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ORIGINAL ARTICLE

Cost-Effectiveness of Polygenic Risk Scores to Guide Statin Therapy for Cardiovascular Disease Prevention

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BACKGROUND: Atherosclerotic cardiovascular diseases (CVDs) are leading causes of death despite effective therapies and result in unnecessary morbidity and mortality throughout the world. We aimed to investigate the cost-effectiveness of polygenic risk scores (PRS) to guide statin therapy for Canadians with intermediate CVD risk and model its economic outlook.

METHODS: This cost-utility analysis was conducted using UK Biobank prospective cohort study participants, with recruitment from 2006 to 2010, and at least 10 years of follow-up. We included nonrelated white British-descent participants (n=96 116) at intermediate CVD risk with no prior lipid lowering medication or statin-indicated conditions. A coronary artery disease PRS was used to inform decision to use statins. The effects of statin therapy with and without PRS, as well as CVD events were modelled to determine the incremental cost-effectiveness ratio from a Canadian public health care perspective. We discounted future costs and quality-adjusted life-years by 1.5% annually.

RESULTS: The optimal economic strategy was when intermediate risk individuals with a PRS in the top 70% are eligible for statins while the lowest 1% are excluded. Base-case analysis at a genotyping cost of $70 produced an incremental cost-effectiveness ratio of $172 906 (143 685 USD) per quality-adjusted life-year. In the probabilistic sensitivity analysis, the intervention has approximately a 50% probability of being cost-effective at $179 100 (148 749 USD) per quality-adjusted life-year. At a $0 genotyping cost, representing individuals with existing genotyping information, PRS-guided strategies dominated standard care when 12% of the lowest PRS individuals were withheld from statins. With improved PRS predictive performance and lower genotyping costs, the incremental cost-effectiveness ratio demonstrates possible cost-effectiveness under thresholds of $150 000 and possibly $50 000 per quality-adjusted life-year.

CONCLUSIONS: This study suggests that using PRS alongside existing guidelines might be cost-effective for CVD. Stronger predictiveness combined with decreased cost of PRS could further improve cost-effectiveness, providing an economic basis for its inclusion into clinical care.

Key Words: cardiovascular disease ■ cause of death ■ lipid ■ morbidity ■ risk factors

Atherosclerotic cardiovascular diseases (CVDs) are some of the leading causes of death in Canada for both men and women.[1] Together, they constitute a large economic burden on the country; in the magnitude of over $10 billion per year.[2,3] Hence, there is a public health and economic desire to improve the prediction of CVD to treat susceptible individuals.

Framingham risk score is widely used as a CVD risk prediction tool and recommended by the Canadian Cardiovascular Society dyslipidemia guidelines of 2016. It derives the 10-year risk of CVD, defined as CVD death, nonfatal myocardial infarctions (MI), ischemic stroke, revascularization, and acute coronary syndromes hospitalizations, from a simple tabulation of risk factors to

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Nonstandard Abbreviations and Acronyms

CVD	cardiovascular disease
ICER	incremental cost-effectiveness ratio
MI	myocardial infarction
PRS	polygenic risk score
QALY	quality-adjusted life-year
WTP	Willingness-to-pay

classify individuals as low (<10%), intermediate (10%–19%), or high risk (≥20%).[4] Statins for primary prevention are prescribed to patients who either fall in high risk; have a statin-indicated condition (clinical atherosclerosis, abdominal aortic aneurysm, certain age with, or duration of diabetes, chronic kidney disease, or familial hypercholesteremia); or other risk factors in conjunction with intermediate risk.[4]

However, traditional risk factors do not capture genetic risk of CVD. Although monogenic patterns of inheritance have been well characterized, such mutations are rare at a population level. As such, the importance of polygenic patterns on CVD heritability is increasingly recognized.[5] Genome-wide association studies (GWASs) have been successful at identifying common genetic variants associated with risk of CVD and can be used to produce polygenic risk scores (PRSs), which reflect individual genetic predisposition of developing CVD.[6] It follows that using genotypic, in addition to phenotypic, factors could yield stronger predictions and risk stratification of disease than either alone.[7,8] Clinical trials and meta-analyses have shown the application of PRSs. These include improved screening strategies, guiding statin therapy to lower LDL-C, and possibly reducing coronary artery disease events by selecting patients who might have the greatest benefits from statins.[7,9–13] Therefore, the application of PRSs to directly target CVD with preventative interventions might have beneficial clinical outcomes with positive health effects, notably by guiding statin therapy.[3,14]

While use of PRSs to guide preventative interventions holds promise, the cost-effectiveness of PRS has not been explored.[14,15] We sought to determine the cost-effectiveness of adding PRS to clinical risk factors to guide statin therapy for the primary prevention of CVD in Canada. The objectives were to estimate the incremental cost-effectiveness ratio (ICER) or cost per quality-adjusted life-year (QALY) gained over a time horizon of 10 years, as well as explore how changes in PRS predictiveness and cost would affect cost-effectiveness.

METHODS

The analytical methods, including selection of the study population, determining statin eligibility, and simulation model were performed in R (version 3.6.3, notable packages include data.table, tidyverse packages, and mice).[16] The source code has been made open source and can be accessed in the Supplemental Material. No institutional review board approval was required. The full Methods are available in the Supplemental Material.

RESULTS

Table 1 presents participant statin eligibility assessed from the 2016 Canadian Cardiovascular Society dyslipidemia guidelines and the optimal PRS strategy.[4] Upper PRS thresholds indicated statin eligibility and lower thresholds represented exclusion due to protective PRSs. As shown in Figure 1, in a study population of 96 111 participants, 81 551 (84.85%) were eligible for statins using the guidelines (without PRS) compared with 90 507 (94.17%) with the PRS at upper and lower thresholds of 70% and 1%, respectively. This combination yielded the greatest number of CVD events (coronary artery disease, subsequently MI and stroke) captured with statin therapy over 10 years relative to the number of statin-eligible participants. The total number of MIs and strokes were 806 and 626, respectively. The guidelines captured 706 MIs (87.60%) and 532 strokes (84.98%), however, when combined with the PRS, 780 MIs (96.77%) and 592 strokes (94.57%) were captured. Although the PRS-guided strategy resulted in an ≈ 9% increase in statin therapy-eligible individuals, the number of captured MIs increased by ≈ 10%.

Using model parameters in Table 2, ICERs using incremental cost per QALYs gained for PRS-guided statin

Table 1. Proposed Algorithm for Statin Prescription Strategies in Cost-Effectiveness Model Incorporating Genetic Risk

CVD risk category	Statin eligibility in the cost-effectiveness model
Dyslipidemia guidelines[4]	
Intermediate FRS (10%–19%)	Yes
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 y and 1 additional CVD risk factor	
Dyslipidemia guidelines and PRS	
Intermediate FRS (10%–19%) without protective PRS≤(lower threshold percentage)	Yes
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 y and 1 additional CVD risk factor	
or risk conferring PRS≥(upper threshold percentage)	
Intermediate FRS (10%–19%) with protective PRS≤(lower threshold percentage)	No

CVD indicates cardiovascular disease; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; and PRS, polygenic risk score.

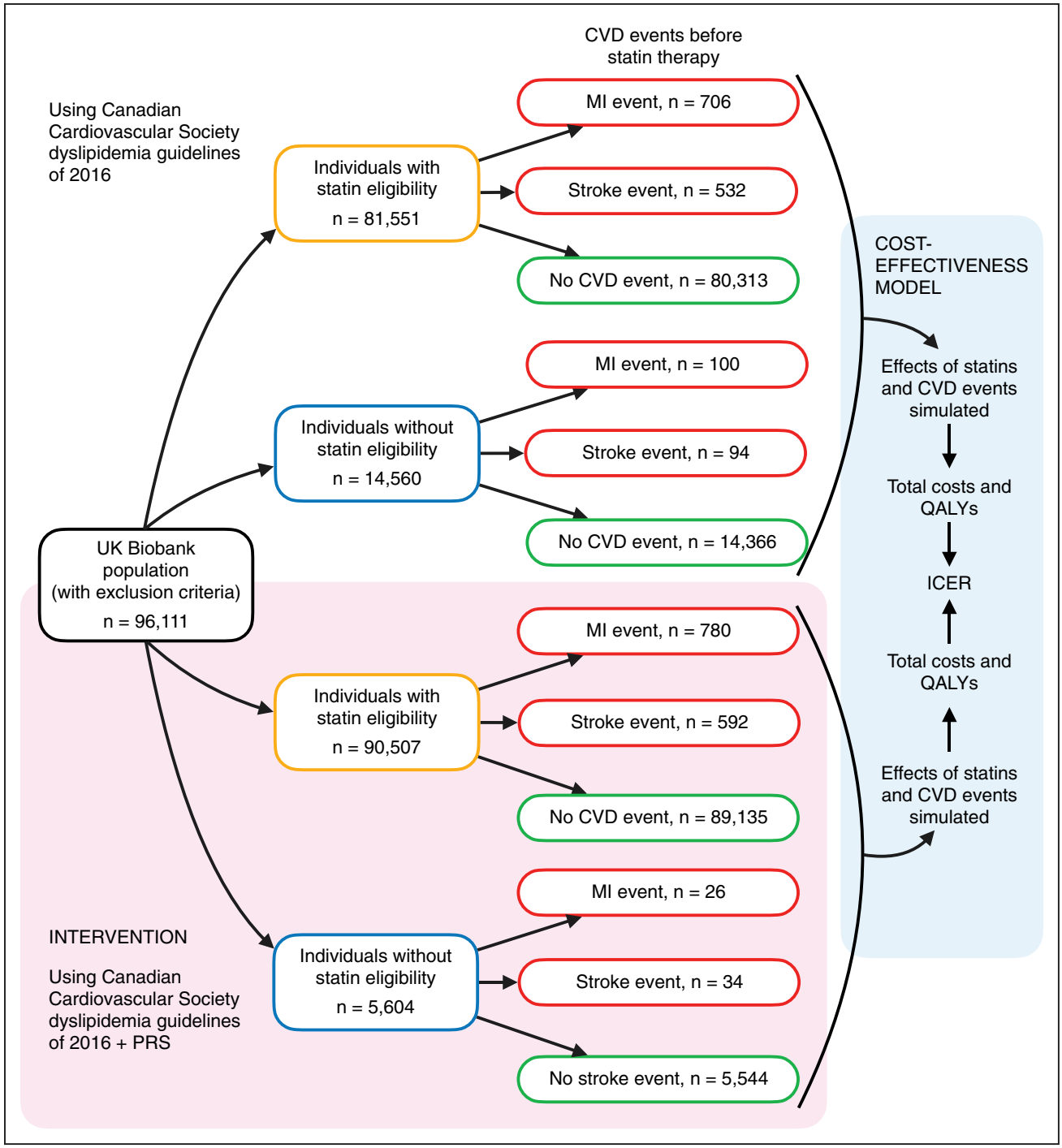

Figure 1. Conceptual diagram of the cost-effectiveness model.
Participants, free from cardiovascular disease (CVD) enter the model and are assigned statin status, guided without PRS via the Canadian Cardiovascular Society dyslipidemia guidelines of 2016 and with polygenic risk score (PRS). The total number of cases were unchanged, but the effects of statins were simulated, and CVD events (myocardial infarction [MI] and stroke) were adjusted accordingly. Costs, benefits, and adverse effects were associated with each state in the 10-year time horizon and calculated using the cost-effectiveness model. ICER indicates incremental cost-effectiveness ratio; and QALY, quality-adjusted life-year.

therapy compared with standard care were produced. The costs and QALYs are shown in Table 3. Based on the cost-effectiveness model, the incremental cost per QALY of the PRS-guided strategy is $172 906 (143 685 USD; 1 Canadian Dollar=0.831 USD) in the base-case scenario when the upper 70% PRS individuals are eligible for statins with the lower 1% excluded.[28] The incremental cost per participant was $127.61 (106.04 USD) and total incremental QALYs were 70.83. Genotyping (and assigning PRSs) each participant ($6 727 770; 5 584 049 USD) was the largest incremental cost followed by increased statin uptake over 10 years for controls

Table 2. Decision Analytical Model Parameters With Ranges Used for Base-Case and Sensitivity Analyses

	Base-case value	Range for sensitivity analysis		Distribution	Source
		Low	High		
Costs					
PRS	$70	$55	$85	Gamma	Assumption
MI (event)	$13 983.78	$10 189.19	$17 778.38	Gamma	[17,18]
Stroke (event)	$63 921.39	$5829.45	$122 013.30	Gamma	[19]
Statins (yearly)	$85.54	N/A	N/A	N/A	[20]
Utilities					
Pre-CVD	Age-dependent	N/A	N/A	N/A	[21]
MI	0.708	0.610	0.806	Beta	[22,23]
Post-MI	0.708	0.610	0.806	Beta	[22,23]
Stroke	0.682	0.584	0.780	Beta	[22,24]
Post-stroke	0.682	0.780	0.584	Beta	[22,24]
Statin disutility	0.000207	0.0001863	0.0002277	Beta	[25]
Other parameters					
Discount rate	0.015	0	0.03	N/A	[3]
RR reduction of statins on MI	0.74	0.73	0.79	Beta	[26,27]
RR reduction of statins on stroke	0.84	0.80	0.89	Beta	[26,27]

CVD indicates cardiovascular disease; MI, myocardial infarction; and PRS, polygenic risk score.

($7 077 624; 5 881 506 USD). In terms of events, the incremental costs of captured strokes increased the greatest due to the larger number of captured events via PRS ($2 702 326; 2 245 633 USD) followed by MI events ($584 754; 485 930.6 USD). Nonetheless, the PRS-mediated statin strategy increased the incremental QALYs of individuals with MI and stroke by 39.19 and 33.50 QALYs, respectively, while only sustaining a penalty of 1.85 QALYs for adverse effects of statins resulting in a net-benefit.

Figure 2 depicts a 1-way sensitivity analysis of independent variations in the effect of statins; discounting; utility of MI and stroke; and cost of PRS, statins, MI, and stroke. The tornado diagram indicates that the lipid lowering effects of statin therapy and cost of genotyping parameters were the largest drivers of the ICER. The former produced a range from $125 696 (104 453 USD) per QALY to $220 116 (182 917 USD) per QALY. Figure 3 shows the probabilistic sensitivity analysis with 10 000 Monte Carlo simulations. Figure 4 is the cost-effectiveness acceptability curve derived from the probabilistic sensitivity analysis, demonstrating a 50% probability of cost-effectiveness falls at a willingness-to-pay (WTP) of approximately $179 100 (148 749 USD) per QALY while tapering at a 90% probability after WTP of $234 600 (194 953 USD) per QALY. The probability of cost-effectiveness under current parameters at WTP of $50 000, $100 000, and $150 000 per QALY, is 0%, 0.8%, and 21.1%, respectively.[29]

A scenario analyses with more predictive PRSs and lower genotyping costs, representing a possibility of the genomics field in shown in Figure 5.[30] The starting point was based on the empirical PRS odds ratio per SD, was conservatively estimated to be 1.275 along with a genotyping cost of $70.[31] A simulated PRS at an odds ratio per SD of 1.3 produced an ICER slightly lower than the base-case scenario; within the range of $160 000 (132 960 USD) per QALY. Maintaining upper and lower PRS statin thresholds of 70% and 1%, respectively, demonstrates the strength of PRS is inversely proportional to the ICER, with the largest cost-savings and QALY-increase between 1.3 odds ratio per SD to 1.5 odds ratio per SD. Lower genotyping costs also demonstrate more cost-effective scenarios. As an additional scenario analysis, the Framingham risk score was adjusted by reclassifying high-risk individuals from 20% to a more lenient 12%, corresponding to an increased 89 449 individuals eligible for statins (approximately the same as the PRS base-case scenario of 90 507). The resulting strategy captured 768 MI events and 591 stroke events corresponding to an ICER of $1 348 942 (1 120 971 USD) per QALY to −1 887 108 (−1 568 187 USD) per QALY, ranging from dominated and extended dominance.

Figure 6 shows a genotyping cost of $0 into the cost-effectiveness model while varying the corresponding upper and lower PRS thresholds for statin eligibility or ineligibility. Since an increasingly larger subset (albeit still a small minority) of the population engaging with direct-to-consumer genetic testing or have existing genotyping information (eg, cancer testing), the public health care system would have this additional information without added expense.[32] Under this scenario, several combinations of upper and lower PRS thresholds of statin strategies guided by the PRS dominated standard care (and therefore improved CVD event prediction) when ≈ 5% or more of the population

Table 3. Summary of Incremental Costs and QALYs from Cost-Effectiveness Model in 96 111 Participants

	Dyslipidemia guidelines	Dyslipidemia guidelines and PRS
Cost group		
Genotyping	$0	$6 727 770
Statin eligible		
MI events	$5 591 072	$6 175 826
Statins for MI, 10 y	$496 161	$548 053
Stroke events	$24 039 678	$26 742 004
Statins for stroke, 10 y	$374 099	$416 152
Statin ineligible		
MI events	$1 374 532	$358 544
Statins for MI, 10 y	$46 763	$11 897
Stroke events	$5 768 905	$1 930 426
Statins for stroke, 10 y	$44 186	$14 664
Controls		
Statins, 10 y	$64 286 817	$71 364 441
Total costs	$102 022 213	$114 286 931
Incremental costs		$12 264 718
Incremental costs per participant		$127.61
QALY group		
Healthy individuals (no CVD)	832 838.1	832 838.1
Statin eligible		
MI prevented	2787.687	3079.243
MI not prevented	3214.504	3549.195
Stroke prevented	1465.755	1630.522
Stroke not prevented	2897.17	3219.815
Statin ineligible		
MI not prevented	800.5957	213.5355
Stroke not prevented	707.8348	253.9235
Statin adverse effects		
Total adverse effects	16.87664	18.73411
Total QALYs	844 352	844 422.8
Incremental QALYs		70.82991
ICER		$ 172906.1 per QALY

CVD indicates cardiovascular disease; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; and QALY, quality-adjusted life-year.

were excluded from statin therapy. Under a $0 genotyping cost worst-case scenario, the ICER is $78 378 (65 132 USD) per QALY when the upper PRS threshold for statin eligibility is 70% and the lower threshold is 1%. However, the thresholds can be easily modulated for a more cost-effective strategy.

When PRS was exclusively used to guide statin therapy, an upper threshold of 85% yielded approximately the same number of statin-eligible participants (N=81 569) as compared with the 2016 guidelines (N=81 551). Seven hundred twenty-nine MIs, compared with 704 in the 2016 guidelines, were captured corresponding to a 3.5% increase in events, but without significant improvement in captured stroke events. After varying the genotyping costs, an ICER of approximately $100 000 per QALY was achieved at $8 and $50 000 per QALY at $5.

Finally, Figure S1 demonstrates the varying effect of statin adherence on cost-effectiveness of the PRS with the strategy (upper and lower thresholds of 70% and 1%, respectively) unchanged. Adherence was ranged from 100% (representing base-case scenario) to 40% to encompass the different values across study designs.[25,33,34] The ICER was between approximately $170 000 (141 270 USD) per QALY and $270 000 (224 370 USD) per QALY.

DISCUSSION

The 2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia strongly recommend statins for high-risk individuals (≥20%) but have more sparing recommendations for intermediate risk (10%–19%). This cost-effectiveness analysis demonstrated that the PRS could guide statin therapy for greater quality-adjusted life expectancy for an intermediate risk population. However, with an ICER of $172 906 (143 685 USD) per QALY, the PRS is not likely cost-effective using commonly accepted WTP thresholds for the Canadian public health system.

Nonetheless, PRSs have a positive, future economic outlook as they are rapidly improving in predictive capacity while demonstrating clinical utility[30,35,36] Additionally, the cost of genotyping has dramatically reduced in the past several years and may continue to become more inexpensive; coupled with the ability of jurisdictions to negotiate more aggressive prices, developing a clinically and economically viable PRS might be within reach.[37–40] Therefore, these 2 trends must be accounted for when understanding the true cost-effectiveness for PRSs. This study demonstrated that WTP thresholds, such as $150 000 per QALY are well within reach under conservative combinations of improved PRS predictiveness and genotyping cost. The WTP threshold of $50 000 per QALY might also possible under the assumption that PRSs will be more predictive and genotyping costs will continue to drop. Conversely, when the Framingham risk score was adjusted to include greater statin eligibility from 20% to 12%, corresponding to the number of individuals via the PRS, the ICER was much more variable and unlikely to demonstrate cost-effectiveness. The impressive effectiveness of statin medications is difficult to challenge and as a result are hard to compete against from an economic perspective.[41]

The PRS is cost-effective with current parameters under 3 scenarios. First, when the public health care payer has existing patient genotypes. Patients are increasingly engaging with direct-to-consumer genetic testing products with a more positive perception.[42] This study demonstrated that individuals could theoretically

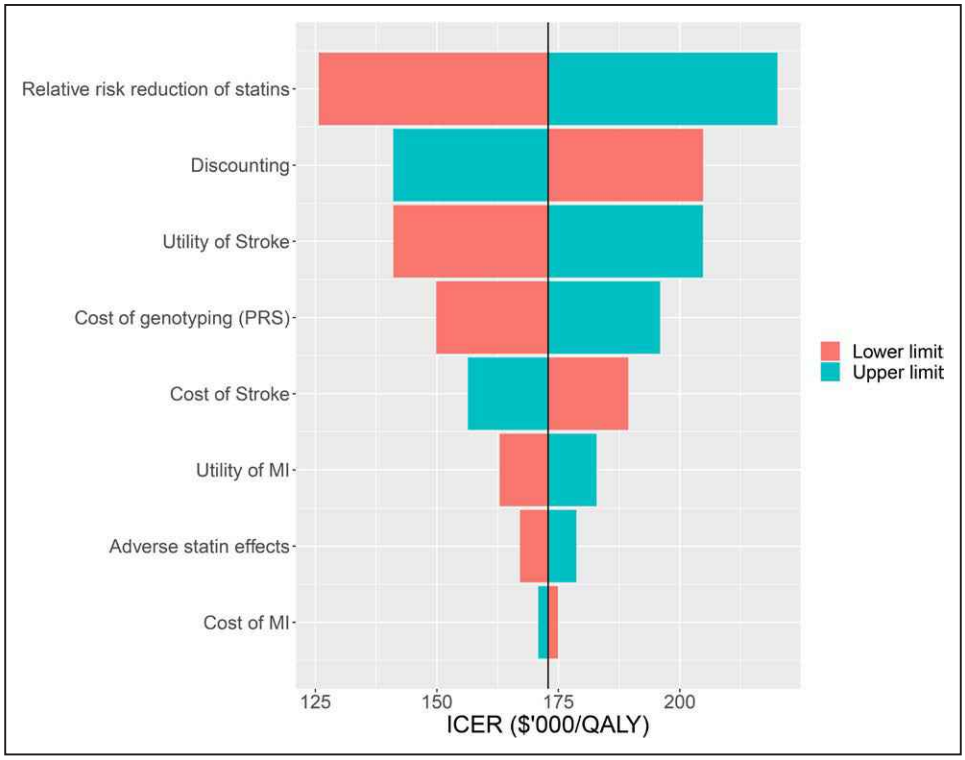

Figure 2. One-way sensitivity analysis.
Model parameters were varied between the ranges, shown in Table 2. The length of each bar indicates the incremental cost-effectiveness ratio (ICER) range associated with the parameter upper and lower limit with the midline as the base-case. PRS indicates polygenic risk score.

advocate for their health using genotyping information as PRS-mediated statin therapy may be cost-saving and clinically effective in specific circumstances. However, the uptake of such tests at the population level is small and likely unviable to many individuals due to cost and privacy concerns.[43] Second, adding unrelated diseases

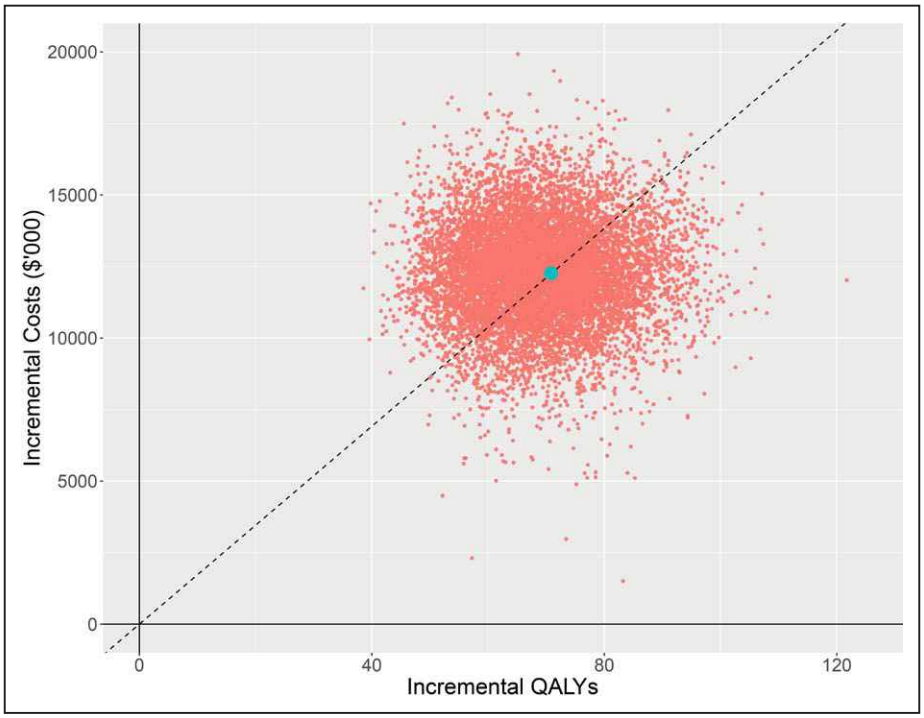

Figure 3. Probabilistic sensitivity analysis.
Ten thousand Monte Carlo simulations using the model parameter ranges, shown in Table 2, were sampled and inputted into the cost-effectiveness model to show the distribution of incremental cost-effectiveness ratio values on a cost-effectiveness plane. QALY indicates quality-adjusted life-year.

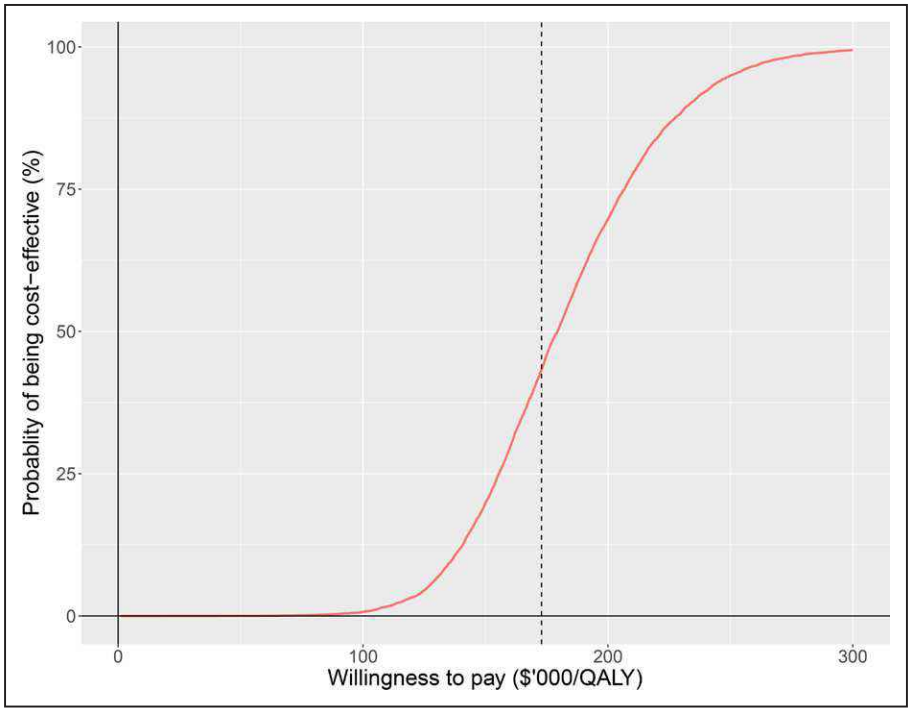

Figure 4. Cost-effectiveness acceptability curve.
Probabilities of cost-effectiveness at willingness-to-pay thresholds were derived from the probabilistic sensitivity analysis incremental cost-effectiveness ratio values using 10 000 bootstrap replications. QALY indicates quality-adjusted life-year.

with a predictive PRS, such as breast cancer, would have the effect of substantially lowering the ICER since the marginal cost associated with generating a second PRS is orders of magnitude smaller than the cost of genotyping itself. Breast cancer screening programs in Ontario where genotyping analysis is provided for select, high

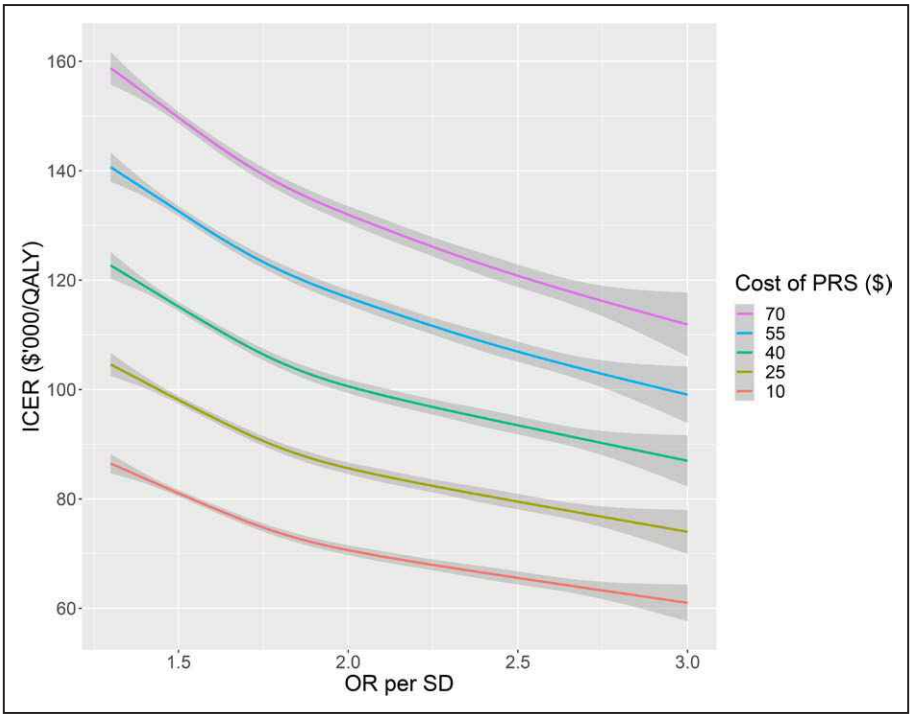

Figure 5. Scenario analysis with incremental cost-effectiveness ratio (ICER) as a function of polygenic risk score (PRS) predictiveness and cost.
Simulated PRS with varying degrees of predictiveness for coronary artery disease, measured by odds ratio (OR) per SD were used for statin prescription assignment and inputted into the cost-effectiveness model. Cost of PRS was lowered in discrete $15 increments. One hundred bootstrap replications were performed to describe the uncertainty around ICER values.

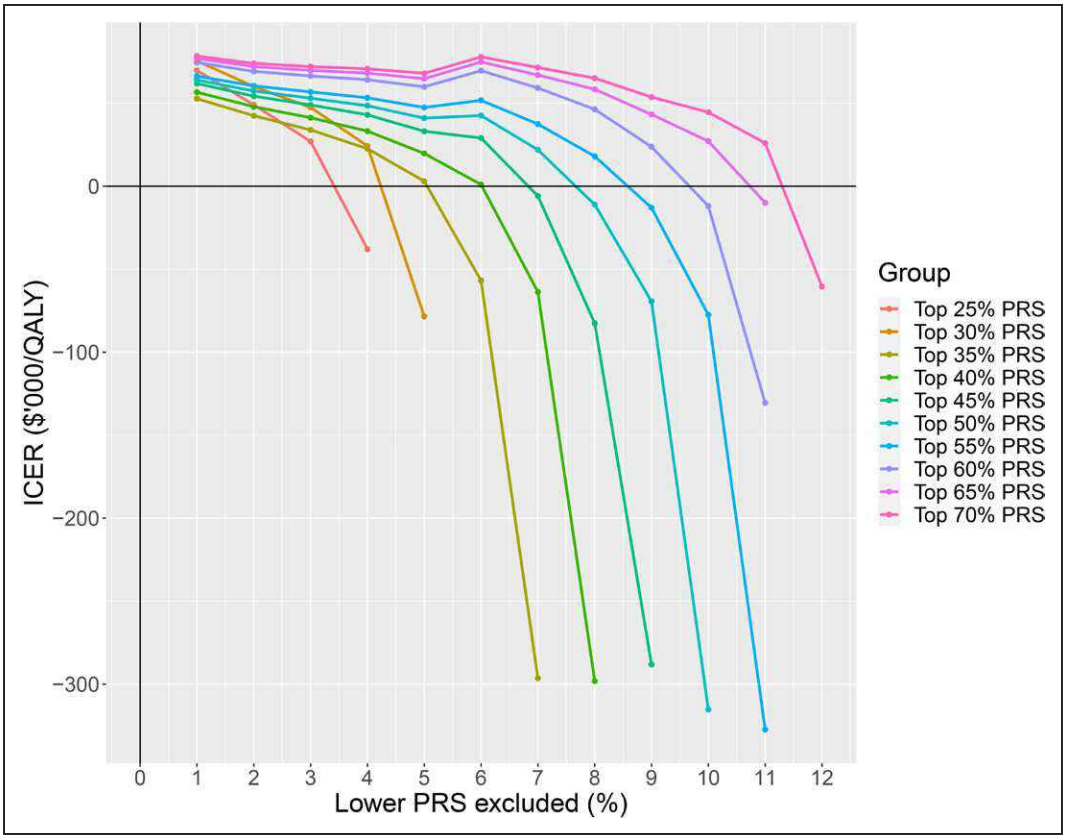

Figure 6. Polygenic risk score (PRS) thresholds for dominance when genotyping has a cost of $0.
Upper and lower PRS threshold combinations were used for statin prescription assignment and inputted in the cost-effectiveness model at a genotyping cost parameter of $0. Positive incremental quality-adjusted life-years (QALYs) were selected to select for strong dominance.

risk patients, can benefit from primary CVD risk stratification using a PRS-guided strategy without any cost to the healthcare system. Third, when PRS is exclusively used to guide statin therapy. The cost of genotyping, especially when lowered, is likely overshadowed by repeated physician visits and lipid profile testing for CVD screening.[4]

The cost-effectiveness study, the first to analyze the PRS in a clinical setting, adhered to best-practice guidelines for conducting and reporting economic evaluations of health care interventions.[44] The decision analytical model used clinical and economic parameters derived from robust and representative Canadian population studies. Direct costs estimates are likely accurate since Canada has transparent data on universal health coverage for hospital care.[45] Almost all costs and benefits for patients undergoing CVD clinical trajectories under a health care payer perspective were implemented. The 10-year time horizon was short for CVD events; however, the prediction model in the 2016 guidelines does not extend beyond this timeframe. Finally, the cost-effectiveness study was derived from the UK Biobank, a longitudinal population study rather than a randomised controlled trial which would otherwise overestimate the incremental benefits.[46–48]

Our study has few limitations. The performance of the PRS is partly dependent on the ethnicity, with the highest among European populations.[49] Since the study sample included white British-descent exclusively, a Canadian-based PRS might not demonstrate the same predictive performance as this study.[50] The UK Biobank also was not located in Canada, which may impart additional, non-genetic differences. Nonetheless, there are current steps taken to improve the diversity of genetic studies.[51] Additionally, the cost-effectiveness model is likely conservative and underestimates the true ICER as it does not account for every CVD outcome that can be treated by statins, thereby grossly overestimating the health care costs and underestimating the clinical benefits of a PRS-guided strategy.[26,52] Conversely, the UK Biobank is a healthier cohort as there is evidence of a "health volunteer" selection bias, resulting in genetic exposures appearing more powerful.[53] While this study exclusively used intermediate CVD risk individuals, it may not yet be representative against a corresponding country-level population. The short, 10-year time horizon was based on the Framingham risk score used in the 2016 guidelines and the UK Biobank length of follow-up. A lifetime horizon would depict the full extent of the PRS and accrued statin benefits, even for secondary prevention. However, this may introduce uncertainty due to the lack of study data for PRS-guided CVD interventions. This study only included only direct medical costs. Indirect costs may be significant,

such as loss of productivity and caregiver costs, which further inflates the ICER estimate.[2] Finally, the base-case assumed individuals with full adherence to statin therapy. To the extent that individuals fail to complete the regimen, this analysis may overstate the cost-effectiveness of the PRS. In the adherence sensitivity analysis, an ICER of under $200 000 (166 200 USD) per QALY is maintained at 70% or above, demonstrating slight robustness but also that cost-effectiveness is affected by statin uptake.

The case for clinical implementation of PRSs is controversial.[54] In this study, a CUA was performed to determine if a single PRS could guide statin therapy cost-effectively compared with using traditional risk factors alone for the prevention of primary CVD events. Although some common WTP thresholds were not met, our results suggest PRSs might be cost-effective in the future, especially if multiple diseases are assessed for prediction using the same set of genotypes. As resources remain scarce while health care costs increase, novel techniques should be considered despite their unique challenges.[55] With decreased genotyping cost and improvements in PRS performance, there exists a real possibility where PRSs can be used in primary care for their clinical and economic utility.[32]

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Supplemental Methods
Figure S1
Source code file (.R)
References[56–61]

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