Journal of the American Heart Association

ORIGINAL RESEARCH

Integrating a Polygenic Risk Score for Coronary Artery Disease as a Risk-Enhancing Factor in the Pooled Cohort Equation: A Cost-Effectiveness Analysis Study

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BACKGROUND: Cardiovascular diseases are the leading cause of death in the United States, yet a significant proportion of adults at high risk remain undetected by standard screening practices. Polygenic risk score for coronary artery disease (CAD-PRS) improves precision in determining the 10-year risk of atherosclerotic cardiovascular disease but health benefits and health care costs associated with CAD-PRS are unknown. We examined the cost-effectiveness of including CAD-PRS as a risk-enhancing factor in the pooled cohort equation (PCE)—the standard of care for determining the risk of atherosclerotic cardiovascular disease—versus PCE alone.

METHODS AND RESULTS: We applied a Markov model on a cohort of 40-year-old individuals with borderline or intermediate 10-year risk (5% to <20%) for atherosclerotic cardiovascular disease to identify those in the top quintile of the CAD-PRS distribution who are at high risk and eligible for statin prevention therapy. Health outcomes examined included coronary artery disease (CAD; ie, myocardial infarction) and ischemic stroke. The model projected medical costs (2019 US$) of screening for CAD, statin prevention therapy, treatment, and monitoring patients living with CAD or ischemic stroke and quality-adjusted life-years for PCE+CAD-PRS versus PCE alone. Deterministic and probabilistic sensitivity analyses and scenario analyses were performed to examine uncertainty in parameter inputs. PCE+CAD-PRS was dominant compared with PCE alone in the 5- and 10-year time horizons. We found that, respectively, PCE+CAD-PRS had 0.003 and 0.011 higher mean quality-adjusted life-years and $40 and $181 lower mean costs per person screened, with 29 and 50 fewer events of CAD and ischemic stroke in a cohort of 10 000 individuals compared with PCE alone. The risk of developing CAD, the effectiveness of statin prevention therapy, and the cost of treating CAD had the largest impact on the cost per quality-adjusted life-year gained. However, this cost remained below the $50 000 willingness-to-pay threshold except when the annual risk of developing CAD was <0.006 in the 5-year time horizon. Results from Monte Carlo simulation indicated that PCE+CAD-PRS would be cost-effective. with the probability of 94% and 99% at $50 000 willingness-to-pay threshold in the 5- and 10-year time horizon, respectively.

CONCLUSIONS: Implementing CAD-PRS as a risk-enhancing factor in the PCE to determine the risk of atherosclerotic cardiovascular disease reduced the mean cost per individual, improved quality-adjusted life-years, and averted future events of CAD and ischemic stroke when compared with PCE alone.

Key Words: coronary artery disease ■ cost-effectiveness ■ polygenic risk score

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Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.025236

For Sources of Funding and Disclosures, see page 13.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Using polygenic risk score for coronary artery disease as a risk-enhancing factor in the pooled cohort equation to guide statin therapy intervention is both cost-effective and cost saving among US adults, from a payer perspective.

What Are the Clinical Implications?

- Using genetic tests to identify high-risk individuals is sustainable, removing cost as a barrier to the widespread adoption of polygenic risk score in cardiovascular disease prevention.
- Experts who develop guidelines and policy makers should consider integrating polygenic risk score in the pooled cohort equation to identify individuals at high risk for developing cardiovascular disease who remain invisible to the current risk assessment methods.

Nonstandard Abbreviations and Acronyms

CAD-PRS	polygenic risk score for coronary artery disease
NMB	net monetary benefit
PCE	pooled cohort equation
PPP	primary prevention population
PRS	polygenic risk score

Atherosclerotic cardiovascular diseases (ASCVDs) are the leading cause of death in the United States and are highly preventable, but identifying all adults at high risk remains a challenge for clinicians. The pooled cohort equation (PCE) is used to determine an individual's 10-year risk of ASCVD, but it does not identify all individuals at high risk, leading to missed opportunities to intervene and prevent adverse health outcomes.[1] Strong evidence shows that a substantial proportion of coronary artery disease (CAD) is attributable to genetic factors,[2] which are not considered in the current PCE. The integration of such genetic risk factors into CAD primary prevention remains limited and the cost-effectiveness is unknown.

To guide preventive therapy interventions, the PCE 10-year risk for ASCVD stratifies individuals into 4 risk categories: low (<5%), borderline (5% to <7.5%), intermediate (≥7.5% to <20%), and high (≥20%).[3] Statin therapy is effective in preventing CAD and is recommended for individuals in the high-risk category.[3] However, for those in the categories of borderline or intermediate risk, the presence of additional risk-enhancing factors, which by definition increase ASCVD risk by at least 2-fold, is needed to guide preventive therapy decisions.[3] Previous work has shown increased 30-day all-cause mortality and worse health outcomes in patients with ST-segment–elevation myocardial infarction in the absence of standard clinical cardiovascular risk factors in the PCE (eg, hypercholesterolemia, diabetes, and smoking) compared with those with risk factors,[4] indicating an urgent need to improve the risk models used to determine ASCVD risk and to guide preventive therapy.

In a large-scale multi-ancestry US-based study, polygenic risk score (PRS) for CAD (CAD-PRS) has been shown to be a strong independent predictor of disease with individuals who fall in the top quintile of the CAD-PRS distribution having an ≈2-fold increased risk of CAD events compared with the remainder of the population (odds ratio [OR], 1.9; [95% CI, 1.8–2.0][1]). Comparable ORs (2.5; [95% CI, 2.4–2.6][5]) were reported from the UK Biobank. As such, the CAD-PRS has been proposed as an additional risk-enhancing factor to the PCE to improve precision in determining an individual's risk, particularly among patients with borderline or intermediate PCE 10-year risk (5% to <20%)[1] who require an additional risk factor to inform prevention therapy decisions.[3] The PRS was developed using large populations and clinical biobanks, and integrates the number of risk variant alleles for an individual weighted by the impact of each allele on disease risk. Applying PRS as a risk-enhancing factor to individuals with borderline or intermediate PCE 10-year risk identifies nearly 17% of additional individuals eligible for prevention therapy compared with only 5.6% with PCE alone based on other risk-enhancing factors (eg, family history).[1]

Establishing the cost-effectiveness of CAD-PRS in a clinical setting may encourage the implementation of PRS testing in standard clinical practices. The purpose of this study was to project health benefits and health care costs associated with including CAD-PRS as a risk-enhancing factor among individuals with borderline or intermediate risk of ASCVD derived from the PCE.

METHODS

Overview

We developed a Markov model to project health care costs, health outcomes, and quality-adjusted life-years (QALYs) of integrating CAD-PRS with PCE in a cohort of 40-year-old individuals in the United States with borderline or intermediate 10-year risk of ASCVD, compared with PCE alone. The model had an annual cycle length with 18 health states (Figure 1) defined to reflect the initial PCE risk strata (high-risk and nonhigh-risk),

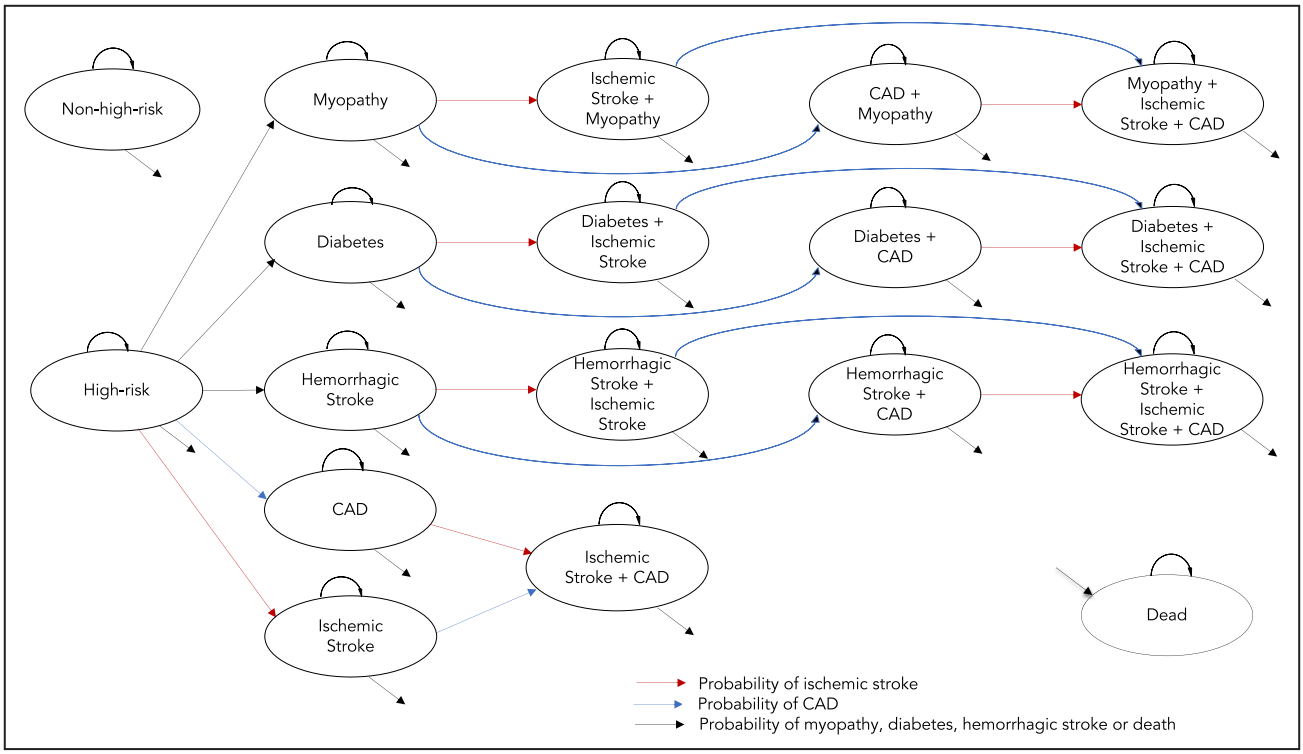

Figure 1. Model structure.
The Markov model structure used in this study is shown with a total of 18 health states. The initial cohort was distributed in 2 groups: high-risk cohort and nonhigh-risk cohort. We defined high risk as individuals in the top quintile of the polygenic risk score (PRS) for coronary artery disease (CAD-PRS) distribution or having other risk-enhancing factor (eg, family history), while the nonhigh-risk group included individuals in the bottom 80% of the CAD-PRS distribution without any risk-enhancing factor. In the pooled cohort equation (PCE)+CAD-PRS strategy, all of the high-risk cohort was initiated on statin preventive therapy to reduce the risk of coronary artery disease (CAD) and stroke, while for the PCE-alone strategy only a proportion of patients with other risk-enhancing factors initiated statins. We accounted for statin side effects such as diabetes, myopathy, and hemorrhagic stroke and subsequent risk of ischemic stroke and CAD. In the PCE-alone strategy, CAD-PRS was not considered as a risk-enhancing factor, so only those with other risk-enhancing factors initiated statins. Health outcomes were not examined for the nonhigh-risk cohort.

health outcomes (CAD and ischemic stroke), statin side effects (diabetes, hemorrhagic stroke, and myopathy), and death. The analysis was performed in a 5- and 10-year time horizon. Our study used published data from the literature and did not use any data that required institutional review board approval. All of the data and supporting materials are provided within the article and supplementary files.

Strategies

We modeled 2 strategies (PCE alone and PCE+CAD-PRS). PCE alone represented current clinical practice that uses conventional risk factors (sex, race, age, blood pressure, lipids, diabetes, and smoking status) to determine an individual's 10-year risk for a first ASCVD event,[3] while the PCE+CAD-PRS strategy included the same risk factors as the PCE-alone strategy with the addition of CAD-PRS as a risk-enhancing factor. In PCE+CAD-PRS, more high-risk individuals were identified and initiated on statin prevention therapy to prevent CAD and ischemic stroke events compared with PCE alone. We assumed that individuals in the top quintile of the CAD-PRS distribution without any risk-enhancing factors remained unidentified by the PCE-alone strategy over the analytical time horizon. Since the risk of a first ASCVD event is estimated at a 10-year period, the impact of age on the disease risk is limited within those 10 years, particularly for a younger cohort of 40 years. However, we performed a scenario analysis with an annual increase in the risk of CAD and ischemic stroke attributable to aging.

Study Population

The study population cohort consisted of individuals with borderline or intermediate PCE risk, defined as high-risk if they were in the top quintile of the CAD-PRS distribution, and the remainder of the cohort defined as nonhigh-risk. Among the high-risk proportion (0.168) of the initial cohort, 34% had other traditional risk-enhancing factors (eg, family history) and were identified by the PCE-alone strategy, but, with the addition of CAD-PRS, the reminder (66%) of the high-risk cohort without traditional risk-enhancing factors was also identified under the PCE+CAD-PRS strategy. Health

outcomes were assessed only among the high-risk proportion of the cohort because of data limitations on individuals with traditional risk-enhancing factors in the nonhigh-risk cohort. We assessed this assumption in the scenario analysis.

Model Structure

At the start of the model, the entire cohort was assumed to be disease free, with 0.168 and 0.832 proportions of the cohort in the high-risk and nonhigh-risk health state, respectively. Per model cycle, the proportion of the cohort in the high-risk health state had a risk of death (age-adjusted natural mortality), CAD, or ischemic stroke, or to remain disease free and high-risk. Under the PCE-alone strategy, only 34% of the cohort in the high-risk health state were identified and initiated statin preventive therapy, while all patients (0.168) were identified under the PCE+CAD-PRS strategy. The proportion of the high-risk cohort who were adherent to the therapy had a reduced risk of CAD and ischemic stroke as a result of the effectiveness of statin therapy in reducing the risk of CAD and stroke but were also at risk for statin side effects (myopathy, diabetes, hemorrhagic stroke). As shown in Figure 1, fractions of the cohort with statin side effects were also at risk for CAD or/and ischemic stroke, and the risk varied by side effect. Although health outcomes were not assessed for the nonhigh-risk proportion of the cohort, we accounted for the risk of death (age-adjusted natural mortality), and those who did not die remained disease-free and nonhigh-risk.

Annual costs were applied to health states to represent the cost incurred in the respective health states, except for the death health state. The cost of screening for ASCVD was applied once at the beginning of the model, as well as the cost for a primary care visit among those with high CAD-PRS (top quintile of the CAD-PRS distribution). The cost of statins was applied only to those who were adherent to prevention therapy per model cycle.

Parameter inputs were derived from published sources with costs estimated from a payer perspective and inflation adjusted to 2019 US$ using the gross domestic product deflator. The relative performance of strategies was assessed using the incremental cost-effectiveness ratio, expressed in US$ per QALY gained, and the cost-effectiveness was determined according to the willingness-to-pay (WTP) threshold equivalent to $50 000.[6] Future costs and QALYs were discounted at an annual rate of 3%. Uncertainty in parameter inputs was assessed using deterministic and probabilistic sensitivity analyses. Analyses were performed at a 5- and 10-year time horizon with half-cycle correction using TreeAge Pro Software 2021 (TreeAge LLC). The CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist was used to prepare the article (Table S2).

Model Parameters

Parameter inputs used in the model are listed in Table 1. The initial distribution of the cohort was based on a retrospective study that examined a large sample (N=47 108) of medical claims from a multi-ancestry population in the United States.[1] Of those, 16 002 were classified as the primary prevention population (PPP) with 5890 having borderline or intermediate PCE 10-year risk of ASCVD. Nearly 17% (987) of individuals with borderline or intermediate 10-year risk were in the top quintile of the CAD-PRS distribution, with 11.07% (652) not taking statin preventive therapy and therefore classified as high-risk based on high CAD-PRS and invisible to current clinical ASCVD risk assessment.[1] Only 5.69% (335) of individuals in the top quintile were taking statin preventive therapy. We assumed these individuals had other risk-enhancing factors (eg, family history) and were therefore identified in both the PCE-alone and PCE+CAD-PRS strategy.

The risk of developing CAD was calculated as the average 10-year risk of ASCVD for individuals with borderline or intermediate risk,[3] with a 1.9-fold increase in risk for being in the top quintile of the CAD-PRS distribution.[1] The risk of ischemic stroke was assumed to be equal to that of the general population since stroke was not considered an outcome in the original study by Aragam et al in 2020,[1] which we used to identify individuals in the top quintile of the CAD-PRS distribution. According the Centers for Disease Control and Prevention, the risk of stroke doubles every decade after the age of 55 years.[46] However, since our baseline cohort was aged 40 years and within the 10-year time horizon, the cohort age will be 50 years, the risk of ischemic stroke was assumed to be constant in both the 5- and 10-year time horizons.

We applied risk reduction on developing CAD[12] and ischemic stroke[13] among individuals taking statin preventive therapy in the top quintile of the CAD-PRS distribution. We assumed 50% of the cohort consistently used statins. Although adherence to statins in primary prevention tends to be low (<50%) and decreases over time,[14] there is evidence of higher adherence to therapy among adults in the United States[15] and individuals who are aware of their high PRS.[47] Those adherent to statins had a risk of developing side effects including myopathy, diabetes, and hemorrhagic stroke.[16] The risk of ischemic stroke and CAD was higher among individuals with diabetes,[7] but only for ischemic stroke among those with hemorrhagic stroke,[11] and there was no increased risk for those with myopathy.

Mortality varied based on the health state. Data for risk of death in the event-free cohort came from the social security life tables (Table S1). Acute stages of the disease (CAD,[17,18] ischemic stroke and hemorrhagic stroke[21,22])

Table 1. Annual Model Parameters

Domain	Description	Baseline (range)*/[95% CI]	Distributions Beta (α, β) Log normal (μ, σ) Gamma (α, β)	Source
Initial distribution	High risk	0.168 (0.159–0.169)	Beta (3250.53, 16147.25)	1
	Nonhigh risk	1-high risk		
CAD†	Probability of CAD	0.013 (0.005–0.022)	Beta (9.33, 697.44)	3
	OR of CAD (high PRS)	1.9 (1.8–2.0)	Log normal (0.64, 0.05)	1
	HR of CAD (with diabetes)	2.00 [1.83–2.19]	Log normal (0.57, 0.22)	7
	Probability of CAD after ischemic stroke	0.017 (0.014–0.019)	Beta (174.59, 10095.92)	8
Ischemic stroke	Probability of ischemic stroke	0.004 (0.003–0.005)	Beta (95.65, 23817.31)	9
	Probability of ischemic stroke after CAD	x1.015		10
	HR of ischemic stroke with diabetes	2.27 [1.95–2.65]	Log normal (0.37, 0.26)	7
	Probability of ischemic stroke post-hemorrhagic stroke	0.057 [0.048–0.068]	Beta (117.64, 1946.26)	11
Statin effectiveness	HR of CAD risk reduction	0.560 [0.400–0.780]	Log normal (–0.58, 0.09)	12
	HR for ischemic stroke risk reduction	0.770 [0.630–0.940]	Log normal (–0.26, 0.08)	13
Adherence	Statin adherence	0.500 (0.4–0.6)	Beta (47.52, 47.52)	14,15
Statin side effects	Probability of myopathy	0.0001 (0.0001–0.0002)	Beta (2397.88, 4793360.99)	16
	Probability of diabetes	0.0015 (0.0010–0.0020)	Beta (847.59, 112165.19)	16
	Probability of hemorrhagic stroke	0.0002 (0.0001–0.0002)	Beta (862.67, 1149370.30)	16
Mortality‡	Probability of death, acute CAD	0.228 (0.182–0.274)	Beta (73.91, 250.27)	17
	Probability of death, post-acute CAD	0.070 (0.067–0.072)	Beta (14100.39, 58209.33)	18
	HR (diabetes and CAD)	1.81 [1.44–2.28]	Log normal (0.69, 0.09)	19
	Probability of death after ischemic stroke or hemorrhagic stroke and CAD	0.075 (0.05–0.1)	Beta (88.72, 1094.73)	Assumption[20]
	Probability of death, acute ischemic stroke	0.100 (0.080–0.120)	Beta (86.34, 777.02)	21
	Probability of death, post-hemorrhagic, or post-ischemic stroke	0.069 (0.055–0.082)	Beta (89.39, 1215.65)	22
	RR (with diabetes and ischemic stroke)	1.67 (1.58–1.76)	Log normal (0.80, 0.18)	23
	Probability, acute hemorrhagic stroke	0.39 (0.33–0.45)	Beta (98.62, 154.25)	21
	HR (diabetes vs no diabetes)	1.68 [1.52–1.87]	Log normal (0.51, 0.09)	19
Utility weights	CAD	0.790 (0.730–0.860)	Beta (118.38, 31.46)	24
	Myopathy	0.917 (0.896–0.938)	Beta (697.06, 54.95)	25
	Diabetes	0.800 (0.620–0.980)	Beta (14.38, 3.59)	26
	Stroke	0.630 (0.440–0.780)	Beta (18.89, 11.09)	24
Disutility weights	Acute CAD	0.041 (0.021–0.062)	Beta (14.69, 343.73)	27
	Acute stroke	0.220 [0.180–0.260]	Beta (90.42, 320.59)	28
	Age disutility	0.004 (0.002–0.006)	Beta (15.30, 3809.93)	29

(*Continued*)

Table 1. Continued

Domain	Description	Baseline (range)*/[95% CI]	Distributions Beta (α, β) Log normal (μ, σ) Gamma (α, β)	Source
Costs (2019, $)	PRS test§	100 (80–120)	Gamma (96.04, 0.96)	Allelica, Inc
	Primary care visit§	114 (91–137)	Gamma (96.04, 0.84)	30
	Statin therapy	132 (106–158)	Gamma (96.04, 0.73)	31
	Background health care costs	4 941 (3953–5930)	Gamma (96.04, 0.02)	32
Acute§				
	Nonfatal CAD	65 442 (43 818–100 531)	Gamma (20.46, 0.0003)	33
	Fatal CAD	18 246 (14 597–21 896)	Gamma (96.04, 0.0053)	34
	Nonfatal ischemic stroke	40 225 (11 539–100 184)	Gamma (3.16, 0.0001)	33
	Fatal ischemic stroke	11 256 (9005–13 507)	Gamma (96.04, 0.0085)	34
	Nonfatal hemorrhagic stroke	38 246 (30 596–45 895)	Gamma (96.04, 0.0025)	35
	Fatal hemorrhagic stroke	18 246 (14 597–21 896)	Gamma (96.04, 0.0053)	34
Follow-up				
	CAD	11 815 (7865–16 186)	Gamma (30.99, 0.003)	36
	Stroke (hemorrhagic/ischemic)	20 005 (16 004–24 006)	Gamma (96.04, 0.0048)	37
	Myopathy	20 438 (16 351–24 536)	Gamma (96.04, 0.0047)	38
	Diabetes	10 026 (8021–12 031)	Gamma (96.04, 0.0096)	39

HR indicates hazard ratio; OR, odds ratio; CAD, coronary artery disease; PRS polygenic risk score; and RR, relative risk.

*Range (+/–20% of the baseline value). The range and 95% CI were used in sensitivity analysis.

†Statin-induced myopathy did not change the risk of coronary artery disease (CAD) and stroke or mortality.[40-43] Further, the risk of CAD did not change after hemorrhagic stroke.[11]

‡Mortality after stroke and CAD is significantly higher compared with only CAD or stroke. In a Medicare study population, >50% of patients with stroke and CAD died in the first year.[20] Because of data limitations and our younger study population, we assumed 75% (50% to 100%) of patients will die in 10 years. We also assumed a higher mortality rate for stroke among individuals with diabetes compared with those without diabetes based on a non-US study. Although no study has been performed in the US population, studies including a meta-analysis showed increased mortality among patients with stroke who had diabetes.[23,44,45]

§Annual cost applied in the first year of the event.

had higher mortality rates compared to chronic stages. Also, mortality was higher among individuals with diabetes,[19] diabetes and CAD,[19] and diabetes and ischemic stroke[44] compared to those without diabetes.

Costs

We considered only medical costs incurred by the payer (Table 1). Costs included PRS testing, statin therapy, in-patient hospitalization for fatal and nonfatal acute events, and follow-up costs after hospital discharge. The cost of genetic testing in the United States has decreased significantly over the years and, the cost varies based on the type of test performed. The one-time cost for PRS testing was based on current prices of genotyping arrays and the required bioinformatic analysis (Source: Allelica, Inc). An additional primary care visit cost was included for the cohort with high CAD-PRS for further genetic counseling.[30] The cost of statin therapy came from online pharmacy prices.[31] We derived costs for treating acute CAD and ischemic stroke from a systematic review of costs associated with major cardiovascular conditions.[33] The cost of acute fatal events included hospitalization and procedures performed for patients who did not survive the acute stage.[34] The cost of recurrent events was calculated as the product of the risk of occurrence and cost of treatment. We included background health care costs per patient-year to account for health care expenditure per capita for a privately insured population.[32]

Health State Utility Values

Utility weights were derived from the literature and assigned to health states to represent the severity of the disease (0=death, 1=perfect health). We assumed fractions of the cohort without any events had perfect health but experienced a disutility attributable to aging.[29] The utility weights for CAD and stroke health states came from a systematic review that examined the utility values for cardiovascular diseases.[24] We applied disutility for acute CAD[27] and stroke[28] events, and utility weights for statin side effects including diabetes[26] and myopathy.[25]

Sensitivity Analysis

We varied parameter inputs over a range of plausible values to identify the main drivers of variation in the incremental net monetary benefit (NMB). Cost variables

included PRS testing, statin therapy, and treatment for CAD, stroke, and statin side effects; and transition probabilities: percentage of the cohort adhering to statins, statin effectiveness in reducing CAD and stroke events, risk of death and developing CAD, ischemic stroke, or statin side effects. For probabilistic sensitivity analysis, we assumed beta, lognormal, and gamma distributions for probabilities, relative risk, hazard and ORs, and cost variables, respectively. The beta distribution bounds the probabilities between 0 and 1, and the gamma distribution restricts costs to >0. We performed 10 000 Monte Carlo simulations, and results are reported using cost-effectiveness planes and cost-effectiveness acceptability curves.

We assessed the value of getting additional information in parameter uncertainty using the population expected value of perfect information (EVPI) approach, which estimates the value of eliminating uncertainty in the model by assuming perfect information. This analysis informs decision makers whether they need to invest more resources to gain additional information. Using 10 000 Monte Carlo simulations, in each iteration, an NMB was calculated with the strategy that maximizes the NMB at a given WTP threshold being preferred to the alternative. EVPI was calculated as the difference between the NMB of the optimal strategy under current uncertainty and the maximum NMB possible per iteration. When the EVPI is equal to zero, this implies that the decision does not change regardless of the new additional information. In this study, the target population was adults between the ages of 40 and 75 years (recommended age for ASCVD screening) without ASCVD, diabetes, or severe hypercholesterolemia (low-density lipoprotein >190 mg/dL) and categorized as at borderline or intermediate risk. To define this population, we estimated that 42% of the current US population fall between the ages of 40 and 75 years based on 2019 census data.[50] We excluded 21% of adults aged 40 to 75 years (13% prevalence of diabetes[48] and 8% prevalence of ASCVD[49] among adults in the United States) to get the PPP. We assumed 37% of the PPP had borderline or intermediate PCE risk based on Aragam et al.[1] We applied a 0.25% annual growth rate in adults aged 40 to 75 years[50] (Figure S1).

Scenario Analysis

Four scenario analyses were performed: (1) we assessed outcomes at different cohort start ages after accounting for the impact of aging on the risk of CAD and ischemic stroke. We applied a 3.5% annual increase in the baseline risk of CAD attributable to aging,[51] and the risk of ischemic stroke increased linearly and doubled every decade after age 55.[46] Results were reported for 5-year, 10-year, and lifetime time horizons. (2) We considered individuals in the bottom 80% of the CAD-PRS distribution (nonhigh-risk) who were eligible for statin prevention therapy since in the base case analysis we only considered high-risk

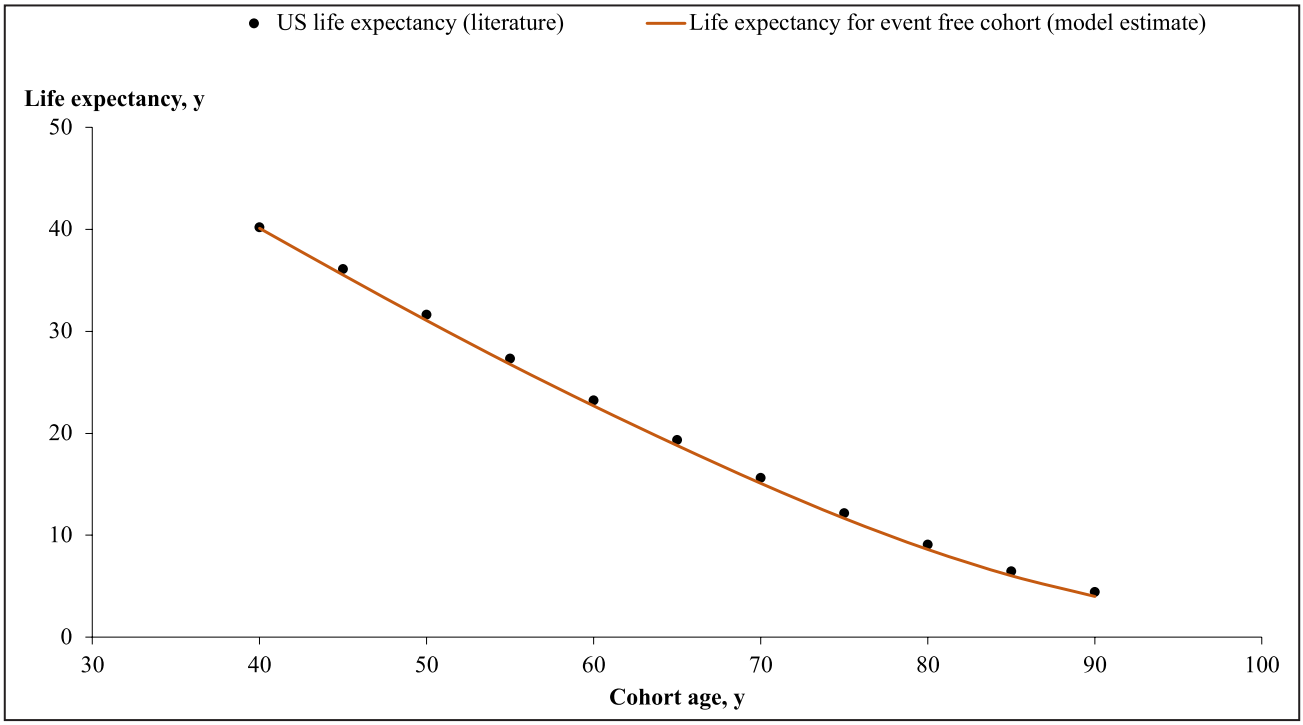

Figure 2. Life expectancy in the US general population compared with the event-free cohort in the model.
Projected life expectancy of the event-free cohort in the model with the mean ages of 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, and 90 years. The projected years of survival were comparable to the life expectancy of Americans with the same age.[52]

individuals in the top quintile. In the study by Aragam et al, 46.8% of individuals in the bottom 80% of the CAD-PRS distribution were eligible for statin prevention therapy based on the American Heart Association statin eligibility guidelines, but only 23.8% received statin prescription. These estimates were only available for the overall sample but not for individuals with borderline or intermediate risk, so we assumed the same percentages applied to all PCE categories including borderline or intermediate.[1] (3) We applied PRS testing only to individuals without any other risk-enhancing factors since the base case analysis tested the whole population of individuals with borderline or intermediate risk to be consistent with the Aragam et al study.[1] By first applying PCE alone and identifying high-risk individuals with other risk-enhancing factors, PRS was applied to fewer targeted individuals and was thus more efficient. (4) We assessed a scenario where PRS has improved predictive performance, being able to identify more individuals in the top quintile of the CAD-PRS distribution with increased risk of developing CAD (expert communication from Allelica, Inc).

Model Validation

We validated the model using an external validation approach by corroborating the life expectancy for the event-free cohort in the model to that of the general population in the United States, and the life expectancy for the cohort with CAD with estimates from the literature. Since no study has examined the cost-effectiveness of PCE+CAD-PRS versus PCE alone among populations at intermediate/borderline risk, primary outcomes (ie, events of CAD and ischemic stroke) were unavailable in the literature to validate the model. Model-projected years of survival were comparable to the life expectancy of Americans in the general population[52] (Figure 2) and after acute CAD[53,54] (Figure 3).

RESULTS

Base Case Analysis

Results for the base case scenario are reported in Table 2. PCE+CAD-PRS had 0.003 and 0.011 more QALYs gained and $40 and $181 lower mean costs per person screened in the 5- and 10-year time horizon, respectively, compared with PCE alone. The breakdown of total and incremental costs is provided in Table S3. In a cohort of 10 000 individuals with borderline or intermediate PCE 10-year risk of ASCVD and not taking statin therapy, PCE+CAD-PRS would prevent ≈29 and 50 events of CAD and ischemic stroke, with an average cost savings of $13 000 and $36 000 per event averted in 5- and 10-year time horizon, respectively (Table 3).

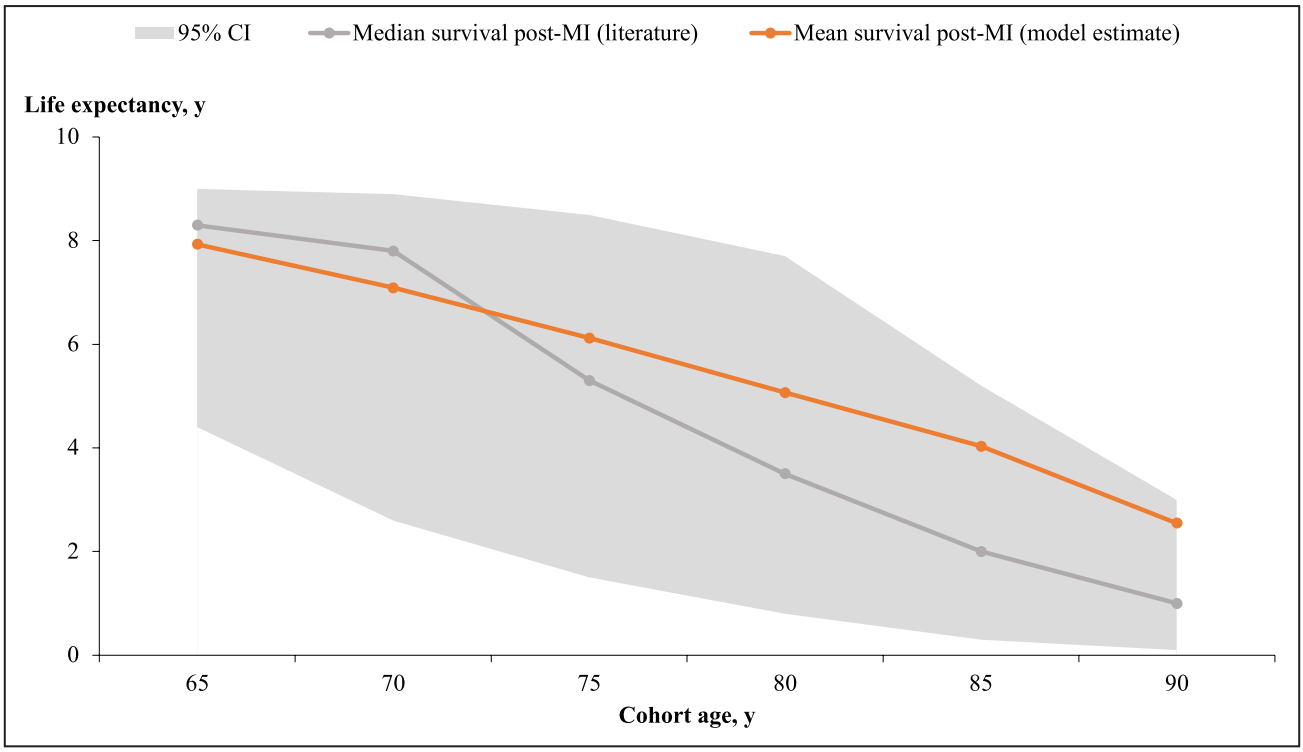

Figure 3. Life expectancy postmyocardial infarction.
Life expectancy of the cohort after acute myocardial infarction (MI) estimated from the model compared with data from the literature.[53,54] We found the life expectancy generated by the model to be within 95% CIs of the life-expectancy values from the literature.

Table 2. Results for the Base Case Analysis (Cost: 2019 US$)

Time Horizon	Strategy	Cost*	Incremental cost	QALYs*	QALYs gained	ICER
5 y	PCE alone	28 932		4.556		
		(23 598–34 586)		(4.485–4.624)		
	PCE+CAD-PRS	28 892	(40)	4.559	0.003	Dominant
		(23 549–34 532)		(4.488–4.627)		
10 y	PCE alone	49 681		8.313		
		(40 590–59 822)		(8.06–8.56)		
	PCE+CAD-PRS	49 500	(181)	8.323	0.011	Dominant
		(40 479–59 610)		(8.08–8.57)		

Base case cost-effectiveness analysis results for 5- and 10-year time horizons in a cohort of 40-year-old Americans with borderline or intermediate risk of atherosclerotic cardiovascular disease. Compared with pooled cohort equation (PCE) alone, PCE+polygenic risk score for coronary artery disease (CAD-PRS) had higher mean quality-adjusted life-years (QALYs; 0.003–0.011) and lower mean costs ($40, $181) per person screened in 5- and 10-year time horizons, respectively. CAD indicates coronary artery disease; and ICER, incremental cost-effectiveness ratio.

*Intervals represent 2.5th to 97.5th percentiles.

One-Way Sensitivity Analysis

Results for 1-way sensitivity analysis are shown in Figures 4 and 5. PCE+CAD-PRS had an incremental NMB of $186 and $711 in the 5- and 10-year time horizon, respectively. The risk of developing CAD, the effectiveness of statin prevention therapy, and the cost of treating CAD had the largest impact on the cost per QALY gained, but PCE+CAD-PRS remained cost-effective (incremental cost-effectiveness ratio <$50 000 WTP threshold) across all parameters' uncertainty in both time horizons except when the annual risk of developing CAD was <0.006 in the 5-year time horizon.

Probabilistic Sensitivity and Value of Information Analysis

Results from Monte Carlo simulation indicated a significant proportion of the joint distribution of incremental effectiveness (QALY gained) and incremental costs on the cost-effectiveness plane fell below the WTP threshold of $50 000 and in the southeast quadrant, indicating that PCE+CAD-PRS was more likely to be effective and cost saving compared with PCE alone (Figure S2). The cost-effectiveness acceptability curves (Figure 6) show that PCE+CAD-PRS would be cost-effective with a probability of 94% and 99% at $50 000 WTP threshold and 98% and 99% at $100 000 WTP threshold in the 5- and 10-year time horizons, respectively. The value of information analysis showed an individual EVPI of $1.56 and $0.09 at $50 000 WTP threshold in the 5- and 10-year time horizons. Figure 7 shows population EVPI values over a range of WTP thresholds. As shown in Figure 6, the probability of cost-effectiveness increased with the increase in WTP, which implies increased decision certainty and decreased EVPI over the WTP thresholds.

Scenario Analysis

PCE+CAD-PRS remained a dominant strategy compared with PCE alone after accounting for the impact of age on the risk of CAD and ischemic stroke. In a cohort of patients with a mean age of 40 years and a 3.5% annual increase in the risk of CAD, we found PCE+CAD-PRS to be cost saving ($50.11, $217.79, and $38.75) in all time horizons (5-year, 10-year, and lifetime), respectively (Table S4). However, cost savings were lower in the lifetime time horizon since more individuals are identified by PCE alone in the long run, and, with longer survival in the PCE+CAD-PRS strategy, the increased health care expenditure reduces the cost advantage of CAD-PRS. In addition, considering the same cohort,

Table 3. Events of CAD and Ischemic Stroke per 10 000 Individuals Screened

Time Horizon	Strategy	CAD	Ischemic Stroke	Events Averted	Cost saved per event averted
5 y	PCE alone	184	31		
	PCE+CAD-PRS	157	29	29	13 000
10 y	PCE alone	344	60		
	PCE+CAD-PRS	297	57	50	36 000

Base case analysis events of coronary artery disease (CAD) and ischemic stroke when the model was applied in 10 000 individuals with borderline or intermediate risk. Pooled cohort equation (PCE)+polygenic risk score for coronary artery disease (CAD-PRS) had ≈29 and 50 fewer events of CAD and ischemic stroke compared with PCE alone, resulting in a cost savings of $13 000 and $36 000 per event averted in 5- and 10-year time horizons, respectively.

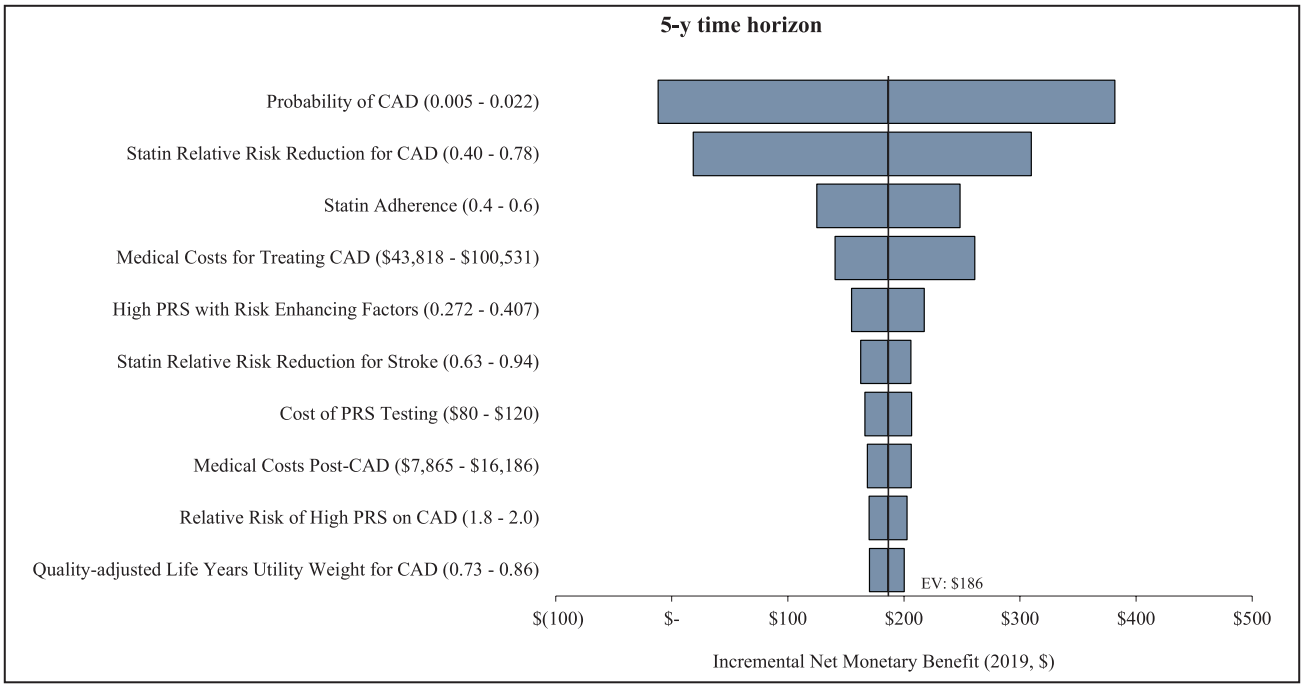

Figure 4. The 5-year incremental net monetary benefit of pooled cohort equation (PCE) alone vs PCE+polygenic risk score for coronary artery disease (CAD-PRS), with PCE+CAD-PRS preferred across all parameter value variations except when the annual risk of developing CAD was <0.006.
CAD indicates coronary artery disease; EV, expected value; and PRS, polygenic risk score.

at 60 years, PRS would no longer be effective but cost more since all high-risk individuals would be identified by PCE alone. The findings were consistent with the base case analysis when we included high-risk individuals in the bottom 80% of the CAD-PRS distribution in the model (Table S6). PCE+CAD-PRS was more

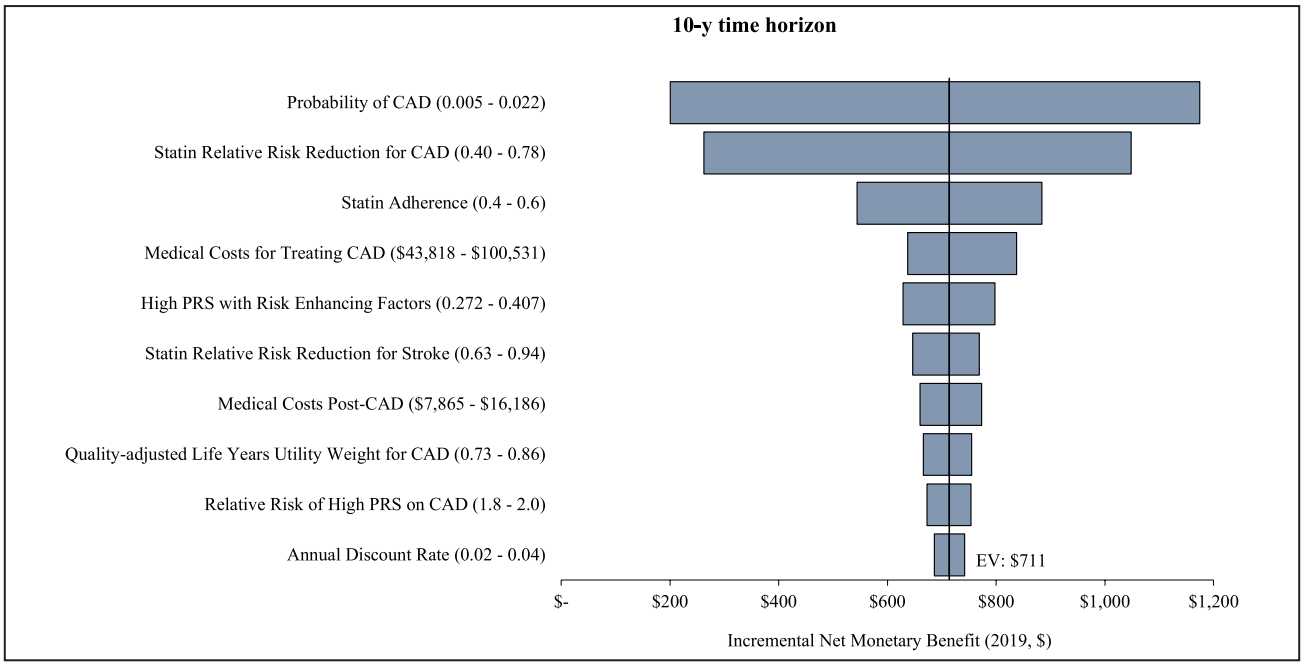

Figure 5. The 10-year incremental net monetary benefit of pooled cohort equation (PCE) alone vs PCE+polygenic risk score for coronary artery disease (CAD-PRS), with PCE+CAD-PRS preferred across all parameter value variations.
Figures 4 and 5 show the incremental net monetary benefit of pooled cohort equation (PCE) alone vs PCE+polygenic risk score for coronary artery disease (CAD-PRS), with PCE+CAD-PRS preferred across all parameter value variations except when the annual risk of developing CAD was <0.006 in the 5-year time horizon.

cost saving compared with the base case ($90 versus $40 and $230 versus $181 for the 5- and 10-year time horizon, respectively) when the cost of PRS testing was applied only to individuals without any PCE risk-enhancing factors (Table S7). Finally, with more high-risk individuals identified and the risk of developing CAD increased up to 3-fold, PCE+CAD-PRS was more cost saving and cost-effective compared with PCE alone in a 5- and 10-year time horizon, respectively (Table S8 and Figure S3). Compared with the base case analysis, PCE+CAD-PRS was cost saving up to >$250 and $550 and improved QALYs by up to >0.007 and 0.023 per person screened in the 5- and 10-year time horizon, respectively.

DISCUSSION

We developed a Markov model to examine health benefits and health care costs associated with integrating CAD-PRS as a risk-enhancing factor in PCE to identify high-risk individuals who are undetected by current clinical practice—PCE alone—and are eligible for statin prevention therapy. We found that PCE+CAD-PRS was cost-effective (incremental cost-effectiveness ratio <$50 000 WTP threshold) and cost saving with higher mean QALYs and lower mean costs per person screened compared with PCE alone in all time horizons. The risk of developing CAD, the effectiveness of statin prevention therapy, and the cost of treating CAD had the largest impact on the cost per QALY gained, which is consistent with previous studies.[55,56]

This study underscores both health and economic benefits of integrating CAD-PRS into risk assessments for ASCVD. More than 29 and 50 CAD and ischemic stroke events were averted by PCE+CAD-PRS compared with PCE alone per 10 000 individuals screened in 5- and 10-year time horizons, respectively. As a result, an average of $13 000 to $36 000 per event averted could be saved between 5- to 10-year time horizons, indicating that the longer the outlook, the more beneficial implementing PRS becomes. Furthermore, from a societal perspective, PCE+CAD-PRS may be even more cost saving when loss of productivity from CAD or stroke events is also considered.[57]

Findings were largely robust to parameter uncertainty, particularly in the longer time horizon of 10 years. The annual risk of developing CAD had the largest impact on the incremental cost-effectiveness ratio in the 5-year time horizon when the risk was <0.6%, which is substantially below the mean risk (1.32%) for the population with borderline and intermediate risk. However, since the larger proportion of the study population was in the group with intermediate risk,[1] this scenario is less likely to occur. In the Monte Carlo simulations, the

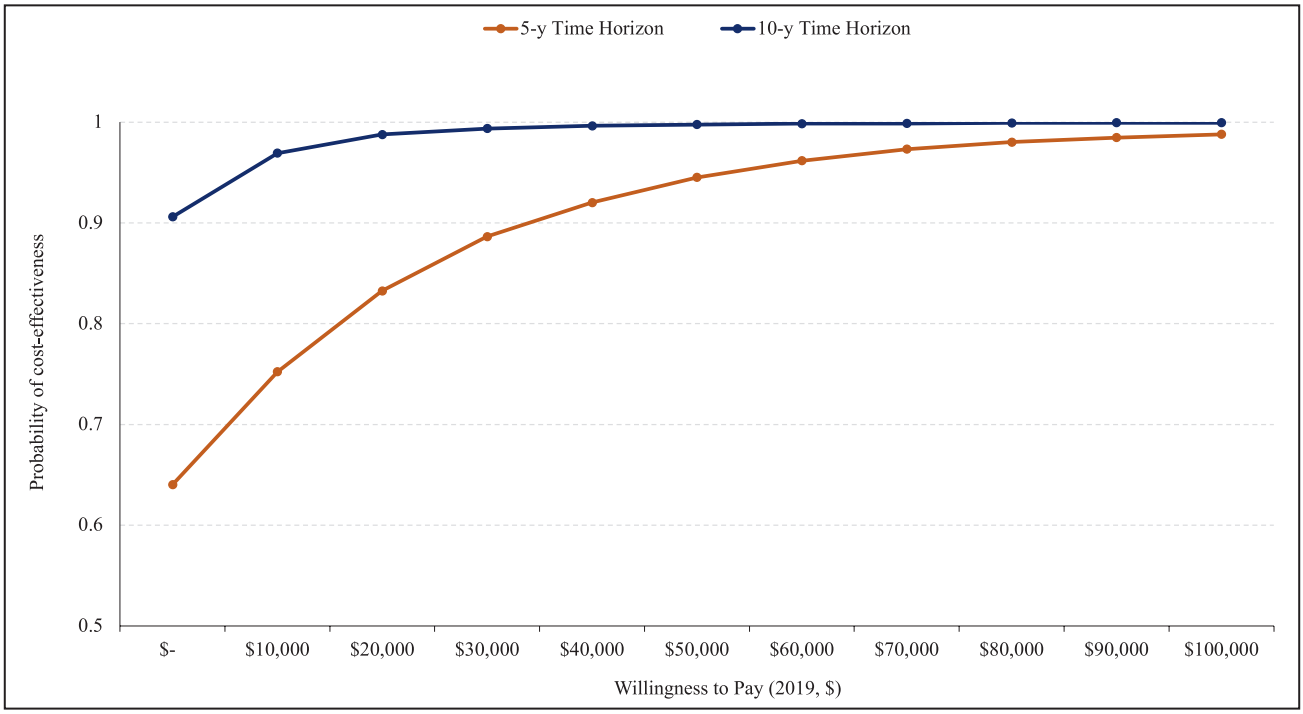

Figure 6. Cost-effectiveness acceptability curves.
Results from the probabilistic sensitivity analysis indicating the probability of the pooled cohort equation (PCE)+polygenic risk score for coronary artery disease (CAD-PRS) being cost-effective at different willingness-to-pay (WTP) thresholds. Compared with PCE alone, PCE+CAD-PRS is likely to be cost-effective with a probability of 94% and 99% at $50 000 WTP threshold and 98% and 99% at $100 000 WTP threshold in 5- and 10-year time horizons, respectively.

probability of cost-effectiveness was >94%, indicating that PCE+CAD-PRS is highly cost-effective compared with PCE alone. Further, the value of information analysis showed that the EVPI decreased with the increase in the WTP threshold suggesting that future research in parameter uncertainty may not be a good value to invest resources. However, since data were collected from the literature and multiple studies, it was not possible to account for potential correlation between parameter inputs, which could have an impact on the EVPI.

CAD-PRS is cost-effective for all ages including young adults given the limitations of traditional risk factors in identifying the risk of ASCVD at a younger age. Our results indicate higher QALYs gained when PCE+CAD-PRS was implemented in a younger cohort (ie, aged 40 years) and followed over a lifetime, primarily attributable to the long-term benefits from prevention of adverse health outcomes over their lifetime (Table S5). Previous work has found that individuals who receive their genetic results are more likely to report positive behavior changes especially in nutiriton.[58] Therefore, implementing CAD-PRS in young adults could have the corollary of improving quality of life in the long run through lifestyle changes.

While our findings are broadly comparable with previous work, they also provide important novel insights on the efficiency of precision medicine, particularly in primary prevention for CAD. In one study, genetic testing was more beneficial when targeting individuals in whom traditional risk factors do not provide an accurate risk assessment.[55] Combining traditional risk factors with genetic testing for a segment of individuals with 17% to 22% 10-year risk reduced the average cost of treating cardiovascular diseases per individual in a population of 100 000 adults by $3.04 in a 10-year follow-up compared with using traditional risk factors on their own.[55] In our study, PCE+CAD-PRS saved >$181 with 0.011 QALYs gained per individual screened, compared with PCE alone after 10 years. This translated to an average of $67 saved per 40-year-old individual in the PPP. Our study identified a higher proportion of high-risk individuals because genetic testing was performed in a larger percentage of patients (36%)—those with 5% to <20% 10-year risk—of the PPP compared with the optimization approach used by Hynninen et al (2019) where genetic testing was performed in only 3% of the population—those with 17% to <22% 10-year risk based on traditional risk factors—and excluding those with <10% 10-year risk from any preventive therapy.[55] In a recent US-based study, PRS testing on individuals with low to borderline (2.5% to 7.5%) 10-year risk was found to not be cost-effective in informing statin therapy decisions.[56] However, these authors only considered individuals with low and borderline 10-year risk and applied genetic testing to classify high-risk individuals for preventive care, whereas guidelines recommend that additional risk-enhancing factors should

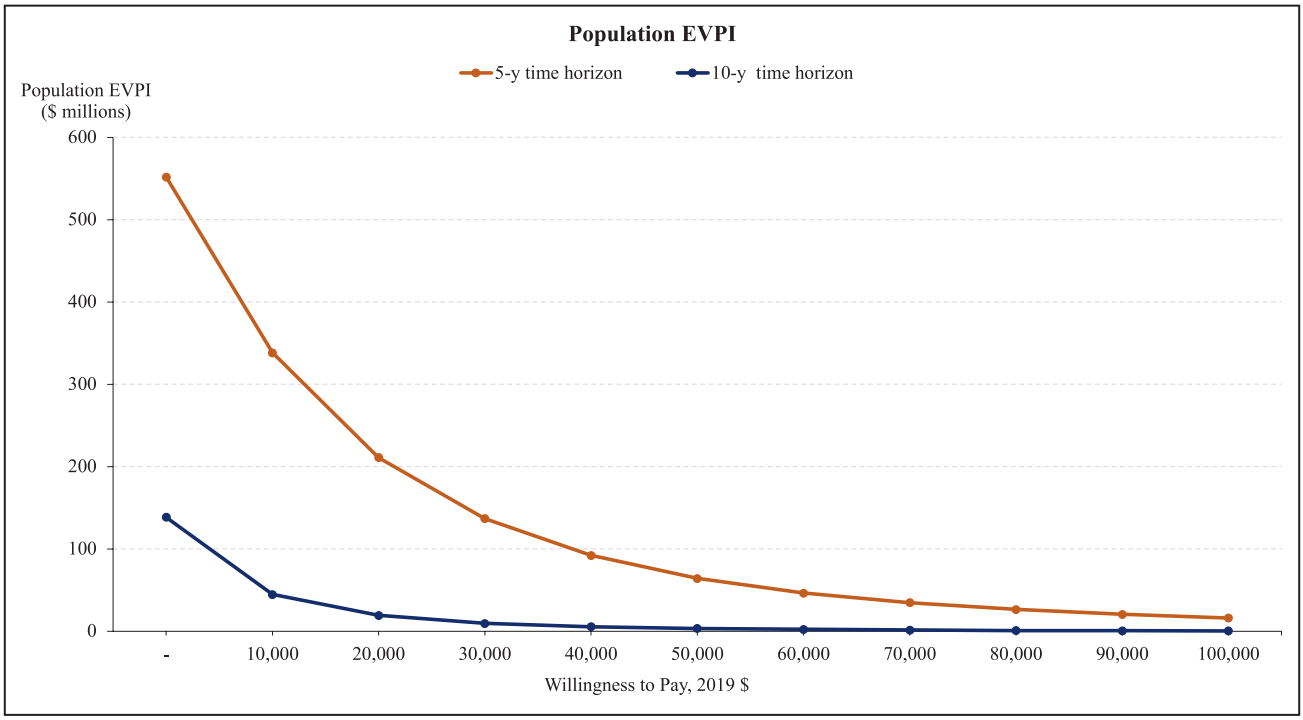

Figure 7. Expected value of perfect information (EVPI) at different willingness-to-pay (WTP) thresholds.
Population EVPI of ≈$64.3 M and $3.53 M at a $50 000 WTP threshold in the 5- and 10-year time horizons. EVPI decreased with increase in WTP thresholds suggesting high certainty in the cost-effectiveness analysis results.

be used in individuals at borderline or intermediate 10-year risk (5% to <20% 10-year risk).[3] Accordingly, in this study, we implemented CAD-PRS as a risk-enhancing factor in the PCE in individuals with borderline/intermediate risk and demonstrate improved health and economic outcomes when focusing on this subgroup.

Limitations

Our study has several limitations. First, alternative preventive therapies were not considered and individuals who experienced statin therapy side effects were assumed to not be taking any preventive therapy. Although alternative prevention strategies including exercising and plant-based diet may reduce the risk of cardiovascular disease, their long-term effectiveness is difficult to measure in a real-world setting because of challenges with adherence, access, and affordability of a healthy diet for the majority of the people in the United States. Preventive therapies such as proprotein convertase subtilisin/kexin type 9 may mitigate the risk of CAD but statin therapy remains the recommended first-line preventive care for cardiovascular diseases in the United States.[3] Second, we assumed that high-risk individuals remained unidentified under the PCE-alone strategy throughout the analytic time horizon and did not initiate any preventive therapy, although age is a strong risk factor for CAD and may inform prevention decisions in the future. However, this assumption did not substantially impact the results since the risk of CAD is usually estimated at 10 years and the risk of stroke is less likely to change before age 55.[46] Third, because of data limitations, our study cohort combined individuals with borderline and intermediate risk although guidelines recommend moderate-intensity statin therapy for those with borderline risk and an additional risk-enhancing factor and high-intensity statin therapy for those with intermediate risk and additional risk-enhancing factor.[3] However, our findings are conservative since we assumed moderate-intensity statin therapy. Fourth, we assumed that patient behavior did not change over the analytical time horizon, while there is some evidence that genetic testing is associated with positive changes in patient behavior.[58] Finally, we did not account for correlation between model parameters, which may have an impact on the findings.

CONCLUSIONS

To inform preventive care decisions for cardiovascular diseases in clinical settings in the United States, we developed a Markov model to examine health benefits and health care costs associated with implementing CAD-PRS as a risk-enhancing factor in the PCE among adults with borderline or intermediate PCE 10-year risk of ASCVD. We found PCE+CAD-PRS to be a highly efficient use of health care resources, with lower costs, higher QALYs, and future events of CAD and ischemic stroke averted when compared with PCE alone. This study supports the growing evidence on the value of PRS in chronic disease prevention.

ARTICLE INFORMATION

Received December 30, 2021; accepted April 6, 2022.

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Sources of Funding

This work was supported by private funding from Allelica, Inc.

Disclosures

Dr Mujwara, P. Di Domenico, Dr Busby, and Dr Bottà are employees of Allelica, Inc. G. Henno is an employee of Pacific Biosciences of California, Inc., and a former employee of Illumina Inc. S. Peng and Dr Schroeder are employees of Illumina, Inc.

Supplemental Material

Data S1
Tables S1–S8
Figures S1–S3
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SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Model

A Markov model was developed to represent ASCVD risk stratification based on CAD-PRS distribution, eligibility for statin preventive therapy, and clinical events. Health states included event free cohort, CAD, ischemic stroke, statin side effects (diabetes, hemorrhagic stroke, and myopathy) and death. We used a Markov model due to its ability to examine alternative strategies and project future costs and health benefits using multiple data sources. This methodology has been implemented in literature to examine strategies, especially when observational data from one source is unavailable to perform statistical analysis. Markov models provide insight in the potential cost-effectiveness of the strategies when data are unavailable to apply more advanced methods such as micro-simulation.[60]

Time horizon

We examined health care costs and health benefits for 5 year and 10 year time horizon to account for benefits of CAD-PRS in both short and long term periods.

Discount rate

We discounted future health care costs and health benefits at 3% to convert future values to present values. Although the discount rate of 3% is recommended.[6] In the sensitivity analysis, we assessed the impact of the discount rate on the incremental cost-effectiveness ratio (incremental costs/incremental effectiveness) by varying the discount rate between 2 and 4%.

Measure of effectiveness

Health benefits were measured as quality-adjusted life years (QALYs) gained. QALYs are a standard measure of health benefits in cost-effectiveness analyses[6] since they measure the quality and quantity of life years gained from an intervention. Health states in the model were assigned utility weights and the sum of weights over the analytic time horizon reflected the total strategy specific QALYs. Utility weights varied based on the health state, severity of the health condition and age of the cohort.

Study perspective

This study was conducted from a payer perspective, which only considered costs incurred by the payer.

Inflation adjustment

The Gross Domestic Product (GDP) deflator was used for inflation adjustment since costs were derived from different studies and time periods. The GDP deflator is a price index which measures the annual change in prices for quantity goods and services produced in the economy. The index is comprehensive as it accounts for government and household consumption, and international trade.

Derivation of annual transition probabilities

Data to inform transition probabilities were derived from the literature and converted into annual probabilities in three steps:

1. Converted the original parameter value into a rate

2. Converted the rate into an annual rate
3. Converted the annual rate into an annual probability

We assumed model parameters to be a random variable that has a Poisson process with constant rate, and the time for occurrence of the next random variable had a negative exponential distribution. Data not reported annually in the data source were first converted to annual rates and then to annual probabilities.[60,61] The relationship between a rate and probability was expressed as: $R = \frac{-\ln(1-p)}{t}$, where R = rate, p = probability, t = time period.

Distribution for probabilistic sensitivity analysis

Beta, gamma, and lognormal distributions were assigned to parameter inputs and used in the probabilistic sensitivity analysis. The beta distribution bounded the probabilities between 0-1 and the gamma distribution restricted costs to >$0.00.[62] As recommended in the guidelines, we assigned lognormal to hazard, relative risk and odds ratios.[63] For beta distribution, we derived the α and β shape parameters using equation (2) and (3). We used the parameter baseline value as the mean and equation (1) to calculate the standard error.

$$se = \frac{u - l}{2\ x\ 1.96} \qquad (1)$$

where se = standard error, u = upper bound value, l = lower bound

$$mean = \frac{\alpha}{\alpha + \beta} \qquad (2) \qquad sd = \sqrt{\frac{\alpha\beta}{(\alpha+\beta)^2(\alpha+\beta+1)}} \qquad (3)$$

For the gamma distribution, we used the baseline value as the mean and equation (1) to estimate the standard deviation, and equations (4) and (5) were used to calculate the shape (α) and rate (β) parameters.

$$mean = \frac{\alpha}{\beta} \qquad (4) \qquad sd = \frac{\sqrt{\alpha}}{\beta} \qquad (5)$$

For the lognormal distribution, we used the baseline value as the mean and equation (1) to estimate the standard deviation and equation (6) to calculate the median, where m is the baseline value and σ is the standard deviation

$$e^{lnm-\frac{\sigma^2}{2}} \quad (6)$$

Model Parameters

Initial distribution

The initial cohort was made up of individuals with borderline/intermediate PCE 10-year risk who do not have any other risk enhancing factors and are not on statin preventive therapy. The borderline/intermediate population was distributed in two categories: high-risk (in the top quintile of the CAD-PRS or have other risk enhancing factors) and non-high-risk (in the bottom 80% of the CAD-PRS and without any risk enhancing factors). Data to inform the initial distribution came from a large retrospective study that used genomic and clinical data of 47,108 individuals in the US to examine the risk of CAD among those in the top quintile of the CAD-PRS distribution compared to the remaining population.[1] The risk of CAD in the top quintile (16.78%) was nearly 2-fold (Adjusted Odds Ratio 1.9 [95% CI 1.8 – 2.0) that of the remaining population. But, among individuals with borderline/intermediate PCE 10-year risk (5 to <20%), over 11.07% were classified as high risk based on CAD-PRS but were not detected by the current clinical practice (PCE-alone) and were not on statin preventive therapy.

Probability of CAD

The probability of CAD was estimated as the average risk of the borderline/intermediate risk population with a 1.9 [95% CI 1.8 – 2.0) times increased risk associated with high PRS (top

quintile of CAD-PRS distribution). The risk of CAD was higher among patients with diabetes (HR: 2.27 [95% CI 1.95-2.65])[14] and those with ischemic stroke (0.17 [95% CI 0.014 – 0.019])[44] This came from meta-analysis and systematic reviews with studies from Europe, Asia and North America. Although parameter values were not derived directly from only US-based studies, we believe meta-analysis estimates are robust but also include studies from the US. The risk of CAD did not significantly change among patients with myopathy[64] or post- hemorrhagic stroke (HR, 1.6 [95% CI 0.3 – 2.9].[15]

Probability of Ischemic Stroke

The risk of Ischemic Stroke was assumed to be at general population level since stroke was not considered as an outcome in the Aragam et al. study,[1] which we based on to identify high risk individuals in the top quintile of the CAD-PRS distribution. In the US, there are nearly 800,000 cases of stroke annually of which nearly 90% are ischemic stroke and occur among adults.[45] With the adult population in the US around 200 million, we estimated the incidence of ischemic stroke was 0.8/200 = 0.004. We assumed that the risk of ischemic stroke was constant in the 5 and 10 year time horizon. According the CDC, the risk of stroke doubles every decade after the age of 55 years[7] but since our initial cohort is 40 years old and the within the 10 year time horizon the cohort age will be 50 years, the risk of ischemic stroke will not have significantly changed.

Statin effectiveness

Statin therapy is widely used as the first-line prevention therapy for CAD among high-risk individuals and it has been shown to be effective in reducing the risk.[65] In this study, we used

simvastatin 20-80mg, which is the used statin in the US with over 42% of all statin prescriptions.[66] However, no studies have examined the efficacy of simvastatin among individuals with high CAD-PRS, so we used the efficacy of pravastatin among individuals in the top quintile of the CAD-PRS distribution. Simvastatin has been shown to be better or comparable to pravastatin in reducing low-density lipoprotein cholesterol.[67,68] Among high risk individual we applied a hazard risk ratio for CAD risk reduction HR: 0.560 [95% CI 0.400 – 0.780])[8] and stroke events HR: 0.770 [95% CI 0.630 – 0.940][9]

Statin side-effects

Statin intolerance and side effects (diabetes, hemorrhagic stroke, and myopathy) may occur in some individuals although the prevalence of these side-effects is low. In one study, a cohort of 10,000 individuals was followed for over five years while on statin, 5-10, 5 and 50-100 had hemorrhagic stroke, myopathy and diabetes respectively.[13] We used these findings to estimate the risk of developing side effects among high-risk individuals on statin.

Adherence to statin

We defined statin adherence as consistent use of statin in a given year. Adherence to statin was assumed to be 50%[10] and constant every year over the analytic time horizon. Although adherence to statin in primary prevention is usually low (<50%), inconsistent, and decreases overtime,[10] we assumed at least 50% of those on statin would adhere to the therapy given evidence of higher statin adherence among adults in the US[11] and higher use of preventive therapy among individuals who know their high PRS.[12]

Utility weights

QALY utility weights were derived from literature to reflect severity of disease in different health states. The utility weights (Median, IQR) for CAD (0.79, 0.73 – 0.86) and Stroke (0.64, 0.44 – 0.78) came from a systematic review that examined the utility value estimates for cardiovascular diseases. The estimates represented a combined value generated from over 350 papers worldwide using different methods.[28] These utility values are robust and comparable to those generated based only on the US population.[29] Utility weights for statin side effects also came from the literature. For diabetes, we used the utility weights from a study that examined healthy utility scores (0.80, 0.620 – 0.980) among type 2 diabetes patients in managed care health plans in the US.[31] For myopathy, we used utility values (0.97, 0.896 – 0.938) from another economic evaluation study focused on statin induced myopathy among patients at high risk of cardiovascular diseases.[32] We applied disutility based on age[27] and acute events (CAD[29] and stroke[30]).

Probability of death

The probability of death for the cohort without CAD, stroke or statin side-effects came from the social security life tables (Table S1).[37] The probability of death at acute CAD [0.228 (0.182 – 0.274)][16] and post-acute CAD [0.070 (0.067 – 0.072)] health states came from US-based studies. Those with diabetes and CAD have an increased risk of death (HR: 1.81 [95% CI 1.44 – 2.28])[20] compared to those without diabetes. Similarly, those with diabetes were at higher risk of death compared to without diabetes (HR: 1.68 [95% CI 1.52 – 1.87]).[20] Mortality after stroke and CAD was significantly high compared to patients with CAD or stroke alone. In a Medicare study population, more than 50% of patients with stroke and CAD died in the first year [47] but not further information was provided beyond that time period. Since the cohort for the current study

is younger, we assumed 50% of patients will die in 10 years. We assumed mortality for stroke increased by 50% among people with diabetes compared to those without diabetes. Although no study has been done on the US population, a meta-analysis of studies out-side the US showed increased mortality among stroke patients with diabetes.[21]

Costs

PRS testing

The cost of genetic testing in the US has reduced significantly over the years.[69] The cost of genetic testing for estimating the PRS for CAD was $100 based on the current prices of genotyping arrays and the required bioinformatics analysis (source: Allelica, Inc).

Primary care provider visit

Patients that undergo genetic testing may require an additional primary care visit to explain the benefits of genetic testing and how this may impact their health outcomes. We applied a median cost of $107 for a primary care visit among patients that fall in the top quintile of the CAD-PRS distribution who are high risk of CAD and may require additional explanation on why they are considered high risk.[22] The estimate came from the Medical Expenditure Panel Survey (MEPS), a nationally representative survey on patient medical expenses.[22]

Statin therapy

The cost of statin therapy was estimated at $132 per patient-year, derived from the current online prices for statin in the US,[23] which is consistent with the literature.[70]

Acute non-fatal CAD, ischemic stroke, and hemorrhagic stroke

The cost of acute non-fatal CAD and ischemic stroke came from a systematic review (N = 114 studies, of which 60 were from the US) of patient-level costs for an acute myocardial infarction and ischemic stroke.[24] A cute costs included costs for a procedure or initial hospitalization costs due to an acute event and costs for the first year. Only costs reported from studies done in the US were considered. For hemorrhagic stroke, the cost was derived from a retrospective study that used medical claims (MarketScan) data examine hospitalization costs for stroke adult patients in the US.[50]

Acute fatal CAD, ischemic stroke, and hemorrhagic stroke

The cost of acute fatal events included costs for hospitalization or any procedures in patients that did not survive the first year from the time the event occurred. The costs came from a retrospective study that used administrative claims data (N = 97.374 hospitalizations) including commercial and Medicare enrollees to estimate the cost of cardiovascular events in the US.[25]

Follow up costs

Patients that survive the first year of an acute event have higher costs compared to the general population or those without prior cardiovascular events. For patients that survived acute CAD, the annual follow up cost value came from a retrospective study that examined medical claims (N = 13,492 patients) to estimate long-term costs for myocardial infarction survivors in the US.[51] Follow up costs for survivors of ischemic stroke came from a systematic review of patient-level costs of major cardiovascular conditions.[24] For hemorrhagic stroke, the cost came from a retrospective study of out-patient costs after first time stroke survival. In this study, costs were

based Medicare reimbursement rates, which are nationally representative of the cost of care.[52] The cost annual cost of diabetes[54] came from a study looking at the economic burden of diabetes in the US. For myopathy[53] the cost came from a study that examined costs among patients with neuromuscular diseases in the US using medical claims data.

Recurrent CAD, ischemic stroke, and hemorrhagic stroke

Patients that survive acute CAD or stroke are at increased risk of recurrent acute CAD or stroke. In the model, we used a 5.3% risk of recurrent acute CAD within the first year among those that survived the first acute CAD event.[71] After the first year, patients remained at high risk although the risk was less than that in the first year. Patients that survived ischemic or hemorrhagic stroke also have an increased risk of recurrent stroke of 6.6% in the first year.[72] After the first year, we assumed a constant annual risk of recurrent CAD or stroke of 0.56%, estimated from a lifetime risk of 20% for a 40 year old individual in the US. The cost of recurrent events was categorized into two (first year after the event occurred, follow up years). We estimated the cost of recurrent events was equal to the product of the probability of an event occurring and the cost of treatment for the event.

Table S1: Age specific annual probability of death

Age	Baseline value	Lower bound value	Upper bound value
40	0.0020	0.0015	0.0024
41	0.0021	0.0015	0.0026
42	0.0022	0.0016	0.0027
43	0.0023	0.0017	0.0029
44	0.0025	0.0019	0.0031
45	0.0027	0.0020	0.0033
46	0.0029	0.0022	0.0036
47	0.0031	0.0023	0.0039
48	0.0034	0.0025	0.0042
49	0.0037	0.0028	0.0046
50	0.0041	0.0030	0.0051
51	0.0044	0.0033	0.0055
52	0.0048	0.0036	0.0061
53	0.0053	0.0040	0.0066
54	0.0058	0.0043	0.0072
55	0.0063	0.0047	0.0079
56	0.0068	0.0051	0.0085
57	0.0074	0.0056	0.0092
58	0.0080	0.0060	0.0100
59	0.0086	0.0064	0.0107
60	0.0092	0.0069	0.0115
61	0.0099	0.0074	0.0124
62	0.0106	0.0080	0.0133
63	0.0113	0.0085	0.0142
64	0.0121	0.0091	0.0151
65	0.0129	0.0097	0.0162
66	0.0139	0.0105	0.0174
67	0.0150	0.0113	0.0187
68	0.0162	0.0122	0.0202
69	0.0175	0.0132	0.0219
70	0.0191	0.0144	0.0238
71	0.0209	0.0157	0.0260
72	0.0229	0.0172	0.0285
73	0.0250	0.0188	0.0312
74	0.0275	0.0207	0.0342
75	0.0303	0.0228	0.0377
76	0.0336	0.0253	0.0418
77	0.0372	0.0280	0.0463

78	0.0411	0.0310	0.0511
79	0.0455	0.0343	0.0565
80	0.0505	0.0381	0.0627
81	0.0563	0.0425	0.0699
82	0.0627	0.0474	0.0778
83	0.0697	0.0527	0.0863
84	0.0774	0.0587	0.0958
85	0.0861	0.0653	0.1065
86	0.0960	0.0729	0.1185
87	0.1071	0.0815	0.1321
88	0.1196	0.0911	0.1472
89	0.1334	0.1018	0.1639
90	0.1486	0.1137	0.1822
91	0.1650	0.1265	0.2019
92	0.1827	0.1404	0.2229
93	0.2016	0.1554	0.2453
94	0.2216	0.1713	0.2689
95	0.2416	0.1873	0.2923
96	0.2613	0.2032	0.3151
97	0.2802	0.2185	0.3370
98	0.2980	0.2331	0.3574
99	0.3142	0.2464	0.3759
100	0.3314	0.2606	0.3954

Table S2: CHEERS Checklist

Section/item	Item No.	Recommendation	Reported on page No./ line No.
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as ‘‘cost-effectiveness analysis’’, and describe the interventions compared.	Title page
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	Abstract page
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Pages 1 – 2
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analyzed, including why they were chosen.	Page 3
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Page 2
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 3
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 3
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 3
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 3
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 2
Measurement of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Page 2 Supplementary material page 2

	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A
Measurement and valuation of preference based outcome	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Page 4-6 Supplementary material, page 11-12
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 3 Supplementary material, page 2, 3
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Page 2, 29 Supplementary material, page 1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Supplementary material, page 1-12
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for	Supplementary material, page 1-12

		handling population heterogeneity and uncertainty.	
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Page 4, 5; 25-27 Supplementary material, page 1-12
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Page 9, 28
Characterizing uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	N/A
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Page 9-11, Supplementary material, page 21-29
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	Page 9 - 15
Other			

Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	N/A
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Conflicts of interest stated

Abbreviations: N/A = Not Applicable

CHEERS Checklist: Items to include when reporting economic evaluations of health interventions.

The ISPOR CHEERS Task Force Report, Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the Value in Health or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage:

http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Citation: Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50

Table S3: Breakdown total and incremental costs by time horizon (costs, 2019 US$)

Cost Component	5 years			10 Years		
	PCE	**PCE+CAD-PRS**	**Incremental Cost**	**PCE**	**PCE+CAD-PRS**	**Incremental Cost**
CAD	1,509.93	1,283.08	(226.85)	3,325.23	2,845.88	(479.35)
Ischemic Stroke	256.42	239.26	(17.16)	633.10	595.16	(37.95)
CAD and Ischemic Stroke	3.43	3.01	(0.42)	23.28	20.50	(2.78)
Myopathy and CAD/Ischemic Stroke	0.02	0.07	0.05	0.13	0.39	0.26
Hemorrhagic Stroke and CAD/Ischemic Stroke	0.08	0.23	0.15	0.36	1.08	0.72
Diabetes and CAD/Ischemic Stroke	0.71	2.10	1.39	3.39	10.08	6.69
Myopathy	0.76	2.26	1.49	2.46	7.34	4.87
Hemorrhagic Stroke	1.16	3.45	2.29	2.61	7.79	5.18
Diabetes	6.43	19.05	12.62	19.59	58.35	38.76
Primary Care Visit	-	23.63	23.63	-	23.63	23.63
Background Health Care	27,136.43	27,166.71	30.28	45,641.77	45,743.16	101.38
Statins	16.67	49.51	32.83	29.03	86.84	57.81
PRS Testing	-	100.00	100.00	-	100.00	100.00
Total	**28,932**	**28,892**	**(40)**	**49,681**	**49,500**	**(181)**

Abbreviations: PCE = pooled cohort equation; PRS = polygenic risk score; CAD = coronary artery disease

Results for the scenario analysis

Table S4: Cost-effectiveness results with impact of age on CAD and ischemic stroke risk* (costs, 2019 US$)

Cohort Age	Time Horizon	Strategy	Mean cost	Incremental Cost	QALYs	QALYs gained	ICER
40	5 years	PCE-alone	29,005.47		4.556		
		PCE+CAD-PRS	28,955.35	(50.11)	4.559	0.003	Dominant
	10 years	PCE-alone	49,974.40		8.307		
		PCE+CAD-PRS	49,756.61	(217.79)	8.318	0.011	Dominant
	Lifetime	PCE-alone	123,028.23		20.197		
		PCE+CAD-PRS	122,989.49	(38.75)	20.268	0.071	Dominant
50	5 years	PCE-alone	29,424.62		4.519		
		PCE+CAD-PRS	29,307.39	(117.23)	4.523	0.004	Dominant
	10 years	PCE-alone	50,413.17		8.161		
		PCE+CAD-PRS	50,091.09	(322.08)	8.175	0.015	Dominant
	Lifetime	PCE-alone	108,320.36		17.572		
		PCE+CAD-PRS	108,267.35	(53.01)	17.619	0.048	Dominant

PCE = pooled cohort equation; PRS = polygenic risk score; QALYs = quality adjusted life years; CAD = coronary artery disease
ICER = Incremental cost-effectiveness ratio

*The risk varied by cohort start age

Table S4 shows mean costs and QALYs per strategy with incremental costs and QALYs gained when we apply a 3.5% annual increase in the baseline risk of CAD and double the risk of ischemic stroke every decade after age 55. In all the time horizons and start age of the cohort, PCE+CAD-PRS was dominant compared to PCE-alone. Beyond age 60 of the cohort, PCE+CAD-PRS is not cost-effective because the risk of CAD among individuals is high enough to be identified by PCE-alone.

Table S5: Cost-effectiveness results with impact of age on CAD and ischemic stroke risk* (costs, 2019 US$)

Cohort Age	Time Horizon	Strategy	Cost	Incremental Cost	QALYs	QALYs gained	ICER
40	5 years	PCE-alone	29,005.47		4.556		
		PCE+CAD-PRS	28,955.35	(50.11)	4.559	0.003	Dominant
	10 years	PCE-alone	49,974.40		8.307		
		PCE+CAD-PRS	49,756.61	(217.79)	8.318	0.011	Dominant
	Lifetime	PCE-alone	122,645.21		20.252		
		PCE+CAD-PRS	122,489.21	(156.00)	20.334	0.082	Dominant
50	5 years	PCE-alone	29,009.92		4.525		
		PCE+CAD-PRS	28,951.06	(58.86)	4.529	0.003	Dominant
	10 years	PCE-alone	49,678.65		8.183		
		PCE+CAD-PRS	49,447.22	(231.43)	8.195	0.012	Dominant
	Lifetime	PCE-alone	107,593.54		17.678		
		PCE+CAD-PRS	107,350.08	(243.45)	17.743	0.065	Dominant
60	5 years	PCE-alone	29,039.21		4.458		
		PCE+CAD-PRS	28,953.53	(85.68)	4.461	0.004	Dominant
	10 years	PCE-alone	49,101.12		7.930		
		PCE+CAD-PRS	48,834.93	(266.19)	7.943	0.013	Dominant
	Lifetime	PCE-alone	89,710.49		14.573		
		PCE+CAD-PRS	89,401.79	(308.70)	14.621	0.048	Dominant
70	5 years	PCE-alone	28,901.37		4.322		
		PCE+CAD-PRS	28,782.82	(118.55)	4.326	0.004	Dominant
	10 years	PCE-alone	47,143.14		7.390		
		PCE+CAD-PRS	46,850.46	(292.68)	7.404	0.014	Dominant
	Lifetime	PCE-alone	68,794.57		10.966		
		PCE+CAD-PRS	68,480.57	(314.00)	10.998	0.032	Dominant

PCE = pooled cohort equation; PRS = polygenic risk score; QALYs = quality adjusted life years; CAD = coronary artery disease
ICER = Incremental cost-effectiveness ratio

*The risk was assumed to be the same per cohort start age

Table S5 shows mean costs and QALYs per strategy with incremental costs and QALYs gained when we double the risk of ischemic stroke every decade after age 55 and apply a 3.5% annual increase in the baseline risk of CAD with each start age having the same baseline risk. PCE+CAD-PRS was dominant compared to PCE-alone in all time horizons.

Table S6: Cost-effectiveness results after including high risk individuals in the bottom 80% of CAD-PRS distribution, (costs, 2019 US$)

Cohort Age	Time Horizon	Strategy	Cost	Incremental Cost	QALYs	QALYs gained	ICER
40	5 years	PCE-alone	32,729.62		4.498		
		PCE+CAD-PRS	32,689.92	(39.70)	4.501	0.003	Dominant
	10 years	PCE-alone	57,577.06		8.095		
		PCE+CAD-PRS	57,396.28	(180.78)	8.105	0.011	Dominant

PCE = pooled cohort equation; PRS = polygenic risk score; QALYs = quality adjusted life years; CAD = coronary artery disease
ICER = Incremental cost-effectiveness ratio

Table S6 shows cost-effectiveness results when the model accounts for individuals in the bottom 80% of the CAD-PRS distribution who may be at high risk due to other risk enhancing factors identified by PCE than high CAD-PRS. Although mean costs are higher and QALYs are lower in this scenario, the incremental costs and QALYs gained are comparable to the base case results since all individuals identified by PCE-alone are also identified by PCE+CAD-PRS.

Table S7: Cost-effectiveness results after restricting PRS testing to only individuals without other risk enhancing factors, (costs, 2019 US$)

Cohort Age	Time Horizon	Strategy	Cost	Incremental Cost	QALYs	QALYs gained	ICER
40	5 years	PCE-alone	32,334.76		4.504		
		PCE+CAD-PRS	32,244.54	(90.22)	4.507	0.003	Dominant
	10 years	PCE-alone	56,751.96		8.117		
		PCE+CAD-PRS	56,522.28	(229.68)	8.128	0.011	Dominant

PCE = pooled cohort equation; PRS = polygenic risk score; QALYs = quality adjusted life years; CAD = coronary artery disease
ICER = Incremental cost-effectiveness ratio

Table S7 shows cost-effectiveness results when the model performs PRS testing only on individuals without other risk enhancing factors who would otherwise be identified by PCE-alone. In this scenario, PCE+CAD-PRS was more cost-saving compared to the base case analysis, implying that restricting PRS testing to only those that need it would improve the efficiency of CAD-PRS.

Table S8: Cost-effectiveness results at different percentages of individuals in the top quintile of the CAD-PRS distribution and increase in risk of CAD – Comparison of PCE+CAD-PRS and PCE-alone, (costs, 2019 US$)

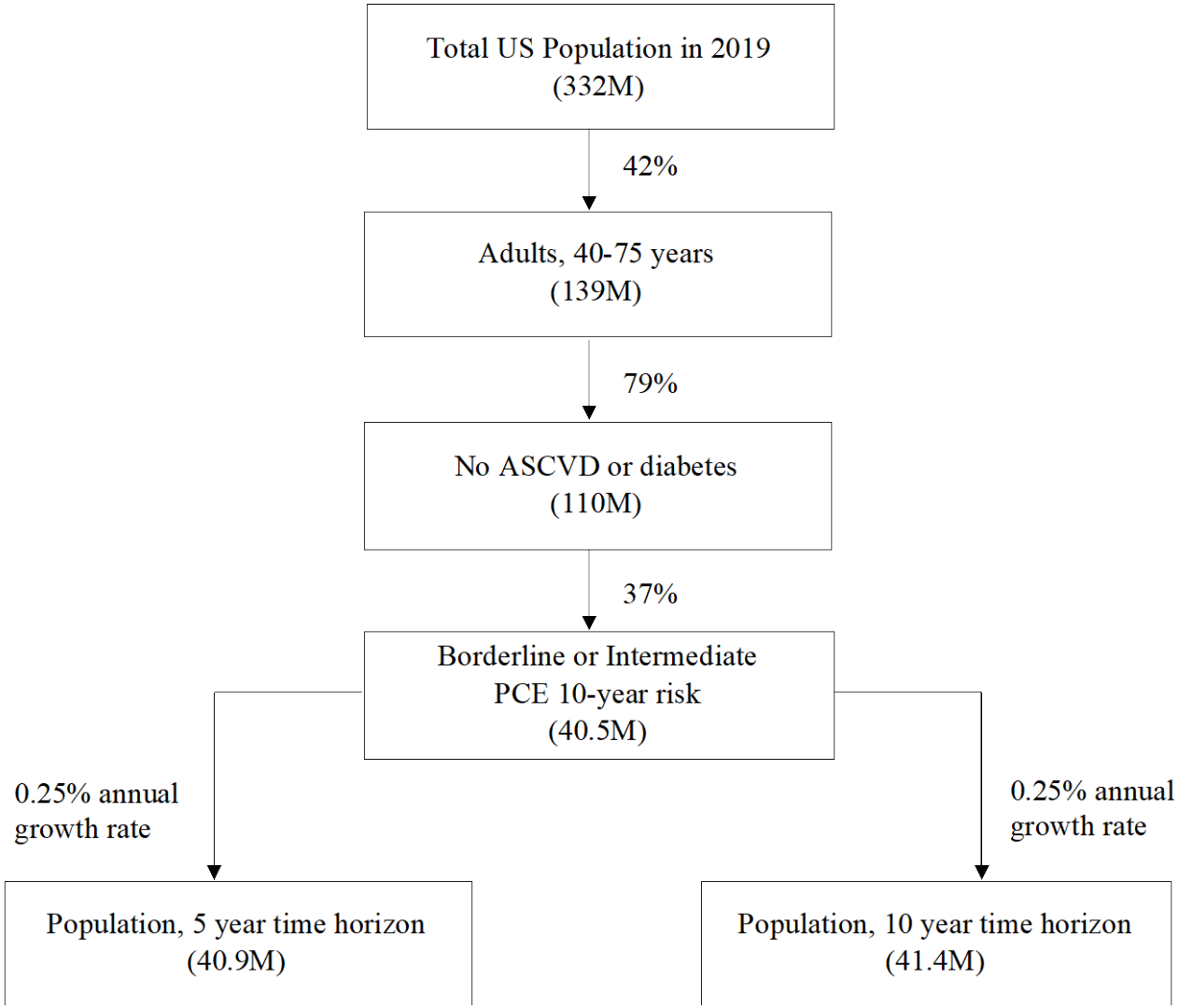
Top 20% CAD-PRS; Risk Increase	Time Horizon	Strategy	Cost	Incremental Cost	QALYs	QALYs gained	ICER
Baseline: 17; 1.9	5 years	PCE-alone	28,932.00		4.556		
		PCE+CAD-PRS	28,892.00	(40.00)	4.559	0.003	Dominant
	10 years	PCE-alone	49,681.00		8.313		
		PCE+CAD-PRS	49,500.00	(181.00)	8.323	0.010	Dominant
17; 2.5	5 years	PCE-alone	29,305.48		4.551		
		PCE+CAD-PRS	29,212.45	(93.03)	4.554	0.004	Dominant
	10 years	PCE-alone	50,380.04		8.292		
		PCE+CAD-PRS	50,109.12	(270.92)	8.305	0.013	Dominant
17; 3.0	5 years	PCE-alone	29,609.19		4.546		
		PCE+CAD-PRS	29,473.77	(135.42)	4.550	0.004	Dominant
	10 years	PCE-alone	50,932.96		8.275		
		PCE+CAD-PRS	50,594.57	(338.39)	8.291	0.016	Dominant
20; 1.9	5 years	PCE-alone	29,222.91		4.552		
		PCE+CAD-PRS	29,156.20	(66.71)	4.555	0.004	Dominant
	10 years	PCE-alone	50,283.86		8.296		
		PCE+CAD-PRS	50,048.81	(35.06)	8.309	0.013	Dominant
20; 2.5	5 years	PCE-alone	29,668.53		4.545		
		PCE+CAD-PRS	29,538.18	(130.35)	4.549	0.005	Dominant
	10 years	PCE-alone	51,118.08		8.271		
		PCE+CAD-PRS	50,775.46	(342.63)	8.287	0.016	Dominant
20; 3.0	5 years	PCE-alone	30,030.95		4.539		
		PCE+CAD-PRS	29,850.02	(180.93)	4.545	0.005	Dominant
	10 years	PCE-alone	51,777.90		8.251		
		PCE+CAD-PRS	51,354.75	(423.14)	8.270	0.019	Dominant

25; 1.9	5 years	PCE-alone	29,671.76		4.545		
		PCE+CAD-PRS	29,563.37	(108.38)	4.549	0.004	Dominant
	10 years	PCE-alone	51,214.26		8.270		
		PCE+CAD-PRS	50,895.44	(318.82)	8.286	0.016	Dominant
25; 2.5	5 years	PCE-alone	30,228.78		4.536		
		PCE+CAD-PRS	30,040.85	(187.93)	4.542	0.006	Dominant
	10 years	PCE-alone	52,257.04		8.239		
		PCE+CAD-PRS	51,803.76	(453.28)	8.259	0.020	Dominant
25; 3.0	5 years	PCE-alone	30,681.81		4.529		
		PCE+CAD-PRS	30,430.65	(251.16)	4.536	0.007	Dominant
	10 years	PCE-alone	53,081.80		8.214		
		PCE+CAD-PRS	52,527.87	(553.93)	8.237	0.023	Dominant

PCE = pooled cohort equation; PRS = polygenic risk score; QALYs = quality adjusted life years; CAD = coronary artery disease
ICER = Incremental cost-effectiveness ratio

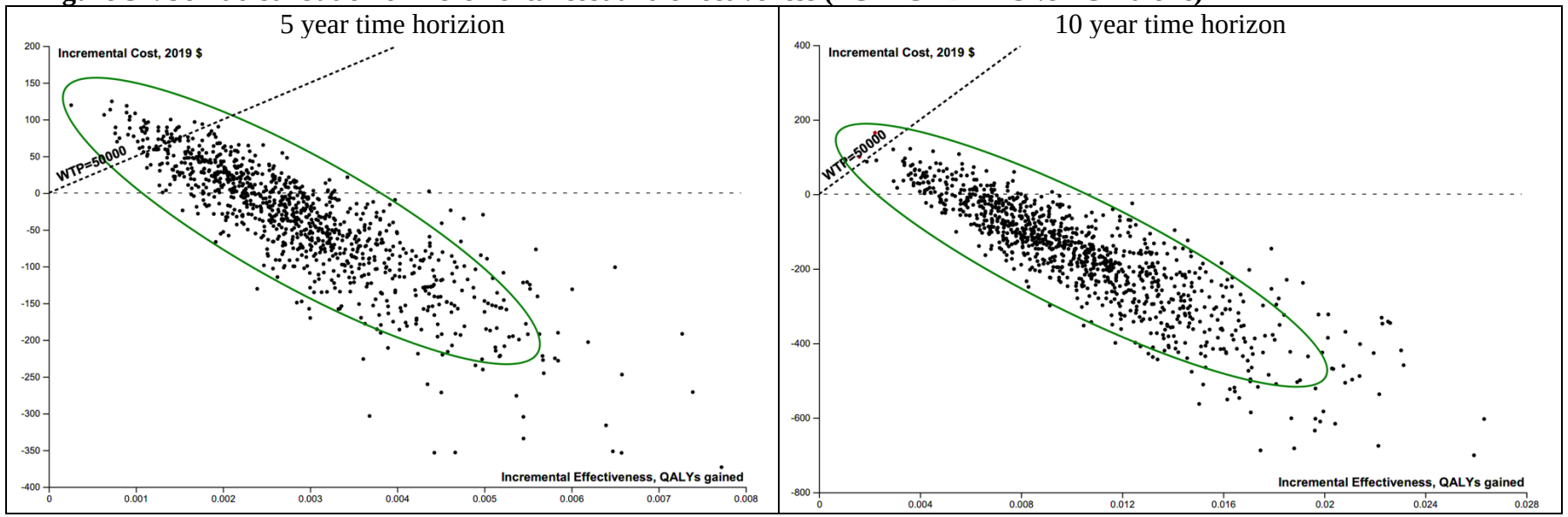
Table S8 shows variation in mean costs and QALYs per strategy, incremental costs and QALYs gained by the percentage of individuals in the top quintile of the CAD-PRS distribution and the increase in the risk of CAD among those in the top quintile of the CAD-PRS distribution. In all the scenarios, PCE+CAD-PRS was dominant compared to PCE-alone. Cost-savings increased with more individuals identified in the top quintile of the CAD-PRS distribution and higher odds of developing CAD.

Figure S1: Target population for expected value of perfect information analysis



Abbreviations: ASCVD = atherosclerotic cardiovascular disease; PCE = pooled cohort equation; M = millions

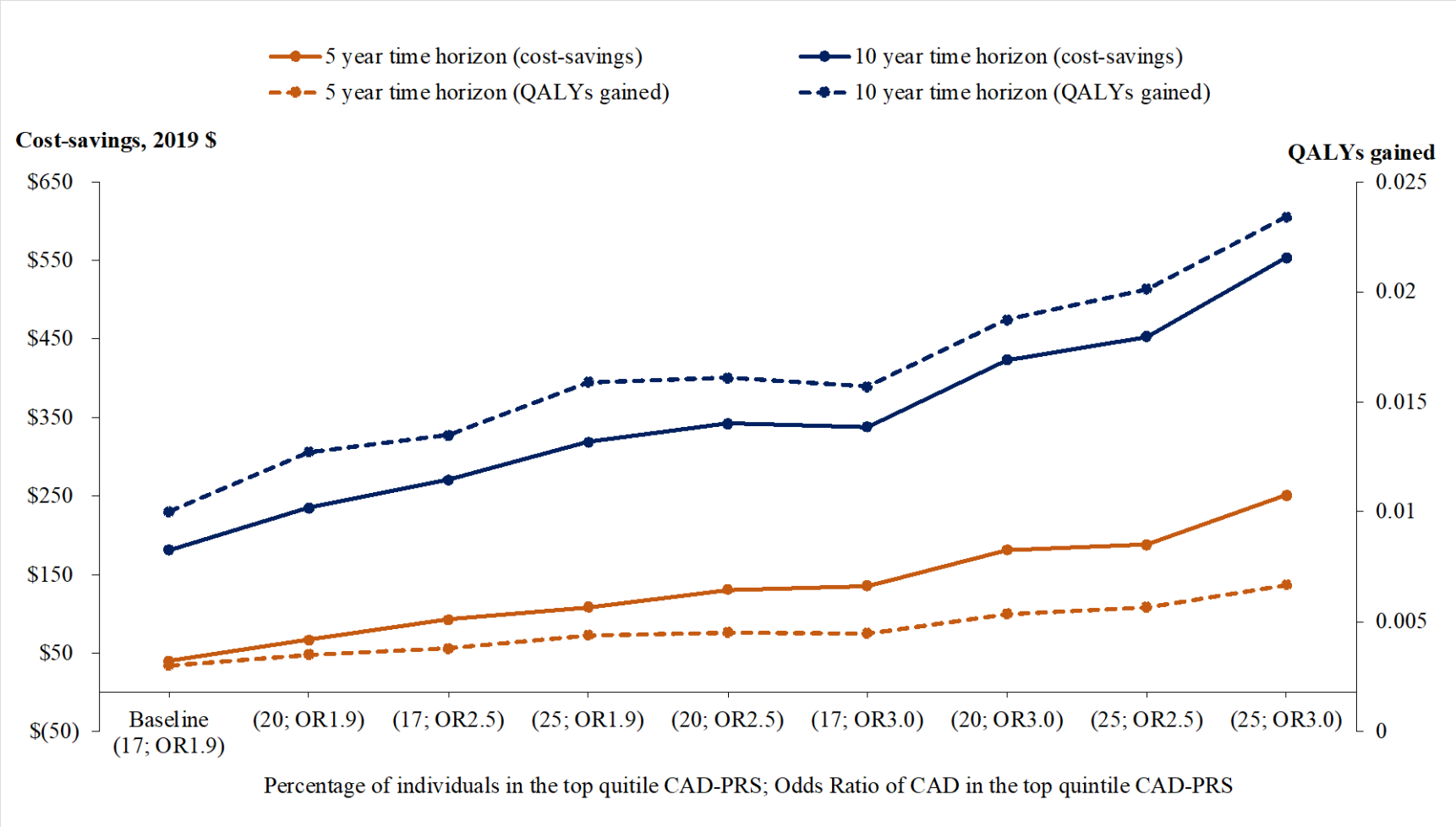
Figure S2: Joint distribution of incremental cost and effectiveness (PCE+CAD-PRS vs PCE-alone)



PCE = pooled cohort equation; PRS = polygenic risk score; CAD = coronary artery disease; QALYs = quality adjusted life years

Figure S2 shows results of the joint distribution of incremental effectiveness (QALY gained) and incremental costs on the cost-effectiveness plane for the 5 year and 10 year time horizon. From figure S2, almost all the distributions are below the WTP threshold of $50,000 and in the southeast quadrant, indicating that PCE+CAD-PRS was more likely to be effective and cost-saving compared to PCE-alone.

Figure S3: Cost-savings and QALYs gained at different percentages of individuals in the top quintile of the CAD-PRS distribution and increase in risk of CAD – Comparison of PCE+CAD-PRS and PCE-alone



PCE = pooled cohort equation; PRS = polygenic risk score; CAD = coronary artery disease; OR = Odds Ratio; QALYs = quality adjusted life years

Figure S3 shows cost-savings and QALYs gained per person screened by implementing PCE+CAD-PRS vs PCE-alone at different percentages of individuals in the top quintile of the CAD-PRS distribution and odds of developing CAD. PCE+CAD-PRS was more cost-saving with higher QALYs gained when 25% of individuals are in the top quintile with 3.0 increased odds of developing CAD.