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Health economic simulation modeling of an AI-enabled clinical decision support system for coronary revascularization

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Abstract

While artificial intelligence (AI) models have been developed to support coronary revascularization decision-making, health economic evaluation of such models has been rare. We conducted a retrospective health economic simulation modeling study using real-world data from 25,942 adult patients with obstructive coronary artery disease in Alberta, Canada to evaluate the economic value of an AI-enabled coronary revascularization decision support system. Clinicians deciding among medical therapy only, percutaneous coronary intervention, and coronary artery bypass grafting were simulated to be provided with AI predictions of 3- and 5-year major adverse cardiovascular events and all-cause mortality. At a willingness-to-pay of $50,000 per quality adjusted life year (QALY), as many as 72.4% of all actual treatment decisions shifted to a different health economically optimized treatment, resulting in an average cost saving of $22,960 and a QALY gain equivalent to up to $22,439 per patient. Even in a conservative scenario where clinicians' AI adoption was assumed to be limited, 53.2% of the actual decisions shifted, resulting in an average QALY gain equivalent to up to $32,214 per patient. AI can potentially optimize the health system level economic value of treatment decisions in the form of reduced costs stemming from fewer future complications and improved patient outcomes.

Introduction

There are typically three treatment options for patients with coronary artery disease (CAD): percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and medical therapy only (MT). Although several large-scale randomized controlled trials have been conducted to compare these treatment options (e.g., SYNTAX[1] – PCI vs. CABG in left main or 3-vessel disease; EXCEL[2] – PCI vs. CABG in left main disease; FREEDOM[3] – PCI vs. CABG in multivessel disease with diabetes; COURAGE[4] – PCI vs. MT in stable CAD) to inform the clinical practice guidelines from the American College of Cardiology and the European Society of Cardiology,[5] clinical equipoise remains in this treatment decision-making because each real-world patient case is unique and the generalizability of the findings from these trials with strict inclusion and exclusion criteria is limited (e.g., a woman from an underrepresented minority group with a unique combination of co-morbidities may not adequately fit any of these trials). The CAD treatment decision becomes particularly challenging when complex disease and unique patient characteristics preclude a straightforward application of clinical practice guidelines. Previous studies have investigated and discussed the treatment decision-making challenges associated with left-main or multivessel disease, co-morbidities, complex coronary anatomies, and patient preference.[5–8]

When evidence-based coronary revascularization decision-making is difficult, artificial intelligence (AI) can potentially present a viable alternative by providing personalized, data-driven insights. Several studies have demonstrated promising performances of AI models that predicted mortality and major adverse cardiovascular event (MACE) outcomes for patients with CAD at various time points ranging from 30 days to 10 years.[9–12] Their patient cohorts varied substantially, ranging from patients who received coronary revascularization to those diagnosed with acute coronary syndrome to those with suspected CAD. Despite their heterogeneity in patient cohort, predictor variables, and predicted outcomes, these studies collectively demonstrate the potential of personalized AI-enabled outcome prediction for patients with CAD.

While AI prediction performance has been investigated in the context of CAD and coronary revascularization, little is known about the economic value that AI can potentially bring to CAD care. Given that economic benefits are crucial to AI adoption in healthcare settings, particularly for health system administrators and payors who would require economic benefits as an important factor in their procurement or reimbursement decisions, this study aimed to perform health economic analysis of an existing AI-enabled clinical decision support system (CDSS) for coronary revascularization. Using a Markov chain simulation model and retrospective patient data, this study assessed the potential economic value of improving coronary revascularization decisions made by interventional cardiologists following diagnostic coronary angiography.

Results

Primary Analysis

Table 1 shows that the net impact of pursuing health economically optimal treatments in Scenario 1, as recommended by Revaz AI, in the test set patients based on lifetime simulations. Revaz AI would have led to a net increase of 4,216 CABG procedures, with a decrease in MT (-597) and PCI (-3,619). Overall, 2,151 of the 7,794 patients (27.6%) remained with their initial treatment, while the remainder shifted. Although shifts occurred in all possible directions, shifts toward CABG were pronounced.

Figure 1a illustrates the net change in system cost and quality adjusted life years (QALY) experienced (valued at the maximum willingness-to-pay of $50,000/QALY) in Scenario 1. The average impact was a cost saving of $22,960 and a QALY gain of 0.449 corresponding to a maximum willingness-to-pay of $22,439. However, the range of shifts was broad and for most patients whose treatment changed the impact was either an increase in costs that was cost effective given an improvement in outcomes or a decrease in costs greater than the willingness-to-pay to avoid a decrease in health-related quality of life (HRQoL). Overall, applying Revaz AI was dominant over standard care as long as it was cost saving and outcome improving (i.e., at any price below $22,960 in this Scenario since Revaz AI improved outcomes on average).

Table 2 and Figure 1b present the results from Scenario 2. As with Scenario 1, patients shifted in all possible directions, but the net flow from MT and PCI to CABG was exaggerated. Consequently, costs increased by $11,644, which included both immediate costs from shifting towards more intensive initial treatments as well as long-term costs due to increased survival. The average QALY gained increased significantly to 0.846, with an acceptable incremental cost-effectiveness ratio of $13,764/QALY.

Table 3 and Figure 1c show the results from Scenario 3. Compared to Scenarios 1 and 2, more patients retained their original treatment but Revaz AI still shifted 4,149 (53.2%) of all treatment decisions even in this conservative Scenario. The decision rule in Scenario 3 was also slightly cost decreasing ($1,910/patient) and resulted in greater QALY gains (0.644

QALY/patient) compared to strict adherence to the economically optimal treatment (Scenario 1) but less than the impact of simply maximizing QALYs gained (Scenario 2).

Secondary Analyses

Figure 2 and Tables 4-6 show the results from the secondary analysis involving all patients in lifetime simulations. All results were similar to the primary analysis results, with the majority of treatment shifts favoring CABG. Scenario 1 led to a cost saving of $25,798 and a QALY gain of $21,072 on average. Scenario 2 resulted in greater QALY gains at the expense of increased costs. Scenario 3 led to substantial QALY gains with small cost savings.

Figure S1 and Tables S1-S3 report the results from the secondary analysis involving test set patients only in 5-year simulations. In Scenarios 1 and 3, Revaz AI caused the number of CABG procedures to decrease, whereas Scenario 2 led to a pronounced increase of CABG and decreases of MT and PCI. Five years was too short to observe substantial QALY gains across all Scenarios. Because of this, most patients (85%) did not shift to a different treatment in Scenario 3. Similar results were found in the secondary analysis involving all patients in 5-year simulations, as shown by Figure S2 and Tables S4-S6.

Table 2Figure 2Table 33 Discussion

Our results show that Revaz AI can improve the cost-effectiveness of actual CAD treatments in most cases, and that even with conservative assumptions regarding the probability of switching treatment decisions (Scenario 3), more than a half of the patients would have their course of treatment altered if Revaz AI were applied. The specifics of the shift will depend on the AI adoption criteria by which physicians weigh cost versus HRQoL for their patients, and the extent to which they are, in practice, willing to allow Revaz AI's recommendations to alter their judgement. Prospective clinical trials are required to determine that willingness in real-world conditions.

Previous Markov simulation-based health economic studies tended to focus on screening tools with a binary diagnostic decision.[13–15] On the contrary, the present study assessed which of the three competing treatment paths was optimal in the presence of considerable uncertainty. As a result, we opted for extensive empirical simulations for each patient to accurately quantify the economic value of Revaz AI, at the expense of substantially increased computational costs. Our work demonstrates that more sophisticated computational techniques can enable health economic analysis of complex health care technologies such as AI-based clinical decision support.

The economic simulation model used treatment costs faced by a typical US healthcare system, and a standard US willingness to pay threshold of $50,000/QALY was used to represent the cost-HRQoL tradeoff decision-making in the US. Different jurisdictions would have different costs as well as different cost effectiveness thresholds, which would change the optimal therapy as recommended by the model in some cases and would alter the willingness to pay for benefits created. While the $50,000/QALY threshold has been common in the literature, higher thresholds ranging from $100,000 to $150,000/QALY have been increasing used in recent years.[16]

Although the treatments shifted in all directions, CABG resulted in the greatest net gains across all three Scenarios in lifetime simulations, in line with the findings from our previous study that applied reinforcement learning to the same data set as this present study.[17]

However, in Scenarios 1 and 3 in 5-year simulations, treatments shifted away from CABG because 5 years was too short to observe improved outcomes relative to the increased upfront costs of CABG. This agrees with many of the major randomized controlled trials previously conducted, including SYNTAX,[18] FREEDOM,[19] BEST,[20] and NOBLE.[21] These trials reported lower costs for CABG than PCI mainly due to fewer repeat revascularizations and rehospitalizations in the long-term, despite CABG's higher upfront costs. To support this finding, Table S7 shows temporally broken-down costs for nine example patients from the primary analysis for whom CABG was cost-minimizing.

Our simulation model can be used in a real-world situation for a new live patient to project the costs and QALYs for the rest of their life or a specific time horizon for each of the three treatment options, since it does not ingest any future data. By comparing the costs and QALYs of each treatment, it is possible to select the health economically optimal treatment in the real-world. Such decision support information can provide an insightful perspective that complements Revaz AI which focuses on patient outcomes rather than economic value.

Despite the rapidly increasing interest in AI innovations in healthcare, there has been a paucity of economic evaluations of health AI technologies in the literature.[22,23] The few studies that have examined the economic value of AI in healthcare tended to focus on medical imaging rather than clinical decision support, and on cost reduction rather than long-term impact.[22] It has also been acknowledged that health economic evaluation of AI is challenging due to its rapid technological advances, lack of generalizability, need for reconfigured clinical workflows, and potential to exacerbate health disparities.[24] The present study makes meaningful contributions to this understudied area of health AI research. Furthermore, health economic evaluations like this present study can potentially facilitate adoption and implementation of AI innovations in healthcare by supporting economic rationale, which is as important as the technology itself for real-world procurement decisions.

This study has several limitations. First and foremost, Revaz AI outcome probabilities were assumed to be a correct representation of the future outcomes for the patient for whom they were generated. Although Revaz AI was trained using a large-scale multi-center data set and its prediction performance is state-of-the-art,[25] any inaccuracy or bias in Revaz AI predictions would reduce the value of Revaz AI in directing care. Additionally, Revaz AI was trained on a data set where clinicians incorporated comprehensive clinical factors and patient preference to arrive at a defined revascularization strategy, which could influence its applicability in a prospective cohort. Given the reliance on the model's accuracy, the results presented here should be interpreted as a ceiling for Revaz AI's potential value.

Second, the results assume that Revaz AI could and would be applied in all cases, and that its optimal treatment recommendations would be followed. In practice, physicians and patients may diverge from Revaz AI's recommendations for several reasons. For example, from a general health system perspective, Revaz AI recommended an overall shift towards increasing CABG volumes, primarily at the expense of PCI, based on lifetime simulations. In practice, this may not be feasible because: 1) the patient may not be a good surgical candidate (e.g., older frail patients) or prefer less invasive procedures; 2) CABG may not be technically feasible due to the coronary anatomy or lesion locations; 3) patients and physicians may choose to weigh the risks of CABG differently than Revaz AI for reasons not discernable in the data ingested by Revaz AI; or 4) the surgical capacity of the health system may be limited. As with the previous limitation, the results from this study should be considered a ceiling, with each case in which an 'optimal' strategy is not pursued reducing the potential overall value of Revaz AI.

Third, while the econometric simulation model relied on trial data (primarily SYNTAX,[1] FREEDOM,[3] and EXCEL[2]) which covered a broad range of populations, the data on which Revaz AI was trained and the population for whom the benefit estimates were calculated represented specifically the population of the province of Alberta, Canada.

Fourth, the trials on which the simulation model was based are more than a decade old, and the more recent ISCHEMIA trial[26] has not yet published economic evaluation results. Any significant developments in MT, PCI, or CABG procedures would also change the economic results.

Fifth, there were many underlying assumptions in the simulation model and three Scenarios (e.g., proportionality of cause-specific deaths to baseline all-cause mortality risk, the QALY threshold of 0.2 in Scenario 3). The computational costs associated with the extensive simulation modeling in this study prohibited complete sensitivity analysis on all assumptions, as each new combination of assumptions and model parameters would require a repeat of the entire simulation.

Sixth, our lifetime simulations assumed that treatment effects would persist for the remainder of each patient's lifetime, beyond the 5-year prediction horizon of Revaz AI. In fact, the vast majority of our patient cohort survived beyond 5 years as depicted in Figure S3 that shows the survival curves for actual and health economically optimal (Scenario 1) treatments in the primary analysis. This is why we censored simulations at 5 years in the secondary analyses, but this unrealistically underestimated the economic benefits of Revaz AI since most patients would survive beyond the first 5 years to experience long-term benefits. Given these respective limitations, the lifetime and 5-year simulations collectively provide complementary findings.

Lastly, this study only focused on the economic value at the patient level stemming from optimized revascularization decisions. Initial infrastructure investments and operational costs related to using Revaz AI at the point of care could be substantial but were excluded.

All these limitations should be addressed with further research, particularly through clinical trials of Revaz AI to observe real-world impacts on clinical decision-making and any changes in patient outcomes as Revaz AI is introduced to clinical practice.

This retrospective health economic simulation modeling study showed that AI-enabled clinical decision support can optimize many coronary revascularization decisions, leading to substantial cost savings and improved patient outcomes, even when limited clinicians' AI adoption was assumed. The findings from this study demonstrate that the economic value of utilizing AI-based decision support can be substantial. Randomized clinical trials are warranted to validate the real-world impacts of Revaz AI on clinician decision-making, costs, and patient outcomes.

Methods

AI-enabled CDSS

We conducted health economic analysis on an existing AI-enabled CDSS named Revaz AI, the development and prediction performance evaluation of which have been described previously.[25] In this study, we evaluated the Revaz AI models that predict the likelihoods of 3- and 5-year all-cause mortality and 3-point MACE (heart failure, myocardial infarction [MI], and stroke) post-diagnostic coronary angiography. These models were developed using a comprehensive data set from over 42,000 patients who underwent coronary angiography at one of the three hospitals with cardiac catheterization labs in Alberta, Canada (Foothills Medical Centre, University of Alberta Hospital, and Royal Alexandra Hospital) from 2009 to 2019, constructed using linked patient data from the APPROACH Registry[27] and administrative health databases. Revaz AI is designed to help decide among PCI, CABG, and MT for patients with obstructive CAD (defined as at least 50% or 70% stenosis in the left main or other coronary vessels, respectively). Patients presenting with ST elevation MI (STEMI) are ineligible for Revaz AI due to its emergent nature that requires immediate PCI.

Patient Cohort

Our economic analysis was based on real-world data from 25,942 patients who underwent diagnostic coronary angiography in Alberta, Canada between 2009 and 2019. This was a subset of the data set used to develop Revaz AI with the following inclusion criteria: 1) 5-year follow-up to enable all outcome predictions, 2) age ≥ 18 years, 3) presentation of non-ST elevation MI (NSTEMI), stable angina, or unstable angina (STEMI was excluded since Revaz AI cannot be used for patients presenting with STEMI, as described in the previous section), and 4) Alberta residents. Table S8 tabulates the patient characteristics used in the simulation model.

The data set of 25,942 patients was randomly partitioned at the patient level into a 70% training set and a 30% test set (7,794 patients). The training set was used to train prediction models, and the primary analysis only utilized the patients in the test set to focus on Revaz AI predictions for patients unseen during model development. The secondary analyses used all 25,942 patients to leverage the larger sample size.

Health Economic Simulation Overview

The simulation model assumed that patients undergoing diagnostic coronary angiography have the possibility of receiving any of the three treatment options: PCI, CABG, and MT. In practice, as shown in Figure S4, there would be multiple decision points and factors which might influence treatment choice. For simplicity, however, this study condensed the decision process to one hypothetical point in which diagnostic angiography has been performed and a treatment decision must now be made.

For each patient in the data set, Revaz AI predicted a set of outcome probabilities conditioned on treatment. Those outcome probabilities were then fed to a Markov simulation model (see Figure S5 for the model structure) with a quarter year cycle length and a lifetime horizon. Each of the three treatment paths was simulated 500 times with the same base outcome probabilities. Once all 1,500 (500 iterations/treatment x 3 treatments) simulations of each patient were completed, we averaged the rest of life costs and QALYs across all 500 iterations for each of the three treatments. The treatment with the best average net monetary benefit when valuing gained quality adjusted life years (QALYs) at $50,000 per QALY, a commonly used willingness-to-pay threshold in health care cost-effectiveness analysis,[28] was deemed 'optimal'. If the optimal treatment was not the treatment actually pursued, the patient was recommended to switch from the actual to the optimal treatment, and the difference in net monetary benefit was the value that could potentially have been created, had Revaz AI been used in selecting the patient's treatment.

Health Economic Simulation Model Details

Patients entered the model at their actual age at the time of angiography and with their actual indication for angiography (stable angina, unstable angina, or NSTEMI), history of MI, and extent of CAD (single vessel [SV], multivessel [MV], or left main [LM]). Event probabilities not directly taken from Revaz AI were extracted from the literature and are shown in Table S9.

The first cycle of the model involved the patient's initial treatment and follow-up. PCI and CABG patients had a risk of peri- or immediate post-operative death, while patients with MT were assumed to survive diagnostic catheterization. Patients could also experience a MACE or death from cardiac or non-cardiac causes in the first cycle.

Following initial treatment, surviving patients were assigned to a stable post-treatment state. From that state, in each subsequent cycle, they could require new or repeat revascularization without an MI (assumed to be due to new or recurrent stable angina), experience a MACE, remain stable, or die of non-cardiac causes. Overall MACE and death probabilities were individual and taken from the Revaz AI predictions for that patient and the selected treatment modality. Patients experiencing a MACE were randomly assigned to one of MI (which could also result in repeat revascularization), stroke, or hospitalization for a new onset of heart failure. Repeat revascularization probabilities were taken from the literature and varied depending on the patient's initial treatment.

Patients assigned to MACE or to revascularization without MI also had a risk of death resulting from that event, in which case they were assigned directly to the death state at the conclusion of the current cycle. Individuals who survived a MACE were assigned back to the stable condition but with altered ongoing costs and quality of life (see next subsections).

Each patient's probability of death concurrent with another event was scaled based on their death risk in that cycle relative to the population average risk in that cycle:

$$P_{(\text{Death from MACE i,c})} = P_{(\text{Cardiac death})} \times P_{(\text{Death i,c})} / P_{(\text{Death c})}$$

$$P_{(\text{Peri-operative death i,c})} = P_{(\text{Peri-operative death})} \times P_{(\text{Death i,c})} / P_{(\text{Death c})}$$

where $P_{(\text{Death from MACE i,c})}$ is the probability of dying conditional on having suffered a MACE in that cycle, where i indicates that a risk is particular to an individual, and c indicates that it is particular to a model cycle. $P_{(\text{Cardiac death})}$ is the expected proportion of all deaths in the cohort based on literature reports of the proportion of PCI or CABG study patients whose proximate cause of death is MI, stroke, or heart failure. $P_{(\text{Peri-operative death})}$ is the population level probability of death either during a revascularization procedure or before discharge from hospital following such a procedure. $P_{(\text{Death i,c})}$ is all-cause death probability for that individual in a given model cycle, and $P_{(\text{Death c})}$ is the average death probability of all patients in that cycle. $P_{(\text{Death from MACE i,c})}$ and $P_{(\text{Peri-operative death i,c})}$ were capped such that their sum could not be greater than 95% of $P_{(\text{Death i,c})}$. The probability of death from other causes was calculated as:

$$P_{(\text{Death other i,c})} = P_{(\text{Death i,c})} - P_{(\text{Death from MACE i,c})} + P_{(\text{Peri-operative death i,c})}$$

so that the overall probability of all cause death in the cycle was preserved as initially forecasted by Revaz AI.

It was assumed that MACE, death, and non-MI-related revascularization rates were higher during the first model cycle, as observed in the Kaplan–Meier curves of SYNTAX[1] and other trials. A higher proportion of 3-year MACE and mortality risks was assigned to the first model cycle, covering initial treatment and short-term recovery. Remaining 3-year mortality and MACE probabilities were then divided evenly across the remaining 11 cycles in that period.

Probabilities from cycles 13 through 20 were calculated by subtracting the individuals' Revaz AI-derived 3-year probability from their 5-year probability and assigning the difference evenly across those 8 cycles. In some cases, Revaz AI's estimated 5-year probabilities of either mortality or MACE were similar to or marginally lower than the same individual's 3-year probabilities. To account for this, lower bound mortality probabilities were calculated based on the annual death risk for members of the Canadian general population aged 65-70, translated into a quarterly probability. Lower bound MACE risks were calculated based on the annual incidence of MI or stroke among Canadians aged 65-70, again translated into quarterly probabilities. Individuals faced the higher of either the lower bound risk or their individual predictions from Revaz AI in each cycle.

In cycles beyond 20, cycle 20 risks were repeated, adjusted based on the change in relative risk of mortality between the patient's starting and current age in the Canadian general population.[29] For example, the annual death probabilities for a 65-69 year old, 70-74 year old, and 75-79 year old in Canada are 1.14%, 1.77%, and 2.90%, respectively. An individual who entered the model at age 65 would have their cycle 20 death risk multiplied by 1.77/1.14 = 1.55 in cycle 21 when they would be 70, and 2.90/1.14 = 2.54 in cycle 41 when they would be 75. Death risk was set to 100% in individuals older than 100 years to account for the lack of quality risk data at extreme ages. This had a minimal impact on overall results, as the probability of surviving to 100 was very low for all patients.

The risk of revascularization without MI was based on initial treatment modality, occlusion type, and observed rates in the literature. Risks were assumed to be tripled in the first cycle. Individuals who required repeat revascularization without MI were returned to their previous state following treatment if they did not experience death in the short term.

In patients assigned to repeat revascularization, either with or without MI, treatment modality was randomly assigned to be one of either PCI or CABG. This assignment was random because updated Revaz AI predictions would depend on changes in patient health state between the initial and repeat treatments, which were not available.

Individual-level Revaz AI risks were consistent across model iterations, but all other parameters were randomly sampled from a normal distribution. Standard deviations were set relative to mean values; for example, a 30% probability with a relative standard deviation of 0.2 had a standard deviation of 6%. Time-related probabilities are reported as annual but were converted into quarterly by the model.

For clarity, Table S10 shows example simulation-level data for five patients from the primary analysis. Table S11 shows the results from five simulation runs for one of the five patients.

Costs

Table S12 reports all costs used in the simulation model in 2024 US dollars. Where necessary, costs were converted to US dollars at purchasing power parity[30] and inflated to 2024 prices using the Bureau of Labor Statistics' Consumer Price Index for Medical Care.[31]

Initial treatment cost and the cost of repeat revascularization during follow-up were based on trial data averaged across the EXCEL, SYNTAX, and FREEDOM trials.[2] MT patients were assumed to receive diagnostic catheterization. Additionally, PCI procedures incurred a consumable cost for second generation drug eluting stents, with the number of stents determined by the type of occlusion. Acute procedure costs were assumed to be gamma distributed, with variance equal to 5 times the mean. Values were simulated at the individual procedure level.

Ongoing post-procedure management costs were taken from the literature and included outpatient care, rehabilitation where necessary, and physician fees. Additionally, patients were assumed to follow a drug regimen for the remainder of their lives based on their diagnosis and treatment. Patients who presented with stable angina and received revascularization were assigned aspirin 325mg, a statin (atorvastatin 40mg), and an ACE inhibitor (lisinopril 5mg). If those patients were assigned to MT, a beta blocker (metoprolol 100mg) and a calcium channel blocker (amlodipine 5mg) were added. For patients who presented with unstable angina or NSTEMI, regardless of treatment, clopidogrel 75mg was added.

Patients who suffered a MACE had additional costs applied. Each MACE had an initial cost of treatment, as well as an ongoing follow-up cost for the remainder of the patient's life. Patients could suffer repeated MACEs of the same type and would accrue acute treatment costs each time, but ongoing costs did not increase with repeat episodes of the same MACE type.

All ongoing costs varied randomly at the simulation level. Draws were normally distributed with a standard deviation equal to 10% of the mean. Half-cycle corrections were applied to ongoing costs in cycles where the patient died.

Utilities

Health related quality of life (HRQoL) was estimated based on a model calibrated using the English general population.[32] Base HRQoL utility was estimated based on patient age and sex, representing a typical utility value for a healthy adult (Figure S6). Modifiers were then applied based on the individual's health conditions and treatment history. Patients could have multiple modifiers applied at once to reflect a history of multiple conditions and the impact of treatment. Cardiac health states were assumed to include MT, and no treatment modifier was applied for patients receiving MT for their condition.

The base utility was multiplied by modifiers indicating whether the patient had received either PCI or CABG in the cycle before or in the past, relative to expected HRQoL under MT (it was assumed that no patient received no intervention). Modifiers were based on reported changes in HRQoL post-treatment for patients in the EXCEL trial.[33] Table S13 summarizes the utility modifiers used in the model.

Base utilities were retained across simulations, but health state modifiers were randomly simulated with a normal distribution and standard deviation equal to 1% of mean. Treatment modifiers were simulated with a normal distribution and a standard deviation equal to 0.5% of the mean.

Primary and Secondary Analyses

The primary analysis focused on the test set patients with lifetime simulations. The secondary analyses investigated: 1) the test set patients with 5-year simulations; 2) all patients with lifetime simulations; and 3) all patients with 5-year simulations. Although the training set had been used to train the prediction models, all patients were used to produce more stable results based on the larger sample size since the focus of this study was health economic simulation rather than accurate estimation of prediction performance. Five-year simulations were conducted to exclude the assumed long-term effects of the selected treatment beyond the longest prediction horizon of Revaz AI, although this would underestimate the true QALY and cost benefits since most patient would survive longer than 5 years, as shown by Figure S3.

Simulation Scenarios

For each primary or secondary analysis, three scenarios were simulated. The same 1,500 simulation runs per patient were used in all three Scenarios to allow for a direct comparison among the Scenarios.

In Scenario 1, physicians were assumed to make the health economically optimal decision while adhering to a maximum willingness-to-pay threshold of $50,000 per QALY. Scenario 2 assumed that physicians maximized patient expected QALY with no cost threshold, because, in practice, physicians are likely less sensitive to health economic measures and primarily interested in maximizing benefit for their individual patients. Scenario 3 was an investigation of AI adoption where physicians pursued their originally selected treatment unless Revaz AI recommended an alternative which added at least 0.2 QALY to the patient's expected rest of life HRQoL. As in Scenario 2, physicians never opted for a treatment that resulted in worse outcomes.

Research Ethics and Reporting Guidelines

This study was conducted in accordance with the Declaration of Helsinki and approved by the Conjoint Health Research Ethics Board at the University of Calgary (REB20-1879). The need for informed consent was waived due to the large number of patients involved in the study.

This study followed the Consolidated Health Economic Evaluation Reporting Standards for Interventions that Use AI (CHEERS-AI)[34] checklist (see Supplementary Information).

Data Availability

The patient data used in this study contains real patient information and cannot be shared without permission from the data custodians, Alberta Health Services and Alberta Health. The simulated data may be shared upon reasonable request.

Code Availability

Our source code for the health economic simulation may be shared upon reasonable request.

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Author Contributions

TM designed and executed the health economic simulation, produced all results, and wrote the manuscript. AP conceived the study and provided feedback on the study design. EB prepared the patient data and Revaz AI predictions for the simulation model. BH, CJM, RW, and BT provided clinical input. CLFS and JL provided technical input related to AI and clinical decision support. JL provided feedback on the study design, wrote the manuscript, and oversaw the project. All authors critically revised the manuscript.

Competing Interests

AP and JL are co-founders and major shareholders of Symbiotic AI, Inc. BH and CJM are minor shareholders of Symbiotic AI, Inc. All other authors have no conflict of interest to declare.

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Tables

Table 1: Actual treatment compared to economically optimal treatment in Scenario 1 in the primary analysis (test set patients only, lifetime simulations). Of the total of 7,794 patients, 5,643 (72.4%) had their actual treatments altered. MT: medical therapy only, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft.

		Actual Treatment		
		MT	**PCI**	**CABG**
Optimal Treatment	**MT**	253	701	142
	PCI	226	970	108
	CABG	1,214	3,252	928
Net Gain/Loss		-597	-3,619	+4,216

Table 2: Actual treatment compared to QALY maximizing treatment in Scenario 2 in the primary analysis (test set patients only, lifetime simulations). Of the total of 7,794 patients, 6,107 (78.4%) had their actual treatments altered. MT: medical therapy only, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft.

		Actual Treatment		
		MT	**PCI**	**CABG**
QALY Maximizing Treatment	**MT**	4	9	0
	PCI	104	550	45
	CABG	1,585	4,364	1,133
Net Gain/Loss		-1,680	-4,224	+5,904

Table 3: Actual treatment compared to 'sticky' physician treatment decisions in Scenario 3 in the primary analysis (test set patients only, lifetime simulations). Of the total of 7,794 patients, 4,149 (53.2%) had their actual treatments altered. MT: medical therapy only, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft.

		Actual Treatment		
		MT	**PCI**	**CABG**
Decision Rule Treatment	**MT**	271	13	0
	PCI	214	2,204	8
	CABG	1,208	2,706	1,170
Net Gain/Loss		-1,409	-2,497	+3,906

Table 4: Actual treatment compared to economically optimal treatment in Scenario 1 in the secondary analysis that analyzed all patients in lifetime simulations. Of the total of 25,942 patients, 18,579 (71.6%) had their actual treatments altered. MT: medical therapy only, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft.

		Actual Treatment		
		MT	**PCI**	**CABG**
Optimal Treatment	**MT**	860	2,417	470
	PCI	881	3,464	428
	CABG	4,009	10,374	3,039
Net Gain/Loss		-2,003	-11,482	+13,485

Table 5: Actual treatment compared to QALY maximizing treatment in Scenario 2 in the secondary analysis that analyzed all patients in lifetime simulations. Of the total of 25,942 patients, 20,200 (77.9%) had their actual treatments altered. MT: medical therapy only, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft.

		Actual Treatment		
		MT	**PCI**	**CABG**
QALY Maximizing Treatment	**MT**	20	51	0
	PCI	464	1,987	202
	CABG	5,266	14,217	3,735
Net Gain/Loss		-5,679	-13,602	+19,281

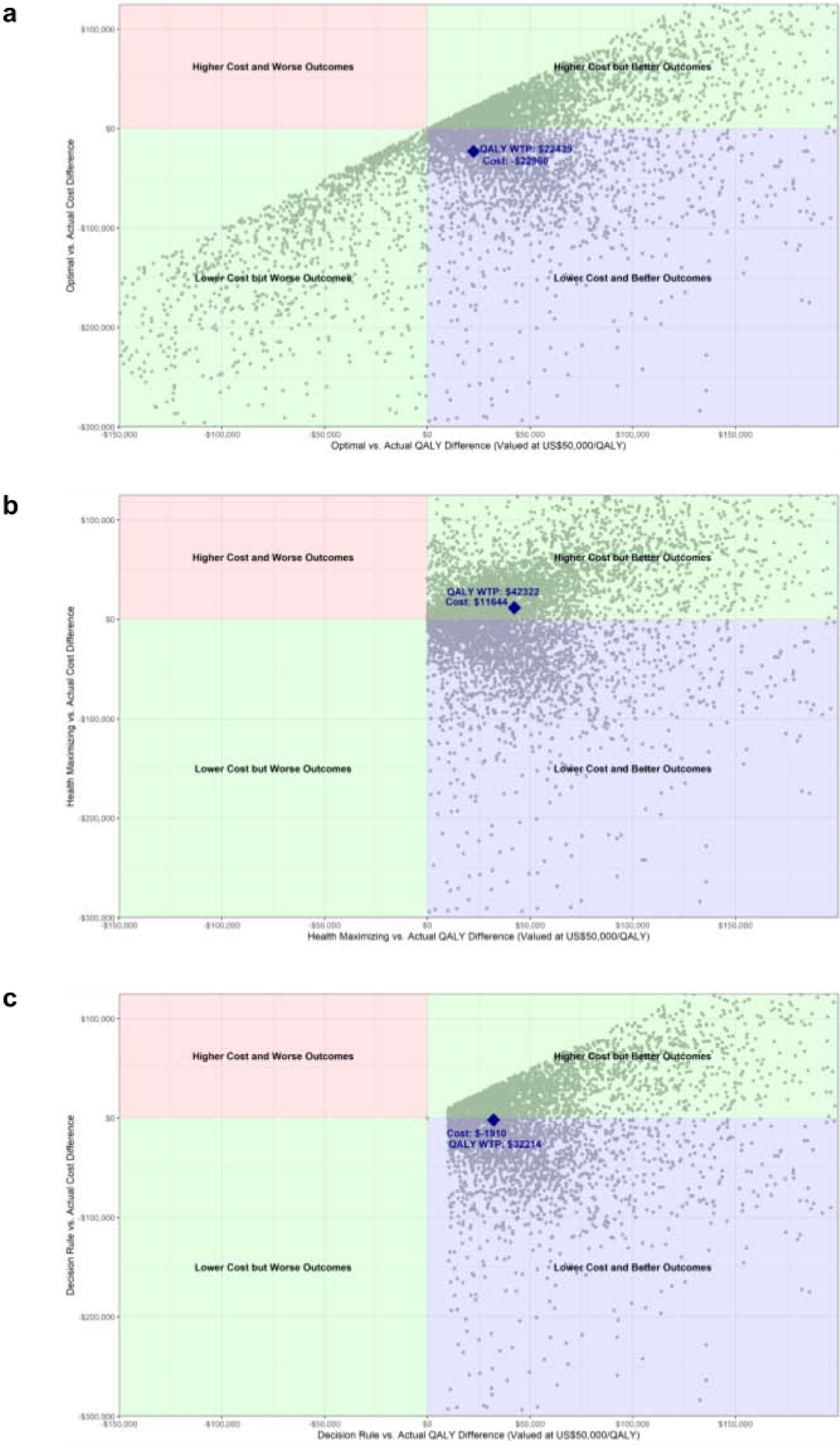
Table 6: Actual treatment compared to 'sticky' physician treatment decisions in Scenario 3 in the secondary analysis that analyzed all patients in lifetime simulations. Of the total of 25,942 patients, 13,451 (51.9%) had their actual treatments altered. MT: medical therapy only, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft.

		Actual Treatment		
		MT	**PCI**	**CABG**
Decision Rule Treatment	**MT**	930	35	1
	PCI	830	7,655	30
	CABG	3,990	8,565	3,906
Net Gain/Loss		-4,784	-7,740	+12,524

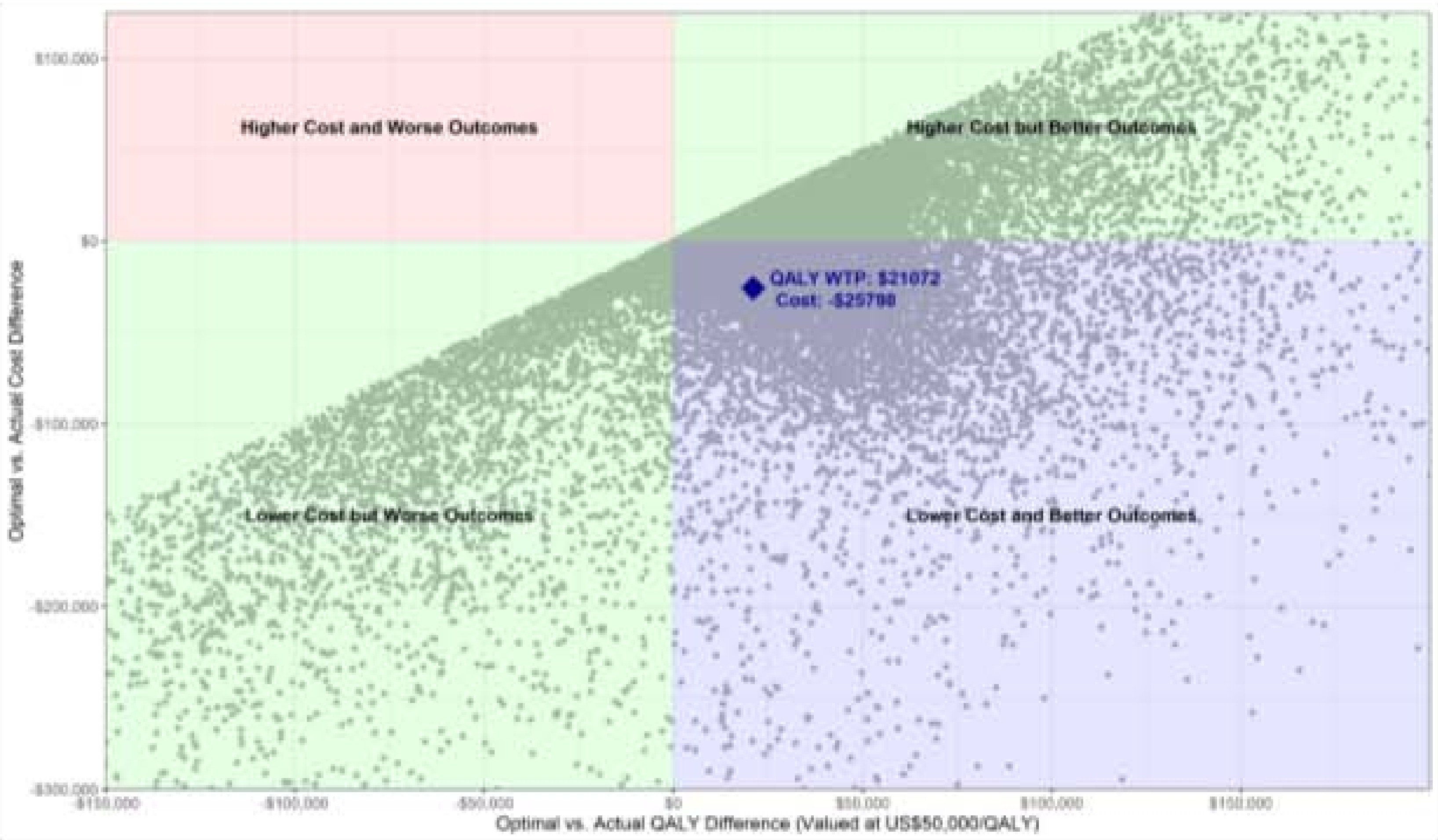
Figure Legends

Figure 1: Impact of Revaz AI on individual cost and health related quality of life outcomes in the primary analysis that analyzed the test set patients only in lifetime simulations for: a) Scenario 1 where the treatment that resulted in the maximum net monetary benefit created over the lifetime of the patient (i.e., QALYs valued at $50,000/QALY minus cost) was deemed optimal, b) Scenario 2 where the treatment that maximized QALY without a cost threshold was deemed 'health maximizing', and c) Scenario 3 where the 'decision rule' was that physicians followed Revaz AI only when there was a QALY gain of at least 0.2. Each point represents an individual patient. The x-axis represents the lifetime QALYs of the selected treatment in each Scenario minus that of the actual treatment, valued at $50,000/QALY. The y-axis represents the lifetime cost of the selected treatment minus that of the actual treatment. The net monetary benefit per patient under a given scenario is equal to mean QALY gain times $50,000/QALY minus mean cost difference (i.e., the two values shown at the blue diamond). WTP: willingness to pay, QALY: quality adjusted life year.

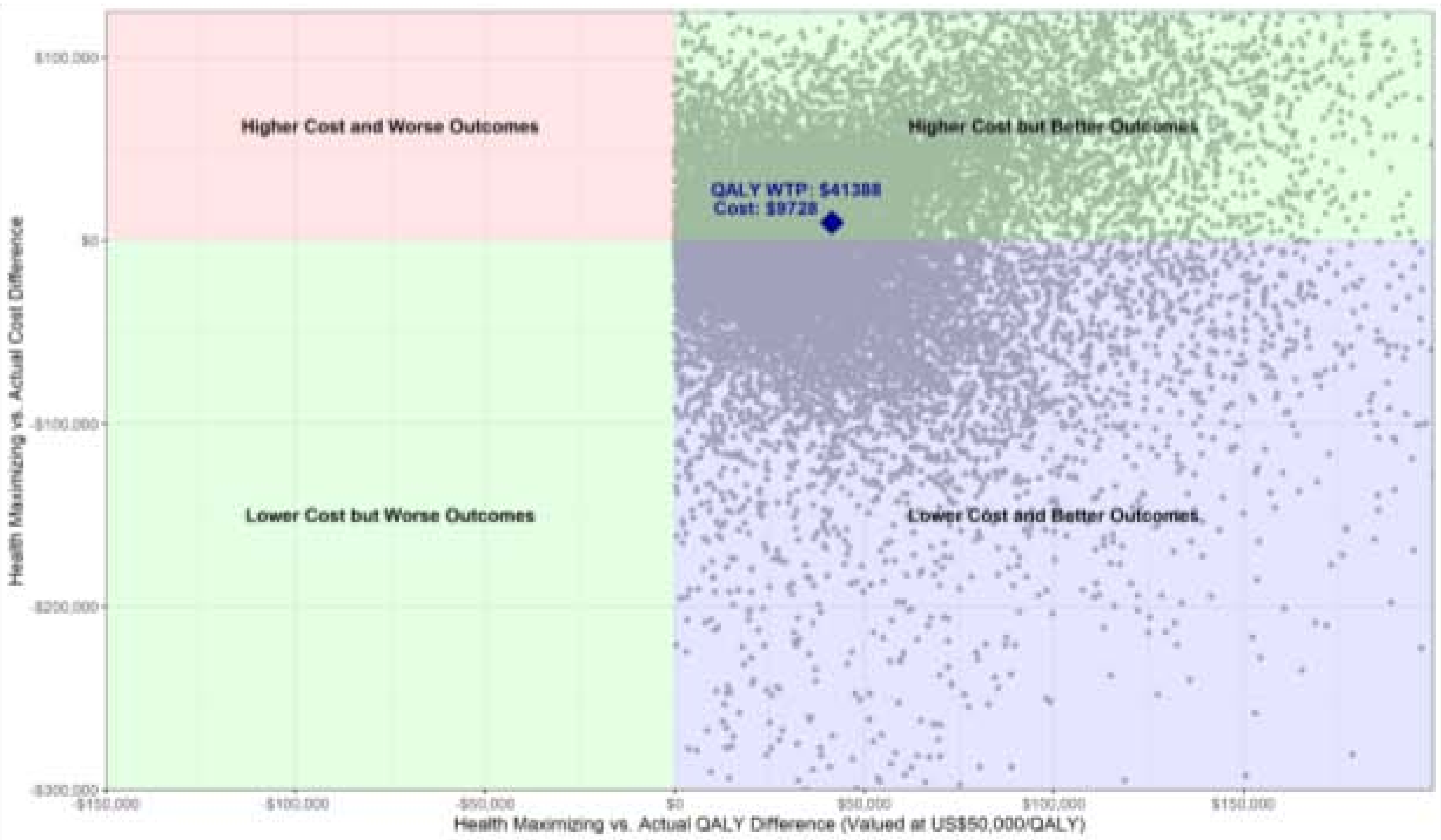
Figure 2: Impact of Revaz AI on individual cost and health related quality of life outcomes in the secondary analysis that analyzed all patients in lifetime simulations for: a) Scenario 1 where the treatment that resulted in the maximum net monetary benefit created over the lifetime of the patient (i.e., QALYs valued at $50,000/QALY minus cost) was deemed optimal, b) Scenario 2 where the treatment that maximized QALY without a cost threshold was deemed 'health maximizing', and c) Scenario 3 where the 'decision rule' was that physicians followed Revaz AI only when there was a QALY gain of at least 0.2. Each point represents an individual patient. The x-axis represents the lifetime QALYs of the selected treatment in each Scenario minus that of the actual treatment, valued at $50,000/QALY. The y-axis represents the lifetime cost of the selected treatment minus that of the actual treatment. The net monetary benefit per patient under a given scenario is equal to mean QALY gain times $50,000/QALY minus mean cost difference (i.e., the two values shown at the blue diamond). WTP: willingness to pay, QALY: quality adjusted life year.


a
Higher Cost and Worse Outcomes
Higher Cost but Better Outcomes
Lower Cost but Worse Outcomes
Lower Cost and Better Outcomes
QALY WTP: $22439
Cost: -$22960
Optimal vs. Actual Cost Difference
Optimal vs. Actual QALY Difference (Valued at US$50,000/QALY)
b
Higher Cost and Worse Outcomes
Higher Cost but Better Outcomes
Lower Cost but Worse Outcomes
Lower Cost and Better Outcomes
QALY WTP: $42322
Cost: $11644
Health Maximizing vs. Actual Cost Difference
Health Maximizing vs. Actual QALY Difference (Valued at US$50,000/QALY)
c
Higher Cost and Worse Outcomes
Higher Cost but Better Outcomes
Lower Cost but Worse Outcomes
Lower Cost and Better Outcomes
Cost: $-1910
QALY WTP: $32214
Decision Rule vs. Actual Cost Difference
Decision Rule vs. Actual QALY Difference (Valued at US$50,000/QALY)

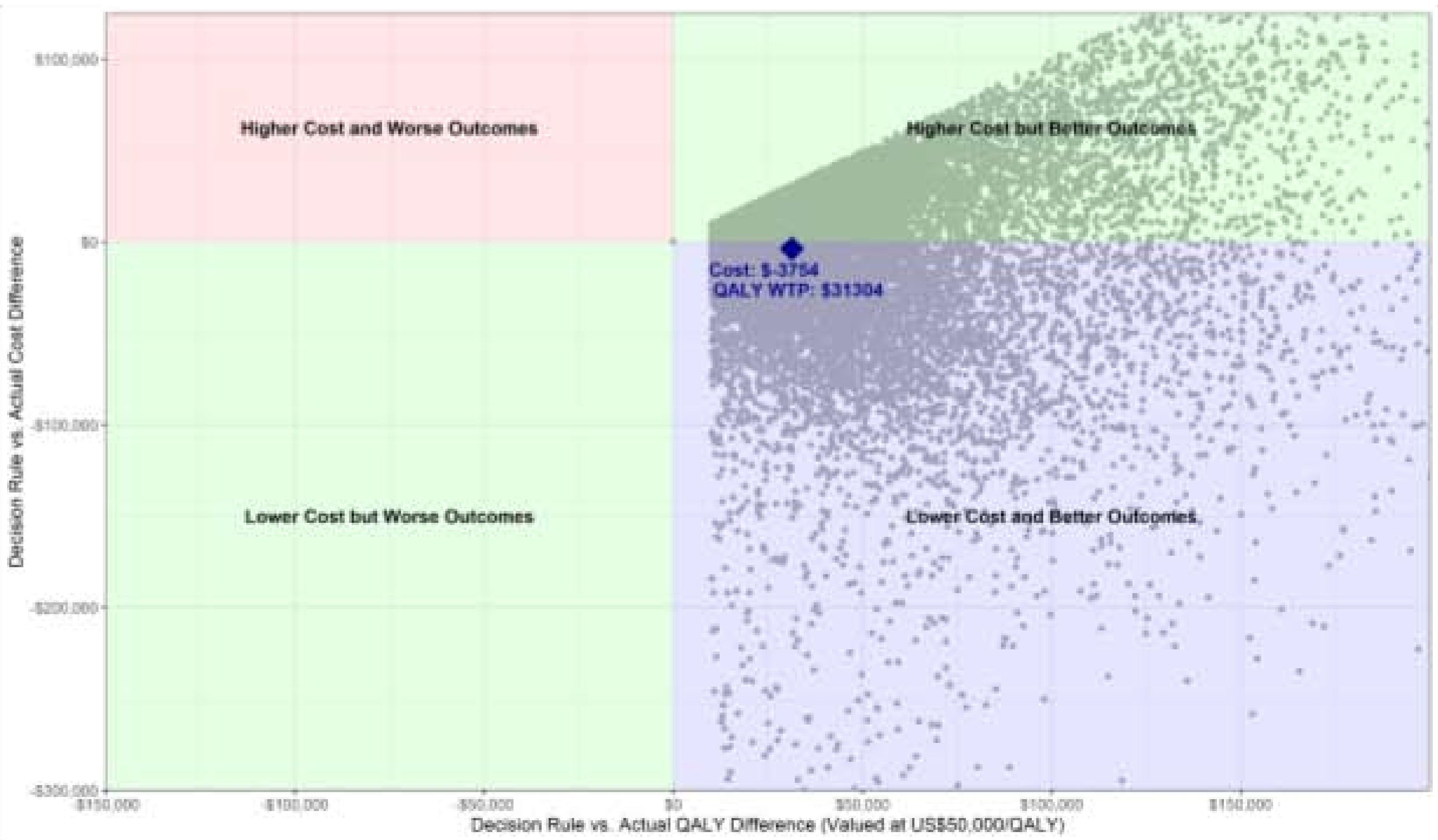
a


Higher Cost and Worse Outcomes
Higher Cost but Better Outcomes
QALY WTP: $21072
Cost: -$25798
Lower Cost but Worse Outcomes
Lower Cost and Better Outcomes
Optimal vs. Actual Cost Difference
Optimal vs. Actual QALY Difference (Valued at US$50,000/QALY)

b


Higher Cost and Worse Outcomes
Higher Cost but Better Outcomes
QALY WTP: $41388
Cost: $9728
Lower Cost but Worse Outcomes
Lower Cost and Better Outcomes
Health Maximizing vs. Actual Cost Difference
Health Maximizing vs. Actual QALY Difference (Valued at US$50,000/QALY)

c


Higher Cost and Worse Outcomes
Higher Cost but Better Outcomes
Cost: $-3754
QALY WTP: $31304
Lower Cost but Worse Outcomes
Lower Cost and Better Outcomes
Decision Rule vs. Actual Cost Difference
Decision Rule vs. Actual QALY Difference (Valued at US$50,000/QALY)