COST-UTILITY ANALYSIS OF USING POLYGENIC RISK SCORES TO GUIDE STATIN THERAPY FOR CARDIOVASCULAR DISEASE

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LAY ABSTRACT

Approximately 1 in 3 Canadians live with at least one genetically linked chronic disease. Together, these diseases constitute a large economic burden on the healthcare system and well-being of individuals. Recent advancements in genetics allow risk prediction of developing complex, but common chronic diseases such as cardiovascular disease. Termed as polygenic risk scores, they have the potential to carry beneficial clinical outcomes such as an improved quality of life. However, the economics is not yet understood. This study determined that when targeting heart attacks, approximately $750,000 is required to gain an additional life-year for an adult. Although this may seem high, the result is closer to an upper-limit estimate than the true cost since polygenic risk scores have more benefits than solely for heart attacks. In the future, when accounting for their entire potential, the cost per life-year is likely to be lower, and perhaps even a money-returning investment.

ABSTRACT

Introduction: There are no economic evaluations to determine the value of PRSs. The objective of this study was to determine if the addition of a PRS to traditional risk factors to guide statin therapy is a cost-effective intervention for the prevention of primary MI cases in the Ontario healthcare payer perspective.

Methods: A PRS cost-effectiveness model was constructed to produce various statin prescription strategies in conjunction with the FRS. Upper PRS thresholds (between 25% to 70%) were set such that individuals falling into them would be eligible for statins while those in lower PRS thresholds (between 1% to 25%) were deemed protected and removed from consideration. The model determined number of incident MIs saved or not saved by statins, costs, quality of life, and the effect of statins on preventing MIs over a 10-year time horizon, discounted at 1.5% annually. One-way sensitivity analysis and a PSA were performed by varying all model parameters. Non-related participants of white British descent from 96,736 participants in the UK Biobank at intermediate risk for cardiovascular disease, determined using the Canadian Cardiovascular Society dyslipidemia guidelines of 2016, were used for the study.

Results: The optimal clinical and economic strategy was one whereby the top 70% PRS individuals are eligible for statins, with the lower 5% PRS excluded. A base-case analysis at a PRS cost of $70 produced an ICER of $747,184.10/QALY, ranging from $525,678.90/QALY to $930,144.40/QALY in a one-way sensitivity analysis. In the PSA, the intervention has approximately a 50% probability of being cost-effective at $750,000/QALY. At a genotyping

cost of $0, statin strategies guided by PRS dominated standard care when at least 12% of the lower PRS individuals were withheld from statins. When the predictive performance of the PRS is increased, the ICER drops drastically depending on the cost of genotyping and statin strategy.

Conclusion: The cost-effectiveness model considers MI cases exclusively and a short, 10-year time horizon which likely overestimate the ICER. However, this study elucidates that the PRS has the potential to be extremely cost-effective in the future.

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LIST OF ABBREVIATIONS AND SYMBOLS

ApoB	Apolipoprotein B
CAD	Coronary artery disease
CVD	Cardiovascular disease
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CUA	Cost-utility analysis
CADTH	Canadian Agency for Drugs and Technologies in Health
DCE	Discrete choice experiments
EE	Economic evaluation
FRS	Framingham risk score
GWAS	Genome-wide association study
HDL	High-density lipoprotein
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
LDL	Low-density lipoprotein
NICE	National Institute for Health and Care Excellence
OR	Odds ratio

PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SNP	Single nucleotide polymorphism
WTP	Willingness-to-pay

1.0. INTRODUCTION

1.1. BASIC CONCEPS OF ECONOMIC EVALUATIONS

In a society of resource scarcity, a multitude of decisions have to be made about allocating healthcare resources to optimise health and economic outcomes.[1] In the pursuit of healthcare system efficiency, these resources are selected such that priority is given to treatments or interventions with the greatest benefit (efficacy or effectiveness) per unit cost.[2] To fulfil this goal, which is central to public health, a set of methods to summarise the costs and benefits of interventions against standard care in a systematic, analytical manner is required.[3]

Economic evaluations (EEs) are studies that can shed light on this objective as they measure the costs and effects of a specific intervention in comparison to another, or more generally, standard care.[3] The definitions of benefits, described below, vary widely depending on the research question and study design, however, costs are universal.[2] It should be noted, these studies are not simply accounting or attempting to cut costs, but rather, to highlight strategies with the intent of maximising benefits while acknowledging that resources are not unlimited. This is important as the least costly intervention might not pose clinical outcomes of suitable standards.[3]

The general framework of EEs poses two criteria; first, both costs and outcomes must be analysed, and second, at least one alternative strategy must be compared against the strategy of interest. Should a study solely examine the costs and benefits of a single strategy, the end result

is a cost-outcome description, not an EE. Subsequently, comparisons of two or more strategies with only cost as an outcome is also only a partial evaluation, known as a cost analysis. The most familiar studies in health science compare two or more strategies while only measuring benefits. Depending on the design, they are, for example, randomised controlled trials (RCTs) or an observational study.[4] Other important parameters in EE are the study perspective, time horizon, and discounting.[4,5]

The study perspective refers to the point of view adopted when deciding which costs and benefits are to be included in the study. This party is responsible for the delivery, payment, and receipt of care. The most comprehensive perspective is societal, which encompasses all direct and indirect (opportunity) costs, including loss of productivity such as reduced wages from the inability to work due to the illness or transportation, and changes in these losses associated with the new intervention. This perspective allows decision makers to compare between programs across the entire economy. However, it biases against individuals who might not be able to work prior to treatment onset due to old age or a pre-existing condition.[6] A more common approach is to use the healthcare payer perspective, which is simply tabulating the costs incurred on the healthcare system. As a result, productivity, lost income, or costs associated with taking care of kin are not included. However, different jurisdictions might have different varieties of health outcome information which are used as indicators of cost-effectiveness. In private healthcare systems, insurance and pharmaceutical companies might use large databases of real-world evidence to track which interventions and programmes deliver health outcomes of interest to subscribers.[6–8] The National Institute for Health and Care Excellence (NICE), based in England, and the Canadian Agency for Drugs and Technologies in Health (CADTH) agencies, which

publish guidelines on health technology assessment (HTA), recommend a public healthcare payer perspective.[5,9]

The time horizon is an important methodological consideration in EEs. It should be long enough to capture the major health and economic consequences relevant to the perspective. For patients, this includes all health states, both intended effects and unintended side-effects. It is common to see time horizons as long as a lifespan to capture the natural course of the condition, but also as short as one year depending on the study design or the sources of the parameters used in the EE. Longer time horizons, especially when extrapolation is necessary, should be performed in tandem with analyses of uncertainty.[4,5] Discounting aims to adjust for the phenomenon that costs and health outcomes that are predicted to occur in the future are usually valued less than present costs. Every subsequent year, the discounting factor increases based on a constant rate such that EE costs and benefits increasingly diminish. The NICE guidelines recommend that costs and health outcomes be discounted at 3.5% per year, while CADTH recommends 1.5% per year.[5,9] Nonetheless, discounting is a heavily debated topic, ranging from the rate itself to whether the same discount rate should be used for costs and health outcomes.[10] Common forms of EE are described below.

1.2. COST-EFFECTIVENESS ANALYSES

The difference between EEs lies in the manner that benefits or outcomes are reported. In a cost-effectiveness analysis (CEA), the outcomes are measured in unidirectional natural units such as lives saved, diagnosed strokes averted, change in a pain score, or change in blood

pressure. There are advantages to this approach. The use of natural units eliminates methodological issues related to outcome evaluation, most prominently observed during utility measurements (see 1.3. Cost-Utility Analyses). The outcomes are also more intuitive to grasp since the study objectives are engrained in the benefits, leading to easier knowledge translation for decision makers.[11] Nonetheless, while the intra-study comparisons between the intervention and comparator are straightforward, this is at the expense of inter-study results comparability, most prominently across different conditions. For example, it is difficult to ascertain the risk and benefits when comparing costs per stroke averted to costs per change in a pain score. The lack of amalgamation of benefits affects the applicability of CEAs because the impact of the intervention is not expressed in a single, common metric. This primary limitation is resolved when a universal method of measuring benefits is enacted.[4,11,12]

1.3. COST-UTILITY ANALYSES

Analogous to CEAs, cost-utility analyses (CUAs) also consider healthcare costs and health effects. However, outcomes of health care interventions are measured in units of health outcome that combine both, quality and quantity of life, and are therefore comparable across different interventions and health conditions.[13] This method produces a single numeric value to combine the duration and the quality of life gained in reference to a health state, known as the quality-adjusted life year (QALY).[2,14]

QALYs are calculated by estimating the total life years gained from a procedure and weighting each year to reflect the quality of life in that year. The quality weights are measured

using health utility values, which are measured based on the population preference.[1,13] They are anchored at 0 and 1, corresponding to death and perfect health, respectively. The conversion from utility values to QALYs is fairly straightforward with the multiplication of the former by the duration spent in its respective state.[15]

Utility values for preference-based measures can be found either directly or indirectly from numerous groups, including members of the general population, patients affected with the specific disease, carers, and health care professionals.[16] Common methods for direct measurements of health states include the standard gamble, time trade-off, and a rating scale. However, they are all resource intensive as they require the accurate development of health state descriptions and access to a representative sample. Since this is not a feasible endeavour for most CUAs, utility values from published literature are used with a gender, age, or disease specific population of interest. Next, indirect, or preference-based health state classification systems, are produced from questionnaires designed to determine respondents' health states with a scoring algorithm. Common examples of such tools include the EQ-5D, the Health and Utilities Index, the Quality of Well-Being scale, and SF-6D.[17]

The limitations to CUA are centred around the benefits aspect of the EE, or more specifically, the utility values and subsequent QALYs. First, there is significant variation in health utilities of a specific states depending on the tool. The standard gamble generally produces higher values compared to the rating scale. Such a variation in health utilities, which are key inputs to EE could alter the cost-effectiveness conclusion. This pattern of dissonance is also found in indirect methods of measuring health states.[14,18] Second, utility values are generally

elicited from the general public, as recommended by agencies such as the NICE and CADTH.[5,16,19] The rationale is that healthcare is (at least partially) publicly funded and members of general public, unlike patients with the disease in question, do not have a vested interest in the EE results. However, since "quality of life" is a vague concept, they might not grasp hypothetical health states compared to patients who have, or are experiencing the condition, leading to different valuations. As a result, the choice of values can impact the conclusion of the CUA.[16,20] Third, QALY values are dependent on the time at which utility values were measured or calculated and therefore, have a time-preference..[14] Although this issue can be solved with discounting, a related problem with respect to time preference comes from the backend analysis of QALYs. When using a differential discounting rate for costs and QALYs, whereby the latter is lower, a technical flaw in the CUA outcome, coined "postponing paradox" takes place. The effect is that continuously postponing an intervention would lead to a more favourable cost-effectiveness conclusion.[21] Fourth, all QALYs are assumed to be equal. However, lower valuation could be attached to later life years than to earlier years which would underestimate the true QALYs of given individuals.[22] Additionally, with the influence of other factors such as the study time horizon or the severity of the health state, individual patient utility values might not be accurately represented.[23] Fifth, there has been concern over the additive structure of utility values across time, such as years, coined as intertemporal utility independence. Although this allows for simplifications in analysis, utilities in different health states that are additively separable suggests their independence. Few issues of this assumption are that utilities values are not independent of each other, resource consumption could vary depending on the health states, and neutrality over the timing of health states is not an accurate depiction of disease trajectory.[24,25] Sixth, health states that are "worse than death" pose difficulties in measurement of

utility values themselves. However, understanding respondents' thought process for these unique health states is the scope of further research.[26] Finally, there are ethical considerations when assigning QALYs on individuals of different ages or livelihoods as CUAs assume utilitarianism, which emphases on the net sum of, or societal benefits without regard to the individual distribution of benefits, as the acceptable doctrine.[27] A balance between community preferences and individual preferences or patient autonomy is challenging, but necessary when decisions regarding clinical judgement and resource allocation are required.[28]

CUA and the associated QALY approach are recommended EEs by a few HTA bodies including NICE and CADTH.[5,9] However, the appeal to using QALYs as a measure of determining cost-effectiveness lies in its comparability across diverse conditions and interventions. Nonetheless, the limitations, especially when different instruments are used, need to be taken into consideration when calculating single values to estimate health states. This will ensure credibility of CUA in decision making.[18]

1.4. COST-BENEFIT ANALYSES

CEAs and CUAs express health benefits in non-monetary units such as changes in blood pressure or QALYs. However, the cost-benefit analysis (CBA) is unique since both, costs and benefits are reported in monetary units. The theoretical framework behind the CBA is welfare economics, whereby the contribution of a certain good to social welfare as a whole is determined by deducting all social costs from all social benefits.[29] In a healthcare context, the final evaluation, or net monetary benefit is calculated by taking the difference in benefits subtracted

by costs of the intervention or program of interest. Benefits are generally measured through willingness-to-pay (WTP) surveys or discrete choice experiments (DCEs). The WTP method requires participants to value healthcare outcomes by asking them how much they are willing to pay to obtain the benefits or avoid the associated costs of illness.[30] In DCEs, participants are asked to state their preference of several scenarios that correspond to the attributes of interventions. Preferences are revealed without participants explicitly being asked to state their preferred level for each individual attribute.[31]

It should be noted that a comprehensive, societal perspective is required when performing a CBA. This enables decision makers to compare the monetary returns on investment of one program against the returns of, for example, another program which could possibly exist in a different area of the economy. Therefore, CBA aims to determine whether an individual intervention offers an overall net welfare gain to society in addition to how this gain compares against alternative interventions.[29,32] CEA and CUA, however, are centred around constrained optimisation whereby individual well-being should be maximised under a budget constraint.[33]

There are several limitations of CBAs, primarily due to the difficulty in cost and benefit measurement. First, accounting for all the costs in a large-scale health intervention is challenging, more so when the program impacts many agencies. Second, public and institutional behavioural change might occur when policies are implemented, flawing original estimates.[34] Third, WTP thresholds are heavily dependent on the characteristics of the individuals. A prominent factor is income because answers correspond to the differential valuation of money

and the health benefits amongst participants.[35] CBAs, while common in other fields, are rare in HTA.[3]

1.5. METHODS OF PERFORMING ECONOMIC EVALUATIONS

To inform decision making for finite resource allocation, the two most common methods of performing EEs are either via RCTs or decision-analytical models, shorthanded to trial-, and model-based, respectively. The rationale of RCTs as vehicles for determining cost-effectiveness is clear; since at least two groups are compared with the sole difference being the intervention of interest, the only additional steps include tabulating costs (and utility values if performing a CUA). Models, however, use pre-existing evidence from multiple sources for clinical, resource use, and outcome data. They create mathematical relationships between various health states to produce clinical pathways characterising the range of possible disease prognoses for simulated patients, with and without the intervention.[4,36]

RCTs are generally commissioned due to lack of high-quality existing evidence in literature on the treatment effect. Therefore, they provide early opportunities to produce reliable estimates of cost-effectiveness data. The individual-level data used in these studies also allow researchers to apply a wide variety of statistical and econometric techniques to test hypotheses between clinical and economic parameters. Additionally, although running RCTs are generally expensive, the marginal cost of adding variables to study the economics of a certain intervention is low. Coupled with the rich data they provide, trial-based EE are a powerful set of methods in HTA. However, general criticisms against the structure of RCTs, derived from their low external

validity, spill over to cost-effectiveness studies as well.[37,38] Their focus is narrow as they are limited by the number of interventions and comparators. This is further problematic when the study population or country of origin is not relevant to other populations or countries. Additionally, since RCT-based EE only use evidence from one study, they fail to incorporate all other relevant evidence such as other trials, observational studies, or real-world evidence.[38]

Decision-analytical models to determine cost-effectiveness of interventions are primarily motivated by the lack of either long-term outcome data or information comparing all relevant treatments within RCTs.[39] Additionally, they are not constrained in the initial study design, but rather, intrinsically modular in structure that allow for the comparison of many treatments and patient trajectories. Mentioned above, although models can draw from a variety of sources for their input parameters, caution must be taken to ensure they are of high quality and relevant to the research question. As a result, it is vital to subject the model to sensitivity analyses to test uncertainty. Assessment of uncertainty also permits a more nuanced set of decision options related to the strategies in the EE compared to the possibly fewer outcomes provided in a trial-based EE. Finally, the modular nature of parameters provides flexibility to characterise the heterogeneity in different patient groups or subgroups of populations.[4]

The simplest decision analytical models found in literature are decision trees. All patient trajectories are laid out with their associated probabilities and outcomes listed at terminal nodes. The mean value of each branch is calculated by summarizing the aforementioned probabilities and outcomes. This method is only practical for interventions with simple prognoses, short time-horizons, and few reoccurring events. Modelling individual heterogeneity and interaction

between individuals are not possible. Next, the most common models found in literature are Markov models, which allow for longer time horizons and events to repeat. Mutually exclusive and exhaustive health states are defined such that simulated individuals cannot occupy more than one at a point in time, or cycle. The simulated participants transition from one state to another based on predefined transition probabilities. Time spent in each state corresponds to a cost and utility, which is then aggregated to determine a summary of an intervention or comparator, followed by the cost-effectiveness. Markov models do not allow for transition probabilities to change and health states that simulated individuals occupy in previous cycles have no effect on the health states occupied in subsequent cycles. Similar to decision trees, interaction between individuals is not possible. Last, individual-based models such as microsimulations, agent-based models, or discrete event simulations resolve the issues faced in decision trees and Markov models. They can program patient history such as previous health conditions or events to more accurately depict health trajectories and allow for individual-individual interaction.[4,36,39,40] However, individual-based models are more challenging to program.

1.6. INTREPRETATION OF ECONOMIC EVALUATIONS

As described in a previous section (1.1. Basic Concepts of Economic Evaluations), formal EEs have the costs and benefits of an intervention strategy in addition to a comparator to objectively assess the value of the former. Since CEAs and CUA are studies that are functions of constrained optimisation, examining the incremental, rather than absolute, costs and health benefits allow clinicians and policymakers to make more rational decisions regarding clinical care and resource allocation.[6,33]

A single metric that allows for comparisons is the incremental cost-effectiveness ratio (ICER), defined as the ratio between the difference in costs (currency) and the difference in health benefits (for example, number of strokes averted, QALYs) of the intervention and comparator. The ICER is not a difference of two cost-benefit ratios. This would have a different meaning and would not allow for incremental comparisons. The interpretation of ICER values is fairly intuitive: a value of $100,000/QALY means that one would expect to gain one QALY for an additional $100,000 spent towards the intervention on the study population. The benefits of CUAs are clear in conjunction with ICER values as different health programs become comparable. Frequently in literature, the abbreviation ICUR is used in lieu of ICER when the EE is a CUA. [6,41]

However, EE and their corresponding ICER values cannot dictate decisions. Rather, they are instruments to inform decision makers about the evidence to either support or reject the reimbursement of an intervention. They can also inform national clinical guidelines or institutional practice standards and governmental research funding directions.[4,5] Implementation is dependent on several known and unknown factors such as the cost-effectiveness threshold (if one exists), the type of decision maker, purpose of the EE, and perspective.[41] Thresholds are a controversial and heavily debated topic in the HTA sphere due to the lack of consistent theoretical and empirical criteria. Unofficial figures are scattered throughout literature but few jurisdictions have explicitly acknowledged a specific value.[42] The analytical method to arrive at a threshold is not clear and any consensus would likely be met with various political and societal hurdles.[41] Canada does not have a threshold.[5] Additionally, should an official threshold exist in

any jurisdiction, it is likely decision makers would feel greater obligations and public pressure to introduce an intervention to the healthcare system.[43] The perspective of an EE is also important because it determines which costs and benefits the authors included in the analysis. Depending on the healthcare system, patients themselves might have different thresholds and could possibly have a higher WTP for improved quality or length of life. Insurance companies might also have multiple thresholds depending on the demands of their subscribers and corresponding plans, which itself is loosely related to personal thresholds.[41]

Results of an EE can also be visualised using a two-dimensional plot referred to as a cost-effectiveness plane with the benefits on the abscissa (x-axis) and the costs on the ordinate (y-axis). Generally, the current practice or standard care is plotted on the origin to ensure that all subsequent datapoints represent incremental values and that the ratio between the coordinate points produces the respective ICER value. New interventions are located on the right or left if they are more or less clinically effective, and above or below the origin if they are more or less costly, respectively.[6] When an intervention is both less costly and clinically beneficial, the datapoint is located on the southeast quadrant is referred as the dominant strategy. Subsequently, a dominated strategy is neither less costly or clinically beneficial and occupies the northwest quadrant. These interventions can be discarded as not cost-effective under any threshold. The majority of studies report interventions that are more costly and clinically beneficial, and as a result, occupy the northeast quadrant. For such interventions, cost-effective thresholds are one of many tools at the disposal of decision makers to determine cost-effectiveness.[44] When more than two datapoints are plotted on the same plane, the resulting line connecting them is the cost-effectiveness frontier. Interventions located to the northwest of a comparator datapoint on the

frontier are strictly dominated by the latter as they are both more costly and less clinically beneficial. Interventions that are northeast of a datapoint on the frontier, having more benefits and costs, are referred to have extended dominance. These terms are relative to the comparator and cost-effectiveness should ideally, but not always, evaluated in conjunction with defined cost-effective thresholds.[4,6,44,45]

1.7. SENSITIVITY ANALYSES

Measuring uncertainty in EEs is paramount to inform decision making in health services as it allows evaluators to assess the methods, increase the study generalisability, make the results more comprehensible during extrapolation, and explore the implications of selecting a particular analytical method amongst alternatives when no widely accepted approach exists.[46]

Base-case analysis refers to the economic model or analysis from the preferred set of parameters and assumptions. In matured fields, accepted methods and assumptions are outlined such that the analysis is referred to as the reference case. This ensures a baseline level of consistency between studies for assessment by, for example, a regulatory agency.[4]

There are numerous forms of sensitivity analysis, which are 2nd order, or parameter uncertainty. Deterministic sensitivity analyses involve varying one (one-way or univariate) or more (multi-variate) parameters simultaneously of an EE to observe their respective effects on the ICER value. Plotting the range of ICER values with each shifted parameter informs decision makers of the main drivers in uncertainty; a variable producing a wide range of ICER values

would cause for further investigation and analysis. Several limitations exist against the deterministic sensitivity analyses. First, the range of values chosen is generally arbitrary, leaving ambiguity as to the importance of a variable and the effect of the corresponding ICERs. Second, deterministic approaches do not take into the account of correlations or non-linearities between two or more variables. This leads to biased estimates of costs and benefits. Last, the results contain no information on the likelihood that a specific range is observed in practice. In fact, tornado diagrams, the plots produced from deterministic sensitivity analyses, might mislead decision makers by overrepresenting variables with large ranges, even if the probability that their true value equalling an extreme value is low frequency. As a result, overly pessimistic factors could cloud judgement.[46–48]

The probabilistic sensitivity analysis (PSA) is a stochastic technique that resolves these issues by assigning each parameter a range and distribution. In a worst-case scenario, no information apart from the minimum-maximum range is known and all distributions are uniform. Generally, the mean, standard deviation, and distribution is known (or specific distribution parameters). Monte Carlo simulations are performed to simultaneously sample a value from each parameter range in the model and produce ICER values. The values can be plotted on a cost-effectiveness plane and the proportion that lie under a certain WTP threshold can be consequently assigned a datapoint on a cost-effectiveness acceptability curve (CEAC). By adjusting the WTP threshold from a minimum to maximum value, many datapoints can populate the CEAC to produce a curve describing the probability of an intervention being cost-effective at a given WTP threshold.[48] It is important to highlight that a PSA does not reduce the uncertainty

of a given EE, but simply represents it more accurately.[47] Both, NICE and CADTH recommend the use of PSA.[5,9]

1.8. CARDIOVASCULAR AND CORONARY ARTERY DISEASE

Atherosclerotic cardiovascular diseases (CVD) are some of the leading causes of death in Canada for both, men and women.[49] Together, they constitute a large economic burden on the country; in the magnitude of $6.4 billion for direct costs and $1.9 billion for indirect costs. The latter is likely underestimated, however, as it includes short-term disability exclusively.[5,50] Hence, there is a public health and economic desire to improve the prediction of CVD onset in order to treat susceptible individuals.

Coronary artery disease (CAD) is a type of CVD that refers to the remodelling and narrowing, or blockage of the coronary arteries via LDL-derived plaque. This process is atherosclerosis and with time, can result in the partial or total restriction of blood flow to the heart. CAD can have various clinical manifestations, including stable angina, unstable angina, MI, or sudden cardiac death.[51] Risk is a function of lifestyle, environmental, and genetic factors with the likely possibly of interaction. Specific risk factors include, but are not limited to, smoking, diabetes mellitus, hyperlipidaemia (increased levels lipids such as triglycerides or low-density lipoprotein [LDL] and decreased levels of high-density lipoprotein [HDL] cholesterol), hypertension, obesity, lack of exercise, and psychosocial stress.[52] The current framework of CVD risk assessment in Canada uses modifiable, phenotypic risk factors such as the aforementioned parameters, some of which are outlined in the Framingham Heart Study.[53–55] Repeated

measurement of these traditional risk factors would improve prediction by accounting for their accumulated nature, such continuous smoking or rising blood pressure.[55] However, genetic factors with predictive capacity can illustrate susceptibility of CAD in addition to the role of environmental interactions which leads to disease onset in the first place.[56,57]

1.9. MODIFIABLE RISK FACTORS IN THE FRAMINGHAM RISK SCORE

The hallmark longitudinal Framingham Heart Study in 1961 formalised phenotypic risk factors that are used in North America as a validated means of predicting CVD.[58] These sex-specific factors include age, total and HDL cholesterol, systolic blood pressure, treatment for hypertension, smoking, and diabetes status.[59] A Framingham risk score (FRS) is outlined in the Canadian Cardiovascular Society dyslipidemia guidelines of 2016 as a 10-year risk percentage which can be derived from a simple tabulation of the aforementioned factors to classify individuals as low (< 10%), intermediate (10 – 19%), and high risk (≥ 20%).[54] Statins are prescribed to patients who either fall in high risk; have a stain-indicated condition (e.g. chronic kidney disease or certain a particular profile of diabetes such as being over the age of 40); or other parameters (e.g. a high waist circumference) in conjunction with intermediate risk.[54]

Although FRSs are ubiquitously used to determine patient CVD risk in clinical settings, they were based on an American population. This has caused a discussion regarding their validity on other populations, which can have large implications in health economic analyses to predict the risk for future CVD events.[60] There are slight deviations depending on the specific cohort, such as ethnicity or sex, however, the FRS are fairly accurate in primary care settings.[61,62]

There are some populations whereby events are overestimated, however, in European, notably British individuals, the FRS is reasonable accurate.[60]

1.10. GENETIC ARCHITECTURE OF CORONARY ARTERTY DISEASE

Hereditary, defined as the proportion of phenotypic variation in a population (not individual) that can be explained by genetic variation, has been shown to confer CAD risk at varying levels of genetic complexity, as described below.[63] Early studies have reported that it increases with greater numbers of affected relatives and onset in a young age.[64] A concordance study with approximately 10,000 twin pairs found that when one sibling died from CAD, the relative hazard of death by CAD for the other was double in males and nearly six times in females. Heritability ranged between 38% to 57% for females and males, respectively.[63,65] A different, older study of nearly 8,000 like-sexed twin pairs reported 53% for both, females and males, however, discrepancy between the two studies has been explained.[66] Family history is a very important factor, such that an increased risk of CAD is at least two-fold when a first-degree relative also has CAD. In populations associated with early-onset CAD, a subset of individuals who had a first-degree relative with CAD had up to a five-fold increased risk of concurring it themselves.[67]

The most basic form of CAD genetic architecture follows a Mendelian pattern of inheritance. For example, familial hypercholesterolaemia is a disorder caused by a single, rare, mutation. However, when observing families with a high incidence of CAD and MI events, they do not appear to fit this Mendelian pattern, suggesting a more complex form of CAD inheritance.

In fact, current evidence suggests that CAD and most common diseases have a genetic architecture that is polygenic in nature rather than the more familiar, monogenic form.[68] The effect can very pronounced, such that 1 in 53 individuals with early-onset CAD have a polygenic contribution of risk at the same magnitude as familial hypercholesterolemia.[69] Nonetheless, the presentation of CAD is likely multifactorial, reflecting the presence of shared genetic and environmental factors.[51,52]

1.11. POLYGENIC RISK SCORES IN CARDIOVASCULAR DISEASE

A polygenic inheritance pattern suggests that many common genetic variants of small effect play a greater role compared to single or few rare monogenic mutations.[70] Genome-wide association studies (GWASs) help identify these variants by analysing subsets of the genome of individuals with and without the disease of interest. Using single-nucleotide polymorphisms (SNP) arrays, the SNPs of cases and controls can be compared against each other to determine which variant is associated with the disease. It is important to note that thresholds of association exist to prevent every variant from being implicated with the disease.[71]

The polygenic risk score (PRS) is a product of GWASs. The risk-conferring SNPs or alleles are summed up and weighted by effect sizes derived from the GWAS results. As a result, the PRS can quantify individual-level risk via a weighted sum of risk-conferring common variants, as shown in Equation 1:[72,73]

$$r_i = \sum_{j=1}^{m} \beta_j x_{ij} \quad (1)$$

whereby r_i represents the value of the risk score for the ith individual, i represents the number of individuals, j is the number of SNPs, β_j ("beta values") is the weight for each SNP that were derived from the GWAS, and x_{ij} is the number of alleles for the j^{th} SNP of the i^{th} individual. The result is a personalised score for each patient which can reflect the relative risk of developing the trait using regression. It follows that using genotypic factors in addition to phenotypic factors could yield a stronger prediction and stratification of disease than phenotypic factors alone.[74,75] This has clinical importance since genetic disposition is the earliest measurable risk factor against all others, for example, serum lipid testing. As a result, PRSs allow clinicians to enact preventative interventions with known benefits in the clinical settings before disease onset. These interventions can vary from changes in lifestyle such as diet and exercise, to pharmacological interventions such as the use of statins.[68]

Clinical trials and meta-analyses have shown the application of PRSs produced improved screening strategies as well as surrogate health endpoints, such as guiding statin therapy to lower low-density lipoprotein levels and possibly CAD events as well as selecting patients who might have the greatest benefits from statins.[74,76–80] Individuals with the highest burden of genetic risk would have the largest relative and absolute clinical benefit from statin therapy.[74,78,79] Therefore, their application to directly target CVD with clear, preventative interventions might have beneficial clinical outcomes with positive health effects, notably by guiding statin therapy.[5,55]

There are several technical limitations which could reduce the predictiveness of the PRS in practice. First, genetic markers cannot intrinsically capture the entirety of a disease phenotype. The former cannot account for the huge variation in the latter. The added burden is that, ideally, all genetic variants affecting the trait of interest should be known and estimated without error. Environmental factors add an additional layer of complexity. Second, since the effects of SNPs that lead to a PRS are produced from a finite number of individuals, the effects might have some degree of sampling error. This is cause for concern since most complex traits, such as CAD, are not products of few genetic variants, but rather, millions. When the effect of each SNP is very small, the accuracy of the estimate could be low.[81] Third, linkage disequilibrium, which is the phenomenon that alleles are non-randomly dispersed in the genome, is necessary to correct in GWASs.[71,81–83] It is possible that a risk conferring SNP is physically close to another SNP, which could result their inheritances to be associated. As a result, both SNPs might be erroneously labelled as risk conferring. Statistical adjustments exist to correct for linkage disequilibrium, however, there is a debate over which method is ideal.[81,83]

2.0. STUDY RATIONALE AND OBJECTIVES

2.1. RATIONALE

The field of medicine is undergoing a paradigm shift whereby personalised therapies, fuelled by 'omics', can have profound implications in the capacity to understand the breadth of disease. Additionally, over the past decade, there has been a rapid increase in the volume, variety, and velocity of individual-level data generation coupled with improved data collection, storage, cleaning, processing and interpretation. With the increasing sample size of GWASs, the validity and clinical utility of PRSs will further improve.[84] Additionally, as public perceptions of genetic testing become more positive, policymakers might find the rise of personalised medicine inevitable and convenient.[85,86]

PRSs hold great promise, from CVD prediction to preventative measures taken by individuals to curb major events.[87] However, as of now, there are no formal EEs surrounding the PRS. Currently, literature on precision or personalised medicine falls short of assessing both, the costs and consequences of the PRS with a suitable comparator. Reporting the low cost of genotyping is a cost description at best, and is therefore not an effective analysis to argue for the value of PRS in the clinic.[55]

2.2. PRIMARY RESEARCH QUESTION

In the UK Biobank cohort, is the addition of the PRS on top of modifiable risk factors to guide statin therapy a cost-effective intervention for the prevention of primary MI cases in the Ontario healthcare payer perspective over a time horizon of 10 years?

2.3. SECONDARY RESEARCH QUESTION

Does the PRS have clinical effectiveness, as assessed by the number of primary MI cases captured by statin therapy over modifiable risk factors alone?

3.0. METHODS

3.1. POPULATION

The UK Biobank is a prospective cohort study, started in 2006 and, until 2010, recruited approximately 500,000 individuals aged 40 to 69 years across the United Kingdom at 22 assessment centres.[88] Due to downstream analyses using the PRS, only non-related participants of white British descent were used. Furthermore, participants were excluded if they had a high (≥ 20%) or low FRS (< 10%), statin-indicated condition, or were on lipid-lowering therapy. Finally, non-incident CAD cases were removed to create a sample size of 96,736 individuals. This study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline.[89]

3.2. DERIVATION OF THE POLYGENIC RISK SCORE

The PRS was derived from 343,725 unrelated British participants in the UK Biobank. For each SNP within a participant's genotype, GWAS summary statistics, from CARDIoGRAMplusC4D, provided weights ("beta values") corresponding to the significance of association between the SNP and CAD.[90,91] A *p*-value threshold of 0.1 was used to capture many SNPs. The ICD-10 and OPCS-4 codes for CAD are defined elsewhere.[70] A linkage disequilibrium window of 300 base pairs was selected to correct for SNP weights. Scores were produced as per the Equation 1 and then normalised to have a mean of 0 and a standard deviation

(SD) of 1. The final result is a PRS for each individual with predictive capacity for CAD.[91] The analysis was performed using PLINK.[91,92]

3.3. STATIN TREATMENT STRATEGIES AND CLINICAL OUTCOME

Following the Canadian Cardiovascular Society dyslipidemia guidelines of 2016, each participant was assigned a FRS to inform treatment decisions.[54] Additional risk factors, such as LDL-C, non-HDL-C, Apo B, low HDL-C, impaired fasting glucose, high waist circumference, smoker, and hypertension were also used. Statin medication status was assigned to each participant as the standard care strategy. Next, various PRS thresholds, from the top 70% down to the top 25%, were treated as risk factors. Additionally, individuals with protective PRS, such as the lowest 25% down to the lowest 1% were removed from statin eligibility. Combinations of the two criteria were sequentially tested to produce different courses of statin program strategies for clinical and economic effectiveness. A generalised algorithm, based on the existing guidelines, incorporating these upper and lower PRS thresholds is shown in Table 1.

3.4. DECISION ANALYTICAL MODEL STRUCTURE AND OUTCOMES

Using the statin strategies described above, a clinical model was developed to determine the effect on the number of MI cases over a 10-year time horizon, corresponding to the validated risk estimates in the Canadian Cardiovascular Society dyslipidemia guidelines.[54] All participants started at perfect health and, if a MI was not recorded, remained in perfect health as controls. However, participants with cases could either fall into the captured and saved MI (statin

successfully prescribed, and MI prevented), captured and unsaved MI (statin successfully prescribed, but MI was not prevented), or uncaptured and therefore, unsaved (statins unsuccessfully prescribed, and MI was therefore not prevented) category. After the MI event, cases transition back to normal life in terms of quality of life and costs. Since identical cohorts with differing statin strategies were subjected to the same health states, multiple variations of PRS interventions could be compared against standard care. Participants transition among stages on a 1-year cycle since cost and utility parameters were measured on a yearly basis. A schematic of the decision analytical model is shown in Figure 1A. If participants had missing data, the multiple imputation by chained equations (predictive mean matching) method was used such that 20 datasets were generated with 30 iterations.[93,94] All simulations, including the effect of the statins and participant transitions were performed in R.[95]

3.5. DATA SOURCES AND PARAMETERS

The clinical parameters, such as participant modifiable risk factors and PRS were directly from the UK Biobank. The effect of statins, costs, and utility values were derived from relevant literature. A key parameter of in the model is the effect of statins on LDL-C reduction and subsequently MI event reduction. For the former, a 54% reduction was used and the latter, a relative risk of 0.76 in major coronary events per 1.0 mmol/L reduction in LDL from a meta-analysis of individual participant data based on a Cholesterol Treatment Trialists' meta-analysis.[96,97] Costs were considered from the Ontario public health care sector perspective and were adjusted to 2019 Canadian dollars using the consumer price index accounting for inflation.[98] Base case analysis costs included direct costs of statins, MIs, and PRS genotyping.

PRS was assumed to cost $70 based on expert knowledge, accounting for materials and human resources but not computational analyses or time spent devising the scripts required to estimate risk. However, a cost of $0 was also considered due to an increasingly larger subset of the population engaging with direct-to-consumer genetic testing or existing genotyping for cancer testing, as the public healthcare system would have this PRS information without expense.[99] Statin therapy, which was assumed to be atorvastatin at 40 mg or 80 mg, were the same cost in the Ontario Drug Benefit Formulary at $85.54/year for the base-case scenario.[100] The PRS odds ratio (OR) was previously found to be 1.211.[91] Additionally, the information conferred from the PRS was assumed to not have additional physician visits, personnel training, or ancillary costs such as computing or data storage fees. The cost of acute MI was $13,983.78, which included all public payer costs during the hospitalisation period. This value was derived from literature with a population similar to the UK Biobank.[101]

Since the UK Biobank did not conduct any utility measurements, quality of life measurements were sourced from literature. A value of 0.708 was assigned to individuals during their year of event, and pre- and post-event years were assumed to be at perfect health (1.00).[102–104] Given that the number of individuals in most of the statin strategies, with and without PRS, were roughly the same, side effects were not included.

Costs, QALYs, and ICERs were calculated for base-case and sensitivity analyses. Costs and QALYs were discounted at a recommended 1.5% discount rate as per the CADTH guidelines for EEs.[5] WTP thresholds were not considered to determine cost-effectiveness due to the unique nature of the PRS intervention.

3.6. SENSITIVITY ANALYSES

Univariate sensitivity analysis was performed to assess the impact of each of the parameters described above, with the respective ICER values plotted on a tornado diagram. Next, a PSA via 10,000 Monte Carlo simulations was performed to estimate a distribution for the model outputs (total costs, total QALYs, and the ICER). The input parameters and respective distributions, which were sampled with replacement and subjected to the model are shown in Table 13. Next, the proportion of PSA ICERs under WTP thresholds from $1,000/QALY to $1,500,000/QALY were used to produce CEACs. Only select strategies of the PRS intervention were subjected to the sensitivity analyses since many prescription combinations could be dominated by standard care. The cost of PRS was excluded from sensitivity analysis since it represents different real-world scenarios rather than uncertainty.

Since the predictive capacity of the PRS is likely to improve in the future and its changes cannot easily be shown in the aforementioned sensitivity analyses, a separate, 2nd order sensitivity analysis was performed.[106] Artificial PRSs predictive for CAD, were generated for all study participants at varying population ORs per SD. The ICER was plotted against OR per SD tuned from approximately 1.3 to 2.5 in increments of 0.1 with 100 bootstraps each to produce 95% confidence intervals (CI). Additionally, to show the trend, a generalised additive model fit was used. The sensitivity analysis was performed at a PRS cost of $70 at various statin strategies, described above (3.3. Statin Treatment Strategies and Clinical Outcome).

4.0. RESULTS

4.1. POPULATION AND STATIN TREATMENT

The baseline characteristics of the UK Biobank subpopulation are shown in Table 2. A total of 96,736 intermediate-risk individuals passed the exclusion criteria, with 3648 CAD cases and 853 MI cases (incidence proportion, 0.882%) over a span of 10 years. The sample included 50,894 women (52.6%) and 45,842 men (47.4%). The validation of PRS, showing the number of CAD cases against each decile is shown in Figure 1. Generally, lower-decile PRS risk bands had fewer cases compared to higher-decile PRS risk bands.

Under standard care, as per the Canadian Cardiovascular Society dyslipidemia guidelines of 2016, 82,083 (84.85%) individuals were eligible for statins with 748 MIs (87.7%) captured with statins. The number of MI cases captured per 1000 statin prescriptions was 9.113, as shown in Table 2. With respect to the statin strategies based on PRS, the number of individuals eligible for statins ranges from 65,318 (67.52%) to 91,148 (94.22%), as shown in Table 3 through Table 12. The former corresponds to a strategy whereby the top 25% PRS individuals are eligible for statins, with the lower 25% PRS excluded, while the latter, top 70% PRS individuals are eligible for statins, with the lower 1% PRS excluded. Invariably, the number of captured MIs is correlated with the number of statin prescriptions, ranging from 650 (76.2%) to 824 (96.6%) with 9.951 to 9.040 MIs per 1000 statin prescriptions, respectively, corresponding to aforementioned strategies. When more statins are prescribed, a greater number of MIs are captured, albeit less precisely.

4.2. COST-EFFECTIVENESS ANALYSIS

Based on clinical outcomes alone, the best statin strategy is one that is most liberal. However, the number of statin prescriptions is directly proportional to the total cost of statins while the number of captured MIs may not continuously drop at the same rate. This was evident in the number of MIs captured per 1000 statin prescription metric.

The economic model was subjected to all combinations of upper and lower PRS thresholds for statin eligibility. Since the cost of PRS, at $70 or $0 represents different scenarios rather than a possible range in cost, the two values were each treated as a base-case analysis. The value of each parameter used in the model is shown in Table 13. At PRS costing $70, the ICERs range enormously as shown in Table 14 through Table 23. However, due to ethical concerns, only strategies with positive incremental QALYs were considered as they would capture more MIs compared to standard of care. With this criterion, the lowest ICER is $747,184.10/QALY, corresponding to the strategy whereby the top 70% PRS individuals are eligible for statins, with the lower 5% PRS excluded. The cost-effectiveness plane with strategies exhibiting a positive incremental QALY, however, is shown in Figure 2. The effect of the lower percent PRS exclusion on the ICER exhibits an increasing trend, as shown in Figure 3, for the same positive-incremental QALY strategies. For upper thresholds between 40% and 70%, the lower percent PRS exclusion from 1% to 5% does not make a drastic difference in the ICERs.

When the cost of the PRS is set to $0 and only positive incremental QALY values are considered, the worst-case scenario ICER is $395,363.67/QALY, representing the strategy

whereby the top 70% PRS individuals are eligible for statins with the lower 1% PRS excluded. The cost-effectiveness plane with strategies displaying positive incremental QALYs is shown in Figure 4. The effect of the lower percent PRS exclusion on the ICER exhibits a decreasing trend. Every PRS strategy exhibits potential for being dominant (clinically superior and cost saving) relative to Canadian Cardiovascular Society dyslipidemia guidelines of 2016, as shown in Figure 5. Some strategies were removed since the difference in QALYs is close to 0. The resultant ICER might not be accurate. To maintain the effect of an ICER less than $0/QALY, the upper PRS percentage threshold of individuals eligible for statins needs to increase while the lower percent PRS of excluded individuals also increases. The $0/QALY effect is dependent the upper PRS percentage threshold. However, when at least 12% of the lower PRS individuals are withheld from statins, the ICER is less an $0/QALY regardless of upper the threshold.

4.3. SENSITIVITY ANALYSES

Amongst the $70 PRS scenario, the lowest ICER value was the strategy whereby the top 70% PRS individuals are eligible for statins, with the lower 5% PRS excluded at $747,184.10/QALY. As a result, this treatment path was subjected to one-way sensitivity analysis by varying the cost and utility of an MI, the discount rate, and effect of statins from the estimates and ranges in Table 13, as shown in Figure 6. The largest drivers of the ICER value, in order, are the rate of discounting, utility of MI, cost of the PRS, the effect of statins, and cost of a MI. At a PRS cost of $0, the worst-case statin strategy is where the top 70% PRS individuals are eligible with the lower 1% PRS excluded. However, a sensitivity analysis was not performed. At base-case parameters, this strategy represented the highest ICER. Any adjustment in the model

parameters would only improve the ICER value, and therefore, would not be an accurate depiction of cost-effectiveness uncertainty at PRS at $0.

Using the parameter ranges shown in Table 13, a PSA was performed on the lowest ICER strategy, whereby the top 70% PRS individuals are eligible for statins, with the lower 5% PRS excluded. A total of 10,000 simulations were performed to determine to range of the incremental costs and incremental QALYs, and plotted on a cost-effectiveness plane, as shown in Figure 7. The dotted line and dot represent an ICER of $747,73/QALY, the base-case analysis value. To determine the cost-effectiveness of the PRS at specific WTP thresholds, a CEAC is shown in Figure 8. The vertical line corresponds to an WTP of $747,184.10/QALY, the base-case analysis value, which has a 48.1% probability of being cost-effective. Since a shift from 1.5% to 3% in the discounting rate had a large effect on the ICER, as shown in Figure 6, a PSA at the latter percent was warranted. Using the same strategy (top 70% PRS individuals are eligible for statins, with the lower 5% PRS excluded), a cost-effectiveness plane and CEAC were generated, as shown in Figure 9 and Figure 10, respectively. The dotted line and dot in Figure 9 represent an ICER of $525,678.90/QALY, the value derived from the one-way sensitivity analysis. The vertical line in Figure 10 corresponds to a WTP the same as the ICER, which has a 49.2% probability of being cost-effective.

Finally, for the secondary, 2nd order sensitivity analysis, the ICER was plotted as a function of different PRS predictiveness, represented by the OR per SD for CAD. Using the optimal base-case at a PRS cost of $70, whereby the top 70% PRS individuals are eligible for statins with the lower 5% PRS excluded is shown in Figure 11. The PRS predictiveness is

represented by the OR per SD for CAD. At a PRS cost of $70, the ICER ranges from approximately $675,000/QALY to $350,000/QALY at ORs per SD of 1.35 to 2.50, respectively. The trend is similar at every PRS cost. As the OR per SD increases, the ICER drops since more individuals with MI cases are correctly assigned to be eligible for statins.

5.0. DISCUSSION

5.1. MAIN FINDINGS

While there are many research articles on the clinical effectiveness of the PRS, with varying levels of defining criteria, there is little evidence on cost-effectiveness.[68,107] As previously defined (1.1. Basic Concepts of Economic Evaluations), formal EEs have costs and benefits of an intervention strategy in addition to a comparator to objectively assess the value of the former.[4] There is currently one study that has preliminary information on the possible cost-effectiveness of a PRS, however, there are limitations to the conclusions since the study design doesn't allow strict comparisons.[108] However, in this study, a decision analytical model was built to demonstrate the cost-effectiveness of the addition of a PRS to modifiable risk factors, as described in the Canadian Cardiovascular Society dyslipidemia guidelines of 2016, to guide statin therapy for the prevention of primary MI cases in Ontario.[54] Using this model, the clinical utility of the PRS, assessed by the number of primary myocardial infarction cases captured by statin therapy over modifiable risk factors alone was also determined.

Many strategies were able to prescribe statins in a manner that captured more MIs compared to the standard guidelines alone, demonstrating the clinical utility of PRS. Although to fully support this idea, a clinical study such as an RCT is required to show a head-to-head comparison with and without PRS. However, there are several variables, described below (5.2. Strengths and Limitations), which could influence the validity of the PRS clinical utility. For example, a greater number of statin prescriptions would mean a proportional increase in adverse

side-effects.[109] However, as shown in Table 3 through Table 12, there are strategies across every upper threshold where the number of individuals eligible for statins is roughly the same (a difference of less than 1%) as the standard care, while capturing more MI cases. This corresponds to a larger ratio of number of MI cases captured per 1000 statin prescriptions. In fact, the same number of cases captured as standard care can be achieved by a lower cumulative number of statin prescriptions, also corresponding to a larger ratio of number of MI cases captured per 1000 statin prescriptions. Reducing the total number of adverse events caused by statins without compromising CVD events could be profound.

The results for the EE require a more nuanced analysis as there are more variables involved. The base-case ICER with the cost of PRS at $70 under in the optimal strategy is $747,184.10/QALY, while at a discounting rate of 3.0%, is $525,678.90/QALY. As the rate of discounting is a controversial topic with a wide range between jurisdictions, an ICER at 3.0% should be considered as a plausible value for decision-makers. There has been advocacy for a rate of 5% as well, however, this was excluded in this EE as the current CADTH guidelines suggest 1.5% with an upper sensitivity analysis threshold of 3.0%.[10]

Nonetheless, based on the one-way sensitivity analysis, as shown in Figure 5, discounting had the largest effect on the ICER due to the 10-year time horizon. The value of costs and QALYs diminish significantly with time. Furthermore, it can be seen that the utility of the MI is also a large driver of the ICER, suggesting that the PRS would be far more cost-effective for severe cases as opposed to mild ones. The cost of PRS, effect of statins, and cost of MI parameters do not have as large of an effect since their variance is lower. The direction of the

ICER and cost of MI are inversely proportional since more cases are captured using the PRS. A greater cost per event means that a larger sum of dollars is saved by preventing those expenses to accrue for the healthcare system. Although the ICERs reported might not be optimal under official or unofficial WTP thresholds such as $50,000/QALY, the possibility that PRS is not cost-effective cannot be supported due to the limitations of the study, described below.[42]

When the cost of PRS is set to $0, regardless of the upper threshold, when the at least 12% of the lower PRS are withheld from statins, the ICER is less an $0/QALY and is dominant against the Canadian Cardiovascular Society dyslipidemia guidelines of 2016.[54]. The difficulty of this analysis arose because when the number of MI cases captured using the PRS and standard guidelines is the same, the difference in QALYs is close to zero and therefore, the model artificially inflates the magnitude of the ICER. As a result, individual ICER values are not reported since discriminating between an artificially negative ICER or a true negative ICER is difficult. A difference of one additional MI case captured between a PRS strategy and standard care is likely noise. However, difference in cases not attributed to noise was not the scope of this study. Although the worst-case scenario is $395,363.67/QALY, there are numerous of strategies with large differences in MI cases compared to standard care where an ICER value of less than $50,000/QALY or even $0/QALY is possible. As a result, achieving more benefits, or an increase in incremental QALYs from MI cases, while reducing costs is a likely possibility in a population where genotypic information is available.

To account for the changes in PRS predictiveness, artificial scores were generated and subjected to the cost-effectiveness model at various costs and statin strategies. In the base-case

optimal strategy, whereby the top 70% PRS individuals are eligible for statins with the lower 5% excluded, there were no combination of parameters that dropped the ICER under $150,000/QALY. There are certain costs that cannot change in this strategy. Statins, which make up the largest fraction of the total costs, must be prescribed. The costs associated with a MI also cannot change. While the number of statin prescriptions or treated MI cases changes with a more predictive PRS, this difference is not negligible compared to the cost of the PRS. The cost-effectiveness of the PRS is very dynamic and dependent on several factors such as the cost and predictiveness of the PRS, as well as the statin strategy implemented. In fact, as the PRS OR per SD increases, the number of statin prescriptions should drop since a stronger, more predictive tool is used to guide the intervention. This implies that the strategy should also change, such as increasing the number of individuals who are deemed to have a protective PRS and therefore removed from statin eligibility. In the current analysis, the prescription strategy was not varied. The dynamic nature of the parameters and the model suggests that introducing the PRS into the clinic is not very straightforward. The ICER value, input costs, and the statin strategy are not independent of each other.

5.2. LIMITATIONS

Although this is the first formal EE performed to assess the cost-effectiveness of the PRS, there are several limitations that need to be taken into account. The sample included white British descent exclusively, which is not generalisable to many jurisdictions, especially Ontario.[110] The performance of the PRS is partly dependent on the ethnicity, with the highest among European populations.[72] This has cause for concern as an Ontario-based PRS might not

demonstrate the same predictive performance as this study. Next, the UK Biobank, while extensive in the number of biomarkers measured at multiple time points, is not designed for HTA studies. Costing data was likely not included due to the logistical challenges when tracking all resource uses at each centre, especially by disease breakdown since CVD conditions are not always mutually exclusive.[111] Additionally, it is unlikely that the heterogeneity of healthcare personnel and treatment protocols across the entire UK can be standardised to produce accurate costing information. In lieu of this data, a top-down approach was implemented using aggregated costs from other studies with similar population characteristics. Utility measurements are not included in the UK Biobank, which limits the ability to measure the difference in clinical benefits before and after an event, and subsequently compromises the calculation of QALYs. The lack of direct or indirect tools to measure utilities also has the consequence of using literature derived from similar populations to estimate the true values.

Frequently, the source studies of EEs are RCTs as it is straightforward to tabulate the costs, benefits, incremental costs, incremental benefits, and ICER.[3,4] However, depending on the design of the RCT, the incremental benefits can be overestimated for the specific risk-reduction intervention. This can happen by reducing the heterogeneity of the recruitment population by avoiding enrolment of patients with other diseases, those whom the disease disappears spontaneously, as well as finding patients who are more likely to have an event of interest, and who are more likely to respond.[112–114] These biasing enrichment factors are not present in longitudinal studies such as the UK Biobank or other study designs that encapsulate the essence of real-world evidence or a true representation of disease in a population.[112] Less MI cases and a reduced effect of the PRS in the UK Biobank produces diminished clinical and economic

valuations. As a result, an ICER of $747,184.10/QALY is likely to lower if an RCT with the PRS intervention is conducted due to the lack of practical, prognostic, and predictive enrichment.[112] Additionally, the lower threshold for the exclusion of statins to reach a dominant ICER value was 12% in this study. However, with a greater number of total cases and more favourable study population, which could be possible in an RCT, the PRS would have greater potential to reduce the number of uncaptured cases. The effect is a lowering of the ICER at a PRS cost of $0 by way of reducing incremental costs and increasing incremental benefits. It should be noted, the enrichments methods are intended to demonstrate the effectiveness of interventions, which is an important purpose of an RCT.[115] However, this study design might be not optimal for an EE, as described above.

The cost-effectiveness model constructed in this study is robust enough to calculate the effect of statins on MI cases by using the intervention of statins targeted by PRS strategies, or standard care, which is outlined by the Canadian Cardiovascular Society dyslipidemia guidelines of 2016.[54] However, the model does not account for every CVD outcome or the breadth of major coronary events that can be treated by statins such as unstable anginas or even nonfatal strokes.[97,116] Increasing the number of total primary events that can be better predicted using the PRS would lead to a decrease in the ICER. With more cases captured via statin therapy, more are prevented compared to standard care. The difference in costs and QALYs over a 10-year time horizon would likely be very large, especially since some major coronary events are costlier and lead to greater utility decrements than nonfatal MIs.[101–103] During the 10-year time horizon, it is also likely that the health of all participants, especially those who experienced an event, would deteriorate.[107] Modelling this effect would also be advantageous for PRS strategies since there

are less individuals who had an uncaptured event compared to standard care. A larger number of healthier individuals in the PRS-guided statin therapy cohort would result in an increased incremental QALY, thereby reducing the ICER.

The 10-year time horizon was chosen for straightforward reasons. The absolute CVD risks found in the Canadian Cardiovascular Society dyslipidemia guidelines of 2016, based on the FRS has a time horizon of 10-years. In order to consistently compare the aforementioned guidelines with PRS strategies, the latter should also have a time-horizon of 10 years. Additionally, the UK Biobank has follow-up data of 10 years. It would be unwise to truncate this timespan since it would reduce the total number of events without providing any benefits as shorter follow-up durations are not accurate depictions of CVD trajectory. A lifetime horizon is ideal to compare both, clinical and economic utility, however, due to the study restrictions, this was not possible.[4,5] The perspective and rate of discounting, which were the public health care payer and 1.5%, respectively, were chosen as per the recommendations in the CADTH guidelines.[5] A societal perspective displays a more holistic image of CVD, especially when spill over costs such as caregiver use and loss of productivity are considered. However, unless these variables are accurately measured, it might not be appropriate to include them as they can distort the ICER. These issues are amplified when different costs are sourced from fragmented sources or databases. Since spill over costs are challenging to measure especially in the UK Biobank, a societal perspective, while more advantageous and informative when done correctly, should be approached with caution.[5,6,117]

5.3. FUTURE DIRECTIONS AND CONSIDERATIONS

The cost-effectiveness model can be improved to use finer resolutions of individual-level data. This study had a clinical outcome of primary MI cases prevented, however, including other primary and secondary CVD events would showcase the effectiveness of the PRS more accurately. Additionally, treatment regimens apart from statins were not modelled. Patients with high CVD risk tend to be on multiple drugs alongside statins, including angiotensin-converting enzyme inhibitors for treating hypertension.[97,108] Many patients also experience statin intolerance or are not responsive to the them for lowering LDL. As a result, they are prescribed protein convertase subtilisin/kexin type 9 inhibitors. Modelling the use of this new class of lipid-lowering medication would improve the generalisability of the results.[118] With respect to the PRS, it is possible that the cost of genotyping will decrease in the years to follow.[119] As shown in the one-way sensitivity analysis in Figure 5, the potential for the ICER lower is not without merit. Adding unrelated diseases with a predictive PRS, such as breast cancer, would have the additional effect of lowering the ICER since the marginal cost associated with generating a second score is likely immensely overshadowed by the cost of genotyping itself. This strategy of having a single genotype associated with multiple, unrelated diseases is not analogous to multiple diseases with one treatment path.[120] The PRS could also increase in predictive performance in the future, having the potential to guide statin therapy more optimally than shown in this study. This would also drop the ICER, as shown in Figure 11.[108] Additionally, this study used a PRS created from genotyping, but scores derived from exome-sequencing can further improve the predictive performance. Rare variants, which may have major effects are seen too infrequently to judge whether they are associated with the phenotype or disease.[121]

However, the cost of exome-sequencing is magnitudes higher than genotyping and therefore poses several downstream restrictions.[122,123] Large scale projects are not as feasible and with less individuals for exome analysis, the capabilities of the PRS would be limited.[123] An EE incorporating a higher PRS derivation cost via exome sequencing in exchange for risk-conferring rare variants would provide valuable information into the trajectory of precision medicine.

In the future, genetic data could be stored alongside clinical records. Widespread use of PRSs to predict disease onset, treatment response, and disease prognosis is a possibility.[106] Before reaching this goal, however, there are ethical considerations that must be resolved.[124] First, the PRS could exacerbate health inequalities due to the ancestry of the study population. Most GWASs have been performed in high-income countries and within these contexts, have included mostly participants of European ancestry. Therefore, their PRS predictive ability is higher than those in underrepresented, non-European ancestries, such as African populations. The underperformance of the PRS for populations which already experience healthcare injustices is a serious ethical challenge. Studying more genetically diverse populations will enhance clinical outcomes and could pose as a solution for these inequalities.[124,125] EEs, especially this study centred around Ontario, would benefit from more diverse, representative populations rather than homogenous populations. Second, PRSs for complex traits could stigmatise certain populations when incorrectly translated to the population. Genetic associations for substance use, intelligence, and anti-social behaviours have been generated.[126–128] Knowledge translation, which can involve oversimplifications and exaggerated claims have devastating consequences. Misinterpretations could amplify pre-existing stigmas against individuals with medical conditions, especially mental disorders. Under the worst-case scenario, discriminatory practices

could take place for employment or insurance purposes in certain jurisdictions. Strict laws should ideally protect the genetic information of individuals.[124] Fair treatment has the possibility of more preventative treatments, which are more cost-effective than reactive measures.[129] Last, this study focused on a PRS associated with CAD on adult populations. Other PRSs for disorders with high heritability, such as schizophrenia, would impose a further set of challenges with prenatal testing or the testing of minors. Adolescents receiving unfavourable PRS feedback for disorders may be at particularly high risk for internalised stigma and potentially detrimental effects associated with negative self-labelling.[130] The negative effects are intensified when deterministic assumptions are made about traits, or when they are unable to modify other, non-genetic risk factors.[124] This amount of variability in human behaviour adds an additional level of complexity when creating EE models. Further research is warranted to fully understand the clinical and economic implications of PRS risk internalisation.

6.0. CONCLUSIONS

The case for clinical implementation of PRSs is controversial.[131] The lack of genetic diversity in large genetic studies in addition to the methods used to produce a PRS results in differing opinions about its clinical utility. In this study, a CUA was performed to determine if a single PRS could guide statin therapy cost-effectively, compared to using modifiable risk factors alone for the prevention of primary MI cases. Although common WTP thresholds were not met, the limitations of the study design and model construction elucidate that PRS is likely to be cost-effective in the future. In a world where healthcare costs are increasing at an ever faster rate while resources are scarce, novel techniques should be considered despite their unique challenges.[1] With the democratisation of genotyping, there exists a real possibility where PRSs can be used in primary care for their clinical and economic utility.[99]

7.0. BIBLIOGRAPHY

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8.0. TABLES

Table 1. Initiation of statin treatment based on CVD risk categories via a combination of the FRS and PRS

CVD risk category	Statin eligibility in the cost-effectiveness model
High FRS (≥ 20%) All	Yes
Intermediate FRS (10% to 19%) without protective PRS ≤ [Lower threshold percentage] LDL-C ≥ 3.5 mmol/L, or non-HDL-C ≥ 4.3 mmol/L, or ApoB ≥ 1.2 g/L, or men ≥ 50 and women ≥ 60 years and 1 additional CVD risk factor, or risk conferring PRS ≥ [Upper threshold percentage]	Yes
Intermediate FRS (10% to 19%) with protective PRS ≤ [Lower threshold percentage]	No
Low FRS (< 10%)	No
Statin-indicated conditions Clinical atherosclerosis, or abdominal aortic aneurysm,	Yes

or DM with age ≥ 40 years, or 15-year DM 1 duration for age ≥ 30 years, or microvascular disease, or chronic kidney disease (age ≥ 50 years) with eGFR < 60 mL/min/1.73 m^2 or ACR > 3 mg/mmol, or LDL-C ≥ 5.0 mmol/L	

Abbreviations: CVD, cardiovascular disease; FRS, Framingham risk score; PRS, polygenic risk score; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ApoB, apolipoprotein B; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ACR, albumin: creatinine ratio.

Although high FRS, low FRS, and statin-indicated conditions CVD risk categories are shown (for holistic illustrative purposes), they are excluded from the study sample, which consists of individuals with intermediate FRS only.

Table 2. Baseline characteristics of UK Biobank subpopulation

	n = 96,736
Age, mean (SD)	58.46 (6.68)
Female, N (%)	50,894 (52.6)
Male, N (%)	45,842 (47.4)
Current smoking, N (%)	9,196 (9.51)
Antihypertensive therapy, N (%)	13,109 (13.6)
Total cholesterol, mean (SD), mmol/L	6.158 (1.07)
LDL-C, mean (SD), mmol/L	3.918 (0.800)
HDL-C, mean	1.473 (0.384)
Systolic blood pressure, mean (SD), mmHg	143.5 (15.9)
FRS, mean (SD), points	13.73 (1.64)
ApoB, mean (SD), g/L	1.121 (0.227)
Creatinine, mean (SD), μmol/L	71.93 (15.0)
Waist circumference, mean (SD), cm	90.81 (12.3)
Hip circumference, mean (SD), cm	103.7 (9.00)

Abbreviations: SD, standard deviation; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FRS, Framingham risk score; ApoB, apolipoprotein B.

Table 3. Clinical parameters of participants on different statin exclusion strategies with PRS greater than 25% as a risk factor

Strategy	Number of MIs captured	Controls given statins	Captured MIs/1000 statin prescriptions
Canadian Cardiovascular Society dyslipidemia guidelines of 2016	748	81,335	9.113
Top 25% PRS eligible for statins with lower threshold excluded:			
1%	776	83,865	9.168
2%	773	83,031	9.224
3%	772	82,194	9.305
4%	767	81,456	9.328
5%	765	80,692	9.391
6%	760	79,899	9.422
7%	755	79,059	9.459
8%	752	78,302	9.512
9%	742	77,456	9.489
10%	739	76,679	9.546

11%	735	75,887	9.593
12%	729	75,100	9.614
13%	722	74,289	9.625
14%	718	73,444	9.682
15%	713	72,680	9.715
16%	706	71,868	9.728
17%	697	71,031	9.717
18%	688	70,222	9.702
19%	683	69,458	9.738
20%	678	68,645	9.780
21%	672	67,863	9.805
22%	666	67,096	9.829
23%	661	66,251	9.879
24%	656	65,440	9.925
25%	650	64,668	9.951

Abbreviations: MI, myocardial infarction; CCSDG16, Canadian Cardiovascular Society dyslipidemia guidelines of 2016; PRS, polygenic risk score

Table 4. Clinical parameters of participants on different statin exclusion strategies with PRS greater than 30% as a risk factor

Strategy	Number of MIs captured	Controls given statins	Captured MIs/1000 statin prescriptions
Canadian Cardiovascular Society dyslipidemia guidelines of 2016	748	81,335	9.113
Top 30% PRS eligible for statins with lower threshold excluded:			
1%	783	84,587	9.172
2%	780	83,753	9.227
3%	779	82,916	9.308
4%	774	82,178	9.331
5%	772	81,414	9.393
6%	767	80,621	9.424
7%	762	79,781	9.461
8%	759	79,024	9.513
9%	749	78,178	9.490
10%	746	77,401	9.546

11%	742	76,609	9.593
12%	736	75,822	9.614
13%	729	75,011	9.625
14%	725	74,166	9.681
15%	720	73,402	9.714
16%	713	72,590	9.727
17%	704	71,753	9.716
18%	695	70,944	9.701
19%	690	70,180	9.736
20%	685	69,367	9.778
21%	679	68,495	11.102
22%	673	67,818	9.826
23%	668	66,973	9.876
24%	663	66,162	9.921
25%	657	65,390	9.947

Abbreviations: MI, myocardial infarction; CCSDG16, Canadian Cardiovascular Society dyslipidemia guidelines of 2016; PRS, polygenic risk score

Table 5. Clinical parameters of participants on different statin exclusion strategies with PRS greater than 35% as a risk factor

Strategy	Number of MIs captured	Controls given statins	Captured MIs/1000 statin prescriptions
Canadian Cardiovascular Society dyslipidemia guidelines of 2016	748	81,335	9.113
Top 35% PRS eligible for statins with lower threshold excluded:			
1%	787	85,262	9.146
2%	784	84,428	9.201
3%	783	83,591	9.280
4%	778	82,853	9.303
5%	776	82,089	9.365
6%	771	81,296	9.395
7%	766	80,456	9.431
8%	763	79,699	9.483
9%	753	78,853	9.459
10%	750	78,076	9.515

11%	746	77,284	9.560
12%	740	76,497	9.581
13%	733	75,686	9.592
14%	729	74,841	9.647
15%	724	74,077	9.679
16%	717	73,265	9.692
17%	708	72,428	9.681
18%	699	71,619	9.666
19%	694	70,855	9.700
20%	689	70,042	9.741
21%	683	69,260	9.765
22%	677	68,493	9.787
23%	672	67,648	9.836
24%	667	66,837	9.881
25%	661	66,065	9.906

Abbreviations: MI, myocardial infarction; CCSDG16, Canadian Cardiovascular Society dyslipidemia guidelines of 2016; PRS, polygenic risk score

Table 6. Clinical parameters of participants on different statin exclusion strategies with PRS greater than 40% as a risk factor

Strategy	Number of MIs captured	Controls given statins	Captured MIs/1000 statin prescriptions
Canadian Cardiovascular Society dyslipidemia guidelines of 2016	748	81,335	9.113
Top 40% PRS eligible for statins with lower threshold excluded:			
1%	796	85,931	9.178
2%	793	85,097	9.233
3%	792	84,260	9.312
4%	787	83,522	9.335
5%	785	82,758	9.396
6%	780	81,965	9.427
7%	775	81,125	9.463
8%	772	80,368	9.514
9%	762	79,522	9.491
10%	759	78,745	9.547

11%	755	77,953	9.592
12%	749	77,166	9.613
13%	742	76,355	9.624
14%	738	75,510	9.679
15%	733	74,746	9.711
16%	726	73,934	9.724
17%	717	73,097	9.714
18%	708	72,288	9.699
19%	703	71,524	9.733
20%	698	70,711	9.775
21%	692	69,929	9.799
22%	686	69,162	9.821
23%	681	68,317	9.870
24%	676	67,506	9.915
25%	670	66,734	9.940

Abbreviations: MI, myocardial infarction; CCSDG16, Canadian Cardiovascular Society dyslipidemia guidelines of 2016; PRS, polygenic risk score

Table 7. Clinical parameters of participants on different statin exclusion strategies with PRS greater than 45% as a risk factor

Strategy	Number of MIs captured	Controls given statins	Captured MIs/1000 statin prescriptions
Canadian Cardiovascular Society dyslipidemia guidelines of 2016	748	86,669	9.146
Top 45% PRS eligible for statins with lower threshold excluded:			
1%	800	86,669	9.146
2%	797	85,835	9.200
3%	796	84,998	9.278
4%	791	84,260	9.300
5%	789	83,496	9.361
6%	784	82,703	9.391
7%	779	81,863	9.426
8%	776	81,106	9.477
9%	766	80,260	9.454
10%	763	79,483	9.508

11%	759	78,691	9.553
12%	753	77,904	9.573
13%	746	77,093	9.584
14%	742	76,248	9.638
15%	737	75,484	9.669
16%	730	74,672	9.681
17%	721	73,835	9.671
18%	712	73,026	9.656
19%	707	72,262	9.689
20%	702	71,449	9.730
21%	696	70,667	9.753
22%	690	69,900	9.775
23%	685	69,055	9.822
24%	680	68,244	9.866
25%	674	67,472	9.891

Abbreviations: MI, myocardial infarction; CCSDG16, Canadian Cardiovascular Society dyslipidemia guidelines of 2016; PRS, polygenic risk score

Table 8. Clinical parameters of participants on different statin exclusion strategies with PRS greater than 50% as a risk factor

Strategy	Number of MIs captured	Controls given statins	Captured MIs/1000 statin prescriptions
Canadian Cardiovascular Society dyslipidemia guidelines of 2016	748	81,335	9.113
Top 50% PRS eligible for statins with lower threshold excluded:			
1%	802	87,412	9.092
2%	799	86,578	9.144
3%	798	85,741	9.221
4%	793	85,003	9.243
5%	791	84,239	9.303
6%	786	83,446	9.331
7%	781	82,606	9.366
8%	778	81,849	9.416
9%	768	81,003	9.392
10%	765	80,226	9.445

11%	761	79,434	9.489
12%	755	78,647	9.509
13%	748	77,836	9.518
14%	744	76,991	9.571
15%	739	76,227	9.602
16%	732	75,415	9.613
17%	723	74,578	9.601
18%	714	73,769	9.586
19%	709	73,005	9.618
20%	704	72,192	9.658
21%	698	71,410	9.680
22%	692	70,643	9.701
23%	687	69,798	9.747
24%	682	68,987	9.789
25%	676	68,215	9.813

Abbreviations: MI, myocardial infarction; CCSDG16, Canadian Cardiovascular Society dyslipidemia guidelines of 2016; PRS, polygenic risk score

Table 9. Clinical parameters of participants on different statin exclusion strategies with PRS greater than 55% as a risk factor

Strategy	Number of MIs captured	Controls given statins	Captured MIs/1000 statin prescriptions
Canadian Cardiovascular Society dyslipidemia guidelines of 2016	748	81,335	9.113
Top 55% PRS eligible for statins with lower threshold excluded:			
1%	809	88,106	9.099
2%	806	87,272	9.151
3%	805	86,435	9.227
4%	800	85,697	9.249
5%	798	84,933	9.308
6%	793	84,140	9.337
7%	788	83,300	9.371
8%	785	82,543	9.421
9%	775	81,697	9.397
10%	772	80,920	9.450

11%	768	80,128	9.494
12%	762	79,341	9.513
13%	755	78,530	9.523
14%	751	77,685	9.575
15%	746	76,921	9.605
16%	739	76,109	9.616
17%	730	75,272	9.605
18%	721	74,463	9.590
19%	716	73,699	9.622
20%	711	72,886	9.661
21%	705	72,104	9.683
22%	699	71,337	9.703
23%	694	70,492	9.749
24%	689	69,681	9.791
25%	683	68,909	9.814

Abbreviations: MI, myocardial infarction; CCSDG16, Canadian Cardiovascular Society dyslipidemia guidelines of 2016; PRS, polygenic risk score

Table 10. Clinical parameters of participants on different statin exclusion strategies with PRS greater than 60% as a risk factor

Strategy	Number of MIs captured	Controls given statins	Captured MIs/1000 statin prescriptions
Canadian Cardiovascular Society dyslipidemia guidelines of 2016	748	81,335	9.113
Top 60% PRS eligible for statins with lower threshold excluded:			
1%	814	88,830	9.080
2%	811	87,996	9.132
3%	810	87,159	9.208
4%	805	86,421	9.229
5%	803	85,657	9.288
6%	798	84,864	9.316
7%	793	84,024	9.350
8%	790	83,267	9.398
9%	780	82,421	9.375
10%	777	81,644	9.427

11%	773	80,852	9.470
12%	767	80,065	9.489
13%	760	79,254	9.498
14%	756	78,409	9.550
15%	751	77,645	9.580
16%	744	76,833	9.590
17%	735	75,996	9.579
18%	726	75,187	9.564
19%	721	74,423	9.595
20%	716	73,610	9.633
21%	710	72,828	9.655
22%	704	72,061	9.675
23%	699	71,216	9.720
24%	694	70,405	9.761
25%	688	69,633	9.784

Abbreviations: MI, myocardial infarction; CCSDG16, Canadian Cardiovascular Society dyslipidemia guidelines of 2016; PRS, polygenic risk score

Table 11. Clinical parameters of participants on different statin exclusion strategies with PRS greater than 65% as a risk factor

Strategy	Number of MIs captured	Controls given statins	Captured MIs/1000 statin prescriptions
Canadian Cardiovascular Society dyslipidemia guidelines of 2016	748	81,335	9.113
Top 65% PRS eligible for statins with lower threshold excluded:			
1%	818	89,574	9.049
2%	815	88,740	9.101
3%	814	87,903	9.175
4%	809	87,165	9.196
5%	807	86,401	9.254
6%	802	85,608	9.281
7%	797	84,768	9.315
8%	794	84,011	9.363
9%	784	83,165	9.339
10%	781	82,388	9.391

11%	777	81,596	9.433
12%	771	80,809	9.451
13%	764	79,998	9.460
14%	760	79,153	9.510
15%	755	78,389	9.540
16%	748	77,577	9.550
17%	739	76,740	9.538
18%	730	75,931	9.522
19%	725	75,167	9.553
20%	720	74,354	9.591
21%	714	73,572	9.612
22%	708	72,805	9.631
23%	703	71,960	9.675
24%	698	71,149	9.715
25%	692	70,377	9.737

Abbreviations: MI, myocardial infarction; CCSDG16, Canadian Cardiovascular Society dyslipidemia guidelines of 2016; PRS, polygenic risk score

Table 12. Clinical parameters of participants on different statin exclusion strategies with PRS greater than 70% as a risk factor

Strategy	Number of MIs captured	Controls given statins	Captured MIs/1000 statin prescriptions
Canadian Cardiovascular Society dyslipidemia guidelines of 2016	748	81,335	9.113
Top 70% PRS eligible for statins with lower threshold excluded:			
1%	824	90,324	9.040
2%	821	89,490	9.091
3%	820	88,653	9.165
4%	815	87,915	9.185
5%	813	87,151	9.242
6%	808	86,358	9.270
7%	803	85,518	9.302
8%	800	84,761	9.350
9%	790	83,915	9.326
10%	787	83,138	9.377

11%	783	82,346	9.419
12%	777	81,559	9.437
13%	770	80,748	9.446
14%	766	79,903	9.496
15%	761	79,139	9.524
16%	754	78,327	9.535
17%	745	77,490	9.523
18%	736	76,681	9.507
19%	731	75,917	9.537
20%	726	75,104	9.574
21%	720	74,322	9.595
22%	714	73,555	9.614
23%	709	72,710	9.657
24%	704	71,899	9.697
25%	698	71,127	9.718

Abbreviations: MI, myocardial infarction; CCSDG16, Canadian Cardiovascular Society dyslipidemia guidelines of 2016; PRS, polygenic risk score

Table 13. Decision analytical model parameters with ranges used for base-case and sensitivity analyses

	Base case	Range for sensitivity analysis		Standard deviation	Distribution	Source
Costs		Low	High			
PRS	$70	$55	$85	$15	Gamma	Assumption
MI (event)	$13,983.78	$10,189.19	$17,778.38	$3,510	Gamma	[101,132]
Statins (yearly)	$85.54	N/A	N/A	N/A	N/A	[100]
Utilities						
Pre-MI	1.00	N/A	N/A	N/A	N/A	Assumption
MI	0.708	0.610	0.806	0.098	Beta	[102–104]
Post-MI	1.00	N/A	N/A	N/A	N/A	Assumption
Other parameters						
Discount rate	0.015	0	0.03	N/A	N/A	[5]
RR reduction of statins on MI	0.74	0.73	0.79	0.03	Beta	[97]

Table 14. Incremental costs, incremental QALYs, and ICERs of UK Biobank subpopulation on different statin exclusion strategies with PRS greater than 25% as a risk factor, costing $70

Strategy	Incremental costs ($)	Incremental QALYs (QALY)	ICER ($/QALY)
Top 25% PRS eligible for statins with lower threshold excluded:			
1%	8,626,597.81	6.189	1,393,861.83
2%	7,976,849.97	5.619	1,419,589.19
3%	7,312,724.04	5.420	1,349,157.12
4%	6,752,215.56	4.305	1,568,351.98
5%	6,152,529.68	3.921	1,569,121.72
6%	5,548,542.66	2.604	2,131,096.78
7%	4,906,213.19	1.610	3,047,286.16
8%	4,318,596.94	0.846	5,105,780.41
9%	3,702,990.54	-1.731	-2,139,791.17
10%	3,098,961.58	-2.339	-1,324,769.22

11%	2,488,917.12	-3.095	-804,153.70
12%	1,895,807.66	-4.599	-412,205.32
13%	1,289,389.74	-6.256	-206,114.62
14%	636,900.39	-7.049	-90,350.50
15%	55,496.32	-8.119	-6,835.39
16%	-552,514.21	-9.438	58,541.72
17%	-1,167,771.13	-11.446	102,021.38
18%	-1,760,702.80	-13.503	130,388.96
19%	-2,341,859.26	-14.621	160,169.30
20%	-2,961,393.40	-16.184	182,988.23
21%	-3,550,980.47	-17.517	202,713.87
22%	-4,128,394.50	-18.897	218,464.74
23%	-4,774,891.20	-19.851	240,530.98
24%	-5,393,758.19	-20.924	257,781.21
25%	-5,975,023.92	-22.406	266,670.07

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PRS, polygenic risk score

Table 15. Incremental costs, incremental QALYs, and ICERs of UK Biobank subpopulation on different statin exclusion strategies with PRS greater than 30% as a risk factor, costing $70

Strategy	Incremental costs ($)	Incremental QALYs (QALY)	ICER ($/QALY)
Top 30% PRS eligible for statins with lower threshold excluded:			
1%	9,161,608.65	7.992	1,146,417.61
2%	8,511,860.81	7.422	1,146,896.67
3%	7,847,734.89	7.223	1,086,532.02
4%	7,287,226.40	6.108	1,193,099.01
5%	6,687,540.53	5.724	1,168,430.93
6%	6,083,553.50	4.406	1,380,702.51
7%	5,441,224.03	3.413	1,594,475.83
8%	4,853,607.78	2.648	1,832,694.55
9%	4,238,001.38	0.072	58,875,966.98
10%	3,633,972.43	-0.537	-6,770,625.80

11%	3,023,927.96	-1.293	-2,339,494.31
12%	2,430,818.50	-2.797	-869,185.41
13%	1,824,400.59	-4.453	-409,685.57
14%	1,171,911.23	-5.247	-223,361.68
15%	590,507.16	-6.316	-93,487.20
16%	-17,503.36	-7.635	2,292.39
17%	-632,760.28	-9.644	65,613.05
18%	-1,225,691.95	-11.701	104,751.54
19%	-1,806,848.42	-12.819	140,954.89
20%	-2,426,382.56	-14.381	168,721.43
21%	-3,015,969.63	-15.715	191,920.46
22%	-3,593,383.65	-17.095	210,203.52
23%	-4,239,880.36	-18.049	234,910.22
24%	-4,858,747.34	-19.121	254,101.79
25%	-5,440,013.08	-20.604	264,033.02

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PRS, polygenic risk score

Table 16. Incremental costs, incremental QALYs, and ICERs of UK Biobank subpopulation on different statin exclusion strategies with PRS greater than 35% as a risk factor, costing $70

Strategy	Incremental costs ($)	Incremental QALYs (QALY)	ICER ($/QALY)
Top 35% PRS eligible for statins with lower threshold excluded:			
1%	9,677,972.04	8.760	1,104,803.32
2%	9,028,224.20	8.190	1,102,341.91
3%	8,364,098.27	7.991	1,046,672.65
4%	7,803,589.79	6.876	1,134,868.24
5%	7,203,903.91	6.492	1,109,672.93
6%	6,599,916.89	5.175	1,275,463.77
7%	5,957,587.42	4.181	1,424,939.26
8%	5,369,971.17	3.417	1,571,665.47
9%	4,754,364.77	0.840	5,657,425.87
10%	4,150,335.81	0.232	17,915,023.84

11%	3,540,291.35	-0.524	-6,754,191.54
12%	2,947,181.89	-2.028	-1,453,052.99
13%	2,340,763.97	-3.685	-635,252.27
14%	1,688,274.62	-4.478	-376,989.76
15%	1,106,870.55	-5.548	-199,506.05
16%	498,860.02	-6.867	-72,645.55
17%	-116,396.90	-8.875	13,114.52
18%	-709,328.57	-10.933	64,882.26
19%	-1,290,485.03	-12.050	107,092.11
20%	-1,910,019.17	-13.613	140,312.55
21%	-2,499,606.24	-14.946	167,239.23
22%	-3,077,020.27	-16.326	188,469.12
23%	-3,723,516.97	-17.281	215,474.50
24%	-4,342,383.96	-18.353	236,605.18
25%	-4,923,649.69	-19.835	248,228.64

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PRS, polygenic risk score

Table 17. Incremental costs, incremental QALYs, and ICERs of UK Biobank subpopulation on different statin exclusion strategies with PRS greater than 40% as a risk factor, costing $70

Strategy	Incremental costs ($)	Incremental QALYs (QALY)	ICER ($/QALY)
Top 40% PRS eligible for statins with lower threshold excluded:			
1%	10,158,873.85	10.734	946,389.94
2%	9,509,126.01	10.164	935,525.31
3%	8,845,000.08	9.966	887,555.97
4%	8,284,491.59	8.851	936,032.48
5%	7,684,805.72	8.466	907,687.72
6%	7,080,818.70	7.149	990,468.23
7%	6,438,489.22	6.155	1,045,993.95
8%	5,850,872.97	5.391	1,085,268.20
9%	5,235,266.58	2.815	1,859,898.08
10%	4,631,237.62	2.206	2,099,281.92

11%	4,021,193.16	1.450	2,772,709.66
12%	3,428,083.70	-0.054	-63,682,360.12
13%	2,821,665.78	-1.710	-1,649,768.09
14%	2,169,176.42	-2.504	-866,330.88
15%	1,587,772.36	-3.574	-444,303.96
16%	979,761.83	-4.893	-200,253.66
17%	364,504.91	-6.901	-52,819.25
18%	-228,426.76	-8.958	25,499.43
19%	-809,583.22	-10.076	80,349.30
20%	-1,429,117.36	-11.638	122,795.75
21%	-2,018,704.44	-12.972	155,621.89
22%	-2,596,118.46	-14.352	180,889.58
23%	-3,242,615.17	-15.306	211,851.06
24%	-3,861,482.15	-16.378	235,766.29
25%	-4,442,747.89	-17.861	248,744.31

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PRS, polygenic risk score

Table 18. Incremental costs, incremental QALYs, and ICERs of UK Biobank subpopulation on different statin exclusion strategies with PRS greater than 45% as a risk factor, costing $70

Strategy	Incremental costs ($)	Incremental QALYs (QALY)	ICER ($/QALY)
Top 45% PRS eligible for statins with lower threshold excluded:			
1%	10,725,287.34	11.678	918,457.23
2%	10,075,539.51	11.108	907,082.07
3%	9,411,413.58	10.909	862,741.50
4%	8,850,905.09	9.794	903,724.75
5%	8,251,219.22	9.410	876,901.66
6%	7,647,232.20	8.092	945,021.90
7%	7,004,902.72	7.099	986,808.97
8%	6,417,286.47	6.334	1,013,095.09
9%	5,801,680.08	3.758	1,543,831.71
10%	5,197,651.12	3.149	1,650,432.37

11%	4,587,606.66	2.393	1,916,744.81
12%	3,994,497.20	0.889	4,491,581.66
13%	3,388,079.28	-0.767	-4,416,276.09
14%	2,735,589.92	-1.561	-1,752,790.88
15%	2,154,185.85	-2.630	-818,939.87
16%	1,546,175.33	-3.949	-391,491.98
17%	930,918.41	-5.958	-156,251.38
18%	337,986.74	-8.015	-42,169.53
19%	-243,169.72	-9.133	26,626.45
20%	-862,703.87	-10.695	80,664.18
21%	-1,452,290.94	-12.029	120,735.56
22%	-2,029,704.96	-13.409	151,371.21
23%	-2,676,201.67	-14.363	186,326.78
24%	-3,295,068.65	-15.435	213,476.57
25%	-3,876,334.39	-16.918	229,131.08

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PRS, polygenic risk score

Table 19. Incremental costs, incremental QALYs, and ICERs of UK Biobank subpopulation on different statin exclusion strategies with PRS greater than 50% as a risk factor, costing $70

Strategy	Incremental costs ($)	Incremental QALYs (QALY)	ICER ($/QALY)
Top 50% PRS eligible for statins with lower threshold excluded:			
1%	11,308,158.24	12.062	937,518.72
2%	10,658,410.40	11.492	927,469.17
3%	9,994,284.48	11.293	884,996.56
4%	9,433,775.99	10.178	926,870.27
5%	8,834,090.12	9.794	902,007.86
6%	8,230,103.09	8.476	970,941.74
7%	7,587,773.62	7.483	1,014,024.45
8%	7,000,157.37	6.719	1,041,902.65
9%	6,384,550.97	4.142	1,541,318.55
10%	5,780,522.02	3.534	1,635,892.95

11%	5,170,477.55	2.778	1,861,405.53
12%	4,577,368.09	1.274	3,593,979.64
13%	3,970,950.17	-0.383	-10,371,026.08
14%	3,318,460.82	-1.176	-2,820,827.48
15%	2,737,056.75	-2.246	-1,218,546.41
16%	2,129,046.23	-3.565	-597,182.48
17%	1,513,789.31	-5.574	-271,603.15
18%	920,857.64	-7.631	-120,678.62
19%	339,701.17	-8.748	-38,830.33
20%	-279,832.97	-10.311	27,140.02
21%	-869,420.04	-11.644	74,664.21
22%	-1,446,834.06	-13.024	111,085.58
23%	-2,093,330.77	-13.979	149,751.93
24%	-2,712,197.76	-15.051	180,200.75
25%	-3,293,463.49	-16.533	199,202.43

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PRS, polygenic risk score

Table 20. Incremental costs, incremental QALYs, and ICERs of UK Biobank subpopulation on different statin exclusion strategies with PRS greater than 55% as a risk factor, costing $70

Strategy	Incremental costs ($)	Incremental QALYs (QALY)	ICER ($/QALY)
Top 55% PRS eligible for statins with lower threshold excluded:			
1%	11,820,963.95	13.642	866,497.93
2%	11,171,216.11	13.072	854,567.34
3%	10,507,090.18	12.873	816,182.55
4%	9,946,581.69	11.759	845,903.30
5%	9,346,895.82	11.374	821,759.93
6%	8,742,908.80	10.057	869,348.79
7%	8,100,579.32	9.063	893,781.45
8%	7,512,963.07	8.299	905,278.33
9%	6,897,356.68	5.723	1,205,262.46
10%	6,293,327.72	5.114	1,230,609.40

11%	5,683,283.26	4.358	1,304,054.80
12%	5,090,173.80	2.854	1,783,487.51
13%	4,483,755.88	1.198	3,744,118.59
14%	3,831,266.52	0.404	9,482,832.49
15%	3,249,862.46	-0.666	-4,881,651.66
16%	2,641,851.93	-1.985	-1,331,097.83
17%	2,026,595.01	-3.993	-507,524.43
18%	1,433,663.34	-6.050	-236,960.30
19%	852,506.88	-7.168	-118,933.82
20%	232,972.74	-8.730	-26,685.60
21%	-356,614.34	-10.064	35,434.77
22%	-934,028.36	-11.444	81,616.84
23%	-1,580,525.06	-12.398	127,479.99
24%	-2,199,392.05	-13.471	163,274.18
25%	-2,780,657.79	-14.953	185,962.17

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PRS, polygenic risk score

Table 21. Incremental costs, incremental QALYs, and ICERs of UK Biobank subpopulation on different statin exclusion strategies with PRS greater than 60% as a risk factor, costing $70

Strategy	Incremental costs ($)	Incremental QALYs (QALY)	ICER ($/QALY)
Top 60% PRS eligible for statins with lower threshold excluded:			
1%	12,369,779.97	14.921	829,035.58
2%	11,720,032.14	14.351	816,680.22
3%	11,055,906.21	14.152	781,230.53
4%	10,495,397.72	13.037	805,047.65
5%	9,895,711.85	12.653	782,102.90
6%	9,291,724.83	11.335	819,715.47
7%	8,649,395.35	10.342	836,359.22
8%	8,061,779.10	9.578	841,739.64
9%	7,446,172.71	7.001	1,063,563.07
10%	6,842,143.75	6.392	1,070,347.71

11%	6,232,099.29	5.637	1,105,644.83
12%	5,638,989.83	4.133	1,364,542.55
13%	5,032,571.91	2.476	2,032,538.61
14%	4,380,082.55	1.682	2,603,352.07
15%	3,798,678.49	0.613	6,199,630.80
16%	3,190,667.96	-0.706	-4,517,696.51
17%	2,575,411.04	-2.715	-948,711.19
18%	1,982,479.37	-4.772	-415,460.03
19%	1,401,322.91	-5.889	-237,937.69
20%	781,788.76	-7.452	-104,912.43
21%	192,201.69	-8.786	-21,877.12
22%	-385,212.33	-10.166	37,893.68
23%	-1,031,709.04	-11.120	92,781.56
24%	-1,650,576.02	-12.192	135,380.92
25%	-2,231,841.76	-13.674	163,213.65

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PRS, polygenic risk score

Table 22. Incremental costs, incremental QALYs, and ICERs of UK Biobank subpopulation on different statin exclusion strategies with PRS greater than 65% as a risk factor, costing $70

Strategy	Incremental costs ($)	Incremental QALYs (QALY)	ICER ($/QALY)
Top 65% PRS eligible for statins with lower threshold excluded:			
1%	12,940,754.86	15.937	812,003.71
2%	12,291,007.02	15.367	799,833.74
3%	11,626,881.10	15.168	766,537.95
4%	11,066,372.61	14.053	787,467.29
5%	10,466,686.74	13.669	765,733.97
6%	9,862,699.71	12.351	798,506.34
7%	9,220,370.24	11.358	811,805.68
8%	8,632,753.99	10.594	814,898.78
9%	8,017,147.59	8.017	999,982.42
10%	7,413,118.64	7.409	1,000,612.56

11%	6,803,074.17	6.653	1,022,595.73
12%	6,209,964.71	5.149	1,206,136.00
13%	5,603,546.79	3.492	1,604,619.65
14%	4,951,057.44	2.699	1,834,670.27
15%	4,369,653.37	1.629	2,682,649.38
16%	3,761,642.85	0.310	12,139,385.26
17%	3,146,385.92	-1.699	-1,852,437.85
18%	2,553,454.26	-3.756	-679,898.88
19%	1,972,297.79	-4.873	-404,713.18
20%	1,352,763.65	-6.436	-210,197.09
21%	763,176.58	-7.769	-98,228.78
22%	185,762.55	-9.149	-20,303.08
23%	-460,734.15	-10.104	45,600.84
24%	-1,079,601.14	-11.176	96,600.33
25%	-1,660,866.87	-12.658	131,208.49

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PRS, polygenic risk score

Table 23. Incremental costs, incremental QALYs, and ICERs of UK Biobank subpopulation on different statin exclusion strategies with PRS greater than 70% as a risk factor, costing $70

Strategy	Incremental costs ($)	Incremental QALYs (QALY)	ICER ($/QALY)
Top 70% PRS eligible for statins with lower threshold excluded:			
1%	13,505,187.40	17.032	792,949.84
2%	12,855,439.56	16.462	780,929.62
3%	12,191,313.63	16.263	749,643.99
4%	11,630,805.14	15.148	767,817.29
5%	11,031,119.27	14.764	747,184.07
6%	10,427,132.25	13.446	775,470.75
7%	9,784,802.77	12.453	785,762.90
8%	9,197,186.52	11.688	786,863.59
9%	8,581,580.13	9.112	941,783.75
10%	7,977,551.17	8.503	938,166.63

11%	7,367,506.71	7.748	950,951.39
12%	6,774,397.25	6.243	1,085,048.53
13%	6,167,979.33	4.587	1,344,696.01
14%	5,515,489.97	3.793	1,453,981.61
15%	4,934,085.91	2.724	1,811,592.21
16%	4,326,075.38	1.405	3,079,864.05
17%	3,710,818.46	-0.604	-6,146,283.67
18%	3,117,886.79	-2.661	-1,171,751.43
19%	2,536,730.33	-3.779	-671,348.18
20%	1,917,196.19	-5.341	-358,962.95
21%	1,327,609.11	-6.675	-198,904.14
22%	750,195.09	-8.055	-93,137.38
23%	103,698.38	-9.009	-11,510.70
24%	-515,168.60	-10.081	51,101.93
25%	-1,096,434.34	-11.563	94,818.83

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PRS, polygenic risk score

9.0. FIGURES

Figure 1. Number of CAD cases as a function of PRS deciles

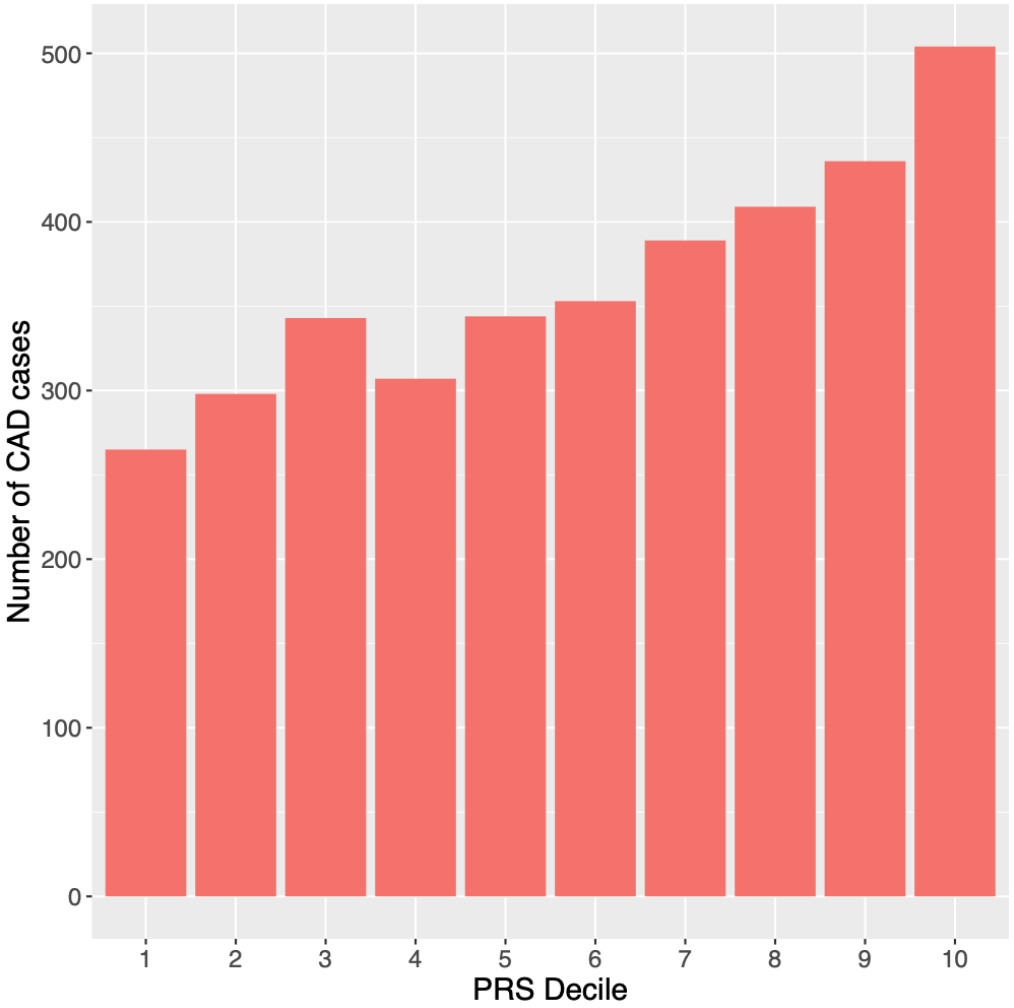


Figure 2. Cost-effectiveness plane of PRS base-cases analysis at $70 genotyping per person

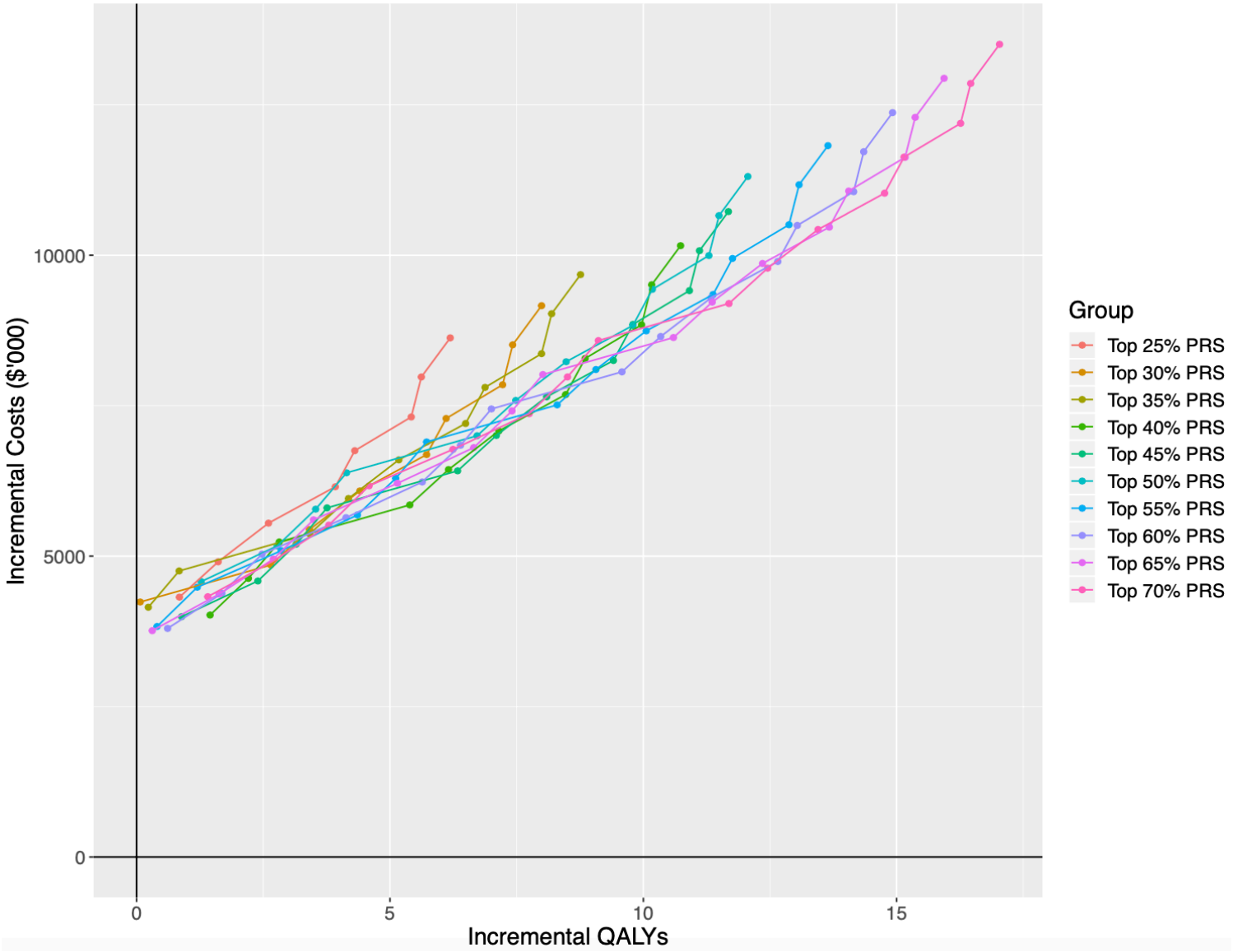


Figure 3. ICER as a function of lower PRS percent exclusion in base-cases analysis at $70 genotyping per person

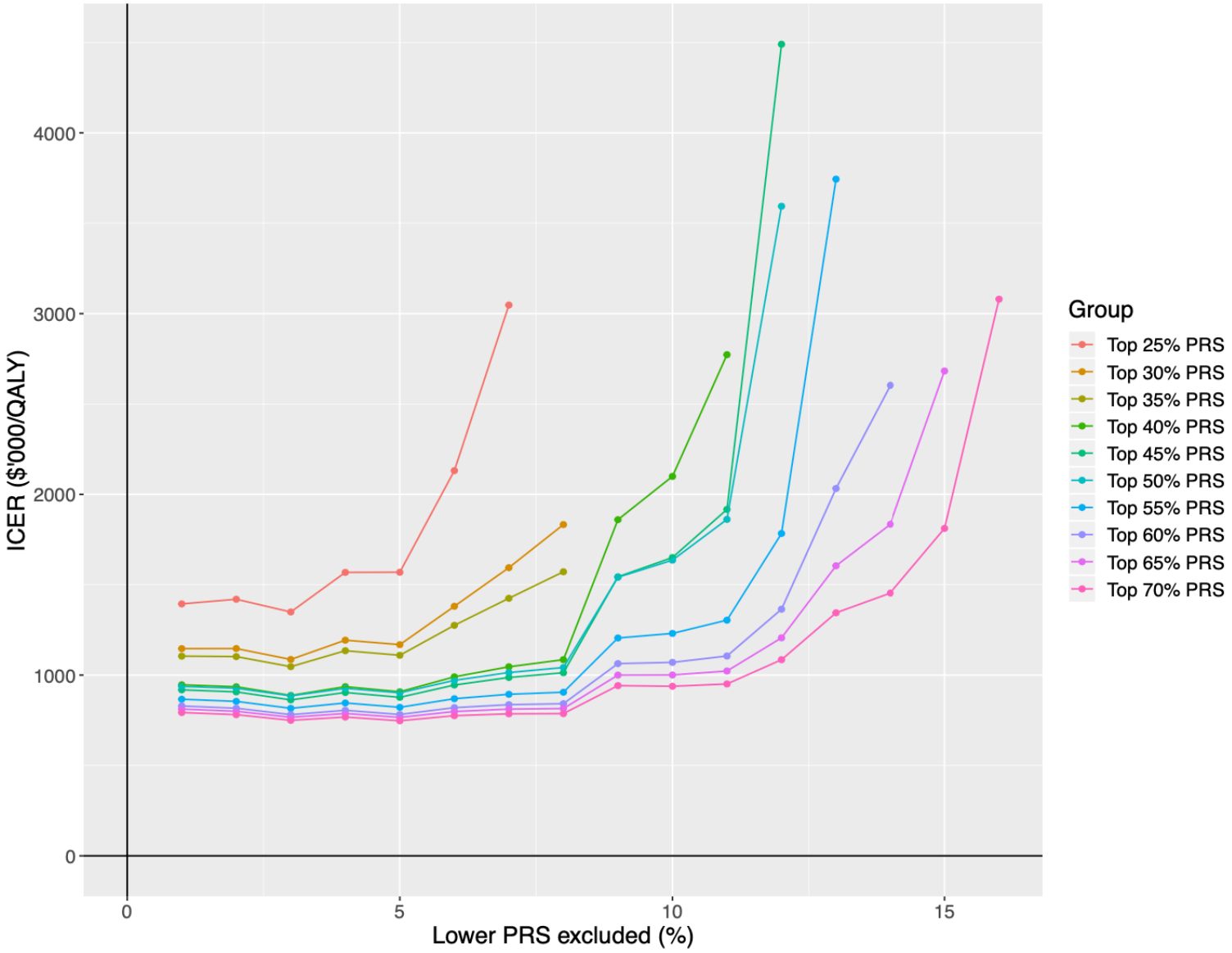


Figure 4. Cost-effectiveness plane of PRS base-cases analysis at $0 genotyping per person

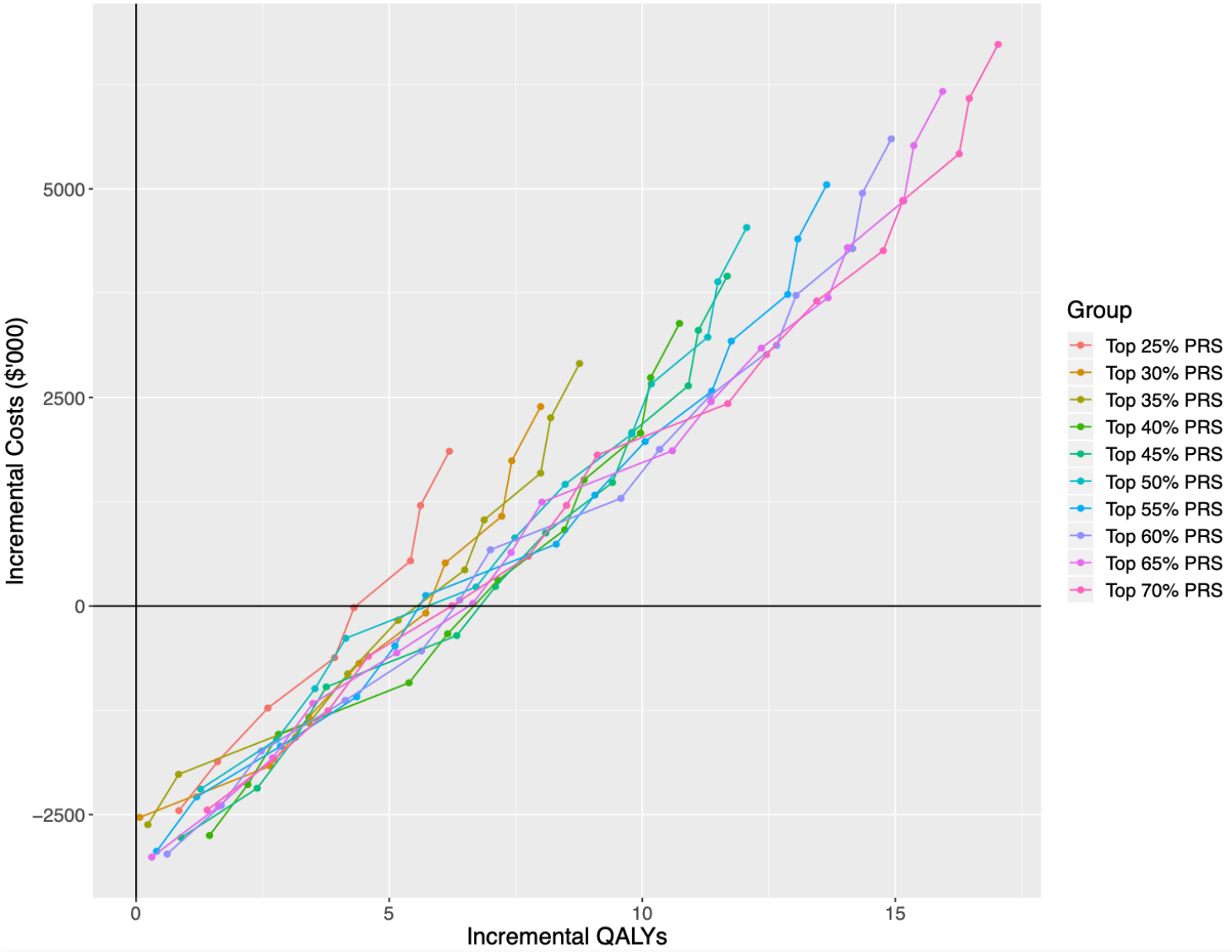


Figure 5. ICER as a function of lower PRS percent exclusion in base-cases analysis at $0 genotyping per person

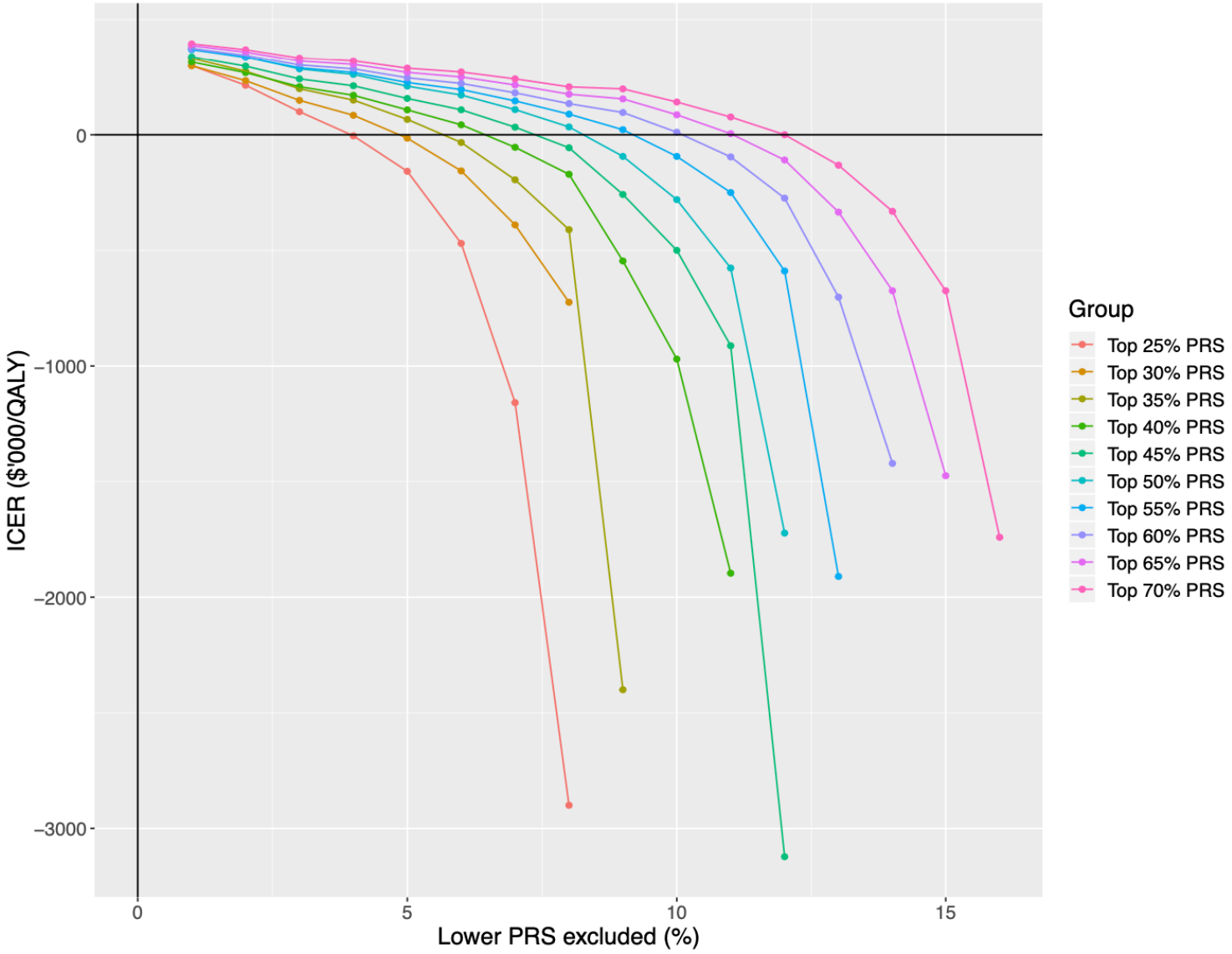


Figure 6. ICER as a function of lower PRS percent exclusion in base-cases analysis at $70 genotyping per person

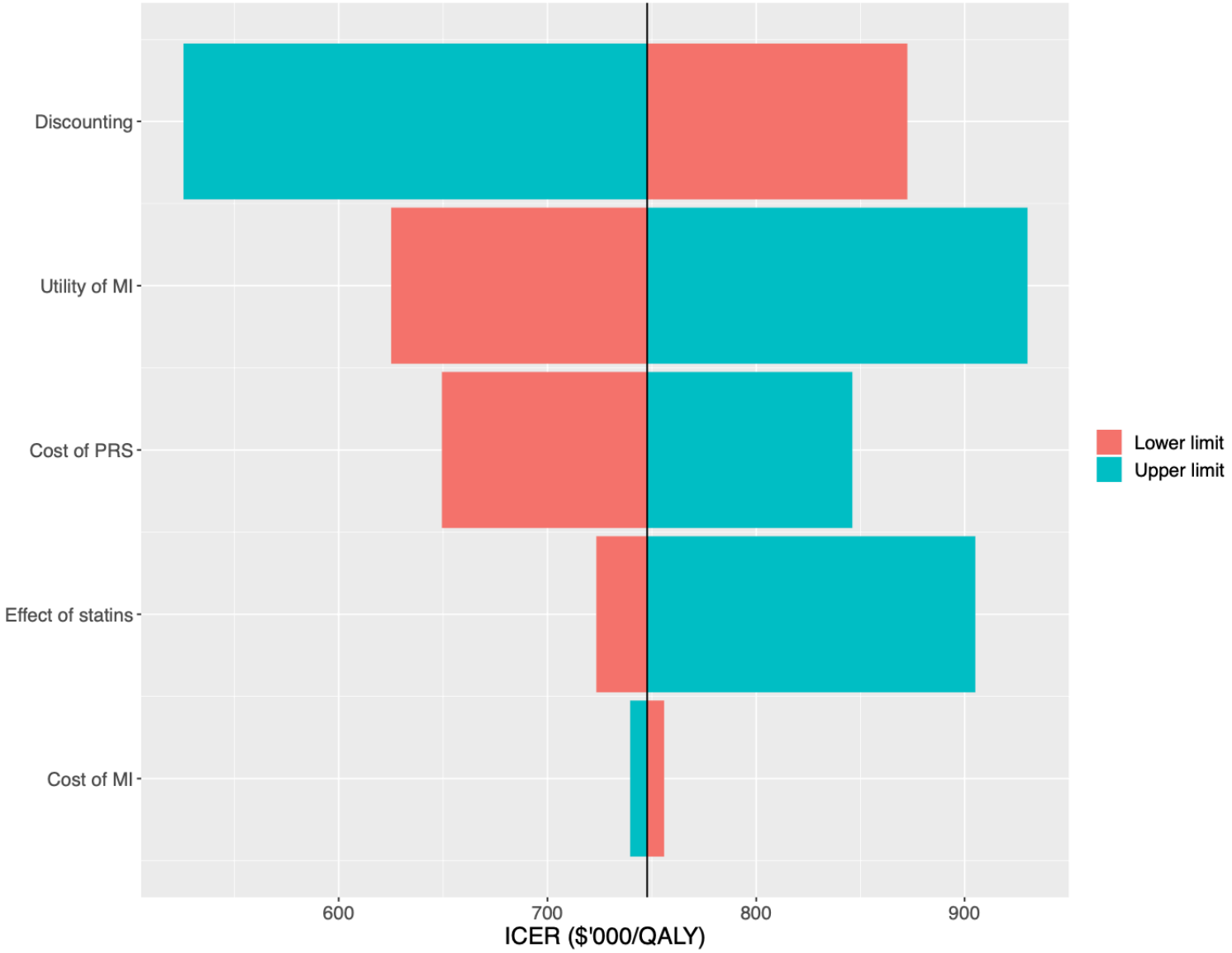


Figure 7. Cost-effectiveness plane of PRS PSA at $70 genotyping per person and a discounting rate of 1.5%

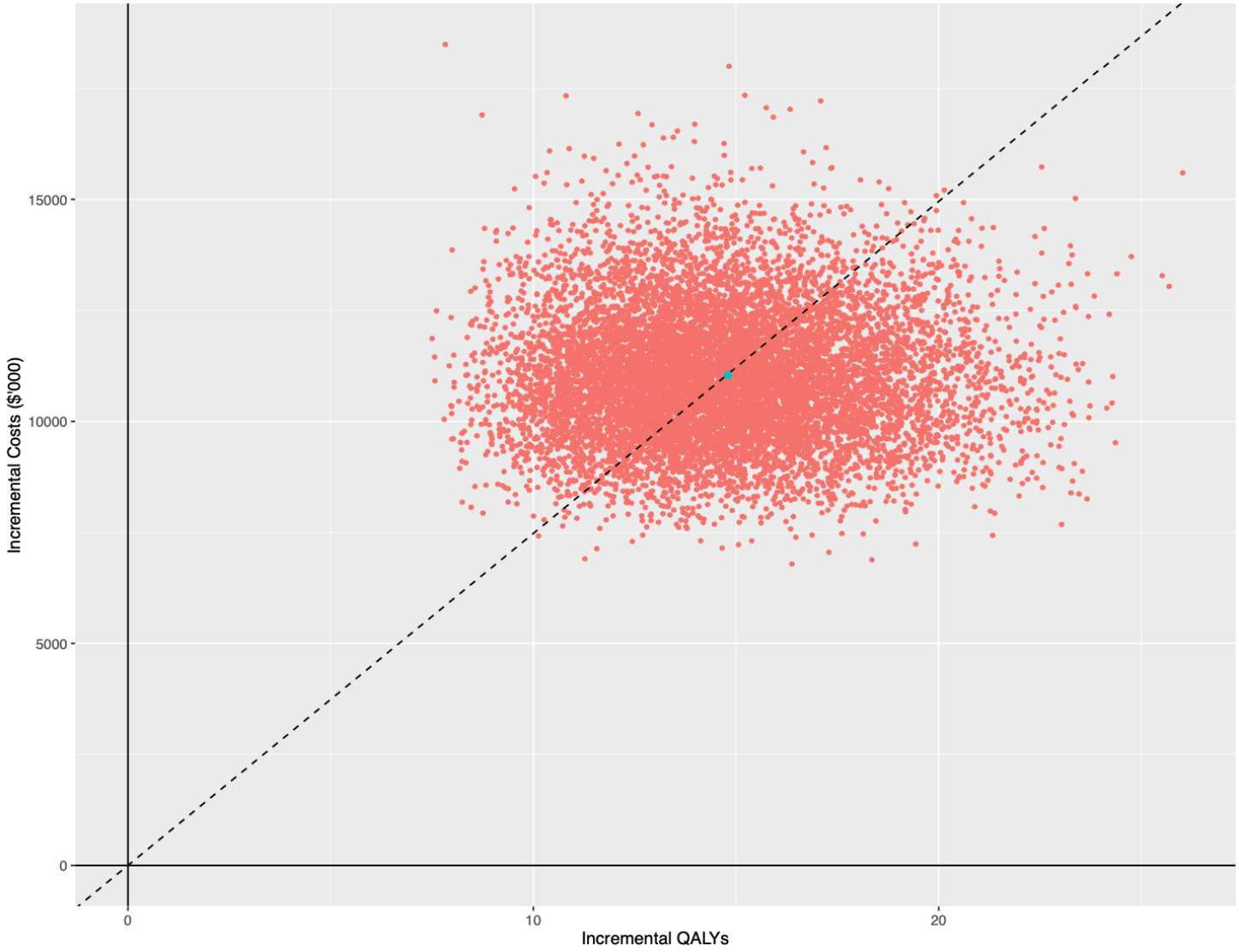


Figure 8. Cost-effectiveness acceptability curve of PRS PSA at $70 genotyping per person and a discounting rate of 1.5%

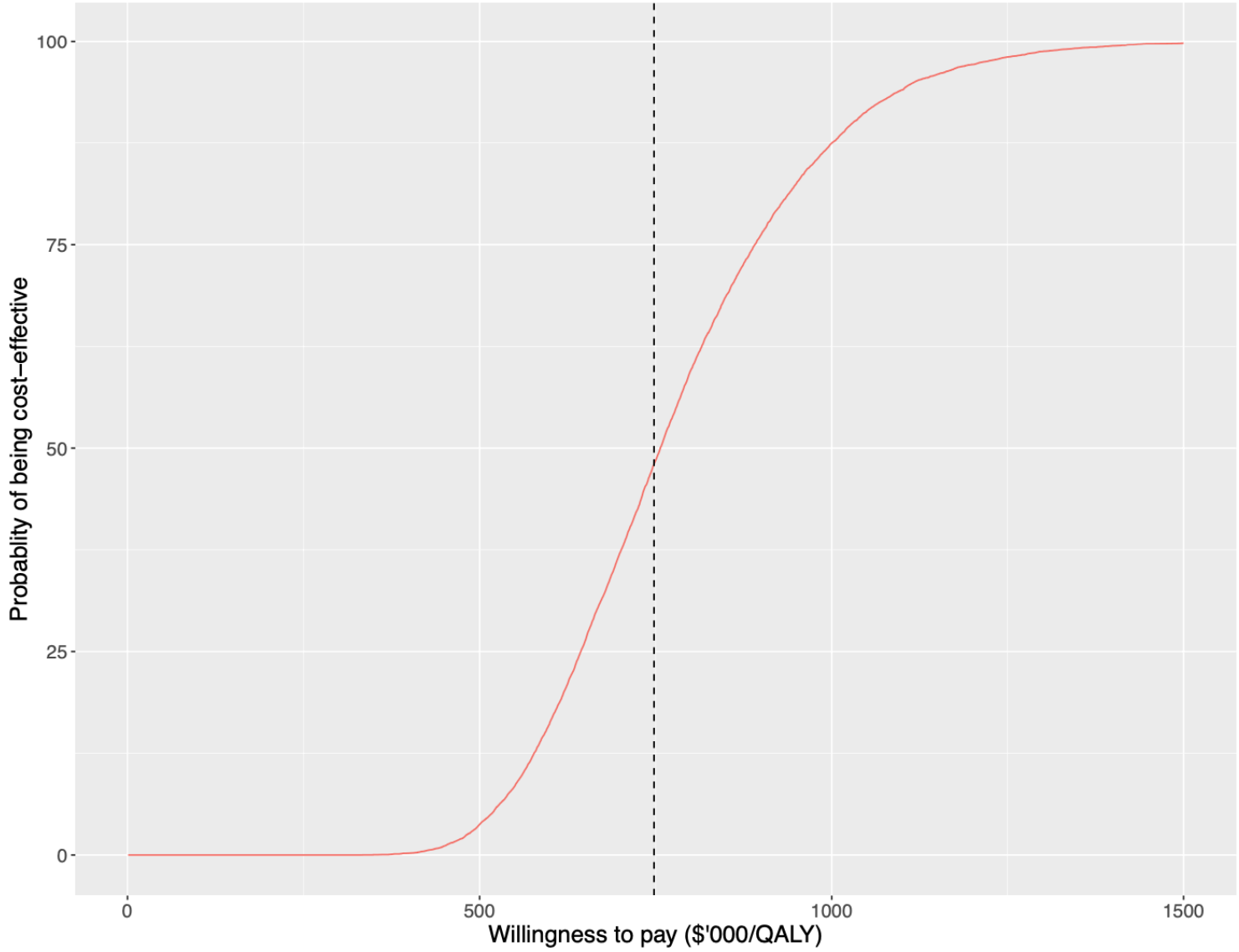


Figure 9. Cost-effectiveness plane of PRS PSA at $70 genotyping per person and a discounting rate of 3.0%

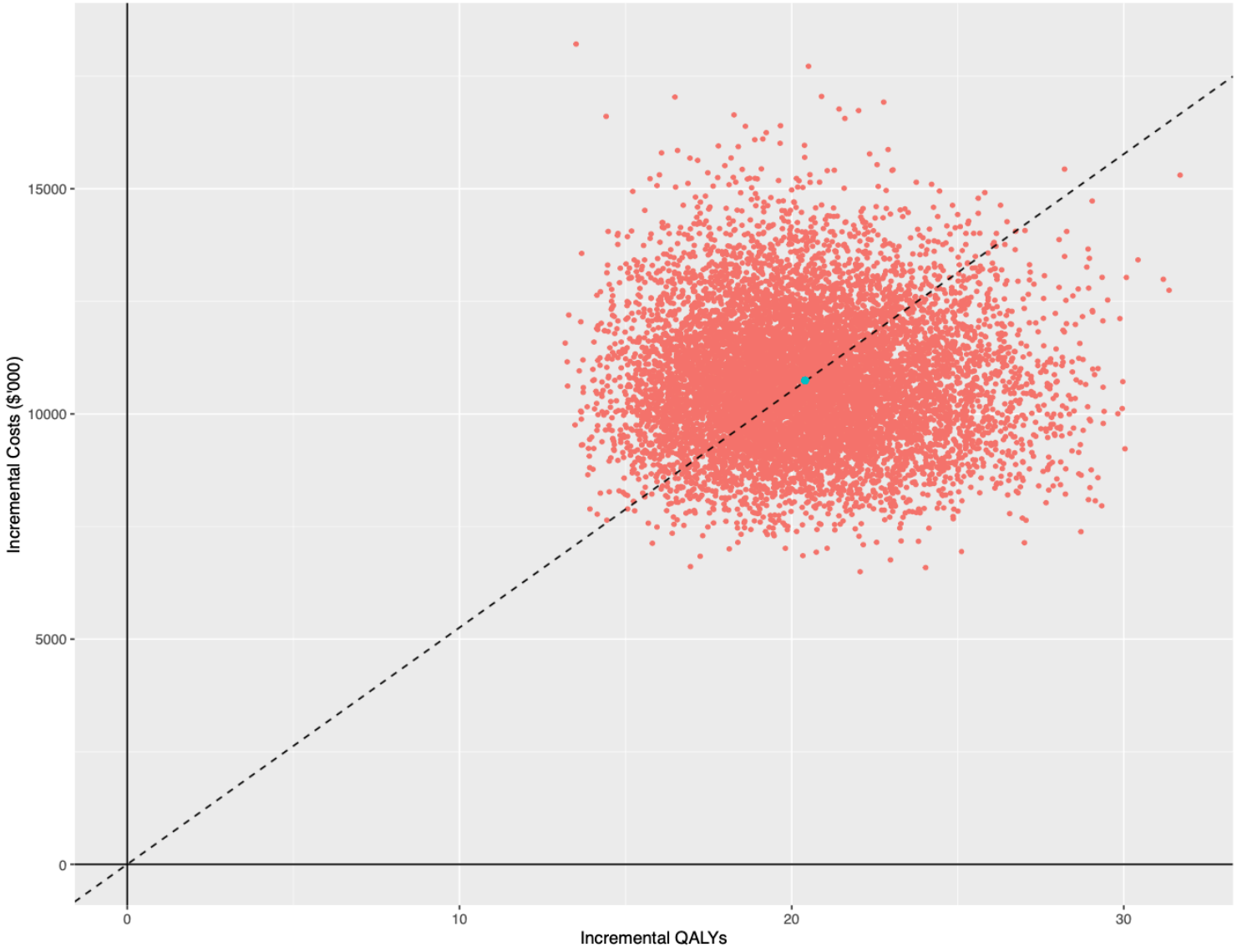


Figure 10. Cost-effectiveness acceptability curve of PRS PSA at $70 genotyping per person and a discounting rate of 3.0%

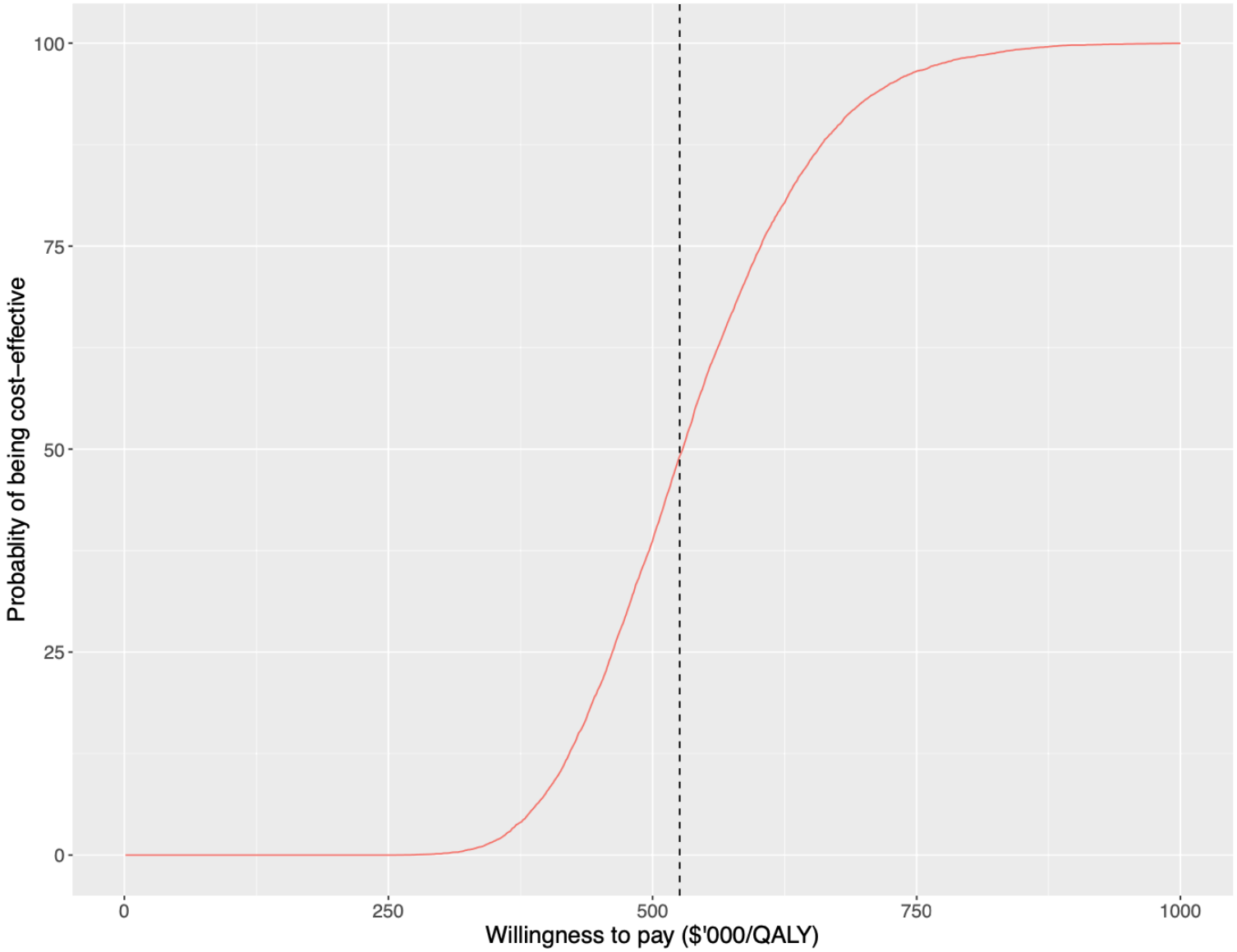
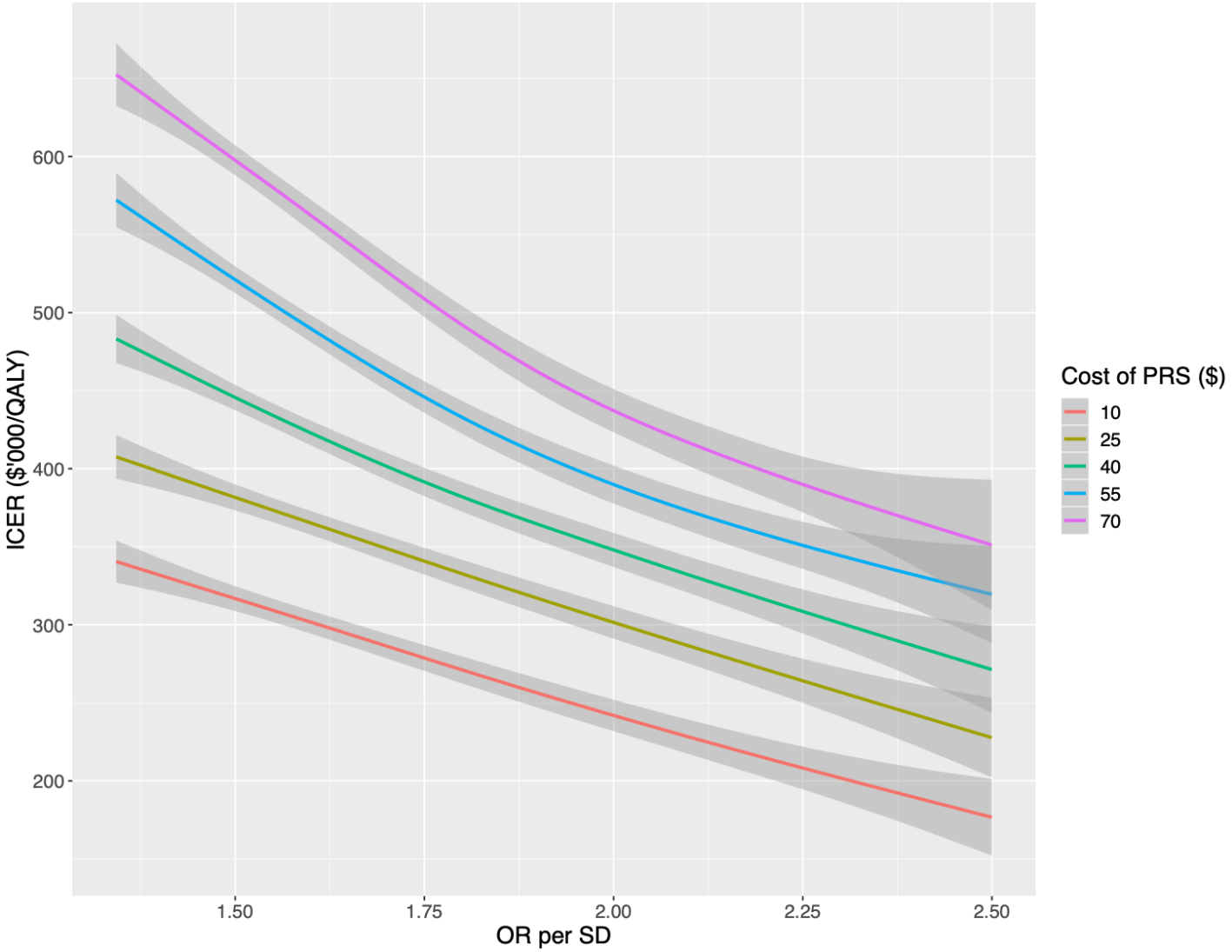


Figure 11. ICER as a function of OR per SD with different genotyping costs with statins for the top 70% PRS individuals and lower 5% PRS excluded



10.0. APPENDIX 1: COST-EFFECTIVENESS MODEL CALCULATIONS

This section provides a step-by-step schematic of the calculations leading to the base-case analysis ICER value ($747,184.10/QALY, corresponding to the strategy whereby the top 70% PRS individuals are eligible for statins with the lower 5% PRS excluded). The parameters are shown in Table 13. The schematic of the clinical model, which is frequently referenced in this section, is shown in Figure 1A.

10.1. COSTS OF THE STANDARD CARE GROUP

In the cohort guided using the Canadian Cardiovascular Society dyslipidemia guidelines of 2016, individuals with statin eligibility (n = 82,083) were subjected to the total cost of statins for 10 years of $800.70, as shown in Table 1A, and the cost of a MI event at $13,983.78. First, the total number of MI events (n = 748) was reduced by 0.5455 (corresponding to reduction of MI events by 'prescribing' statins) and multiplied by $13,983.78. The total cost of MI events was $5,594,276.00 and the total cost of the corresponding statins for 10 years was $523,822.50. The total cost of statins who were eligible (n = 81,335) but had no event was $65,126,005.00. There were no further costs associated with individuals eligible for statins without an MI event.

Individuals without statin eligibility (n = 14,653) required a more nuanced analysis. First, the total cost of MI events (n = 105) was $1,439,660.00. There was no reduction due to statins since this group was not eligible for pharmacological intervention. However, statin therapy was started at the year of the event till the end of the 10-year time horizon. The cost of statins was

therefore dependent on the year of MI, as per Table 1A. The total cost of statins for individuals who were initially not eligible for statins in the standard care group and subsequently had an MI (n = 105) was $48,813.90. Individuals who were not eligible for statins with no MI event had no costs (n = 14,548).

10.2. COSTS OF THE POLYGENIC RISK SCORE INTERVENTION GROUP

In the cohort guided using the Canadian Cardiovascular Society dyslipidemia guidelines of 2016 in addition to the PRS, the cost of genotyping at $70 was applied as a one-time cost for all participants in the 10-year duration. The total was $6,771,520.00. Individuals with statin eligibility (n = 87,964) were subjected to the same $800.70 cost of statins for 10 years, as shown in Table 1A and the cost of a MI event at $13,983.78. The total number of MI events (n = 813) was reduced by 0.5455 and multiplied by $13,983.78. The total cost of MI events was $6,080,410.00 and the total cost of the corresponding statins for 10 years was $569,341.90. The total cost of statins who were eligible (n = 87,151) but had no event was $69,782,953.00. There were no further costs associated with individuals eligible for statins without an MI event.

For individuals without statin eligibility (n = 8,772), the total cost of MI events (n = 40) was $548,441.80. There was no reduction due to statins since this group was not eligible for pharmacological intervention. Analogous to the standard care group, statin therapy was started at the year of the event till the end of the 10-year time horizon, as per Table 1A. The total cost of statins for individuals who were not eligible for statins in the PRS intervention group and

subsequently had an MI (n = 40) was $19,088.30. Individuals who were initially not eligible for statins with no MI event had no costs (n = 14,548).

10.3. QUALITY-ADJUSTED LIFE YEARS OF THE STANDARD CARE GROUP

The QALYs in the cohort using the Canadian Cardiovascular Society dyslipidemia guidelines of 2016 revolve around MI cases as they are the sole adverse events. The UK Biobank cohort started with perfect health with utility values of 1.00. Individuals with statin eligibility and a MI event (n = 748) could take two trajectories based on the reduction of their event by statins. Approximately 54.55% of these cases were prevented and therefore, remained at perfect health for 10 years. The total QALYs for individuals who had a MI prevented was 3399.876. However, approximately 45.45% of cases experienced an MI. During the year of event, utility dropped to 0.708 and subsequently restored to perfect utility for the rest of the time horizon barring discounting, as per Table 2A. The QALYs associated with an individual who had a MI is dependent on the time of event. The total QALYs of individuals with statin eligibility with a MI event was 3874.418. Individuals without statin eligibility and a MI event (n = 105) had no possibility of reduced events. Their trajectory was identical to individuals who were on statin therapy but nonetheless, experienced a MI, as per Table 2A. The total QALYs for this group was 1016.401.

All other individuals did not experience a MI. This included non-cases with statin eligibility (n = 81,335) and without statins (n = 14,548) who had perfect health for the entire 10-

year time horizon. Their trajectories were identical to MI cases that were prevented by statins. The total QALYs for controls was 910,011.

10.4. QUALITY-ADJUSTED LIFE YEARS OF THE POLYGENIC RISK SCORE INTERVENTION GROUP

The QALYs in the cohort using the Canadian Cardiovascular Society dyslipidemia guidelines of 2016 in addition to PRS also revolve around MI cases. Approximately 54.55% of individuals with statin eligibility and a MI event (n = 813) were prevented and therefore, remained at perfect health for 10 years. The total QALYs for individuals who had a MI prevented was 3695.32. However, approximately 45.45% of cases experienced a MI and followed a utility trajectory as per Table 2A. The total QALYs of individuals with statin eligibility with a MI event was 4211.257. Individuals without statin eligibility and a MI event (n = 40) have a trajectory identical to individuals who were on statin therapy but nonetheless, experienced a MI, as per Table 2A. The total QALYs for this group was 398.8826.

All other individuals did not experience a MI. This included non-cases with statin eligibility (n = 87,151) and without statins (n = 8,732) who had perfect health for the entire 10-year time horizon. Their trajectories were identical to MI cases that were prevented by statins. The total QALYs for this set of controls was also 910,011 since the total number of non-MI cases is constant. The driver for the nonzero incremental QALY is the number of MI cases prevented due to statins.

10.5. INCREMENTAL COST-EFFECTIVENESS RATIO CALCULATION

The incremental cost was calculated by taking the difference of the standard care group costs summation and the PRS intervention group costs summation. The incremental QALYs were calculated in a similar manner, as shown in Table 3A. The final ICER, $747,729.90, was the ratio of the two values.

Figure 1A. Schematic of the statin eligibility clinical model

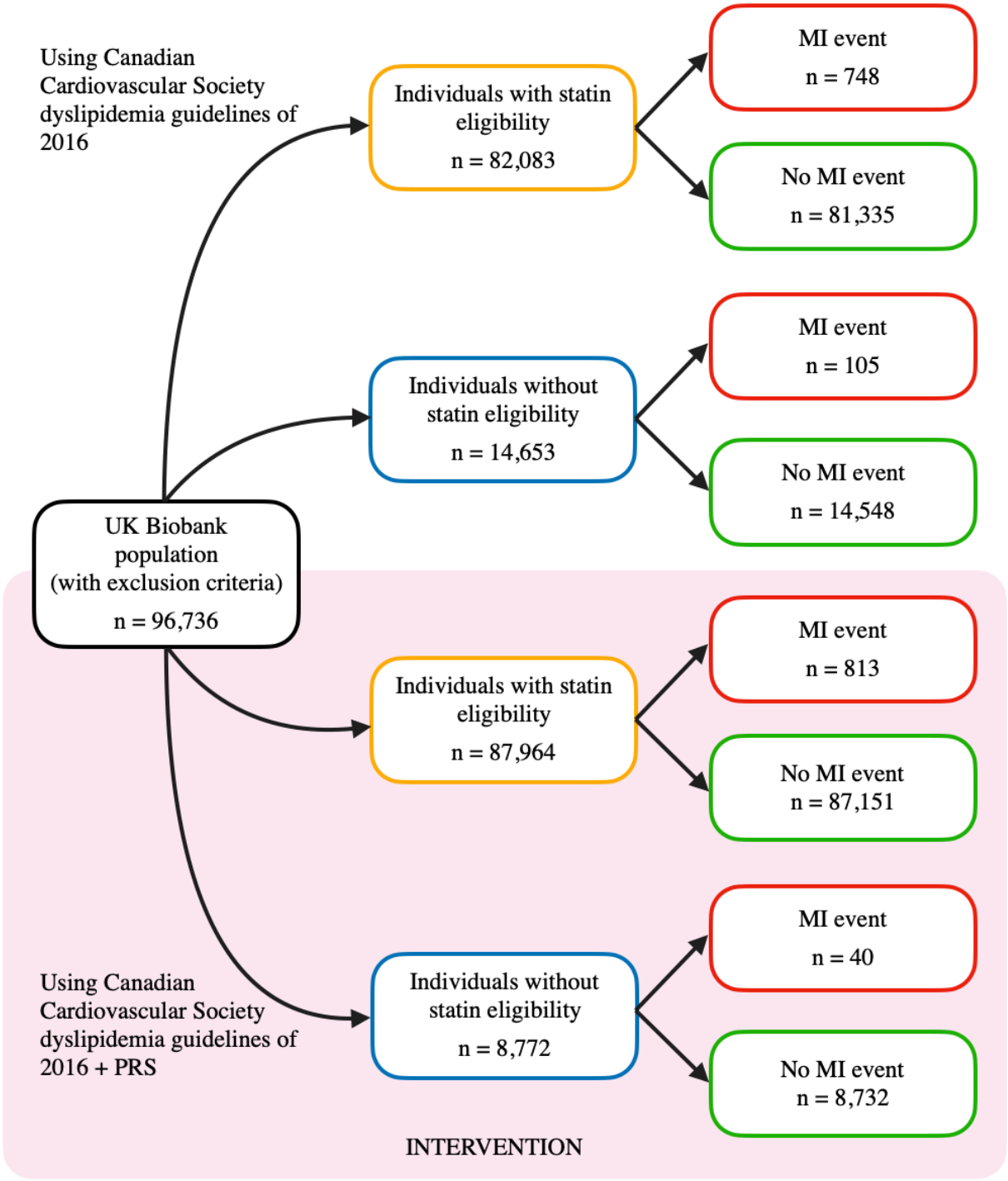


Table 1A. Cost of statins per year with a discounting rate of 1.5%

Year	Discounting factor	Cumulative cost of statin ($ CAD)
1	1.000	85.54
2	0.9852	169.82
3	0.9707	252.90
4	0.9563	334.70
5	0.9422	415.30
6	0.9283	494.70
7	0.9145	572.90
8	0.9010	650.00
9	0.8877	725.90
10	0.8746	800.70

Table 2A. Utility trajectories of MI cases with a discounting rate of 1.5%

Year of MI	Utility value per subsequent year after MI									
1	0.708	0.985	0.971	0.956	0.942	0.928	0.915	0.901	0.888	0.875
2	1.000	0.708	0.985	0.971	0.956	0.942	0.928	0.915	0.901	0.888
3	1.000	1.000	0.708	0.985	0.971	0.956	0.942	0.928	0.915	0.901
4	1.000	1.000	1.000	0.708	0.985	0.971	0.956	0.942	0.928	0.915
5	1.000	1.000	1.000	1.000	0.708	0.985	0.971	0.956	0.942	0.928
6	1.000	1.000	1.000	1.000	1.000	0.708	0.985	0.971	0.956	0.942
7	1.000	1.000	1.000	1.000	1.000	1.000	0.708	0.985	0.971	0.956
8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.708	0.985	0.971
9	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.708	0.985
10	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.708

Table 3A. Breakdown of total costs, total QALYs, incremental costs, incremental QALYs, and ICER

Description of cost or QALY	Value
Canadian Cardiovascular Society dyslipidemia guidelines of 2016:	
Costs	
Cost of MI cases, statin prescribed	$5,594,276.00
Cost of statins for MI cases, statin initially prescribed	$523,822.50
Cost of MI cases, statin not prescribed	$1,439,660.00
Cost of statins after MI cases, statin initially not prescribed	$48,813.90
Cost of statins for non-MI cases	$65,126,005.00
Total costs associated with standard care	$72,732,577.40
QALYs	
QALYs of MI cases, statin prescribed and prevented	3,399.876 QALYs
QALYs of MI cases, statin prescribed and not prevented	3,874.418 QALYs
QALYs of MI cases, statin not prescribed	1,016.401 QALYs
QALYs of controls	910,011 QALYs
Total QALYs associated with standard care	918,301.70 QALYs
Canadian Cardiovascular Society dyslipidemia guidelines of 2016 in addition to PRS:	
Costs	
Cost of genotyping	$6,771,520.00
Cost of MI cases, statin prescribed	$6,080,410.00

Cost of statins for MI cases, statin initially prescribed	$569,341.90
Cost of MI cases, statin not prescribed	$548,441.80
Cost of statins after MI cases, statin initially not prescribed	$19,088.30
Cost of statins for non-MI cases	$69,782,953.00
Total costs associated with intervention	$83,771,754.00
QALYs	
QALYs of MI cases, statin prescribed and prevented	3,695.320 QALYs
QALYs of MI cases, statin prescribed and not prevented	4211.257 QALYs
QALYs of MI cases, statin not prescribed	398.8826 QALYs
QALYs of controls	910,011 QALYs
Total QALYs associated with PRS intervention	918,316.5 QALYs
ICER calculations	
Incremental costs	$11,039,177.30
Incremental QALYs	14.76359 QALYs
ICER	$747,729.90/QALY