and severe hemophilia A and B incident cohort – sensitivity analyses

	Price	Cost-Effectiveness Threshold	Incident cases (#)	Gene Therapy Applied	Private payer payment for Gene Therapy	Total population return for private payer cure	No. of patients who reach age 65	Cure applied at age 65	Public payer cost	Total population return for public payer
Without HealthCoin										
Case 1	$250,000	@$100,000/QALY	375	0	$0	$0	188	0	$0	$0
	$500,000	@$200,000/QALY								
	$1,000,000	@$400,000/QALY								
Case 2	$1,000,000	@$500,000/QALY								
Case 3	$250,000	@$25,000/QALY								
	$1,000,000	@$200,000/QALY								
	$1,500,000	@$300,000/QALY								
Case 4	$500,000	@$100,000/QALY								
	$1,000,000	@$200,000/QALY								
With HealthCoin										
Case 1	$250,000	@$100,000/QALY	375	375	$57,663,573	$92,712,295	285	0	$36,086,427	$10,739,618
	$500,000	@$200,000/QALY			$105,083,006	$164,936,309		0	$82,416,994	$20,317,525
	$1,000,000	@$400,000/QALY			$199,921,871	$309,384,337		0	$175,078,129	$39,652,285
Case 2	$1,000,000	@$500,000/QALY			$212,996,735	$310,895,678	260	0	$162,003,265	$34,859,578
Case 3	$250,000	@$25,000/QALY			$54,286,808	$89,712,220	300	0	$39,463,192	$3,871,454
	$1,000,000	@$200,000/QALY			214759392	354073205		0	$160,240,608	$22,755,138
	$1,500,000	@$300,000/QALY			309152497	505136624		0	$253,347,503	$33,641,318
Case 4	$500,000	@$100,000/QALY			116091013	181491399	274	0	$71,408,987	$8,609,128
	$1,000,000	@$200,000/QALY			208325766	315270277		0	$166,674,234	$16,461,169

Discussion

HealthCoin will provide adequate incentive to participate in the market for any private payer with a cost-effectiveness valuation of $100,000/QALY or above. Payers who value a QALY for more than $100,000 will not need HealthCoin to enter the market because the return in

investment is already positive with value-based pricing. Because the efficacy rate is high and patients are given gene therapy at age 18, private payers have incentive to enter the market above a valuation of $100,000 per QALY. A QALY is typically valued between $50,000 and $150,000 in the US market, so in this market, we can expect that payers will engage in a HealthCoin market, given the assumptions of the primary model.[27]

With HealthCoin in the market there is an expected increase in quality of life and mortality expected for moderate and severe patients. Hemophilia is characterized by three levels of severity, but there are subsets of patients among severe patients with inhibitors to standard factor treatment or many severe bleeds who are higher cost with a lower quality of life and higher mortality. This model examines the price and HealthCoin feasibility for all moderate and severe patients. If gene therapy were targeted to the highest cost patients, private payers would be incentivized to enter the market for higher cost-effectiveness thresholds, holding all other model assumptions the same. Conversely, if the manufacturer price is higher than $250 thousand and the product is only approved on the market for a subset of patients with higher severity (i.e., higher bleed rates, higher mortality, lower quality of life), HealthCoin may still be appropriate for the market because the value of gene therapy will be higher for the overall health sector and individual stakeholders, holding all other variables in the model the same.

The sensitivity analyses revealed that the payer price will have a significant impact on the feasibility and prices of HealthCoin, given the assumptions in the primary model. There are many analyst projections of the potential price for gene therapies for hemophilia, primarily between $1,000,000 and $1,500,000, but getting above $2,000,000.[28] In this model, we focus on $1,500,000 as the highest price to demonstrate analyst projections in the market price range. We did not need to test a higher price point because, given the assumptions in the primary model, the

lifetime net values are negative for all cost-effectiveness thresholds per QALY that we tested. If price reaches this point, there may not be a reason for HealthCoin because the price is too high for Medicare to participate in the market. In case 3, where patients are treated at age 1 with lifetime duration of efficacy, there is potential for HealthCoin to increase access when the cost-effectiveness threshold is $300,000/QALY for a price of $1.5 million. Like the primary model this is likely to be a higher threshold than stakeholder in the US market consider for decision-making. A Price of $1.5 million or higher may be cost prohibitive for private and public payers in the market for investment in the treatment with or without HealthCoin unless valuations of a QALY are very high compared to the benchmark in the literature.

Uncertainty about efficacy over time could incentivize payer to participate in HealthCoin markets for lower valuations of a QALY because the expected benefit over time is reduced. Payers need a greater benefit to enter the market in the form of greater compensation from HealthCoin. Decreased efficacy means increased costs per patient from breakthrough bleeds, reductions in quality of life for patients, and reductions in survival to the age of 65 and the number of patients that payers can rely on for receiving compensation upon their enrollment in Medicare.

Administering the treatment at a younger age has the opposite impact on the primary model that uncertainty around efficacy has. Treating earlier reduces lifetime cost, increases quality of life for ages 1 to 18, and increases survival overall. While the clinical trials have been for adults to date, patients are diagnosed with hemophilia in the first couple years of life, providing opportunity for greater savings if efficacy and safety can be demonstrated in a younger population.

Limitations

The primary limitation of the probabilistic model we have created to understand the feasibility and impact of HealthCoin are the limited clinical data and potential bias in the health care costs that result from inability to identify the severity of disease.

Because the gene therapies in hemophilia are still in development, there is uncertainty around the potential age of treatment, duration of efficacy, and efficacy across all patients or severities. We assume the efficacy will be durable today but do sensitivity analyses in case it degrades. We assume the clinical trial efficacy remains consistent across all patients, despite limited samples in the early trial phases of the current gene therapies in development. Additionally, gene therapies are currently administered to adults with hemophilia, but we do a sensitivity for administration at age 1 because it is unclear if gene therapies will always remain restricted for pediatric patients.

In the dataset, we did not have an indicator of severity, which may have underestimated costs for the moderate and severe hemophilia patients, whose costs are expected to be higher than the mild patients, also included in the analyzed sample. This could have important implications for the price point a manufacturer selects. Payers may have a much higher willingness to pay for the most severe patients because of significantly higher annual costs. Increasing the cost of patients today would increase INMB and the net value expected from the treatment. Additionally, patients with mild hemophilia were removed from the cost of the general population without hemophilia, which could bias those costs. The Marketscan claims databases are also based on a large convenience sample; because the sample is not random, it may contain biases or fail to generalize well to other populations.

4.5 Conclusion

The value of gene therapy for moderate and severe hemophilia A and B may be high enough for some private payers to invest without HealthCoin, but at a price of $250,000 per patient, HealthCoin will be feasible for all stakeholders in the market for a reasonable cost-effectiveness threshold of $100,000/QALY per year. If gene therapies launch on the market with a higher price, approval for younger patients, approval for higher cost and mortality subset of patients, or the product does not have duration of efficacy, HealthCoin will be feasible for significantly different cost-effectiveness thresholds. The sensitivity analysis reveals that there are reasonable assumptions that can be made across the variables in the model that change the feasibility and distribution of costs and benefits with HealthCoin in the market. As there is increased information in the market, HealthCoin should be considered as a potential means to increase access for younger patients.

Additionally, because there is switching between private payers in the United States payer market, where there are payers of different sizes, with different population mixes, and varied average expected time a patient is covered on a plan, we expect different assessments of the cost risk that treating a patient with hemophilia poses. Cost exposure risk profiles for individual payers, based on their size and the attributes of patients with hemophilia on their plans, could provide greater insight into differences that may exist among private payers in willingness to engage in HealthCoin. As we gain more information about gene therapies in hemophilia, cost-effectiveness thresholds for a QALY in hemophilia patients, and payer assessment of budget risk in this market, the HealthCoin model can be refined to more closely reflect true costs and benefits. Price and duration of efficacy will be significant drivers in the need and feasibility of HealthCoin for private payers and Medicare, respectively.

3.6 Appendix

APPENDIX A: Expected Costs and Benefits Across Sensitivity Scenarios

Table 4.8 - Expected QALY and cost before and after gene therapy for each sensitivity analysis case in a moderate and severe incident cohort of hemophilia A and B patients

	No Gene Therapy		*Gene Therapy*		*Difference: Gene - No Gene*	
	E(QALY)	**E(Cost)**	**E(QALY)**	**E(Cost)**	**Δ E(QALY)**	**Δ E(Cost)**
Case 1: Treatment at age 18, constant efficacy (90%)	20.78	$453,480	23.21	$393,517	2.44	-$59,964
Case 2: Treatment at age 18, decreasing efficacy (90% to 50% lifetime)			22.72	$411,448	1.94	-$42,032
Case 3: Treatment at age 1, constant efficacy (90%)			25.38	$309,628	4.60	-$143,852
Case 4: Treatment at age 1, decreasing efficacy (90% to 50% lifetime)			24.76	$322,969	3.99	-$130,511

Table 4.9 - Lifetime INMB by sensitivity analysis case before cost of gene therapy for an incident cohort of moderate and severe hemophilia A and B patients

Incremental NMB	***Case 1***	***Case 2***	***Case 3***	***Case 4***
@$25,000/QALY	$120,858	$90,566	$258,920	$230,145
@$50,000/QALY	$181,753	$139,099	$373,988	$329,780
@$100,000/QALY	$303,541	$236,166	$604,123	$529,049
@$200,000/QALY	$547,119	$430,300	$1,064,394	$927,586
@$300,000/QALY	$790,697	$624,433	$1,524,666	$1,326,124
@$400,000/QALY	$1,034,274	$818,567	$1,984,937	$1,724,662
@$500,000/QALY	$1,277,852	$1,012,701	$2,445,208	$2,123,199

APPENDIX B: Expected Net Value Across Sensitivity Scenarios Overall and by Payer

Table 4.10 - Case 1. Returns to private and public payers in gene therapy for moderate and severe hemophilia A and B among a birth cohort by a private payer until the age of 85

	With - Without Gene Therapy		*Cost-Effectiveness Threshold*	*INMB*	*Net Value by Gene Therapy Price Points*			
	Δ E(QALY)	**Δ E(Cost)**			**$250K**	**$500,000**	**$1 Million**	**$1.5 Million**
Lifetime until the age of 85	2.44	-$59,964	@$25,000/QALY	$120,858	-$129,142	-$379,142	-$879,142	-$1,379,142
			@$50,000/QALY	$181,753	-$68,247	-$318,247	-$818,247	-$1,318,247
			@$100,000/QALY	$303,541	$53,541	-$196,459	-$696,459	-$1,196,459
			@$200,000/QALY	$547,119	$297,119	$47,119	-$452,881	-$952,881
			@$300,000/QALY	$790,697	$540,697	$290,697	-$209,303	-$709,303
			@$400,000/QALY	$1,034,274	$784,274	$534,274	$34,274	-$465,726
			@$500,000/QALY	$1,277,852	$1,027,852	$777,852	$277,852	-$222,148
Lifetime until the age of 65 (private payer perspective)	1.96	-$54,635	@$25,000/QALY	$102,785	-$147,215	-$397,215	-$897,215	-$1,397,215
			@$50,000/QALY	$150,934	-$99,066	-$349,066	-$849,066	-$1,349,066
			@$100,000/QALY	$247,233	-$2,767	-$252,767	-$752,767	-$1,252,767
			@$200,000/QALY	$439,830	$189,830	-$60,170	-$560,170	-$1,060,170
			@$300,000/QALY	$632,428	$382,428	$132,428	-$367,572	-$867,572
			@$400,000/QALY	$825,025	$575,025	$325,025	-$174,975	-$674,975
			@$500,000/QALY	$1,017,622	$767,622	$517,622	$17,622	-$482,378
Age 65 to 85 (public payer perspective)	0.51	-$5,328	@$25,000/QALY	$18,074	-$231,926	-$481,926	-$981,926	-$1,481,926
			@$50,000/QALY	$30,819	-$219,181	-$469,181	-$969,181	-$1,469,181
			@$100,000/QALY	$56,309	-$193,691	-$443,691	-$943,691	-$1,443,691
			@$200,000/QALY	$107,289	-$142,711	-$392,711	-$892,711	-$1,392,711
			@$300,000/QALY	$158,269	-$91,731	-$341,731	-$841,731	-$1,341,731
			@$400,000/QALY	$209,249	-$40,751	-$290,751	-$790,751	-$1,290,751
			@$500,000/QALY	$260,230	$10,230	-$239,770	-$739,770	-$1,239,770

Table 4.11 -Case 2. Returns to private and public payers in Gene Therapy for moderate and severe hemophilia A and B among a birth cohort by a private payer until the age of 85

	With - Without Gene Therapy		*Cost-Effectiveness Threshold*	*INMB*	*Net Value by Gene Therapy Price Points*			
	Δ E(QALY)	**Δ E(Cost)**			**Price of $250K**	**$500,000**	**$1 Million**	**$1.5 Million**
Lifetime until the age of 85	1.94	-$42,032	@$25,000/QALY	$90,566	-$159,434	-$409,434	-$909,434	-$1,409,434
			@$50,000/QALY	$139,099	-$110,901	-$360,901	-$860,901	-$1,360,901
			@$100,000/QALY	$236,166	-$13,834	-$263,834	-$763,834	-$1,263,834
			@$200,000/QALY	$430,300	$180,300	-$69,700	-$569,700	-$1,069,700
			@$300,000/QALY	$624,433	$374,433	$124,433	-$375,567	-$875,567
			@$400,000/QALY	$818,567	$568,567	$318,567	-$181,433	-$681,433
			@$500,000/QALY	$1,012,701	$762,701	$512,701	$12,701	-$487,299
Lifetime until the age of 65 (private payer perspective)	1.60	-$38,755	@$25,000/QALY	$78,270	-$171,730	-$421,730	-$921,730	-$1,421,730
			@$50,000/QALY	$117,785	-$132,215	-$382,215	-$882,215	-$1,382,215
			@$100,000/QALY	$196,815	-$53,185	-$303,185	-$803,185	-$1,303,185
			@$200,000/QALY	$354,875	$104,875	-$145,125	-$645,125	-$1,145,125
			@$300,000/QALY	$512,935	$262,935	$12,935	-$487,065	-$987,065
			@$400,000/QALY	$670,995	$420,995	$170,995	-$329,005	-$829,005
			@$500,000/QALY	$829,055	$579,055	$329,055	-$170,945	-$670,945
Age 65 to 85 (public payer perspective)	0.36	-$3,278	@$25,000/QALY	$12,296	-$237,704	-$487,704	-$987,704	-$1,487,704
			@$50,000/QALY	$21,314	-$228,686	-$478,686	-$978,686	-$1,478,686
			@$100,000/QALY	$39,351	-$210,649	-$460,649	-$960,649	-$1,460,649
			@$200,000/QALY	$75,425	-$174,575	-$424,575	-$924,575	-$1,424,575
			@$300,000/QALY	$111,499	-$138,501	-$388,501	-$888,501	-$1,388,501
			@$400,000/QALY	$147,572	-$102,428	-$352,428	-$852,428	-$1,352,428
			@$500,000/QALY	$183,646	-$66,354	-$316,354	-$816,354	-$1,316,354

Table 4.12 - Case 3. Returns to private and public payers in Gene Therapy for moderate and severe hemophilia A and B among a birth cohort by a private payer until the age of 85

	With - Without Gene Therapy		*Cost-Effectiveness Threshold*	*INMB*	*Net Value by Gene Therapy Price Points*			
	Δ E(QALY)	**Δ E(Cost)**			**$250K**	**$500,000**	**$1 Million**	**$1.5 Million**
Lifetime until the age of 85	4.60	-$143,852	@$25,000/QALY	$258,920	$8,920	-$241,080	-$741,080	-$1,241,080
			@$50,000/QALY	$373,988	$123,988	-$126,012	-$626,012	-$1,126,012
			@$100,000/QALY	$604,123	$354,123	$104,123	-$395,877	-$895,877
			@$200,000/QALY	$1,064,394	$814,394	$564,394	$64,394	-$435,606
			@$300,000/QALY	$1,524,666	$1,274,666	$1,024,666	$524,666	$24,666
			@$400,000/QALY	$1,984,937	$1,734,937	$1,484,937	$984,937	$484,937
			@$500,000/QALY	$2,445,208	$2,195,208	$1,945,208	$1,445,208	$945,208
Lifetime until the age of 65 (private payer perspective)	4.07	-$138,524	@$25,000/QALY	$239,233	-$10,767	-$260,767	-$760,767	-$1,260,767
			@$50,000/QALY	$339,942	$89,942	-$160,058	-$660,058	-$1,160,058
			@$100,000/QALY	$541,359	$291,359	$41,359	-$458,641	-$958,641
			@$200,000/QALY	$944,195	$694,195	$444,195	-$55,805	-$555,805
			@$300,000/QALY	$1,347,031	$1,097,031	$847,031	$347,031	-$152,969
			@$400,000/QALY	$1,749,867	$1,499,867	$1,249,867	$749,867	$249,867
			@$500,000/QALY	$2,152,703	$1,902,703	$1,652,703	$1,152,703	$652,703
Age 65 to 85 (public payer perspective)	0.57	-$5,328	@$25,000/QALY	$19,687	-$230,313	-$480,313	-$980,313	-$1,480,313
			@$50,000/QALY	$34,046	-$215,954	-$465,954	-$965,954	-$1,465,954
			@$100,000/QALY	$62,764	-$187,236	-$437,236	-$937,236	-$1,437,236
			@$200,000/QALY	$120,199	-$129,801	-$379,801	-$879,801	-$1,379,801
			@$300,000/QALY	$177,635	-$72,365	-$322,365	-$822,365	-$1,322,365
			@$400,000/QALY	$235,070	-$14,930	-$264,930	-$764,930	-$1,264,930
			@$500,000/QALY	$292,506	$42,506	-$207,494	-$707,494	-$1,207,494

Table 4.13 - Case 4. Returns to private and public payers in Gene Therapy for moderate and severe hemophilia A and B among a birth cohort by a private payer until the age of 85

	With - Without Gene Therapy		*Cost-Effectiveness Threshold*	*INMB*	*Net Value by Gene Therapy Price Points*			
	Δ E(QALY)	**Δ E(Cost)**			**$250K**	**$500,000**	**$1 Million**	**$1.5 Million**
Lifetime until the age of 85	3.99	-$130,511	@$25,000/QALY	$230,145	-$19,855	-$269,855	-$769,855	-$1,269,855
			@$50,000/QALY	$329,780	$79,780	-$170,220	-$670,220	-$1,170,220
			@$100,000/QALY	$529,049	$279,049	$29,049	-$470,951	-$970,951
			@$200,000/QALY	$927,586	$677,586	$427,586	-$72,414	-$572,414
			@$300,000/QALY	$1,326,124	$1,076,124	$826,124	$326,124	-$173,876
			@$400,000/QALY	$1,724,662	$1,474,662	$1,224,662	$724,662	$224,662
			@$500,000/QALY	$2,123,199	$1,873,199	$1,623,199	$1,123,199	$623,199
Lifetime until the age of 65 (private payer perspective)	3.59	-$127,233	@$25,000/QALY	$216,419	-$33,581	-$283,581	-$783,581	-$1,283,581
			@$50,000/QALY	$305,605	$55,605	-$194,395	-$694,395	-$1,194,395
			@$100,000/QALY	$483,977	$233,977	-$16,023	-$516,023	-$1,016,023
			@$200,000/QALY	$840,721	$590,721	$340,721	-$159,279	-$659,279
			@$300,000/QALY	$1,197,464	$947,464	$697,464	$197,464	-$302,536
			@$400,000/QALY	$1,554,208	$1,304,208	$1,054,208	$554,208	$54,208
			@$500,000/QALY	$1,910,952	$1,660,952	$1,410,952	$910,952	$410,952
Age 65 to 85 (public payer perspective)	0.42	-$3,278	@$25,000/QALY	$13,726	-$236,274	-$486,274	-$986,274	-$1,486,274
			@$50,000/QALY	$24,175	-$225,825	-$475,825	-$975,825	-$1,475,825
			@$100,000/QALY	$45,072	-$204,928	-$454,928	-$954,928	-$1,454,928
			@$200,000/QALY	$86,866	-$163,134	-$413,134	-$913,134	-$1,413,134
			@$300,000/QALY	$128,660	-$121,340	-$371,340	-$871,340	-$1,371,340
			@$400,000/QALY	$170,453	-$79,547	-$329,547	-$829,547	-$1,329,547
			@$500,000/QALY	$212,247	-$37,753	-$287,753	-$787,753	-$1,287,753

APPENDIX D: Feasible HealthCoin Valuation's Across Sensitivity Scenarios

Table 4.14 - Case 1. HealthCoin Valuation						
		Case 1				
Price	Cost-Effectiveness Threshold	(EINMB NE Private)	Price - (EINMB NE Private)/S	HealthCoin Low	HealthCoin High	Midrange Value for HealthCoin
$250,000	@$25,000/QALY	$102,785	$194,017	$3,647	$250,000	$126,823
	@$50,000/QALY	$150,934	$130,560			
	@$100,000/QALY	$247,233	$3,647			
	@$200,000/QALY	$439,830	-$250,180			
	@$300,000/QALY	$632,428	-$504,007			
	@$400,000/QALY	$825,025	-$757,833			
	@$500,000/QALY	$1,017,622	-$1,011,660			
$500,000	@$25,000/QALY	$102,785	$523,495	$79,299	$500,000	$289,649
	@$50,000/QALY	$150,934	$460,039			
	@$100,000/QALY	$247,233	$333,125			
	@$200,000/QALY	$439,830	$79,299			
	@$300,000/QALY	$632,428	-$174,528			
	@$400,000/QALY	$825,025	-$428,355			
	@$500,000/QALY	$1,017,622	-$682,182			
$1,000,000	@$25,000/QALY	$102,785	$1,182,452	$230,602	$1,000,000	$615,301
	@$50,000/QALY	$150,934	$1,118,996			
	@$100,000/QALY	$247,233	$992,082			
	@$200,000/QALY	$439,830	$738,256			
	@$300,000/QALY	$632,428	$484,429			
	@$400,000/QALY	$825,025	$230,602			
	@$500,000/QALY	$1,017,622	-$23,225			
$1,500,000	@$25,000/QALY	$102,785	$1,841,409			
	@$50,000/QALY	$150,934	$1,777,953			
	@$100,000/QALY	$247,233	$1,651,039			
	@$200,000/QALY	$439,830	$1,397,213			
	@$300,000/QALY	$632,428	$1,143,386			
	@$400,000/QALY	$825,025	$889,559			
	@$500,000/QALY	$1,017,622	$635,732			

Table 4.15 - Case 2. HealthCoin Valuation						
		Case 2				
Price	Threshold	(EINMB NE Private)	Price - (EINMB NE Private)/S	HealthCoin Low	HealthCoin High	Midrange Value for HealthCoin
$250,000	@$25,000/QALY	$78,270	$247,781			
	@$50,000/QALY	$117,785	$190,767			
	@$100,000/QALY	$196,815	$76,739			
	@$200,000/QALY	$354,875	-$151,319			
	@$300,000/QALY	$512,935	-$379,376			
	@$400,000/QALY	$670,995	-$607,433			
	@$500,000/QALY	$829,055	-$835,490			
$500,000	@$25,000/QALY	$78,270	$608,494			
	@$50,000/QALY	$117,785	$551,480			
	@$100,000/QALY	$196,815	$437,451			
	@$200,000/QALY	$354,875	$209,394			
	@$300,000/QALY	$512,935	-$18,663			
	@$400,000/QALY	$670,995	-$246,720			
	@$500,000/QALY	$829,055	-$474,777			
$1,000,000	@$25,000/QALY	$78,270	$1,329,919			
	@$50,000/QALY	$117,785	$1,272,905			
	@$100,000/QALY	$196,815	$1,158,876			
	@$200,000/QALY	$354,875	$930,819			
	@$300,000/QALY	$512,935	$702,762			
	@$400,000/QALY	$670,995	$474,705			
	@$500,000/QALY	$829,055	$246,648	$246,648	$1,000,000	$623,324
$1,500,000	@$25,000/QALY	$78,270	$2,051,344			
	@$50,000/QALY	$117,785	$1,994,330			
	@$100,000/QALY	$196,815	$1,880,302			
	@$200,000/QALY	$354,875	$1,652,244			
	@$300,000/QALY	$512,935	$1,424,187			
	@$400,000/QALY	$670,995	$1,196,130			
	@$500,000/QALY	$829,055	$968,073			

Table 4.16 - Case 3. HealthCoin Valuation						
		Case 3				
Price	Threshold	(EINMB NE Private)	Price - (EINMB NE Private)/S	HealthCoin Low	HealthCoin High	Midrange Value for HealthCoin
$250,000	@$25,000/QALY	$239,233	$13,479	$13,479	$250,000	$131,740
	@$50,000/QALY	$339,942	-$112,594			
	@$100,000/QALY	$541,359	-$364,741			
	@$200,000/QALY	$944,195	-$869,035			
	@$300,000/QALY	$1,347,031	-$1,373,329			
	@$400,000/QALY	$1,749,867	-$1,877,622			
	@$500,000/QALY	$2,152,703	-$2,381,916			
$500,000	@$25,000/QALY	$239,233	$326,444			
	@$50,000/QALY	$339,942	$200,371			
	@$100,000/QALY	$541,359	-$51,776			
	@$200,000/QALY	$944,195	-$556,070			
	@$300,000/QALY	$1,347,031	-$1,060,364			
	@$400,000/QALY	$1,749,867	-$1,564,657			
	@$500,000/QALY	$2,152,703	-$2,068,951			
$1,000,000	@$25,000/QALY	$239,233	$952,374			
	@$50,000/QALY	$339,942	$826,300			
	@$100,000/QALY	$541,359	$574,153			
	@$200,000/QALY	$944,195	$69,860	$69,860	$1,000,000	$534,930
	@$300,000/QALY	$1,347,031	-$434,434			
	@$400,000/QALY	$1,749,867	-$938,728			
	@$500,000/QALY	$2,152,703	-$1,443,021			
$1,500,000	@$25,000/QALY	$239,233	$1,578,303			
	@$50,000/QALY	$339,942	$1,452,230			
	@$100,000/QALY	$541,359	$1,200,083			
	@$200,000/QALY	$944,195	$695,789			
	@$300,000/QALY	$1,347,031	$191,496	$191,496	$1,500,000	$845,748
	@$400,000/QALY	$1,749,867	-$312,798			
	@$500,000/QALY	$2,152,703	-$817,092			

Table 4.17 - Case 4. HealthCoin Valuation						
		Case 4				
Price	Threshold	(EINMB NE Private)	Price - (EINMB NE Private)/S	HealthCoin Low	HealthCoin High	Midrange Value for HealthCoin
$250,000	@$25,000/QALY	$216,419	$46,023			
	@$50,000/QALY	$305,605	-$76,208			
	@$100,000/QALY	$483,977	-$320,670			
	@$200,000/QALY	$840,721	-$809,595			
	@$300,000/QALY	$1,197,464	-$1,298,519			
	@$400,000/QALY	$1,554,208	-$1,787,443			
	@$500,000/QALY	$1,910,952	-$2,276,368			
$500,000	@$25,000/QALY	$216,419	$388,653			
	@$50,000/QALY	$305,605	$266,422			
	@$100,000/QALY	$483,977	$21,960	$21,960	$500,000	$260,980
	@$200,000/QALY	$840,721	-$466,965			
	@$300,000/QALY	$1,197,464	-$955,889			
	@$400,000/QALY	$1,554,208	-$1,444,813			
	@$500,000/QALY	$1,910,952	-$1,933,738			
$1,000,000	@$25,000/QALY	$216,419	$1,073,913			
	@$50,000/QALY	$305,605	$951,682			
	@$100,000/QALY	$483,977	$707,220			
	@$200,000/QALY	$840,721	$218,295	$218,295	$1,000,000	$609,148
	@$300,000/QALY	$1,197,464	-$270,629			
	@$400,000/QALY	$1,554,208	-$759,553			
	@$500,000/QALY	$1,910,952	-$1,248,478			
$1,500,000	@$25,000/QALY	$216,419	$1,759,173			
	@$50,000/QALY	$305,605	$1,636,942			
	@$100,000/QALY	$483,977	$1,392,480			
	@$200,000/QALY	$840,721	$903,556			
	@$300,000/QALY	$1,197,464	$414,631			
	@$400,000/QALY	$1,554,208	-$74,293			
	@$500,000/QALY	$1,910,952	-$563,218			

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Chapter 5. DISCUSSION

The following is a brief chapter to summarize the primary findings of the dissertation, the importance for stakeholders, wider potential policy implications, and recommendations for building stronger evidence for HealthCoin literature.

5.1 Summary of Findings

This dissertation primarily focused on the potential feasibility and impact of introducing HealthCoin to two markets with new and developing SLA treatments. Although hemophilia gene therapies are not yet on the market, CAR T has faced reimbursement challenges in the market, as Medicare and the private market continue to innovate in payment methods to attempt to align the cost with the benefits realized.[1] In addition to r/r ALL, CAR T has been approved in diffuse large b-cell lymphoma and is being tested in peritoneal mesothelioma. As more indications are approved for CAR T products, their budget impact will increase and the need for aligned financial incentives will continue to grow in importance.

Aim 1: *The underfunding of high cost single/limited administration treatments in commercial health plans compared to Medicare*

Aim 1 demonstrated a discontinuous increase in the treatment rate at age 65 for surgical procedures with a decreasing trend prior to the discontinuity, consistent with underfunding of SLA treatments. There was no such discontinuity in the chronic falsification group. This research provides evidence that further research is needed for the impact of the patient lifetime in specific disease states that could provide further clarity on the potential underfunding for single or limited administration high cost therapies from private payers.

Aim 2: *Distribution of costs and benefits of chimeric antigen receptor T-cell (CAR T) therapies for refractory and relapsed acute lymphoblastic leukemia (r/r ALL) pediatric patients and HealthCoin's potential role*

HealthCoin is feasible in the r/r ALL market for CAR T where the cost-effectiveness threshold per QALY is $50,000. Without CAR T therapy, 3.1 of the 20.1 average number of expected cases for incident 15-year-olds will live to 65. With CAR T therapy 11.4 patients are expected to live to 65. Because there are no 15-year-old patients on Medicare they will not fund the CAR T therapy prior to introducing HealthCoin, and private payers are not financially incentivized to pay for CAR T therapy when valuing a QALY at, or below, $50,000. When the cost-effectiveness threshold is $100,000/QALY and higher, private payers pay to administer the CAR T treatment without the intervention because the benefits expected under the age of 65 is adequate to incentivize payment at the list price of $475,000.

Aim 3: *The distribution of health care costs and benefits of potential gene therapies for patients with hemophilia A and B over their lifetimes and the potential role of HealthCoin*

HealthCoin is feasible in the moderate and severe hemophilia A and B markets, where the cost-effectiveness threshold per QALY is $100,000 or greater when the price is $250,000 for the gene therapy. With HealthCoin in the market, private investment in gene therapy is expected to be about $58 million with a return for the total population while on private insurance of about $93 million. The public payer would invest $36 million and the return while patients are enrolled in Medicare will be around $11 million.

5.2 Importance of Findings

HealthCoin is a financial instrument intended to provide private payers with incentives to pay for treatment based on the impact to the entire lifetime of the patient, rather than the time the patient is on the private plan. Patients and payers are the most impacted stakeholders, but we primarily discuss financial implications for payers because of their decision-making power for funding the SLA treatment.

Demonstrating Underfunding

The first aim did not definitively demonstrate underfunding of treatments as patients approach Medicare. However, the results were suggestive that underfunding may persist with a more precise study. The primary importance that emerged from the first aim is that there is a need for more research to determine if the incentives for underfunding are resulting in delayed or denied payment for single or limited administration treatments. There is especially a need for specific indications where new high cost SLA therapies such as gene and cell therapies are emerging, and where there is not a significant mortality difference between treatments.

Major Financial Stakeholders

Payers. Fundamentally, the free-rider problem Aim 1 attempted to demonstrate is hypothesized to stem from future medical savings from a given treatment being distributed over all payers the patient will have while medical savings are incurred and QALYs gained are realized. This dissertation demonstrated private payers would benefit from the redistribution of costs for SLA therapies in hemophilia and r/r ALL from a single private payer perspective. Although Aim 1 did not definitively demonstrate a discontinuity due to underfunding, it is difficult to draw strong conclusions about how the potential underfunding incentives impact

behavior now and for future SLA therapies of higher cost and along the patient's lifetime. The probabilistic models demonstrate HealthCoin could incentivize a more value-based approach for private payers with a singular perspective under the age 65. From the perspective of a segmented private market, greater value may exist for small payers, especially for orphan diseases where it is not always possible to rely on a market average of expected benefits before the patient reaches age 65 because of limited payer exposure to the disease population.

A study published in 2011 found roughly 21% of patients on private insurance switch insurers each year.[2] Patients can switch or lose coverage entirely at certain times throughout their lifetime, or use another government sponsored insurance, such as Medicaid or VA care. These scenarios present a greater risk in never receiving future medical savings from treatment, reducing the private payers expected realized benefits per patient treated. Considering these factors and building payer specific assumptions for each disease state into future research will demonstrate where HealthCoin could benefit the market most.

Medicare. Medicare would have a larger role for the payment of SLA therapies if HealthCoin existed in the market and would increase the number of Medicare participants in the long run, avoiding future medical costs for high morbidity conditions. The tradeoff for the larger investment is a healthier population from earlier access to treatments expected to have lifetime benefits. In the cases of the primary CAR T and gene therapy models, net benefit from HealthCoin across both payer stakeholders is expected to be positive, and Medicare is always willing to participate. In the case where an SLA therapy is not expected to provide a net benefit across the patient's lifetime compared to a standard of care, Medicare is not willing to participate.

5.3 Policy Implications

Increased Access

HealthCoin has the potential to increase and expedite SLA treatments to the level of access that would be expected if payers were considering the entire lifetime of the patient for value-based decision-making. The probabilistic models in r/r ALL and hemophilia demonstrated that HealthCoin would be feasible in the market and increase investment of private payers in SLA treatments for cost-effectiveness thresholds of $50,000/QALY and ≥$100,000/QALY, respectively. The World Health Organization suggests cost-effectiveness thresholds of 1-3 times of gross domestic product per capital, giving the US a suggested valuation threshold of about $59,531 to $178,593.[3,4] If estimations of cost-effectiveness valuations per QALY are similar to what the WHO recommends, HealthCoin should be viable in both the r/r ALL and hemophilia markets, to increase investment and re-distribute the costs of administration along all payers the patient encounters.

The r/r ALL market is characterized by high mortality rates, whereas hemophilia is a lifetime chronic disease where mortality is only reduced 10 years on average from the general population, but costs are higher than the general population and quality of life suffers from bleeds.[5,6] Alternatively, both are orphan indications with a current standard of care for treatment that is not as efficacious as the SLA treatment in addressing mortality or morbidity.[7,8] In both cases, HealthCoin could facilitate a redistribution of costs and benefits to align the health care sector more with value-based payment. The models demonstrate that HealthCoin is likely to be successful at different cost-effectiveness valuation thresholds, which suggests understanding that threshold across the market and diseases will be important to pricing and implementing HealthCoin by disease state.

Overall Policy Implications

HealthCoin is a viable idea to address incentives for underfunding in the private market but will require an investment in understanding payer cost-effectiveness thresholds for specific payers and real-world outcomes for SLA treatments to appropriately price HealthCoin. As a greater number of SLA therapies enter the market, the need for a financial instrument such as HealthCoin will increase as more high cost products providing lifetime efficacy become available and Medicare benefits more from investments made in the private payer setting.

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