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ORIGINAL ARTICLE

Cardiovascular Genetic Risk Testing for Targeting Statin Therapy in the Primary Prevention of Atherosclerotic Cardiovascular Disease

A Cost-Effectiveness Analysis

See Editorial by Pandya

Jamie Jarmul, PhD
Mark J. Pletcher, MD, MPH
Kristen Hassmiller Lich, PhD
Stephanie B. Wheeler, PhD, MPH
Morris Weinberger, PhD
Christy L. Avery, PhD
Daniel E. Jonas, MD, MPH
Stephanie Earnshaw, PhD
Michael Pignone, MD, MPH

BACKGROUND: It is unclear whether testing for novel risk factors, such as a cardiovascular genetic risk score (cGRS), improves clinical decision making or health outcomes when used for targeting statin initiation in the primary prevention of atherosclerotic cardiovascular disease (ASCVD). Our objective was to estimate the cost-effectiveness of cGRS testing to inform clinical decision making about statin initiation in individuals with low-to-intermediate (2.5%–7.5%) 10-year predicted risk of ASCVD.

METHODS AND RESULTS: We evaluated the cost-effectiveness of testing for a 27-single-nucleotide polymorphism cGRS comparing 4 test/treat strategies: treat all, treat none, test/treat if cGRS is high, and test/treat if cGRS is intermediate or high. We tested a set of clinical scenarios of men and women, aged 45 to 65 years, with 10-year ASCVD risks between 2.5% and 7.5%. Our primary outcome measure was cost per quality-adjusted life-year gained. Under base case assumptions for statin disutility and cost, the preferred strategy is to treat all patients with ASCVD risk >2.5% without cGRS testing. For certain clinical scenarios, such as a 57-year-old man with a 10-year ASCVD risk of 7.5%, cGRS testing can be cost-effective under a limited set of assumptions; for example, when statins cost $15 per month and statin disutility is 0.013 (ie, willing to trade 3 months of life in perfect health to avoid 20 years of statin therapy), the preferred strategy (using a willingness-to-pay threshold of $50 000 per quality-adjusted life-year gained) is to test and treat if cGRS is intermediate or high. Overall, the results were not sensitive to assumptions about statin efficacy and harms.

CONCLUSIONS: Testing for a 27-single-nucleotide polymorphism cGRS is generally not a cost-effective approach for targeting statin therapy in the primary prevention of ASCVD for low- to intermediate-risk patients.

Key Words: cardiovascular disease ■ clinical decision making ■ genetic testing ■ quality-adjusted life-year ■ risk factors

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WHAT IS KNOWN

- Cardiovascular genetic risk testing provides the opportunity to more precisely identify individuals at high risk for developing atherosclerotic cardiovascular disease.
- It is unclear whether cardiovascular genetic risk score testing produces important differences in clinical decision making regarding statin initiation or ultimately improves cardiovascular outcomes.
- Clinical decision analysis and cost-effectiveness modeling can be used to explicitly compare alternative clinical options regarding their relative downstream risks, benefits, and costs.

WHAT THE STUDY ADDS

- Testing for a 27-single-nucleotide polymorphism cardiovascular genetic risk score is generally not a cost-effective approach for targeting statin therapy in the primary prevention of atherosclerotic cardiovascular disease for low- to intermediate-risk patients.
- The cost-effectiveness of cardiovascular genetic risk score testing is sensitive to assumptions about statin disutility and statin cost, age, sex, 10-year atherosclerotic cardiovascular disease risk, and willingness-to-pay threshold.

Over 1.2 million Americans experience a first atherosclerotic cardiovascular disease (ASCVD) event (myocardial infarction [MI], coronary heart disease death, or stroke) every year.[1] Statins, a group of highly efficacious lipid-lowering agents, significantly reduce the risk of MI, stroke, and coronary heart disease (CHD) death and are recommended as preventive therapy in nondiabetic, ASCVD-free individuals who have a 10-year predicted ASCVD risk (calculated using the pooled cohort equations) ≥7.5%.[2,3] However, the pooled cohort equations alone may not be optimal for guiding statin treatment decisions in individuals close to the 7.5% treatment threshold, given the wide variance inherent in individual-level risk estimates and variation in patient preferences for daily medication use.[4–7] Furthermore, the 7.5% threshold is based on expert opinion, rather than evidence from cost-effectiveness analyses.[2]

Apart from the 7.5% threshold, the 2013 American College of Cardiology/American Heart Association guidelines on ASCVD risk reduction suggest testing for nontraditional risk factors—such as coronary artery calcium (CAC), ankle–brachial index, and high-sensitivity C-reactive protein—to provide information about other aspects of risk not covered by traditional risk factors, such as atherosclerotic burden or vessel reactivity, and to assist clinicians and patients during shared decision making about statin initiation.[3] Although there is no consensus on which nontraditional risk factors are most clinically useful or how to interpret risk factor test results in the context of existing ASCVD-predicted risk estimates, decision modeling can be used to help determine clinical utility of testing for new nontraditional risk factors such as CAC.[8,9]

Cardiovascular genetic risk testing provides the opportunity to more precisely identify individuals at high risk for developing ASCVD for whom preventive therapy, such as statins, can be directed.[10–16] An individual's cardiovascular genetic risk score (cGRS) may reflect genetic susceptibility to accelerated atherosclerosis potentially related to errors in cholesterol metabolism, thrombosis, and other endothelium-related factors.[17] In 2015, Mega et al[18] demonstrated a significant, independent association between a 27-single-nucleotide polymorphism (SNP) cGRS and cardiovascular disease outcomes after accounting for traditional ASCVD risk factors. However, it is unclear whether its impact on predicted risk produces important differences in clinical decision making regarding statin initiation or ultimately improves cardiovascular outcomes.[10–16]

In the absence of large, generalizable randomized controlled trials comparing clinical management with and without additional testing for novel risk factors, clinical decision analysis and cost-effectiveness or cost-utility modeling can be used to explicitly compare alternative clinical options regarding their relative downstream risks, benefits, and costs.[8,19,20] In this study, we used modeling to evaluate the clinical utility and cost-effectiveness of cGRS testing for targeting statin therapy in the primary prevention of ASCVD.

METHODS

The cost-effectiveness model described below will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. However, the structure, inputs, and assumptions of the model have been described in sufficient detail both here and in previous publications for interested analysts to reproduce the model. Because of the nature of this study, an institutional review board approval was waived.

Overview and Model Structure

The UNC-RTI CHD Prevention Model is a state-transition Markov model that can be used to compare incidence of ASCVD events, mortality, quality of life, and costs with and without a prevention intervention, such as aspirin or statin therapy, for specific clinical scenarios over a lifetime horizon. A detailed description of the model and validation has been published elsewhere.[8,21–24] Briefly, a specific clinical scenario is defined by age, sex, and ASCVD risk factors, including systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, smoking status, and antihypertensive medication use (Appendix A in the Data Supplement). A cohort of 10 000 individuals with defined characteristics begins in the healthy state and then transitions every 12 months as described in Figure 1A. Myopathy, angina, MI, and stroke are modeled as separate health states. Costs, quality of life, and mortality rates differ in each state. The probabilities of transitioning

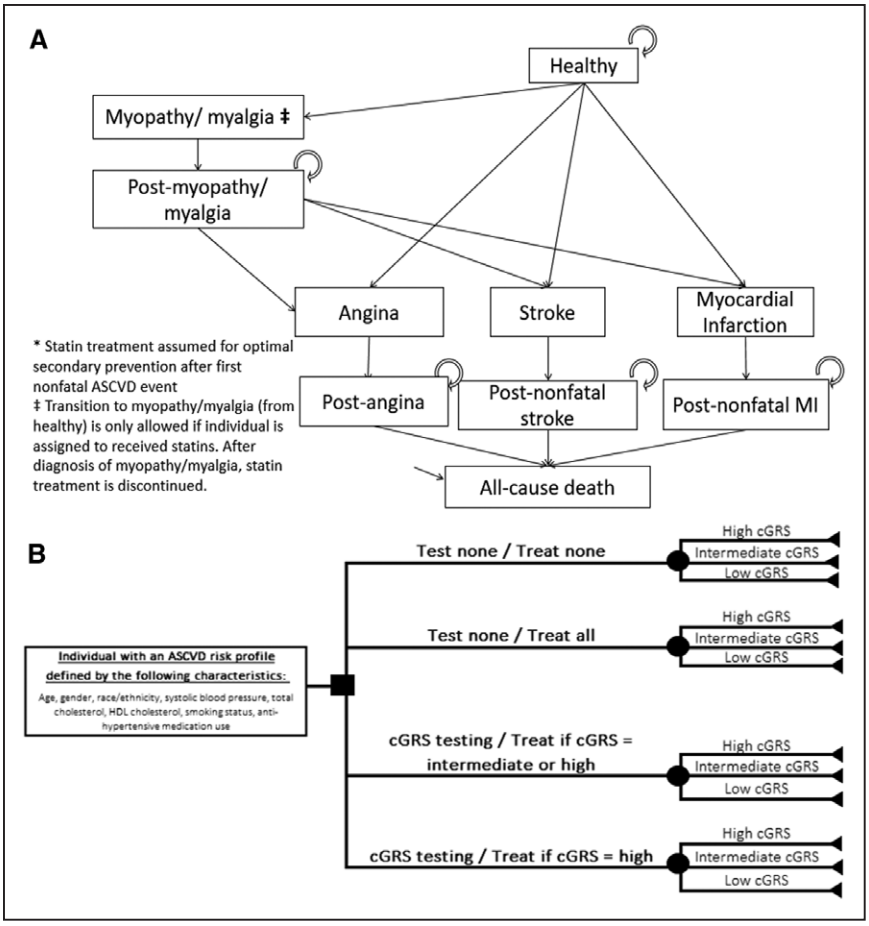

Figure 1. Model design, including diagram of health states for Markov state-transition model (A) and decision tree for test/treat intervention options (B).
ASCVD indicates atherosclerotic cardiovascular disease; cGRS, cardiovascular genetic risk score; and MI, myocardial infarction.

from healthy to angina, MI, and stroke are determined by the Framingham risk models for each of those health states (Appendix F in the Data Supplement; Tables 2 through 4).[25]

We updated the UNC-RTI CHD Prevention Model to include cGRS testing strategies. Specifically, we used the model to compare 4 different interventions:

1. Two strategies where statin prescribing does not depend on results of cGRS testing (treat none and treat all) and
2. Two strategies for which a cGRS test is ordered and statins are prescribed only if the cGRS is above a threshold (treat if cGRS is intermediate or high and treat if cGRS is high; Figure 1B).

Statin prescribing was assumed to be differential for 10 years, but cumulative costs and quality-adjusted life-years (QALYs) were simulated across a full lifetime horizon to fully account for the consequences of a life saved or MI prevented by statins during those first 10 years of differential treatment. We assumed that after 10 years, most individuals have increased enough in risk that the decision about initiating statin treatment would no longer depend on the baseline risk or results of genetic testing. Thus, after 10 years, all individuals are assumed to be on statins for primary prevention, if not already on statins for secondary prevention. We have previously used these methods to model cost-effectiveness of CAC scanning.[8,21–24]

Our primary outcomes were ASCVD events, life-years, QALYs, costs, and the incremental cost-effectiveness ratio measured in cost per QALY gained. Life-years, QALYs, and costs were discounted at 3% per annum. We identified preferred strategies under the assumption that society is willing to pay ≤$50 000 per QALY gained. Our secondary outcome measures were (1) net benefit (in QALYs) defined as the balance of benefits and harms for a strategy over the lifetime horizon at a willingness-to-pay (WTP) threshold of <$50 000 per QALY and (2) gain in QALYs.

cGRS Testing Parameters

Costs for genetic risk testing vary based on the number of SNPs genotyped and the laboratory at which the genotyping is performed.[26] We assumed, based on expert opinion, a base case cost of $100 but varied the cost between $1 and $1000 in sensitivity analyses.[27] We also added the cost of one physician visit to discuss cGRS test results with patients.

For each of our base case clinical scenarios, we accounted for the expected distribution of cGRS using a prediction model derived from Add Health data to estimate the proportion of scores falling into categories of low risk, intermediate risk, and high risk, using methods described previously.[28,29] The expected distribution of cGRS was not associated with the other ASCVD risk factors. We then estimated posttest risk for angina, MI, and CHD death in these categories using cGRS-specific relative risks and previously described methods (Appendix F in the Data Supplement; Tables 1 through 4).[18,29,30] We assumed that the risk of stroke did not vary with cGRS.

Statin Treatment Parameters

In our base case scenario, we assumed that statins can be obtained at a cost of $4 per month (2017 Walmart Retail

Table 1. Base Case Model Parameters and Ranges for Deterministic and Probabilistic Sensitivity Analyses

Parameters	Base Case	Range	Source
Costs for incident events*			
Myocardial infarction	$41797	±20%	Pletcher et al[8], Menzin et al[35]
Stroke	$54847	±20%	Pletcher et al[8], Leibson et al[38]
Myalgia/myopathy	$398	±20%	Pletcher et al[8]
Angina	$16777	±20%	Pletcher et al[8]
Ongoing costs for postevent health states*			
Postmyocardial infarction	$5091	±20%	Pletcher et al[8], Menzin et al[35]
Post-stroke	$14607	±20%	Pletcher et al[8], Leibson et al[38]
Post-angina	$7323	±20%	Pletcher et al[8]
Testing costs			
Cardiovascular genetic risk test	$100	$1–$1000†	Expert opinion
Cost of one physician visit (to discuss cGRS test results)	$70.46	±20%	Pletcher et al[8]
Treatment costs*			
Statin therapy, generic	$4/mo	$2/mo–$60/mo	Pletcher et al[8], Pandya et al [41]
One physician visit	$70.46	±20%	Pletcher et al[8]
Lipid panel	$23.49	±20%	Pletcher et al[8]
Health state utilities*			
Healthy	1.0	Not varied in SA	Assumed
MI	0.859	±0.0311	Pletcher et al[8]
Post-MI	1.0	Not varied in SA	Pletcher et al[8]
Stroke	0.771	±0.1505	Pletcher et al[8]
Post-stroke	0.771	±0.1542	Pletcher et al[8]
Angina	0.929	0.40–1.0	Pletcher et al[8]
Post-angina	0.997	0.68–1.0	Pletcher et al[8]
Statin treatment–related disutilities*			
Daily statin therapy	0.001	0–0.02	Hutchins et al[7], Pletcher et al[8]
Myalgia/myopathy	0.017	0–0.1†	Pletcher et al[8]
Effects of statin treatment			
RR: CHD death	0.80	0.76–0.85	Mihaylova et al[31]
RR: stroke	0.85	0.80–0.89	Mihaylova et al[31]
RR: angina	0.74	0.71–0.77	Mihaylova et al[31]
RR: myocardial infarction	0.74	0.71–0.77	Mihaylova et al[31]
IR: myalgia/myopathy	0.001	0–0.05†	Pignone et al[21]
Expected distribution of cGRS			
Proportion expected to have low cGRS	8%	…	Add Health data‡
Proportion expected to have intermediate cGRS	86%	…	Add Health data‡
Proportion expected to have high cGRS	6%	…	Add Health data‡
Relative risk for CHD outcomes associated with cGRS categories			
Low cGRS	1.0	…	Mega et al[18]
Intermediate cGRS	1.31	1.19–1.49	Mega et al[18]
High cGRS	1.72	1.53–1.92	Mega et al[18]
Statin effect modification			
RR: CHD death	High cGRS: RR=0.40 Intermediate/low cGRS RR=0.83	…	Calculation (see Appendix B in the Data Supplement)
RR: myocardial infarction	High cGRS: RR=0.48 Intermediate/low cGRS RR=0.76	…	Calculation (see Appendix B in the Data Supplement)
RR: angina	High cGRS: RR=0.48 Intermediate/low cGRS: RR=0.76	…	Calculation (see Appendix B in the Data Supplement)

cGRS indicates cardiovascular genetic risk score; CHD, coronary heart disease; IR, incidence rate; MI, myocardial infarction; RR, relative risk; USD, United States Dollars; and SA, sensitivity analysis.

*Costs from the study by Pletcher et al[8] updated to USD 2016 (not shown). Additional references for model costs and utilities provided in Appendix C in the Data Supplement.

†Range is based on expert opinion; value shown is upper range for deterministic sensitivity analysis.

‡Unpublished Add health (National Longitudinal Study of Adolescent to Adult Health) analysis.

Prescription Program Drug List) and that taking a statin pill every day is associated with a small reduction in quality of life (disutility of 0.001). The disutility of daily statin use represents any reason that a patient might prefer not to take a pill daily, such as inconvenience or reduction in self-conception of health but does not include adverse effects.[7]

We also assumed that statin therapy triggers one additional physician visit and lipid panel per year. Furthermore, we assumed that statins are associated with relative reductions in risk of MI (26%), angina (26%), stroke (15%), and CHD death (20%), as well as increased risk of myopathy (absolute rate of 0.001 cases per year).[31] Associated cost, mortality, and disutility are applied for the current 1-year cycle, and it is assumed that statins are discontinued. We also assumed immediate discontinuation of statins in 31% of individuals to simulate the effect of nonadherence to treatment.[32]

There is evidence that statin initiation is associated with a small but statistically significant increase in hemoglobin A1C (HbA1C) and new diagnoses of diabetes mellitus with high-dose therapy.[33] The short-term cardiovascular risks are implicitly accounted for in the statin efficacy estimates from clinical trials.[31] The long-term cardiovascular risks associated with this small increase in HbA1C are not well understood.[33] Thus, in this model, we assumed no long-term risk of diabetes mellitus that may be associated with the slight increase in HbA1C because of statin initiation.

Table 2. Description of Scenario Analyses

Scenario	Statin Cost	Statin Disutility	cGRS Test Cost	RR for Intermediate and High cGRS*	Interpretation
Base case	$4/mo	0.001	$100	1.31; 1.72	Base case assumptions
1	$4/mo	0.001	$1	1.31; 1.72	Less-expensive cGRS test
2	$4/mo	0.011	$100	1.31; 1.72	Patient with stronger preference against daily statin therapy
3	$15/mo	0.011	$100	1.31; 1.72	Patient with stronger preference against daily statin therapy and more-expensive statin therapy
4	$15/mo	0.011	$1	1.31; 1.72	Patient with stronger preference against daily statin therapy and more-expensive statin therapy but less-expensive cGRS test
5	$4/mo	0.001	$100	3.93; 5.16	Hypothetical cGRS test with improved prediction of CHD outcomes
6	$4/mo	0.001	$1	3.93; 5.16	Hypothetical cGRS test with improved prediction of CHD outcomes that is also less expensive

cGRS indicates cardiovascular genetic risk score; CHD, coronary heart disease; and RR, relative risk.
*Compared with low cGRS (reference).

Event and Health State Costs

Total costs were assessed from the US healthcare system perspective, adjusted to the year 2016 using consumer price indices (medical care component). Acute care costs within the UNC-RTI CHD Prevention Model were estimated using data on hospital charges from the Healthcare Utilization Project database and converted to costs using hospital charge-to-cost ratios (Table 1).[21–24,34] In addition to the acute care costs, we assumed that each patient who survived an acute event would also incur one half of the estimated ongoing annual costs of care for the first year. Costs for subsequent years were based on ongoing costs of care that were drawn from the medical literature.[35–39] Additional references for these model assumptions and a complete Consolidated Health Economic Evaluation Reporting Standards checklist are provided in Appendixes C and E in the Data Supplement.

ASCVD Risk Factor Profiles

We created 5 ASCVD risk factor profiles to illustrate important findings from our base case and scenario analyses: (1) a 57-year-old man at 7.5% risk (profile 1); (2) a 65-year-old woman at 7.5% risk (profile 2); (3) a 45-year-old woman at 2.5% risk (profile 3); (4) a 45-year-old woman at 5% risk (profile 4); and (5) a 45-year-old woman at 7.5% risk (profile 5; Appendix A in the Data Supplement). We selected these profiles to illustrate the effect of varying sex (profile 1 versus 2), age (profile 2 versus 5), and baseline ASCVD risk on outcomes (profile 3 versus 4 versus 5).

For interested readers, we have also included the base case results for 21 additional ASCVD risk profiles ranging from 0.25% to 7.5% 10-year ASCVD risk in the Data Supplement (Appendix G in the Data Supplement; Tables 1 and 2).

Sensitivity Analyses

We varied incidence of myopathy, disutility for myopathy, and statin effect modification in a 1-way deterministic sensitivity analysis (Table 1). There is some evidence to suggest that individuals with high cGRS have a larger relative risk reduction for CHD events when taking statins compared with individuals at low and intermediate cGRS.[40] To investigate the influence of statin effect modification, we increased the relative risk reduction associated with statin treatment for individuals with high cGRS while proportionally reducing the relative risk reduction associated with statin treatment for individuals with low and intermediate cGRS. We chose to increase the relative risk reduction for individuals with high cGRS by 3-fold to illustrate the sensitivity of results to statin effect modification rather than test the exact relative risk reduction values published by Natarajan et al (calculation described in detail in Appendix B in the Data Supplement).

We performed a 2-way sensitivity analysis of statin disutility and statin cost by varying the cost of statins from $2 per month to $200 per month and the disutility of daily statin use from 0 to 0.10.[7,41] For context, a disutility of 0.02 is equivalent to 10 weeks of perfect health traded away to avoid 10 years on statins.[7] Hutchins et al found that the majority of individuals (87%) have a statin disutility of 0, but we tested values up to 0.10 to demonstrate the sensitivity of the results to higher levels of statin disutility.

We completed the same 2-way sensitivity analysis for profiles 1 to 5 to demonstrate the importance of specific ASCVD risk factors, in addition to 10-year ASCVD risk, on the preferred strategies for different combinations of statin cost and disutility. For interested readers, we have also shown how the 2-way sensitivity table changes when using a WTP threshold of $50 000 per QALY gained versus $100 000 per QALY (Appendix D in the Data Supplement).

To examine the role of statin cost, statin disutility, and cGRS test characteristics, we show scenario analyses that vary statin cost, statin disutility, cost of cGRS testing, and the strength of the relationship between the 27-SNP cGRS and cardiovascular disease outcomes (Table 2).

We conducted a probabilistic sensitivity analysis using second-order Monte Carlo simulation (n=1000 trials) to determine the effect of parameter uncertainty on the probability of cost-effectiveness for the scenario analyses (Table 2). Parameter ranges are reported in Table 1. We parameterized costs using γ distributions, disutilities using β distributions, and relative risks using lognormal distributions.[42] Finally, we

show cost-effectiveness acceptability curves for the 57-year-old man (profile 1) for 2 statin cost/disutility combinations from the 2-way sensitivity analysis (cost=$15 per month, disutility=0.011; cost=$15 per month, disutility=0.013) to illustrate how the probability of cost-effectiveness changes with WTP threshold.[43]

RESULTS

Base Case Assumptions

Under base case assumptions, treating all patients without any cGRS testing was cost saving and dominated all other test/treat strategies for a cohort of 10 000 57-year-old men at 7.5% ASCVD risk (Table 3) over a lifetime horizon. Compared with treating no one, the cohort of 10 000 men experienced 53 fewer MIs, 1 fewer strokes, 139 fewer cases of angina, and 23 fewer CHD deaths but 65 more cases of myopathy. When treating all patients with statins, the total statin costs over a lifetime horizon were $949 per patient and the total costs (including other healthcare costs) were $146 545 per patient. Treating none of the patients had total statin costs of only $229 per patient but total overall costs of $147 003 per patient.

Treating all patients without cGRS testing was also cost-saving and dominated all other strategies for a cohort of 10 000 65-year-old women with 7.5% 10-year ASCVD risk (Table 4; profile 2). For the 45-year-old women at 2.5%, 5%, and 7.5% 10-year ASCVD risk, the recommendation was to treat all with no cGRS testing, and the gain in QALYs associated with that strategy (compared with treat none) increased with increasing 10-year ASCVD risk (base case scenario; Table 4). Furthermore, the gain in QALYs associated with treating all 65-year-old women at 7.5% 10-year ASCVD risk is lower than the gain in QALYs associated with treating all 45-year-old women at 7.5% 10-year ASCVD risk. For profiles 1 to 5, under base case assumptions, the probability of cost-effectiveness of treat all with no cGRS testing compared with treat none with no cGRS testing was 100%.

We analyzed 11 additional ASCVD risk profiles representing risk levels between 2.5% and 7.5% (Appendix G in the Data Supplement; Table 1) and found that the preferred test/treat strategy under base case assumptions for all profiles was also to treat all patients without cGRS testing. For a set of example low-risk profiles ranging from 0.25% to 1.0% 10-year ASCVD risk, we found that the preferred test/treat strategy varied depending on both risk and specific ASCVD risk profile (Appendix G in the Data Supplement; Table 2). For all the profiles at 1.0% risk, the preferred test/treat strategy was to treat all without any cGRS testing; however, at 0.5% 10-year ASCVD risk, the preferred test/treat strategy was different across ASCVD risk profiles. For example, the base case preferred strategy for a 40-year-old woman at 0.5% risk was to treat none without cGRS testing, whereas the base case preferred strategy for a 45-year-old woman at 0.5% risk was to test and treat only if cGRS is high (Appendix G in the Data Supplement; Table 2, profiles 20–21). At 0.25% 10-year ASCVD risk, the preferred strategy for all example profiles was treat none without any cGRS testing.

Table 3. Model Outcomes Over a Lifetime Horizon for 10 000 57-y-old Men With 7.5% 10-y ASCVD Risk (Profile 1)

	Treat None	Treat if cGRS=High	Treat if cGRS=Intermediate or High	Treat All
No. of individuals on statins	0	615	9230	10 000
CVD events per 10 000 individuals				
Cases of angina	1958	1948	1828	1819
Myocardial infarction	1413	1409	1364	1360
Stroke	530	530	530	529
CHD death	838	837	817	815
Statin-induced myopathy	0	4	60	65
Outcomes (discounted at 3%/y)				
Total life-years (per person)	20.006	20.024	20.240	20.257
Total QALYs (per person)	14.515	14.525	14.649	14.659
Costs (discounted at 3%/y)				
Total cost of cGRS testing	0	$1 704 600	$1 704 600	0
Total lifetime cost of statin therapy (per person)	$229	$272	$892	$949
Total costs (per person)	$147 003	$146 963	$146 568	$146 545

ASCVD indicates atherosclerotic cardiovascular disease; cGRS, cardiovascular genetic risk score; CHD, coronary heart disease; CVD, cardiovascular disease; and QALY, quality-adjusted life-years.

Table 4. Preferred Strategy: Incremental Net Benefit and Probability of Cost-Effectiveness of Base Case and Scenario Analyses for 45-y-old Woman at 2.5%, 5%, and 7.5% ASCVD Risk; 65-y-old Woman at 7.5% ASCVD Risk, and a 57-y-old Man at 7.5% ASCVD Risk

	45-y-old Woman			65-y-old Woman	57-y-old Man
	2.5%	5%	7.5%	7.5%	7.5%
Base case scenario: statin disutility=0.001; statin cost=$4/mo; cGRS test cost=$100					
Preferred strategy	Treat all (strong dominance)*	Treat all (strong dominance)	Treat all (strong dominance)	Treat all (strong dominance)	Treat all (strong dominance)
Gain in QALYs†	0.043	0.077	0.084	0.061	0.144
Probability of CE, %‡	100	100	100	100	100
Scenario analysis 1: statin disutility=0.001; statin cost=$4/mo; cGRS test cost=$1					
Preferred strategy	Treat all (strong dominance)	Treat all (strong dominance)	Treat all (strong dominance)	Treat all (strong dominance)	Treat all (strong dominance)
Gain in QALYs	0.043	0.0770	0.084	0.061	0.144
Probability of CE, %	100	100	100	100	100
Scenario analysis 2: statin disutility=0.011; statin cost=$4/mo; cGRS test cost=$100					
Preferred strategy	Treat none	Treat all	Treat all	Treat all	Treat all (strong dominance)
Gain in QALYs	…	0.004	0.010	0.004	0.079
Probability of CE, %	55	70	85	83	100
Scenario analysis 3: statin disutility=0.011; statin cost=$15/mo; cGRS test cost=$100					
Preferred strategy	Treat none	Treat if cGRS=high (strong dominance)	Treat if cGRS=intermediate/high (strong dominance)	Treat none	Treat all (strong dominance)
Gain in QALYs	…	0.004	0.012	…	0.079
Probability of CE, %	79	43	90	71	100
Scenario analysis 4: statin disutility=0.011; statin cost=$15/mo; cGRS test cost=$1					
Preferred strategy	Treat none	Treat if cGRS=intermediate/high (strong dominance)	Treat if cGRS=intermediate/high (strong dominance)	Treat none	Treat all (strong dominance)
Gain in QALYs	…	0.004	0.012	…	0.079
Probability of CE, %	82	43	91	75	100
Scenario analysis 5: statin disutility=0.001; statin cost=$4/mo; cGRS test cost=$100; RR_cGRS=3×					
Preferred strategy	Treat all ($26 158/QALY gained)	Treat all ($6555/QALY gained)	Treat all ($4838/QALY gained)	Treat all (strong dominance)	Treat all (strong dominance)
Gain in QALYs	0.043	0.076	0.083	0.061	0.140
Probability of CE, %	91	100	100	100	100
Scenario analysis 6: statin disutility=0.001; statin cost=$4/mo; cGRS test cost=$1; RR_cGRS=3×					
Preferred strategy	Treat all ($27328/QALY gained)	Treat all ($6614/QALY gained)	Treat all ($4870/QALY gained)	Treat all (strong dominance)	Treat all (strong dominance)
Gain in QALYs	0.043	0.076	0.083	0.061	0.140
Probability of CE, %	90	100	100	100	100

ASCVD indicates atherosclerotic cardiovascular disease; CE, cost-effectiveness; cGRS, cardiovascular genetic risk score; QALY, quality-adjusted life-years; and RR, relative risk.

*Strong dominance indicates that the strategy listed is more effective (higher QALYs) and less costly than the next most effective strategy.

†Gain in QALYs=difference between preferred strategy and treat none.

‡Probability of CE is taken from the probabilistic sensitivity analysis for each of these scenarios and risk profiles.

One-Way Sensitivity Analyses: Incidence of Myopathy, Disutility of Myopathy, and Statin Effect Modification

We conducted a 1-way sensitivity analysis of key model parameters using 10 000 57-year-old men at 7.5% ASCVD risk. The base case recommendation to treat all without any cGRS testing did not change with varying the incidence or disutility of myopathy throughout the ranges listed in Table 1. Furthermore, assuming a statin effect modification did not change the recommendation to treat all without any cGRS testing.

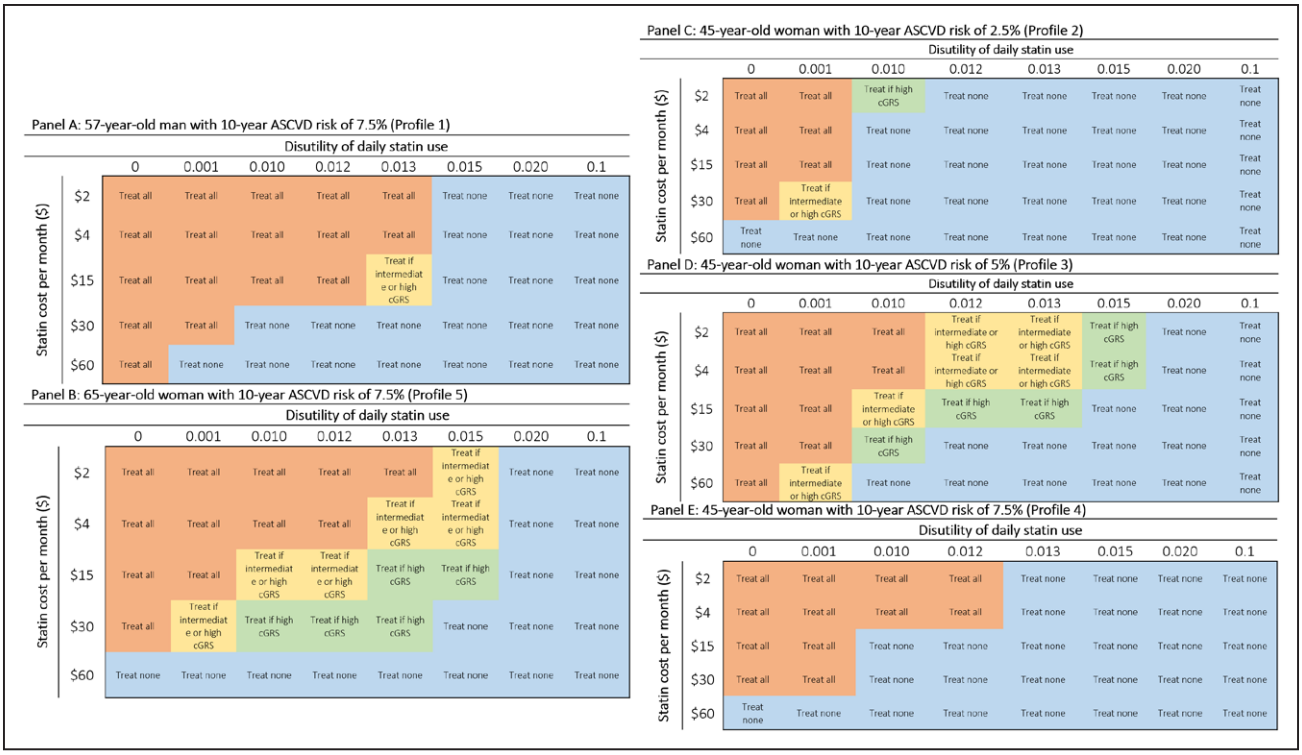

Figure 2. Two-way sensitivity analysis of statin cost and disutility of daily statin use for profiles 1 through 5 (A through E) with $100 cGRS test.
ASCVD indicates atherosclerotic cardiovascular disease; and cGRS, cardiovascular genetic risk score.

Two-Way Sensitivity Analysis: Statin Disutility Versus Statin Cost

The specific combinations of statin disutility and statin cost that lead to cGRS testing as a preferred strategy were uncommon and dependent on the ASCVD risk factors for the specific profile considered (Figure 2). For example, for the 57-year-old man at 7.5% risk, only one combination of statin disutility/statin cost combinations led to a cGRS testing strategy being preferred (profile 1; Figure 2A). None of the statin disutility/statin cost combinations led to a preferred strategy that involved cGRS testing for the 65-year-old woman at 7.5% ASCVD risk (profile 4; Figure 2B). However, cGRS testing was preferred for several statin disutility/statin cost combinations for the 45-year-old woman with 7.5% 10-year ASCVD risk (profile 3; Figure 2C).

Scenario Analyses: cGRS Testing Cost, Statin Disutility, Statin Cost, and RR Associated With CHD Outcomes

Varying the cGRS testing cost alone did not change the preferred test/treat strategy for the ASCVD profiles considered (Table 4; scenario #1 versus base case). However, when statin disutility was increased, cGRS testing became the preferred strategy for the 45-year-old women at 5% and 7.5% 10-year ASCVD risk if cGRS testing cost was decreased (scenario 4 versus scenario 2) along with an increase in the cost of statins (scenario 3 versus scenario 2). When both statin disutility and statin cost were increased compared with base case assumptions, the cost of cGRS testing did not affect the preferred strategy for any of the profiles shown. Finally, under base case assumptions for statin disutility and statin cost, increasing the strength of the association between the cGRS results and CHD outcomes (to simulate a hypothetical better cGRS test) did not affect the preferred strategy, even when the hypothetical better cGRS test was inexpensive (scenarios 5 and 6 versus base case). In general, treat none is preferred when the cost and disutility of statins are high.

Probabilistic Sensitivity Analysis

For the 57-year-old man at 7.5% risk (profile 1) using base case assumptions (scenario 1), the probability of cost-effectiveness for treat all is 100% when compared with the next best strategy (test and treat if cGRS is intermediate or high), at a WTP threshold of $50 000 per QALY. Figure 3 shows the cost-effectiveness acceptability curves for the 57-year-old man at 7.5% risk (profile 1) for 2 combinations of statin cost and disutility to illustrate the importance of statin disutility on the relationship between WTP threshold and probability of cost-effectiveness. For the first combination of statin

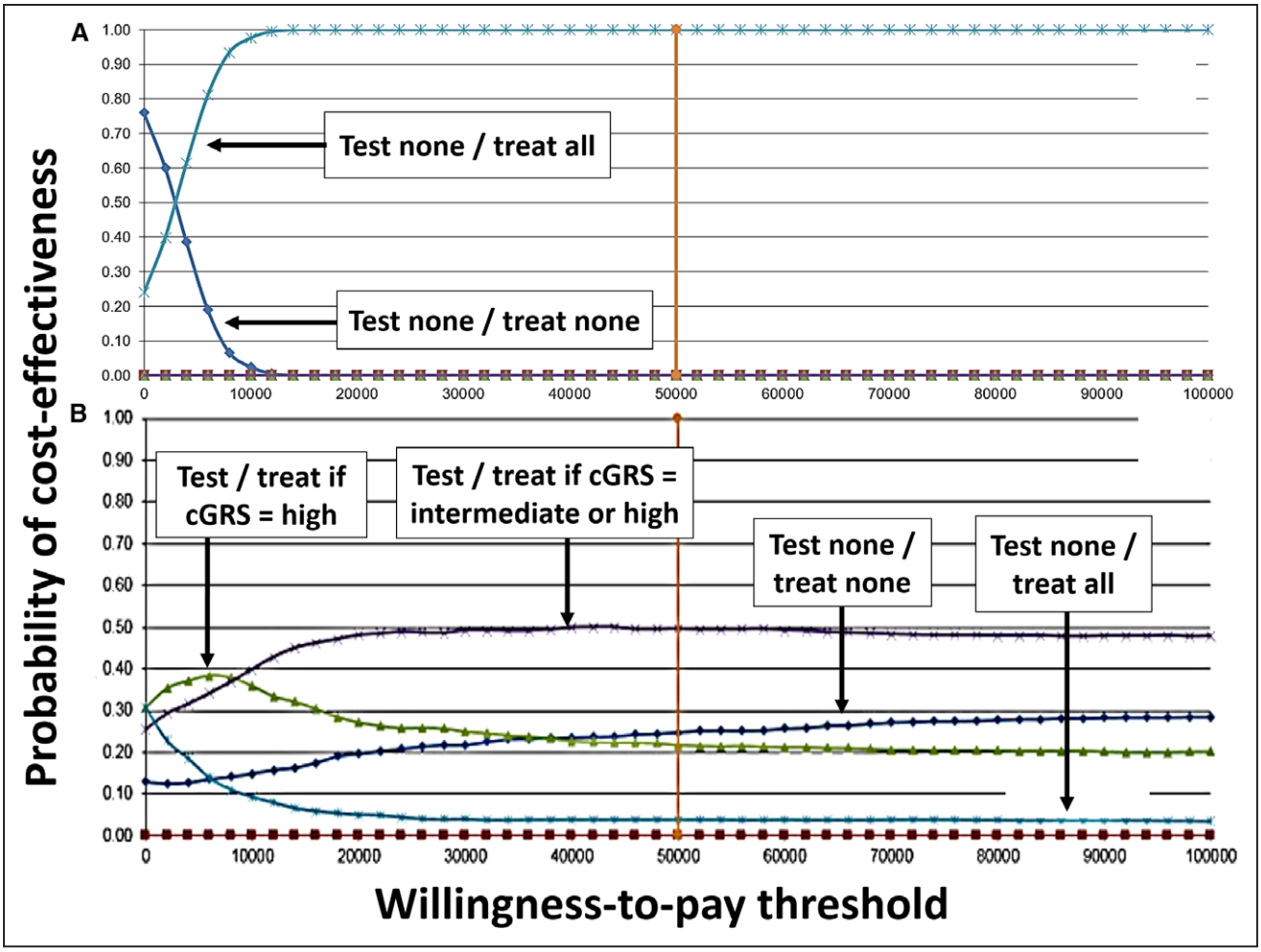

Figure 3. Impact of statin disutility on CEACs.
Impact of statin disutility on cost-effectiveness acceptability curves for 57-y-old man with 10-y atherosclerotic cardiovascular disease risk of 7.5% for 2 combinations of statin cost ($15/mo) and disutility: (**A**) statin disutility=0.011 and (**B**) statin disutility=0.013. cGRS indicates cardiovascular genetic risk score.

cost/disutility (Figure 3A), none of the cGRS testing strategies are preferred at any WTP threshold. In Figure 3B, the statin cost is the same, but statin disutility is higher. Here, the preferred strategy is dependent on the WTP threshold. For example, the preferred strategy for WTP thresholds between $0 per QALY gained and around $9000 per QALY gained is test and treat if cGRS is high, compared with WTP thresholds >$9000 per QALY gained, for which the preferred strategy is test and treat if cGRS is intermediate or high. Furthermore, the probability of cost-effectiveness for each test/treat strategy is closer for Figure 3B, indicating that uncertainty in parameter assumptions plays an important role in determining the preferred test/treat strategy at different WTP thresholds.

The probability of cost-effectiveness for the preferred strategies varied considerably across profiles and scenarios (Table 4). In general, when statin disutility and statin cost were set at their base case assumptions (base case, scenarios 1, 5, and 6), the probability of cost-effectiveness for the preferred strategy (assuming a WTP threshold of $50 000 per QALY gained) of treat all was either at or close to 100%. For the scenarios in which a cGRS testing strategy was preferred, the probability of cost-effectiveness for that strategy ranged from 43% to 91%, indicating substantial parameter uncertainty even for this most favorable scenario for cGRS testing.

DISCUSSION

In a set of clinical scenarios of individuals with 10-year predicted ASCVD risk ranging from 2.5% to 7.5%, obtaining a cGRS test to target statin therapy for primary prevention of ASCVD was not a cost-effective strategy at a WTP of $50 000 per QALY gained. Instead, we found that the preferred strategy is to treat all patients with statins under base case assumptions of low-cost statins and low statin disutility. However, cGRS testing

can be cost-effective under a small set of assumptions related to statin cost and statin disutility that depend on sex, age, 10-year ASCVD risk, and WTP threshold.

In our example of a 45-year-old woman with 10-year ASCVD risk of 2.5%, the preferred strategy under base case assumptions is to treat all without any testing. Although this 10-year ASCVD risk is much lower than current thresholds for recommended statin therapy, our findings are consistent with the work of Pandya et al[41] that demonstrate that 10-year ASCVD risk thresholds <5% for recommending statin can be cost-effective. We chose to limit our analysis to individuals with 10-year ASCVD risk of ≤7.5% because at higher levels of risk, treat all is the preferred strategy even with wide variation in assumptions about statin disutility and cost.

Furthermore, the sensitivity of our results to statin cost and statin disutility is consistent with previous work on the cost-effectiveness of statin therapy in intermediate-risk patients.[8,41] A recent study found that the prevalence of statin disutility >0.01 (trading away 5 weeks of perfect health to avoid 10 years on statins) was ≈7.4%, with 87% of individuals being unwilling to trade any length of time to avoid statin therapy.[7] Given that net benefit from statin therapy relies heavily on assumptions about statin disutility, it may be reasonable to ask patients how much the idea of taking a daily preventive medication bothers them during shared decision making regarding statin initiation. In the absence of knowledge about an individual patient's disutility for taking daily preventive medications, we can assume that the conditions under which cGRS testing is the preferred strategy are uncommon during routine clinical practice.

When we examined the 2-way sensitivity analysis (statin disutility versus statin cost) for the 65-year-old woman at 7.5% 10-year ASCVD risk (profile 4), we did not find any combinations of statin disutility and statin cost that led to a cGRS testing strategy being preferred. In contrast, cGRS testing was preferred for the 45-year-old woman at 7.5% 10-year ASCVD risk for many combinations of statin disutility and statin cost. These findings demonstrate the importance of the underlying clinical risk factors that determine 10-year ASCVD risk, especially age. When simulating a lifetime horizon, the treated 45 year old has more years to accumulate benefit from cGRS testing compared with a 65 year old. Conversely, the untreated 45 year old also has more years to avoid disutility of treatment compared with the 65 year old. Thus, it is important to be able to make risk-based and preference-based decisions about cGRS testing (as well as testing for other novel biomarkers). Future work should be done to test the best way to operationalize in clinical practice.[44]

Although the 27-SNP cGRS test is an independent predictor of ASCVD outcomes, the strength of the association is small.[18] Other approaches to targeting statin therapy, such as the selective use of imaging (CAC scanning), are substantially better at improving discrimination and reclassification in intermediate-risk patients.[6] However, although CAC scanning improves risk prediction, it has also been shown to be cost-effective only under a limited set of assumptions for statin disutility and cost.[8,9] In the future, other versions of cGRS tests may need to focus on incorporating gene variants related to the cardiovascular risk pathways that do not overlap with traditional risk factors, such as inflammation and thrombosis.[11]

Our work has some limitations. We did not attempt to account for any change in a patients' adherence or motivation to improve lifestyle factors based on receipt of genetic risk information because of limited evidence supporting this assumption. Furthermore, we did not explicitly account for new-onset diabetes mellitus in the model. However, as previously stated, although there is evidence that statin initiation is associated with a small but statistically significant increase in HbA1C and new diagnoses of diabetes mellitus, the cardiovascular benefits outweigh the risks, at least in the short term.[33] And, it is unclear whether there are long-term microvascular implications associated with the small increase in HbA1C or slightly earlier diagnosis of diabetes mellitus. We also did not attempt to account for any patient-level differences in risk for myopathy. Current evidence suggests that there may be some increased risk when used in combination with certain drugs or with certain patients (individuals of Asian origin or with functional variations of the *SLCO1B1* gene).[45]. However, we do not explicitly model differences in ethnicity in our model, and the 27-SNP genetic risk score does not include information about the functional status of the *SLCO1B1* gene. Thus, we chose not model any subpopulations with increased risk for myopathy. Finally, we chose to show results for only 5 clinical profiles, which limits generalizability of our results. Future work could extend the current analysis to include a full set of clinical profiles that is representative of some population of interest.

Decision modeling and cost-effectiveness analyses are methods used to explicitly compare alternative clinical options regarding their relative downstream risks, benefits, and costs. In March 2017, the National Academy of Science and Medicine published a framework for evaluation of genetic tests that endorsed the use of clinical decision analysis as a way to assess both clinical utility and cost-effectiveness of new genetic tests.[27] The work presented here is an example of the type of analysis that can help identify conditions under which genetic risk testing may (or may not) be a cost-effective approach for tailoring decisions about initiation of preventive therapies for individual patients.

Results from decision analyses can also be used to decide whether to invest in large-scale and expensive clinical trials to definitively assess the clinical utility of cGRS testing or whether to invest in commercialization. For example, the 27-SNP cGRS test used in this analysis is not currently marketed, and commercialization would require investment in the equipment and processes necessary to assure analytic validity.[46,47] The test developer would need to charge a high enough price for the test to ensure return on investment for research and development. However, depending on the price, our findings demonstrate that the cost of cGRS testing and the strength of association between the cGRS and CHD outcomes play a limited role in determining the overall clinical utility of cGRS testing for guiding statin therapy.

CONCLUSIONS

Our analyses demonstrate that cGRS testing is not a cost-effective approach for targeting statin therapy in the primary prevention of ASCVD in patients with 10-year ASCVD risk of ≥2.5%. Although there are a small set of combinations of parameters under which cGRS testing strategies would be preferred, these are unlikely to be encountered in routine clinical practice.

ARTICLE INFORMATION

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Correspondence

Jamie Jarmul, PhD, UNC School of Medicine, 321 S Columbia St, Chapel Hill, NC 27599. E-mail jbell6@med.unc.edu

Affiliations

Department of Health Policy and Management, Gillings School of Public Health (J.J., K.H.L., S.B.W., M.W.), UNC School of Medicine (J.J., D.E.J.), Department of Epidemiology, Gillings School of Public Health (C.L.A.), Carolina Population Center (C.L.A.), and Cecil G. Sheps Center for Health Services Research (D.E.J.), University of North Carolina-Chapel Hill. Department of Internal Medicine, Dell Medical School, University of Texas-Austin (M.P.). Department of Epidemiology and Biostatistics (M.J.P.) and Department of Medicine (M.J.P.), University of California, San Francisco.

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Disclosures

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Cardiovascular Genetic Risk Testing for Targeting Statin Therapy in the Primary Prevention of Atherosclerotic Cardiovascular Disease: A Cost-Effectiveness Analysis

Jamie Jarmul, Mark J. Pletcher, Kristen Hassmiller Lich, Stephanie B. Wheeler, Morris Weinberger, Christy L. Avery, Daniel E. Jonas, Stephanie Earnshaw and Michael Pignone

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SUPPLEMENTAL MATERIAL

Appendix A: ASCVD risk factors for the clinical profiles

	57-year-old man	45-year-old woman			65-year-old woman
	Profile 1: 7.5%	Profile 2: 2.5%	Profile 3: 5%	Profile 4: 7.5%	Profile 5: 7.5%
TC	215 mg/dL	167 mg/dL	255 mg/dL	275 mg/dL	160
HDL	45 mg/dL	45 mg/dL	45 mg/dL	45 mg/dL	45
SBP	125 mmHg	120 mmHg	120 mmHg	120 mmHg	131
Smoker?	No	Yes	Yes	Yes	No
On anti-HTN meds?	No	No	No	Yes	Yes

Appendix B: Calculation of statin efficacy for statin effect modification analysis

We applied this calculation to the statin efficacy assumptions for CHD death, MI and angina. We will go through the calculation for CHD death as an example. The base case assumption for the relative risk of CHD death with statin treatment was 0.80. Natarajan et al. found that the relative risk reduction associated with statin therapy was increased for only individuals at high cardiovascular genetic risk compared to those with intermediate and low genetic risk. In order to test whether statin effect modification affected our results, we tested the assumption that individuals with high cGRS have 3 times more relative risk reduction with statins compared to individuals with low or intermediate cGRS. We then used prevalence data for the distribution of the 27-SNP cGRS to determine the proportion of individuals expected to have low, intermediate and high cGRS and "re-distributed" the relative risk of 0.80 (Pletcher 2011; Cook 2007). We have reported the actual values for statin relative risk used in this sensitivity analysis for low/intermediate cGRS and high cGRS in Table 1.

Appendix C: Additional references for the UNC-RTI CHD Prevention Model (from Table 1)

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Russell MW, Huse DM, Drowns S, Hamel EC, Hartz SC. Direct medical costs of coronary artery disease in the united states. Am J Cardiol. 1998;81:1110-1115

Nease RF, Jr., Kneeland T, O'Connor GT, Sumner W, Lumpkins C, Shaw L, Pryor D, Sox HC. Variation in patient utilities for outcomes of the management of chronic stable angina. Implications for clinical practice guidelines. Ischemic heart disease patient outcomes research team. JAMA. 1995;273:1185-1190.

Appendix D: Comparison of willingness-to-pay thresholds (Panel A: $50,000/QALY gained and Panel B: $100,000/QALY gained) for 57-year-old man with 7.5% 10-year ASCVD risk

Panel A: Willingness-to-pay threshold of $50,000/QALY gained

Statin cost per month ($)	Disutility of daily statin use: 0	0.001	0.010	0.012	0.013	0.015	0.020	0.1
$2	Treat all	Treat all	Treat all	Treat all	Treat all	Treat none	Treat none	Treat none
$4	Treat all	Treat all	Treat all	Treat all	Treat all	Treat none	Treat none	Treat none
$15	Treat all	Treat all	Treat all	Treat all	Treat if intermediate or high cGRS	Treat none	Treat none	Treat none
$30	Treat all	Treat all	Treat none	Treat none	Treat none	Treat none	Treat none	Treat none
$60	Treat all	Treat all	Treat none	Treat none	Treat none	Treat none	Treat none	Treat none

Panel B: Willingness-to-pay threshold of $100,000/QALY gained

Statin cost per month ($)	Disutility of daily statin use: 0	0.001	0.010	0.012	0.013	0.015	0.020	0.1
$2	Treat all	Treat all	Treat all	Treat all	Treat all	Treat if intermediate or high cGRS	Treat none	Treat none
$4	Treat all	Treat all	Treat all	Treat all	Treat all	Treat if high cGRS	Treat none	Treat none
$15	Treat all	Treat all	Treat all	Treat all	Treat if intermediate or high cGRS	Treat none	Treat none	Treat none
$30	Treat all	Treat all	Treat all	Treat if intermediate or high cGRS	Treat if high cGRS	Treat none	Treat none	Treat none
$60	Treat all	Treat all	Treat if high cGRS	Treat none	Treat none	Treat none	Treat none	Treat none

Appendix E: CHEERS checklist (Husereu 2013)

Item	In this study:
Title and abstract	
1: Title	Cardiovascular genetic risk testing for targeting statin therapy in the primary prevention of atherosclerotic cardiovascular disease: a cost-effectiveness analysis
2: Abstract	See Abstract
Introduction	
3: Background and objectives	See Background
Methods	
4: Target population and subgroups	Non-diabetic, ASCVD-free individuals with 10-year ASCVD risk between 2.5% and 7.5%
5: Setting and location	US health care system
6: Study perspective	Health care system perspective
7: Comparators	1- Treat all with statins 2- cGRS testing/ treat with statins if cGRS is intermediate or high risk 3- cGRS testing/treat with statins if cGRS is high risk 4- Treat none with statins
8: Time horizon	Lifetime horizon. This is appropriate because we are evaluating a prevention intervention and the effect on all-cause mortality.
9: Discount rate	3%/year for costs and outcomes. This is a typical discount rate for primary prevention intervention and lifetime horizon.
10: Choice of health outcomes	Quality-adjusted life-years (QALYs) and discounted total costs
11: Measurement of effectiveness	Synthesis-based estimates for statin efficacy from MIhaylova 2012
12: Measurement and valuation of preferences-based outcomes	Statin disutility: Hutchins 2015 Health state disutilities: Dehmer 2015; Pletcher 2014
13: Estimating resources and costs	Literature-based estimates Microcosting
14: Currency, price date and conversion	USD, different price dates, all converted to 2016
15: Choice of model	Decision-analytic Markov model

16: Assumptions	See Methods
17: Analytical methods	See Methods
Results	
18: Study parameters	See Table 1
19: Incremental costs and outcomes	Costs were discounted 3%/year Discounted life-years and quality-adjusted life-years (QALYs)
20: Characterizing uncertainty	One-way, two-way and probabilistic sensitivity analyses
21: Characterizing heterogeneity	Use of multiple clinical profiles
Discussion	
22: Study findings, limitation, generalizability, current knowledge	See Results and Discussion
Other	
23: Source of funding	There was no external funding provided for this analysis.
24: Conflicts of interest	There are no conflicts of interest for any study contributors.

* 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.

Appendix F. Table 1. Post-test ASCVD risks for the five clinical scenarios

Clinical scenario	Pretest ASCVD risk	cGRS category	Post-test cGRS risk
1- 57-year-old man at 7.5% risk	7.5%	Low	5.6%
		Intermediate	7.5%
		High	9.7%
2- 45-year-old woman at 2.5% risk	2.5%	Low	1.9%
		Intermediate	2.5%
		High	3.2%
3- 45-year-old woman at 5% risk	5.0%	Low	3.7%
		Intermediate	5.0%
		High	6.4%
4- 45-year-old woman at 7.5% risk	7.5%	Low	5.6%
		Intermediate	7.5%
		High	9.7%
5- 65-year-old woman at 7.5% risk	7.5%	Low	5.6%
		Intermediate	7.5%
		High	9.7%

Appendix F. Table 2. Post-test incidence for non-fatal MI used in UNC-RTI CHD Prevention Model.

Clinical scenario	Pretest nonfatal MI incidence	cGRS category	Post-test nonfatal MI incidence
1- 57-year-old man at 7.5% risk	0.0051	Low	0.0038
		Intermediate	0.0051
		High	0.0066
2- 45-year-old woman at 2.5% risk	0.0019	Low	0.0014
		Intermediate	0.0019
		High	0.0110
3- 45-year-old woman at 5% risk	0.0044	Low	0.0033
		Intermediate	0.0044
		High	0.0056
4- 45-year-old woman at 7.5% risk	0.0050	Low	0.0037
		Intermediate	0.0050
		High	0.0064
5- 65-year-old woman at 7.5% risk	0.0017	Low	0.0012
		Intermediate	0.0017
		High	0.0021

Appendix F. Table 3. Post-test incidence for fatal CHD used in UNC-RTI CHD Prevention Model.

Clinical scenario	Pretest fatal CHD incidence	cGRS category	Post-test fatal CHD incidence
1- 57-year-old man at 7.5% risk	0.0022	Low	0.0016
		Intermediate	0.0022
		High	0.0028
2- 45-year-old woman at 2.5% risk	0.00009	Low	0.00007
		Intermediate	0.00009
		High	0.00011
3- 45-year-old woman at 5% risk	0.00032	Low	0.00024
		Intermediate	0.00032
		High	0.00041
4- 45-year-old woman at 7.5% risk	0.00039	Low	0.00029
		Intermediate	0.00039
		High	0.00050
5- 65-year-old woman at 7.5% risk	0.00069	Low	0.00051
		Intermediate	0.00069
		High	0.00088

Appendix F. Table 4. Post-test incidence for angina used in UNC-RTI CHD Prevention Model.

Clinical scenario	Pretest angina incidence	cGRS category	Post-test angina incidence
1- 57-year-old man at 7.5% risk	0.0121	Low	0.0090
		Intermediate	0.0121
		High	0.0155
2- 45-year-old woman at 2.5% risk	0.0041	Low	0.0031
		Intermediate	0.0041
		High	0.0053
3- 45-year-old woman at 5% risk	0.0079	Low	0.0059
		Intermediate	0.0079
		High	0.0101
4- 45-year-old woman at 7.5% risk	0.0088	Low	0.0066
		Intermediate	0.0088
		High	0.0113
5- 65-year-old woman at 7.5% risk	0.0064	Low	0.0047
		Intermediate	0.0064
		High	0.0082

Appendix G. Table 1. Preferred test/treat strategies for additional ASCVD risk profiles using base case parameters

Profile	Age (years)	Gender	TC/HDL (mg/dL)	SBP (mmHg)	On anti-HTN meds?	Smoker?	10-year ASCVD risk	Preferred strategy (base case scenario)
1	57	Man	215/45	125	No	No	7.5%	Treat all
2	45	Woman	167/45	120	No	Yes	2.5%	Treat all
3	45	Woman	255/45	120	No	Yes	5.0%	Treat all
4	45	Woman	275/45	120	Yes	Yes	7.5%	Treat all
5	65	Woman	160/45	131	Yes	No	7.5%	Treat all
6	40	Man	235/40	140	No	No	2.5%	Treat all
7	40	Man	220/45	125	No	Yes	5.0%	Treat all
8	40	Man	262/45	130	No	Yes	7.5%	Treat all
9	45	Man	225/45	120	No	No	2.5%	Treat all
10	45	Man	187/45	120	No	Yes	5.0%	Treat all
11	50	Man	180/50	115	No	No	2.5%	Treat all
12	50	Man	260/45	120	No	No	5.0%	Treat all
13	55	Woman	230/45	120	No	No	2.5%	Treat all
14	55	Woman	195/45	120	No	Yes	5.0%	Treat all
15	57	Man	140/62	100	No	No	2.5%	Treat all
16	57	Man	180/50	115	No	No	5.0%	Treat all

Appendix G. Table 2. Additional low ASCVD risk profiles (base case parameters vs. increased statin disutility)

Profile	Age (years)	Gender	TC/HDL (mg/dL)	SBP (mmHg)	On anti-HTN meds?	Smoker?	10-year ASCVD risk (%)	Preferred strategy (base case)	Preferred strategy (increased statin disutility)*
17	40	Woman	160/52	100	No	No	0.25%	Treat none	Treat none
18	45	Woman	145/60	100	No	No	0.25%	Treat none	Treat none
19	40	Man	147/60	90	No	No	0.25%	Treat none	Treat none
20	40	Woman	180/45	109	No	No	0.50%	Treat none	Treat none
21	45	Woman	160/46	105	No	No	0.50%	Treat if cGRS = high	Treat none
22	40	Man	160/45	100	No	No	0.50%	Treat if cGRS = high	Treat none
23	40	Woman	213/45	130	No	No	1.0%	Treat all	Treat none
24	45	Woman	200/45	121	No	No	1.0%	Treat all	Treat all
25	40	Man	185/45	120	No	No	1.0%	Treat all	Treat if cGRS = high
26	45	Man	170/50	100	No	No	1.0%	Treat all	Treat none

*statin disutility = 0.005 (base case = 0.001)