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

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ABSTRACT

Atherosclerotic cardiovascular disease (ASCVD) is among the top causes of death in the US. Although research has shown that ASCVD has genetic elements, the understanding of how genetic testing influences its prevention and treatment has been limited. To this end, we develop a simulation framework to estimate the risk for ASCVD events due to clinical and genetic factors. We model the health trajectory of patients stochastically and determine treatment decisions with and without genetic testing. Since the cholesterol level of patients is one controllable risk factor for ASCVD events, we model cholesterol treatment plans as a Markov decision process. By simulating the health trajectory of patients, we quantify the effect of genetic testing in optimal cholesterol treatment plans. As precision medicine becomes increasingly important, having a simulation framework to evaluate the impact of genetic testing becomes essential.

1 INTRODUCTION

Genetic tests are recently developed tools that could be used to improve medical assessments and to identify patients at risk of certain diseases. A genetic risk score (GRS) could help characterize individuals who might receive the greatest benefit from treatment. One condition with known genetic components is Atherosclerotic cardiovascular disease (ASCVD), constituted of coronary heart disease (CHD) and stroke (MacRae et al. 2016). While the role of genetic testing in the prevention and treatment of ASCVD has been limited, the development of the new GRS could make genetics central to daily cardiovascular care (Natarajan et al. 2017). The risk for ASCVD events is mainly composed of demographic, behavioral, and clinical factors (Goff et al. 2014). Among these, the cholesterol level of patients is one factor that can be managed. The objective of this work is to understand how optimal cholesterol treatment plans change with the addition of genetic information and to evaluate how the cost-effectiveness of genetic testing changes with respect to the population tested. This is done by combining Markov decision process (MDP) modeling and stochastic simulation.

2 MODELING FRAMEWORK

We consider a large representative sample of the US population composed of adult White or African-American patients from 40 to 75 years old. The health trajectory of every patient in this population is simulated over a 10-year planning horizon. Patients receive genetic testing if a GRS has reasonable chance of changing their treatment at the first year of the study, according to the US Preventive Services Task Force statin guidelines (Bibbins-Domingo et al. 2016).

Before the start of the simulation, I calculate the risk for ASCVD events of every patient at each year using risk scores that are and are not informed by genetic information. Although no information of the risk for stroke events due to genetic factors is available, I assume that the risk for CHD events due to genetic

factors can be measured using a GRS. To ensure the number of CHD and stroke events in the simulation match those of the national statistics, I calibrate the number of events predicted by the risk scores. Transition probabilities are estimated based on each risk score to determine the treatment strategies.

In my work, I model cholesterol treatment plans as a finite-horizon MDP. Two treatment plans are developed for each patient in our population: (i) one based on clinical information and (ii) another based on clinical and genetic information. At the beginning of every year, each patient receives one of the following three treatment options: no treatment, moderate intensity statins, or high intensity statins. The objective of each MDP is to determine the treatment strategy that maximizes the expected discounted quality-adjusted life-years. The treatment plans are compared in a simulation-based framework.

Since genetic variants play a role on patients' health (independent of whether or not they have received genetic testing), the health trajectory of every patient evolves according to the risk score informed by clinical and genetic information. I compare the outcomes of each patient under both treatment strategies at every replication and year of the simulation. Finally, I estimate the lifetime effects of the treatment decisions on each patient.

All analyses are performed with R (v3.5.0 The R Foundation for Statistical Computing, Vienna AT). The computations are made using 50 Intel Xeon CPUs and 256GB of RAM. To capture the heterogeneity in the population and observe low-probability events, the simulation is replicated 750 times. A single replicate of the simulation requires approximately 5 seconds of computing time.

3 RESULTS AND CONCLUSIONS

Out of a population of 93.55 million patients, 16.17 million patients would receive a genetic test at the first year of the study. While most of the population have slightly lower risk scores after the addition of genetic information, I found that the GRS also helps characterize patients at increased risk for CHD events. The policies derived with clinical and genetic information prevented 86 more CHD events and saved 390 more QALYs while costing $3.13 billion less than the policies derived with just clinical information. I 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 least cost-effective if performed on female individuals only. It is most cost-effective if performed on people who are less than 50 years old. Yet, the incremental cost-effectiveness ratio of the policies derived with clinical and genetic information compared to the policies derived with clinical information only is considerably higher than the commonly used cost-effectiveness thresholds (Neumann et al. 2014).

While the role of genetics is promising in many applications, it remains rather unclear. The understanding of the potential impact of genetics on disease management becomes crucial as precision medicine continues to become increasingly important.

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