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A SIMULATION MODEL TO EVALUATE THE IMPLICATIONS OF GENETIC TESTING IN CHOLESTEROL TREATMENT PLANS

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ABSTRACT

Atherosclerotic cardiovascular disease (ASCVD) is among the leading causes of death in the US. While it is known that ASCVD has familial and genetic components, understanding the role of genetic testing in the prevention and treatment of the cardiovascular disease has been limited. To this end, we develop a simulation framework to estimate the risk for ASCVD events due to clinical and genetic factors. One controllable risk factor for ASCVD events is the cholesterol level of patients. Cholesterol treatment plans are modeled using Markov decision processes. By simulating the health trajectory of patients, we determine the impact of genetic testing in optimal cholesterol treatment plans. As precision medicine and genetic testing become increasingly important, having such a simulation framework becomes essential.

1 INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD), constituted of coronary heart disease (CHD) and stroke, is among the leading causes of death in the US (Heron 2018). CHD accounts for approximately 43.8% of deaths attributable to cardiovascular diseases in the US followed by stroke, which accounts for nearly 16.8% of deaths. Among Americans with at least 20 years of age, it is estimated that 16.5 million (6.3%) have CHD and 7.2 million (2.7%) have had a stroke (Benjamin et al. 2018). While it is known that ASCVD has familial and genetic components, understanding the role of genetic testing in its prevention and treatment has been limited (MacRae and Vasan 2016; Jarmul et al. 2018). However, the development of a new genetic risk score (GRS) that helps predict ASCVD and the benefit of treatment could make genetics central to daily cardiovascular care (Mega et al. 2015; Khera et al. 2016; Natarajan et al. 2017).

The risk for ASCVD events is primarily composed of demographic, behavioral, and clinical factors. Among the risk factors for ASCVD events, the cholesterol level of patients is one component that can be controlled (Goff et al. 2014). Several clinical guidelines recommend that the risk for ASCVD events should be followed to guide the usage of statin cholesterol-lowering drugs (Bibbins-Domingo et al. 2016; Stone et al. 2014). Incorporating the GRS to the risk for ASCVD events would improve risk prediction. Improving risk prediction would in turn improve cholesterol treatment. Nevertheless, it remains unknown if the benefits of genetic testing are large enough and its costs are low enough to be used in clinical practice.

Our study has the following objectives: (i) determine the potential public health impact of large-scale genetic testing to inform the use of cholesterol-lowering drugs; and (ii) evaluate how the cost-effectiveness of genetic testing changes with respect to the population tested. We model cholesterol treatment plans using finite-horizon Markov decision processes (MDPs). The treatment plans are compared in a simulation framework. This allows us to asses different aspects of our model with great flexibility (Glover et al. 2018).

This paper is organized as follows. We begin by providing a review of the relevant literature in Section 2. In Section 3, we present our simulation framework along with our selection of data and parameters to characterize a population of adults in the US. We present our results in Section 4. Finally, conclusions and future research directions are discussed in Section 5.

2 LITERATURE REVIEW

The relevant literature to this research lies in the following fields: (1) risk prediction models that incorporate genetic information; (2) treatment decision models for patients at risk of cardiovascular diseases; and (3) simulation models that incorporate patients' risk of cardiovascular diseases. We highlight some prominent papers in each category and briefly describe how our proposed methodology differs from them.

Risk prediction models that incorporate genetic information have been previously developed in the literature. Sun et al. (2007) presented a model to improve the prognosis of breast cancer using genetic and clinical markers. Abraham and coauthors created a predictive model for Celiac disease based on genome-wide single nucleotide polymorphisms profiles (Abraham et al. 2014). The authors also presented an extensive analysis of multiple statistical models for the prediction of Celiac disease, diabetes, and Crohn's disease using genome-wide single nucleotide polymorphisms profiles (Abraham et al. 2013). Although these models use genetic information to predict the risk for adverse events, none of them have been used to improve decision making.

Treatment decision models for patients at risk of cardiovascular diseases have also been previously developed in literature (Cooper et al. 2006). Hauskrecht and Fraser (2000) modeled ischemic heart disease treatment plans using a partially observable Markov decision process (POMDP). Denton and coauthors constructed an MDP model to determine the optimal time for starting cholesterol medications in patients with diabetes (Denton et al. 2009). Mason et al. (2014) extended this work by determining the optimal timing of blood pressure and cholesterol medications in patients with diabetes. Schell et al. (2016) developed a method to approximate optimal hypertension treatment policies derived with an MDP. Nevertheless, none of these models incorporate genetic information to guide treatment plans.

Researchers have also developed simulation models to evaluate therapies for patients at risk of cardiovascular diseases. Liu et al. (2018) created a system dynamics model to study the cost-effectiveness of different diabetes treatment options. Fonarow et al. (2017) used a simulation model to project the lifetime costs and quality-adjusted life-years (QALYs) and evaluate the cost-effectiveness of evolocumab when added to standard cholesterol background therapy. Pandya and coauthors developed a microsimulation model to estimate the cost-effectiveness of various 10-year ASCVD risk thresholds that could be used in the American College of Cardiology and the American Heart Association's (ACC/AHA) cholesterol treatment guidelines (Pandya et al. 2015). Other simulation studies that consider patients' risk for cardiovascular diseases include (Cannon et al. 2017) and (Ferranti and de Freitas Filho 2011). These papers differ from ours in that none of them incorporate the risk for cardiovascular events due to genetic factors. Our research is a step towards understanding the impact of genetic testing in the prevention and treatment of ASCVD.

3 SIMULATION FRAMEWORK

We use a large representative sample of the US population to understand the implications of genetic testing. To find a group for whom genetic testing is most likely to influence their care, we use the US Preventive Services Task Force (USPSTF) statin guidelines (Bibbins-Domingo et al. 2016). We model the health status of each patient as a Markov chain and simulate their state trajectory over a 10-year planning horizon. The trajectory of a single patient in our modeling framework is summarized in Figure 1.

Before the start of the simulation, we calculate each patient's 1-year risk for ASCVD events at each year $t = 0, 1, \ldots, T-1$ using risk scores that are and are not informed by genetic information. We then estimate transition probabilities based on each risk score. The transition probabilities are used to determine treatment strategies using clinical information only and clinical and genetic information.

We compare the outcomes of every patient under each treatment strategy at every replication $k = 1, 2, \ldots, K$ and year t. Since genetic variants play a role in each patient's health (independent of whether or not they have received genetic testing), the health trajectory of each patient progresses from year t to year $t+1$ according to the risk score informed by clinical and genetic information. Finally, we estimate the lifetime effects of the treatment strategies on every patient, represented by the terminal time period T. The simulation ends once the planning horizon of each patient is simulated K times.

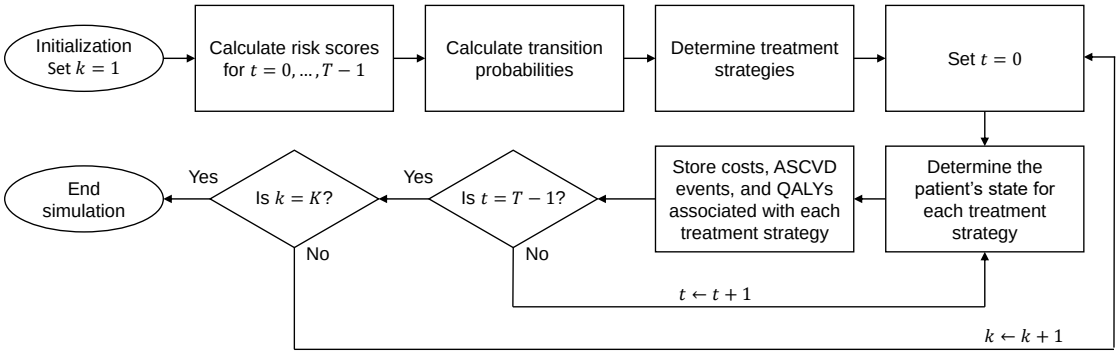

Figure 1: Summary of simulation framework for a single patient.

We describe our data, risk scores, and treatment strategies in more detail in the following subsections.

3.1 Data

We use data from the National Health and Nutrition Examination Survey (NHANES) from 2009 to 2014 to parameterize our model (Centers for Disease Control and Prevention 2017). Our sample is composed of adult Caucasian and African-American patients from 40 to 75 years old with no history of ASCVD and a low-density lipoprotein (LDL) of less than 190 mg/dL.

To obtain our population, we first impute missing data using the MissForest package in R (Stekhoven and Buhlmann 2012). We then create a synthetic dataset based on the NHANES sampling weights that represent the approximately 93.55 million people who meet the eligibility criteria. We use nonparametric classification and regression trees and the synthpop package in R to generate the synthetic dataset (Nowok et al. 2016). Since risk factors may change over time, we estimate their progression over the 10-year planning horizon with linear regression. We regress systolic blood pressure (SBP), high-density lipoprotein (HDL), LDL, and total cholesterol (TC) on age, gender, race, smoking status, diabetes status, and cholesterol treatment status to predict their change over time. Based on clinical expertise, we code every cholesterol-lowering drug as a moderate intensity statin with the exception of atorvastatin and rosuvastatin, which are coded as high intensity statins.

Our final population is determined on the basis of the USPSTF statin guidelines (Bibbins-Domingo et al. 2016). Based on discussions with our clinical collaborators, we perform genetic testing on any patient whose risk for ASCVD events at the first year of our study would be sufficiently different after the addition of genetic information. Please refer to Marrero et al. (2019) for a complete description of the population that receives genetic testing.

3.2 Risk Scores

The risk for ASCVD events due to clinical factors of each patient per year is measured using an existing pooled cohort equations (PCE) risk score (Goff et al. 2014). This risk score is based on a proportional hazards model with age, gender, race, smoking status, diabetes status, SBP, HDL, and TC as explanatory variables. Based on clinical expertise, we assume independence among the ASCVD events. Moreover, we assume that 60% of the ASCVD risk is due to CHD events (Benjamin et al. 2018).

While no information of the risk for stroke events due to genetic factors is available, based on communications with clinical collaborators we assume that the risk for CHD events due to genetic factors can be measured using a GRS. We assume the GRS of each patient does not change over time. Previous studies have shown that the risk for CHD due to genetic factors is nearly independent from the risk for CHD due to clinical factors (Khera et al. 2016; Khera et al. 2018; Natarajan et al. 2017). Past research has also found that the distribution of genetic scores is near normal (Khera et al. 2018; Mega et al. 2015). This allows us to model the genetic score of each patient in our population as a standard Gaussian random variable. We then estimate the GRS as the odds ratio for CHD events per standard deviation of the genetic score, as estimated by Khera et al. (2018). The PCE risk increases by an odds ratio of 1.67 per standard deviation of the genetic score (Khera et al. 2018; Abraham et al. 2016).

We assume the event rate predicted by the PCE risk score as true at a population level (Goff et al. 2014). Hence, the average risk for ASCVD events in the population is expected to remain unchanged after the addition of genetic information. Since the distribution of odds ratios is asymmetric, the GRS would likely change the average risk for CHD events at a population level. To account for this, we develop a correction factor for the genetic risk scores. We define this correction factor as the ratio of the mean odds for CHD due to clinical factors to the mean odds for CHD due to clinical and genetic factors at the first year of our study. Combining the two components of the risk for CHD events, we can then estimate the risk for ASCVD events due to clinical and genetic factors, or the GenePCE risk score.

3.3 State Space

Our simulation model uses a state-space representation to fully describe the characteristics of every patient at each year t. A state $s_t \in \mathcal{S}$ consists of a patient's demographic information, laboratory measurements, health status, and GRS at year t. Each patient's demographic information and laboratory measurements are incorporated into our state in the form of the PCE risk score. The demographic information encompasses the patient's age, race, and sex. The laboratory measurements include measurements of the patient's untreated SBP, HDL, TC, smoking status, and diabetes status. We assume each patient's health status can be classified at the beginning of each year into one of the following: (1) healthy (no history of CHD or stroke); (2) history of CHD but no adverse event in the current period; (3) history of stroke but no adverse event in the current period; (4) history of CHD and stroke but no adverse event in the current period; (5) survived a CHD event in the current period; (6) survived a stroke in the current period; (7) death from a non-cardiovascular disease related cause; (8) death from a CHD event in the current period; (9) death from a stroke in the current period; and (10) dead. We also assume that all patients have a healthy status at the beginning of our simulation.

3.4 Action Space

We limit our action space $\mathcal{A}$ to three treatment options: no treatment, moderate intensity statins, or high intensity statins. The treatment that patients receive each year depends on their current and future states. Once a treatment choice $a_t \in \mathcal{A}$ is made at the beginning of year t, we assume it has a near-immediate effect on each patient's health. We incorporate this effect by estimating the relative risk reduction due to treatment choice a_t. The estimates of the effect of cholesterol-lowering statins drugs on ASCVD events are derived from Collins et al. (2016).

3.5 Transition Probabilities

We use $p_t(\tilde{s}_t|s_t,a_t)$ to denote the transition probability from state s_t to state $\tilde{s}_t$, after taking action a_t at the beginning of year t. To calculate the transition probabilities, we first estimate the PCE risk score (risk for ASCVD events due to clinical factors) and GenePCE risk score (risk for ASCVD events due to clinical and genetic factors). As in previous studies, we assume that if patients have a history of CHD or stroke, they are more likely to have additional ASCVD events (Schell et al. 2016; Marrero et al. 2019). To account

for this, we multiply the patient's CHD odds by 3 if the patient has a history of CHD, multiply the stroke odds by 2 if the patient is at least 60 years old and has a history of stroke, and multiply the stroke odds by 3 if the patient has a history of stroke and is less than 60 years old (Brønnum-Hansen 2001; Burn et al. 1994). The risks for CHD and stroke are adjusted if the patient receives treatment. For people who have an event in a given year, we calculate the probability for this event to be fatal by applying fatality likelihoods to the post-treatment risk for CHD and stroke (Lloyd-Jones et al. 2009; Sussman et al. 2013). We calculate the fatality likelihoods as the ratio of known fatal event rates from the National Center for Health Statistics to the overall event rates predicted by the PCE risk, adjusted for age and gender (National Center for Health Statistics 2017). In addition, we incorporate the probability of non-ASCVD mortality using life-tables (Arias et al. 2017).

3.6 Rewards and Costs

We define the reward $q_t(s_t, a_t)$ as the quality of life (QoL) associated with the patient's health status at state s_t minus the burden from treatment choice a_t at year t. During our study, we assume that the QoL weight depends only on the patient's health status. We obtain the QoL weights and burden from the treatment choices used during our analyses from previous studies (Fryback et al. 1993; Pignone et al. 2006; Pignone 2007; Pandya et al. 2015). To evaluate the lifetime effect of the treatment choices, we assume the terminal condition of a patient can be computed as the product of the patient's expected lifetime, a mortality factor that accounts for the effect of ASCVD events on future mortality, and a terminal QoL weight (Fryback et al. 1993; Pignone et al. 2006; Pignone 2007; Arias et al. 2017; Pandya et al. 2015).

The cost of fatal and non-fatal ASCVD events, history of ASCVD events, medications, and genetic testing are also obtained from existing literature (O'Sullivan et al. 2011; Medical Expenditure Panel Survey 2015; GoodRx 2017; Color Genomics 2018). All the cost parameters in our analyses are adjusted for inflation from the original citations. All QoL weights and costs are discounted by 3%.

3.7 Treatment Strategies

To evaluate the impact of genetic testing, we model the process of sequentially determining cholesterol treatment medications over the 10-year planning horizon as a finite-horizon discrete-time MDP (Puterman 2014). We develop two MDP policies for each patient in our simulation, one based on clinical information only and another based on clinical and genetic information.

The objective of each MDP is to determine the treatment strategy that maximizes the expected discounted QALYs, based on the available information. We obtain optimal cholesterol treatment plans by solving the set of dynamic programming equations:

$$v_t(s_t) = \max_{a_t \in \mathcal{A}} \left\{ \sum_{\tilde{s}_t \in \mathcal{S}} p_t(\tilde{s}_t | s_t, a_t) \left[q_t(\tilde{s}_t, a_t) + \lambda v_{t+1}(\tilde{s}_t) \right] \right\},$$

for $s_t \in \mathcal{S}$, and $t = 0, 1, \ldots, T-1$, where $\lambda = 0.97$ is the discount factor of the model. Given a terminal condition $v_T(s_T)$, we can find the optimal treatment strategy by recursively computing the value functions $v_t(s_t)$ for $t = 0, 1, \ldots, T-1$ and $s_t \in \mathcal{S}$.

Both MDPs share the same states, transition probabilities, and rewards as our simulation model. However, the MDP model developed with clinical information only does not include genetic information when treatment decisions are made.

3.8 Model Evaluation

Our simulation framework allows for an estimation of the benefit of treatment plans with and without genetic information in a flexible and realistic way. Given the patient's initial state s_0, our simulation framework

enables us to approximate the total expected QALYs obtained from each treatment plan as:

$$v_0(s_0) \approx \frac{1}{K} \sum_{k=1}^{K} \sum_{t=0}^{T-1} \lambda^t q_{t,k}(s_{t,k}, a_{t,k}) + \lambda^T v_T(s_{T,k}),$$

where $q_{t,k}(s_{t,k}, a_{t,k})$ is the QoL associated with the patient's health status minus the treatment harm from $a_{t,k}$ at state $s_{t,k}$, year t, and replication k, $v_T(s_{T,k})$ is the terminal condition as defined in the MDP formulation at state $s_{T,k}$, $\lambda = 0.97$ is the discount factor of the model, and K is the total number of replications in our simulation model.

3.9 Calibration and Validation

To ensure the number of fatal and non-fatal CHD and stroke events in our simulation match those of the national statistics, we calibrate the amount of events predicted by the risk scores. Mortality from second cardiovascular events and known overdiagnosis of cardiovascular diseases is accounted for by decreasing the fatal event rates reported by the National Center for Health Statistics by 50% (Govindan et al. 2014). We estimate the overall event rates predicted by the risk scores by simulating the first year of the 10-year planning horizon of every patient following the USPSTF statin guidelines 50 times. We also run a baseline simulation in which the study population is untreated and the event rates are calibrated with national data (National Center for Health Statistics 2017). The calibration of our model was verified by a clinical researcher at the University of Michigan Medical School.

Our simulation was built with high face validity by discussing the parameters and logic with experts in the field. Our co-author, a practicing clinician at the University of Michigan Hospital and researcher at the Veterans Affairs Ann Arbor Healthcare System, helped to validate our model. Additionally, our estimates of the effect of genetic information on the risk for CHD events were discussed with geneticists at the Massachusetts General Hospital and the Department of Medicine at Harvard Medical School.

All analyses are performed with R (v3.5.0 The R Foundation for Statistical Computing, Vienna AT) (R Core Team 2016). The computations are made using 50 Intel Xeon CPUs and 256GB of RAM. A single replicate of our simulation requires approximately 5 seconds of computing time.

4 RESULTS

The number of replications needed to capture the heterogeneity in our population and to observe low-probability events is first evaluated. We study how the average QALYs saved and cost incurred per patient change by incorporating genetic information into treatment plans as we increase the number of replications. The effect of genetic information on each patient's PCE risk at the first year of our study is then investigated. Subsequently, we estimate the number of CHD events averted, QALYs saved, costs incurred, and cost per QALY saved following both treatment strategies, compared to no treatment. Lastly, we evaluate the impact of performing genetic testing in patients below and above 50 years old and in male and female patients while varying the cost of genetic testing from \$0 to \$400. See Marrero et al. (2019) for the implication of genetic testing in current practice and additional analyses.

4.1 Selection of Number of Replications

Before investigating the impact of genetic testing in a representative sample of the US population, we derive the number of replications to run our simulation model empirically. We observe that the average QALYs saved and cost incurred after 750 replications are close to the average QALYs saved and cost incurred at 2,000 replications with small variation (Figure 2). Based on this, we choose to run the simulation $K = 750$ times for all analyses.

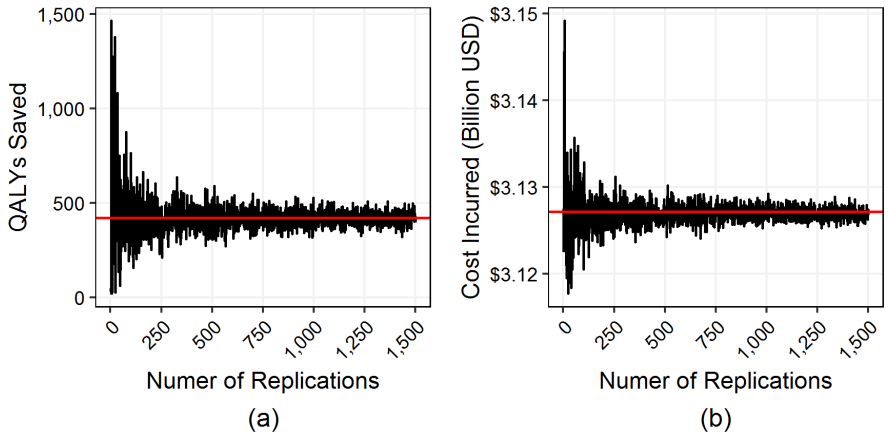

Figure 2: Convergence of QALYs saved and cost incurred due to genetic testing in simulation. Figure 2(a) illustrates the average QALYs saved due to genetic testing using from 1 to 1,500 replications. Points in Figure 2(b) represent the average cost incurred due to genetic testing using from 1 to 1,500 replications. The red horizontal lines in plots show the average QALYs saved and cost incurred at 2,000 replications.

4.2 Comparison of Risk Scores

Out of a population of 93.55 million patients, 16.17 million (17.29%) patients receive a genetic test at the first year of our study. Even though genetic information does not change the overall rate of events in the population, it may change the individual risk scores of patients. The genetic information of patients alters their risk for ASCVD events and may change their treatment plans. Figure 3 shows an overall comparison of the PCE and GenePCE risk scores at the first year of our study. We observe that genetic information helps identify individuals at increased risk for ASCVD events. However, it can be noticed that most of the population have GenePCE risk scores slightly lower than PCE risk scores.

4.3 Impact of Genetic Testing

Table 1 summarizes the health outcomes and costs of both treatment strategies compared to no treatment. We observe that the policies informed with clinical and genetic information averted 86 more CHD events and saved 390 more QALYs than the policies informed with clinical information only. Patients with GenePCE scores higher than PCE scores may require a more intense treatment than they would have received without genetic information. Conversely, patients for whom the GenePCE score is lower than the PCE score may require less treatment under the GenePCE score than given without genetic information.

After genetic testing, the cost of treatment decreases by $9.42 million. Since genetic testing provides information about which patients should receive higher treatment intensity, the cost due to ASCVD events decreases by $2.59 million using clinical and genetic information. Nonetheless, the policies derived using clinical and genetic information have an additional cost of $3.14 billion due to genetic testing ($200 per test in our base case). These cost estimates lead to an increase of nearly 3.13 billion USD in the total cost of the policies informed with clinical and genetic information. Understanding which population benefits the most from genetic testing may result in better health outcomes and lower costs.

4.4 Population and Genetic Testing Cost Analysis

By performing genetic testing on different populations, we are able to further identify which individuals would benefit the most from a genetic test. Both treatment strategies are well below the commonly used cost-effectiveness thresholds for all populations and testing costs, when compared to no treatment (Neumann

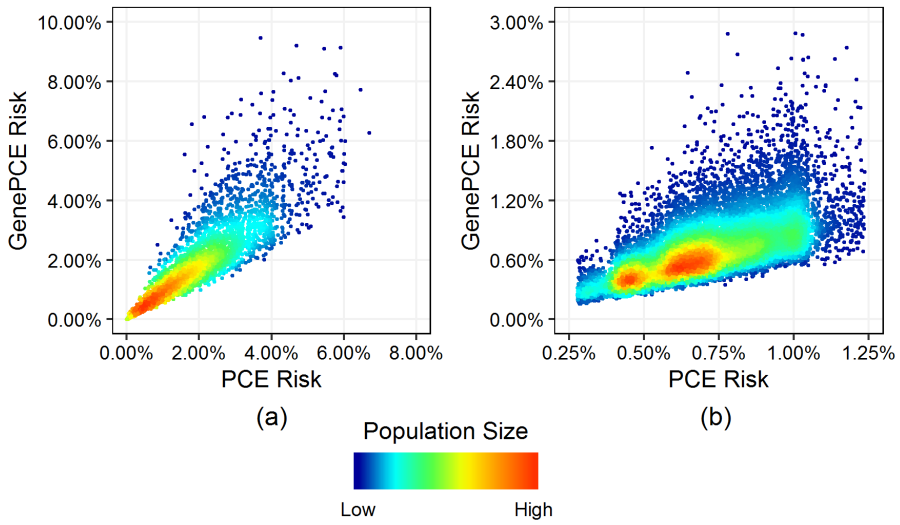

Figure 3: Comparison of PCE and GenePCE risk scores. The population size is represented with the color gradient (dark blue indicates the smallest population sizes and dark orange indicates the biggest population sizes). Figure 3(a) shows the risk scores of the whole population (93.55 million people). Figure 3(b) shows the risk scores of the patients that receive a genetic test during the first year of our study (16.17 million people).

et al. 2014). We find that the policies informed with clinical and genetic information are cost-saving compared to the policies informed with clinical information only if there is no cost associated with genetic testing. Genetic testing is most cost-effective if performed on people who are less than 50 years old. It is least cost-effective if performed on female individuals only. However, the incremental cost-effectiveness ratio (ICER) of the policies informed with clinical and genetic information compared to the policies derived with clinical information only is considerably higher than the regularly used cost-effectiveness thresholds in all scenarios (Neumann et al. 2014). The results of our population and genetic testing cost analysis are included in Figure 4.

5 CONCLUSIONS AND FUTURE WORK

In this paper, we presented a simulation framework to evaluate the implications of genetic testing on optimal cholesterol treatment plans using a 10-year planning horizon. We applied this framework to a large sample representative of an adult population in the US. Although our simulation required longer running times

Table 1: Population health outcomes at the end of the 10-year time horizon. The policies informed with clinical information only and with clinical and genetic information are compared to no treatment. Results are averages over 750 replications. Values within parenthesis indicate the standard deviation across replications.

Information Considered	Clinical	Clinical and Genetic
Moderate intensity treatment, patient-years	121,875 (25,979)	155,512 (30,085)
High intensity treatment, patient-years	149,188,644 (276,853)	149,153,543 (277,348)
CHD events averted by treatment	275,038 (30,272)	275,124 (30,298)
QALYs saved	4,286,972 (241,950)	4,287,362 (242,010)
Total cost, billion USD	$27.81 ($2.49)	$30.94 ($2.49)
Cost/QALY saved, USD	$6,488 ($840)	$7,216 ($874)

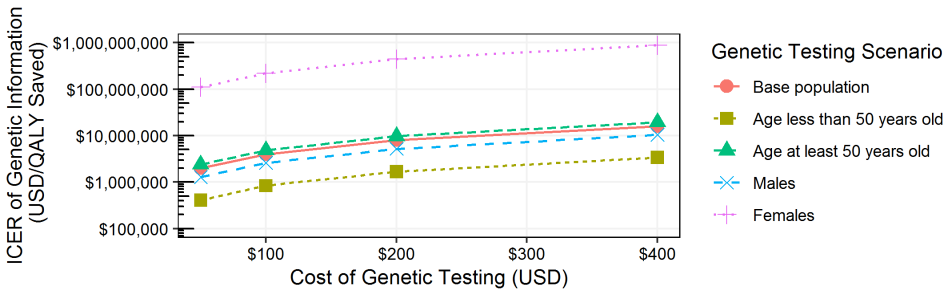

Figure 4: Incremental cost-effectiveness ratio (ICER) of genetic information in different populations and costs of genetic testing. Points indicate the ICER of genetic information at genetic testing costs of $50, $100, $200, and $400 per test. The base population represents performing genetic testing according to clinical expertise and the USPSTF statin guidelines. A base-10 logarithmic scale was used in the vertical axis for illustration purposes. Minor tick marks in the vertical axis represent 10% increases between the major tick marks.

than simpler models (such as Markov cohort models), it enabled us to asses different aspects of our model with great flexibility.

While we have modeled genetic testing based on the USPSTF statin guidelines and clinical expertise, two key extensions of this work are to identify the population that would benefit the most from genetic information and when to perform such a test. We leave these questions for future work (Marrero, Lavieri, and Sussman 2019). It might also be worthwhile to limit the amount of treatment recommended by the MDPs so that optimal treatment plans are cost-effective.

This work could also be extended by incorporating other cholesterol-lowering drugs (such as fibrates). We chose statins because they are the most commonly used cholesterol-lowering drugs and there is reliable data about their benefit. Another extension of this work could be to incorporate the effect of genetic testing on hypertension treatment or aspirin use. The same genetic test could be used to guide decisions of multiple conditions at once. However, risk prediction plays a smaller role in hypertension treatment decisions and the clinical benefit of aspirin is now unclear (McNeil et al. 2018).

Although there are multiple extensions of this simulation model, we have developed a framework to evaluate the impact of genetic testing on optimal cholesterol treatment plans. Our simulation framework may also be used to evaluate other treatment strategies such as the USPSTF guidelines or the ACC/AHA statin guidelines in practice (Bibbins-Domingo et al. 2016; Goff et al. 2014; Marrero et al. 2019). We sought to find treatment strategies that maximized the expected discounted QALYs due to their popularity in quantifying the health-related benefits gained from clinical interventions (Fonarow et al. 2017; Glover et al. 2018; Jarmul et al. 2018; Mason et al. 2014). Other objective functions (such as cost alone, or more general utility functions) may be used to find treatment plans.

While our model may not be straightforward to implement at its current stage, it serves as a first step towards quantifying the effect of genetic information in general treatment guidelines. In fact, current guidelines already require risk calculation. We believe that when a GRS is already calculated, incorporating these results would be technically feasible. As genetic information becomes increasingly available, having such a framework becomes crucial.

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