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$)

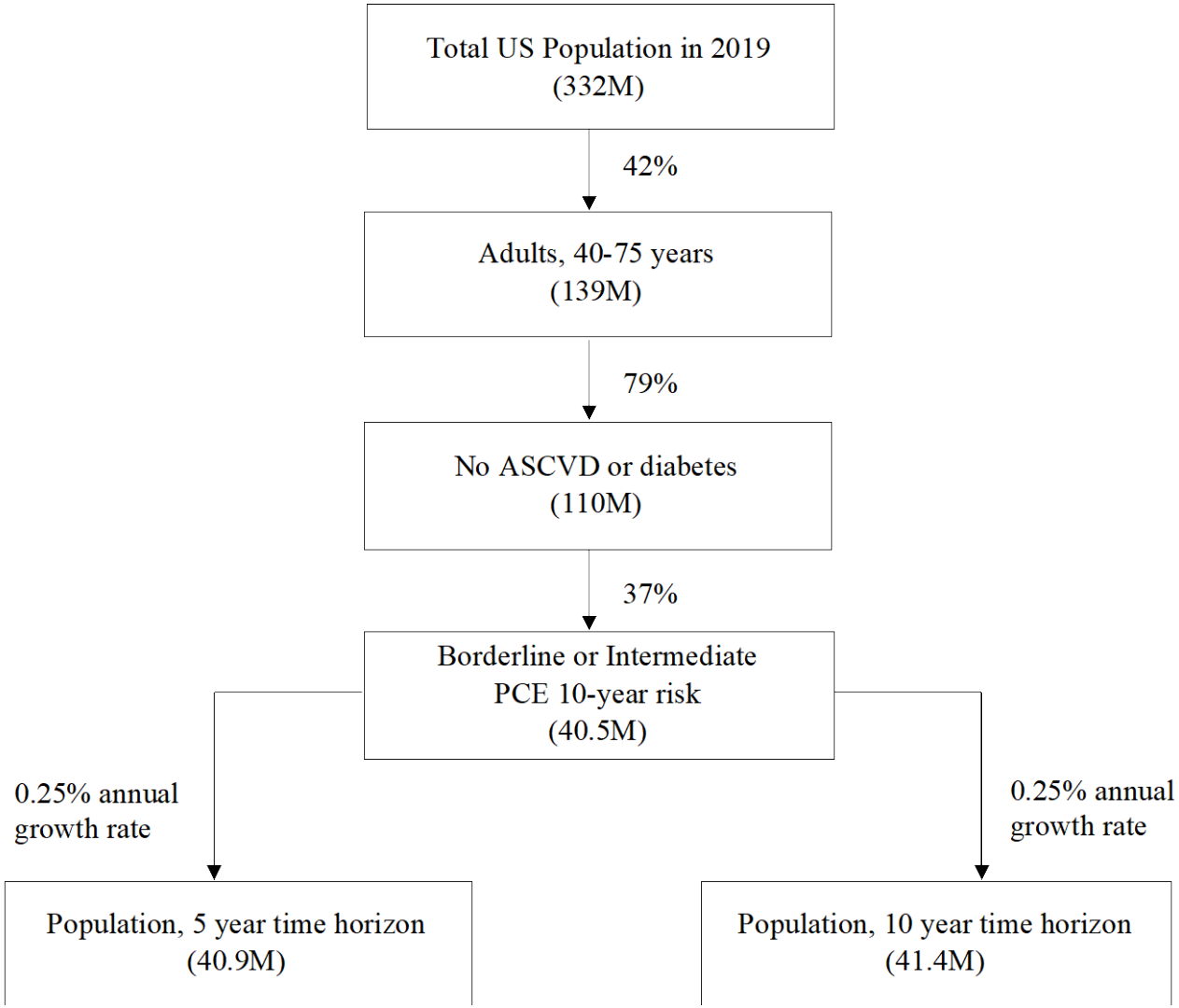
Top 20% CAD-PRS; Risk Increase	Time Horizon	Strategy	Cost	Incremental Cost	QALYs	QALYs gained	ICER
Baseline: 17; 1.9	5 years	PCE-alone	28,932.00		4.556		
		PCE+CAD-PRS	28,892.00	(40.00)	4.559	0.003	Dominant
	10 years	PCE-alone	49,681.00		8.313		
		PCE+CAD-PRS	49,500.00	(181.00)	8.323	0.010	Dominant
17; 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

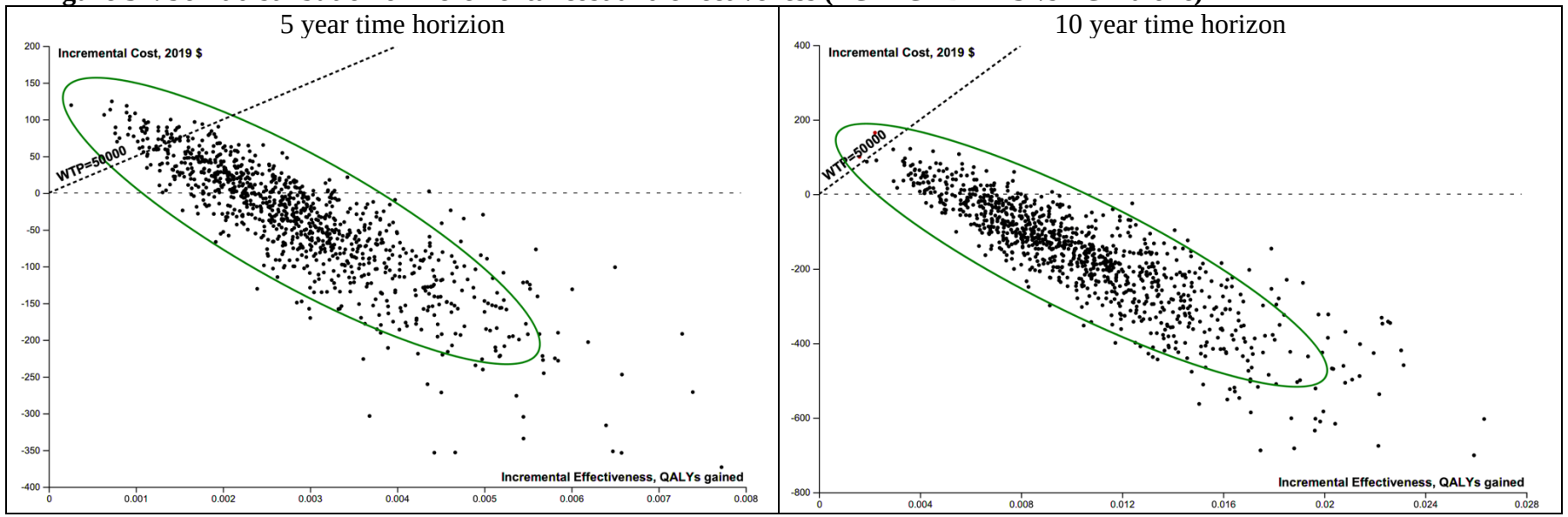
Table S8 shows variation in mean costs and QALYs per strategy, incremental costs and QALYs gained by the percentage of individuals in the top quintile of the CAD-PRS distribution and the increase in the risk of CAD among those in the top quintile of the CAD-PRS distribution. In all the scenarios, PCE+CAD-PRS 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

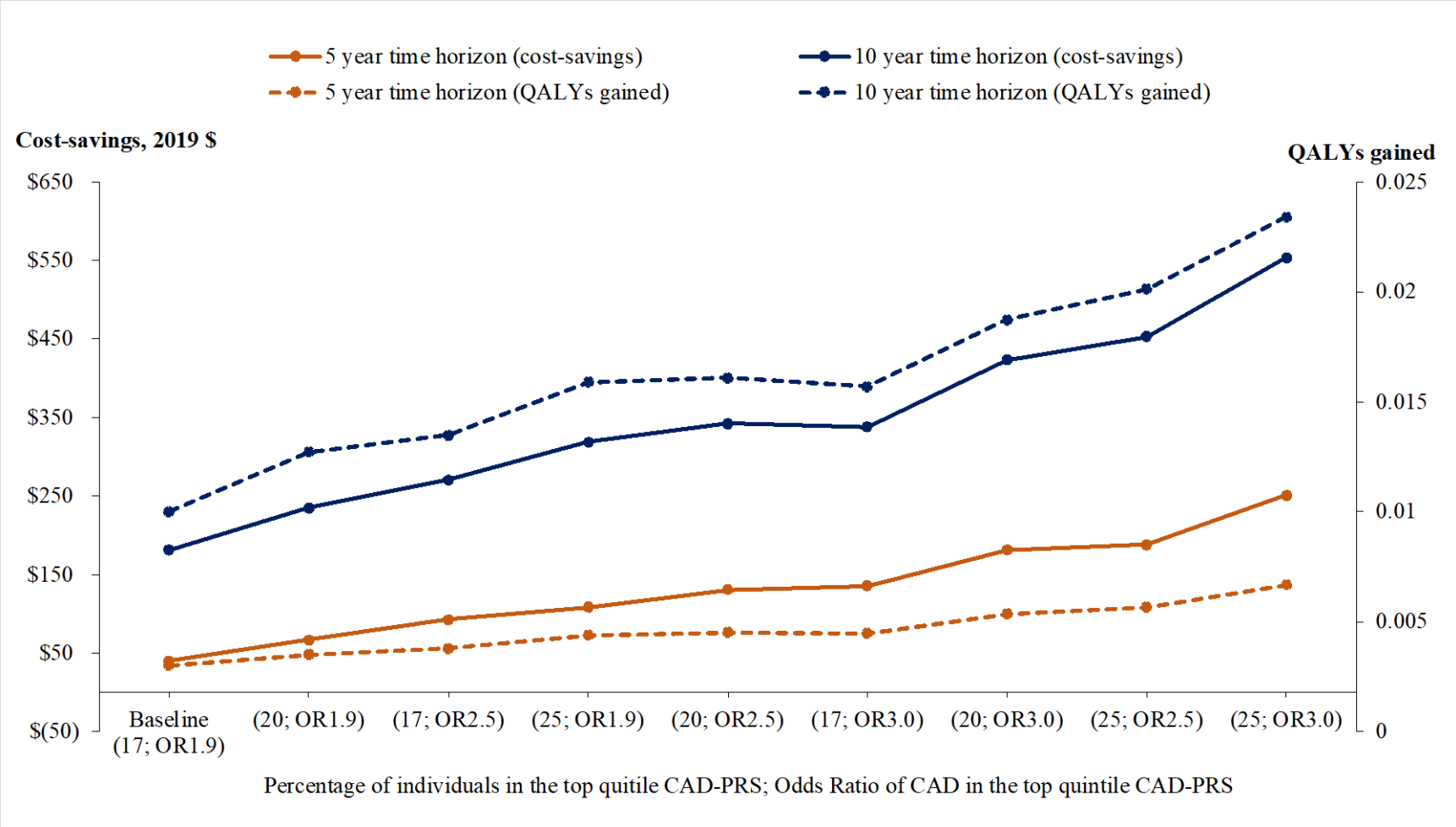
Figure S2: Joint distribution of incremental cost and effectiveness (PCE+CAD-PRS vs PCE-alone)



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.