THE CLINICAL UTILITY AND COST-EFFECTIVENESS OF CARDIOVASCULAR GENETIC RISK TESTING FOR TARGETING STATIN THERAPY IN THE PRIMARY PREVENTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Jamie Aileen Jarmul

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor in Philosophy in the Department of Health Policy and Management in the Gillings School of Global Public Health.

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Approved by:

Morris Weinberger

Michael Pignone

Christy Avery

Kristen Hassmiller Lich

Stephanie Wheeler

ABSTRACT

Jamie Aileen Jarmul: The clinical utility and cost-effectiveness of cardiovascular genetic risk testing for targeting statin therapy in the primary prevention of atherosclerotic cardiovascular disease
(Under the direction of Morris Weinberger)

This three-paper dissertation examined the clinical utility and cost-effectiveness of testing for cardiovascular genetic risk, using a previously developed 27-SNP cardiovascular genetic risk score (cGRS), to target statin therapy in the primary prevention of atherosclerotic cardiovascular disease (ASCVD).

In the first paper, I tested the association between the 27-SNP cGRS and 10-year ASCVD outcomes in black and white non-diabetic, ASCVD-free participants from the ARIC study. After adjusting for traditional ASCVD risk factors, I found that intermediate and high cGRS was associated with a 1.32-fold (95% CI: 0.97-1.79) and 1.47-fold (95% CI: 1.03-2.10) higher risk of 10-year pooled ASCVD events, respectively; however, the improvement in risk prediction was small. In the second paper, I used an unbiased model selection algorithm with 10-fold cross-validation to determine the expected distribution of the 27-SNP cGRS in a multi-ethnic, nationally representative sample of individuals, the Add Health study. I found that race/ethnicity was the only statistically significant predictor of cGRS, explaining a fair amount of the variation (CV r^2= 0.177), and that the risk increase associated with high expected cGRS was modest (approximately 30% increase in 10-year predicted ASCVD risk, comparable to the risk increase associated with being 5 years older). In the third paper, I updated the UNC-RTI CHD Prevention

Model to investigate whether testing for the 27-SNP cGRS is a cost-effective strategy for targeting statin therapy in the primary prevention of ASCVD. I found that obtaining a 27-SNP cGRS test to prevent some patients from being prescribed a statin was generally not a cost-effective strategy for a set of clinical scenarios of individuals with 10-year predicted ASCVD risk ranging from 2.5% to 7.5%.

In conclusion, I found that a 27-SNP cGRS is independently associated with 10-year ASCVD outcomes in a diverse population; however, the absolute change in updated 10-year ASCVD predicted risk estimates is modest. More importantly, through the work completed in the dissertation, I can conclude that, when compared to no genetic risk testing, obtaining cardiovascular genetic risk information by testing for a 27-SNP cGRS is generally not a cost-effective strategy for targeting statin therapy in the primary prevention of ASCVD.

To my husband, Jonathan, for his constant love and support, and our two boys, Jordan and James, for always being the best part of my day. To my parents, Margery and Doug, and my in-laws, David and Champa, for their love, support and babysitting.

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LIST OF ABBREVIATIONS

ADD HEALTH	National Longitudinal Study of Adolescent to Adult Health
ARIC	Atherosclerosis Risk in Communities
ASCVD	Atherosclerotic cardiovascular disease
CAC	Coronary artery calcium
CGRS	Cardiovascular genetic risk score
CHD	Coronary heart disease
CV	cross-validated
CVD	cardiovascular disease
GWAS	genome-wide association study
HDL	high density lipoprotein
ICER	Incremental cost-effectiveness ratio
LD	linkage disequilibrium
LDL	low density lipoprotein
MI	Myocardial infarction
NNT	Number needed to treat
PCEs	Pooled Cohort Equations
QALY	quality-adjusted life years
SBP	systolic blood pressure
SNP	Single nucleotide polymorphism
TC	total cholesterol

CHAPTER 1: BACKGROUND

1.1. Cardiovascular disease risk prediction and primary prevention with statins

In the US, atherosclerotic cardiovascular disease (ASCVD) is responsible for one out of every three deaths and, in 2008, accounted for nearly $300 billion in health care costs (Roger 2011). By 2030, up to 40% of Americans are expected to have ASCVD and medical costs attributable to ASCVD are projected to double (Mozaffarian 2015). ASCVD, which includes fatal coronary heart disease (CHD), non-fatal myocardial infarction (MI), and ischemic stroke, can lead to substantial morbidity and reductions in quality of life. Thus, primary prevention of ASCVD is critical to reduce the population burden of ASCVD and improve overall population health.

Statins, a group of highly efficacious lipid-lowering agents, significantly reduce the risk of MI, stroke and all-cause mortality (Chou 2015). The 2013 American Heart Association (AHA)/American College of Cardiology (ACC) ASCVD risk reduction guidelines recommend moderate to high intensity statin therapy for primary prevention in nondiabetic, ASCVD-free individuals with 10-year predicted ASCVD risk >7.5%, calculated using the Pooled Cohort Equations (PCEs) (Goff 2013; Stone 2013). The PCEs, published along with the ASCVD primary prevention guidelines, calculate predicted 10-year ASCVD risk using the traditional risk factors age, sex, race/ethnicity, systolic blood pressure, total cholesterol, HDL cholesterol, anti-hypertension treatment, smoking status and presence of diabetes as inputs (Goff 2013). Based on these guidelines, approximately 45 million Americans without pre-existing ASCVD or diabetes are currently eligible for statin therapy (Pencina 2014). Of these, 10.4 million are newly eligible

for statin therapy when compared statin recommendations from the previous ATP-III guidelines (Pencina 2014). Consequently, the PCEs and 2013 AHA/ACC guidelines on ASCVD risk reduction have been the subject of significant controversy (Amin 2014; Martin 2014). Some experts have questioned the use of the PCEs because they have been showed to significantly overestimate the risk of ASCVD events in several external cohorts (Ridker and Cook, 2013). Furthermore, in individuals near the recommended 7.5% statin treatment threshold, the number needed to treat (NNT) to prevent CVD outcomes is high (NNT to prevent one CVD death: 217; NNT to prevent one MI: 108; NNT to prevent one all-cause death: 244); thus, many individuals will be treated and few will benefit (Chou 2015).

The 2013 AHA/ACC ASCVD risk reduction guidelines suggest that additional testing for nontraditional risk factors, such as coronary artery calcium (CAC), high sensitivity C-reactive protein, and ankle-brachial index, may be useful prior to statin initiation, as a part of the shared decision-making process with patients (Stone 2013). Furthermore, additional tests may be helpful to assess other aspects of risk not covered by traditional risk factors, such as atherosclerotic burden or vessel reactivity. However, interpreting results from nontraditional risk factor testing in the context of baseline ASCVD risk estimates is challenging, and the relative importance of different nontraditional risk factors is a topic that has been widely debated (Yeboah 2016; Zamarano and del Val 2016; Nasir 2015).

1.2. Using cardiovascular genetic risk information to improve cardiovascular disease risk prediction

The use of cardiovascular genetic risk information in ASCVD risk prediction and clinical decision-making is an area of intense research and debate (Kullo 2016; Goldstein 2014; Paynter 2016; Tikkanen 2013; Krarup 2015; Shah 2016). Genetic risk scores aggregate information about

the effect of many genetic variants (single nucleotide polymorphisms, or SNPs) on disease outcomes (Smith 2015). An individual's cGRS may reflect an individual's genetic susceptibility to accelerated atherosclerosis, related potentially to errors in cholesterol metabolism, thrombosis and/or other endothelium-related factors (Vasan 2006).

One advantage of using genetic information for risk stratification is that an individual's genetic markers of increased ASCVD risk are present from birth and fixed throughout an individual's lifetime. Genetic testing could potentially be used to identify "healthy" (no cardiovascular risk factors), younger individuals that have increased cardiovascular genetic risk. In these individuals, early initiation of lifestyle interventions or statin therapy to prevent or slow progression of atherosclerosis could reduce lifetime risk of ASCVD (Thanassoulis 2013).

Early papers looking at 21-SNP cGRS' reported statistically significant, but small magnitude, improvements in area under the curve, after being incorporated along with traditional risk factors into risk prediction models (Morrison 2007; Ripatti 2010; Thanasoullis 2012; de Vries 2015). In 2015, Mega et al. demonstrated a statistically significant association between a 27-SNP cGRS and CHD outcomes (nonfatal and fatal MI), after adjusting for traditional cardiovascular risk factors (Mega 2015). Furthermore, Mega et al. reported that individuals with higher cGRS experience a greater absolute risk reduction from statin therapy compared to individuals with a low cGRS.

Despite Mega et al's intriguing results, we believe there are gaps that merit evaluation. First, Mega et al. used pooled data from several randomized clinical trials examining statin efficacy, which included primarily individuals of European ancestry; as such, the association between the 27-SNP cGRS and CHD outcomes may not replicate across populations, particularly African

Americans or in population-based settings (Franchescini 2014). Furthermore, Mega et al's analysis was limited by the relatively short follow-up period in the statin efficacy trials (maximum 5 years). Last, the 27-SNP cGRS was developed based on SNPs that had been shown to be related to incident CHD, but not ischemic stroke, in prior GWAS studies (Mega 2015). Thus, there may not be a significant association between the 27-SNP cGRS and pooled ASCVD outcomes, which includes non-fatal MI, fatal CHD and ischemic stroke. Because individuals of African ancestry suffer disproportionally from stroke compared to other ASCVD outcomes (Guetierrez 2014), inclusion of stroke as an endpoint provides valuable additional insight into downstream health outcomes associated with non-traditional cardiovascular disease risk factors in diverse populations.

More importantly, it is unclear whether cardiovascular genetic risk testing alters clinical decision-making or ultimately improves cardiovascular disease outcomes. One recently published randomized controlled trial found that providing cardiovascular genetic risk information to patients resulted in more prescriptions of statins and significantly lower LDL levels compared to patients that had not been provided cardiovascular genetic risk information (Kullo 2016). While this may suggest that providing genetic risk information increases patients' acceptance and/or adherence to therapy, the follow-up period was short (6 months) and thus difficult to know if these effects will continue over longer periods of time.

1.3. Dynamic risk prediction and clinical decision-making

Applying population-based ASCVD risk prediction equations, such as the PCEs, to individual patients can become problematic because these risk scores are only accurate risk estimates for an individual on average and have high intrinsic variance for cardiovascular risk

prediction when applied in a specific patient (McEvoy 2014). We can improve individual-level risk prediction by integrating information that is obtained by testing for nontraditional or novel risk factors into existing ASCVD risk estimates (Kooter 2011; Pletcher 2011).

Re-estimating the ASCVD risk prediction models with the nontraditional risk factor included is one approach for combining the new information provided by the nontraditional risk factor with existing information about traditional risk factors (Yeboah 2016; McClelland 2015; Antioches 2016; Ruwanpathirana 2015). However, this approach is time consuming and requires a large data set that includes baseline risk factor measurement as well as sufficient duration of follow-up to capture ASCVD outcomes. Furthermore, re-estimating ASCVD risk prediction models to include the novel risk factor will only give us the population-average effect of the nontraditional risk factor on the variation in ASCVD events, which is unlikely to help improve risk stratification within subgroups of the population, which may have differing expected distributions of the novel risk factor (McEvoy 2014; Amin 2014; Yeboah 2015).

Dynamic risk prediction is a more flexible approach than completely re-estimating ASCVD risk prediction models. Dynamic risk prediction is when a baseline risk estimate-such as the PCEs—is updated using individualized information about the expected distribution of a novel risk factor for a given individual (Pletcher 2011; Jarmul 2015). This allows the same baseline risk estimate to be used regardless of the novel risk factor to be integrated. We can improve individual-level prediction in specific patients in whom the expected distribution of a novel risk factor is substantially different than for the average individual within the population.

Once we know the expected distribution of a novel risk factor, we can integrate information about the novel risk factor into existing risk prediction models to produce expected

post-test risk estimates for individual patients (Kooter 2011; Pletcher 2011; Pletcher 2013; Jarmul 2015). Thus, dynamic risk prediction allows us to translate improved risk prediction offered by novel risk factors into actionable information that physicians can use to guide clinical decision-making around preventive therapies, such as statins or aspirin.

1.4. Using decision analysis and cost-effectiveness modeling to assess clinical utility of predictive risk information

Measures that are typically used to assess clinical utility of novel risk factors prediction include measures of reclassification (net reclassification index, integrated discrimination improvement), discrimination (area under the curve, c-statistic), and calibration (difference between observed and predicted risks). However, these measures do not sufficiently capture the trade-offs associated with clinical decision-making that is necessary to obtain the new information used in the model. Furthermore, the risks and costs associated with up-classification and down-classification are not necessarily equivalent and should be balanced against the expected benefits as a part of the clinical decision-making process (Pletcher 2011).

Clinical decision analysis and cost-effectiveness analysis are methods to explicitly define a set of clinical options and weigh the downstream risks, benefits and costs of each. Furthermore, through deterministic and probabilistic sensitivity analyses, decision-makers can consider the decision options while considering the effects of parameter uncertainty and stochastic variation in the estimates (Briggs 2012). These tools can be especially powerful for evaluating primary prevention or screening strategies, which are difficult to evaluate using randomized controlled trials because long-term follow-up is generally required to capture the benefits associated with the intervention. In particular, evaluation of several test/treat strategies for targeting prevention

interventions may be infeasible to evaluate in an RCT due to large sample size that would be required to adequately power comparisons between all the study arms (Pletcher 2011).

For these reasons, cost-effectiveness analyses are frequently conducted to evaluate test/treat strategies; however, the tests that are being investigated are generally diagnostic or prognostic tests, as opposed to tests that provide predictive information. When evaluating tests that provide predictive risk information, it is crucial to consider whether there are established baseline risk estimates ('pretest risk') and how the new predictive risk information should be integrated into baseline risk estimates to produce updated risk estimates ('post-test risk'). Failure to adequately consider pre-existing knowledge of baseline risk, such as information about clinical risk factors or established risk prediction models, may lead modelers and decision-makers to over-estimate the value of the additional risk information provided by the predictive test.

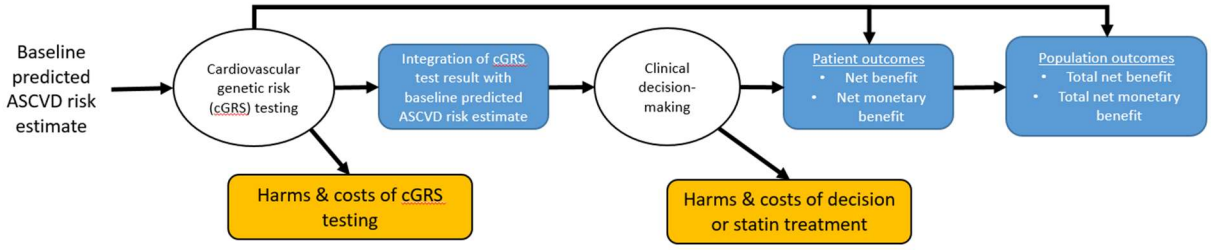
Previous work has been done to model the cost-effectiveness of CAC scanning (Pletcher 2014; Roberts 2015), as well as the comparative-effectiveness of CAC scanning compared to CRP testing (Galper 2015). However, the cost-effectiveness analysis of CAC scanning by Pletcher et al. is the only analysis to explicitly model the integration of CAC results into pre-existing risk estimates to update transition probabilities based on expected CAC scan results; results from this analysis indicated that targeting statin therapy based on CAC scanning is generally not a cost-effective strategy, except under certain favorable statin assumptions (Pletcher 2014). In contrast, the analysis from Roberts et al did not consider CAC distribution in combination with pre-existing risk estimates, and found that CAC scanning to target statin therapy was generally cost-saving and dominated other statin treatment strategies (Roberts 2015). While these results were produced using different cost-effectiveness models, and thus not directly comparable, it is

reasonable to suggest that the more aggressive conclusions found by Roberts et al. may have been the result of over-estimation of the risk information provided by CAC beyond traditional ASCVD risk factors.

Clinical validity assesses whether a relationship exists between a genetic test and a clinical phenotype.

Figure 1: Conceptual Framework

Cost-effectiveness assesses incremental cost per unit outcome, compared to an alternative option



1.5. Conceptual framework

The conceptual framework in Figure 1 shows the steps necessary to determine whether obtaining additional predictive risk information, in the form of testing for a novel risk factor, should be used for guiding clinical decisions regarding prevention interventions. First, a novel risk factor must be independently associated with the outcomes of interest. Second, the novel risk factor should be clinically useful, meaning that information provided by the novel risk factor should be actionable, change clinical decision-making, and improve health outcomes. Third, for the information provided by the novel risk factor to be cost-effective, the improvement in health outcomes (resulting from the change in clinical decision-making) should be able to be achieved at a cost that is acceptable to a decision-maker in a resource-constrained environment. The work presented in this dissertation thesis will follow this framework to address the question of

whether testing for a 27-SNP cGRS is a cost-effective strategy for targeting statin therapy in the primary prevention of ASCVD.

CHAPTER 2: ASSOCIATION BETWEEN A 27-SNP CGRS AND ASCVD OUTCOMES IN A DIVERSE, POPULATION-BASED COHORT STUDY

2.1. Background

Prediction of ASCVD risk is important to aid clinical decision-making regarding initiation of preventive therapies, such as whether to prescribe statins or aspirin. Risk prediction algorithms, such as the PCEs or Framingham equations, rely primarily on a set of traditional risk factors, including age, sex, blood pressure, lipid levels and smoking (Goff 2013). Many novel, independent ASCVD risk factors have been identified, but whether they merit inclusion in risk assessment and clinical decision-making algorithms remains controversial and the subject of much ongoing research (Cainzos-Achirica 2015; Yeboah 2016; Zamarano 2016).

One area of intense research is the use of cardiovascular genetic risk information in clinical decision-making (Kullo 2016; Paynter 2016; Tikkanen 2013; Krarup 2015; Shah 2016). Early papers evaluating 21-SNP cGRS reported statistically significant, but small magnitude, improvements in area under the curve, after incorporating traditional risk factors (Morrison 2007; Ripatti 2010; Thanassoulis 2012; de Vries 2015). In 2015, Mega et al. demonstrated a statistically significant association between a 27-SNP cGRS and CHD outcomes (nonfatal and fatal MI), after adjusting for traditional cardiovascular risk factors, over average follow-up time of 3.6 years (Mega 2015).

However, the 27-SNP cGRS from Mega et al. was developed and validated in individuals primarily of European ancestry; thus, the observed association between the 27-SNP cGRS and

CHD outcomes may not replicate across populations, particularly to populations of African ancestry (Franchescini 2014). Furthermore, the 27-SNP cGRS was developed based on SNPs that had been shown to be related to incident CHD, but not ischemic stroke, in prior GWAS studies (Mega 2015). Thus, there may not be a significant association between the 27-SNP cGRS and pooled ASCVD outcomes, which includes non-fatal MI, fatal CHD and ischemic stroke. Because individuals of African ancestry suffer disproportionally from stroke compared to other ASCVD outcomes (Guetierrez 2014), inclusion of stroke as an endpoint provides valuable additional insight into downstream health outcomes associated with non-traditional cardiovascular disease risk factors in diverse populations.

The Atherosclerosis Risk in Communities (ARIC) study is a prospective, population-based study of the etiology and natural history of atherosclerosis in black and white individuals from four communities in the United States. The ARIC study provides an excellent opportunity to investigate the association between the 27-SNP cGRS, incident CHD and pooled ASCVD outcomes in a diverse, population-based cohort.

2.2. Methods

2.2.1. Data Source

The ARIC study is an ongoing prospective cohort study of atherosclerosis and its clinical sequelae in black and white individuals living in four U.S. communities (Jackson, Mississippi; Forsyth County, North Carolina; suburbs of Minneapolis, Minnesota; Washington County, Maryland) (ARIC Investigators 1989). Four ARIC field centers randomly selected and recruited a cohort sample of ~4,000 individuals aged 45-64 from their communities (total n= 15,792). Participants received a comprehensive baseline examination, including medical, social and

demographic data at visit 1 in 1987-1989. After visit 1, three triennial exams were conducted and a fifth visit occurring between 2011 and 2013. Participants were contacted semi-annually by telephone for follow-up to assess health status of the cohort.

2.2.2. Study Cohort

We included all individuals with visit 1 data who consented to allow use of genetic data for research (n= 12,219). We excluded participants with congestive heart failure (defined using the Gothenburg criteria) (n= 545), prevalent coronary heart disease (CHD) (n=584), diabetes (n=1,118), or prevalent stroke (n= 204) at visit 1. Prevalent diabetes, CHD, and stroke was classified using ARIC investigator definitions (White 1996). We excluded individuals who reported statin use at any of the four visits to examine the role of cGRS in primary prevention of ASCVD (n=1,304). We excluded an additional 312 participants due to missing data on covariates (systolic blood pressure, total cholesterol, HDL cholesterol, anti-hypertensive medication use and current smoking status), for a final sample size of 8,884 (Appendix 3).

2.2.3. Measures

Key dependent variables: non-fatal myocardial infarction (MI), fatal CHD, and ischemic stroke

Our primary outcome variable was time-to-first ASCVD event, and our secondary outcome variable was time-to-first CHD event. Incident CHD events included definite or probable non-fatal MI and definite CHD death. Pooled ASCVD events included all pooled CHD events, as well as definite or probable non-fatal ischemic stroke and definite or probable fatal ischemic stroke. Incident CHD was determined by follow-up telephone surveys and by surveying discharge lists from local hospitals and death certificates for potential cardiovascular events (White 1996). All identified events were adjudicated by ARIC investigators. Details on

ascertainment and classification of CHD events have been published elsewhere (White 1996). Individuals who did not experience an event within 10 years were censored at date of death, last known contact (if lost to follow-up) or after 10 years of follow-up time.

Key independent variables: cardiovascular genetic risk

We calculated the 27-SNP cGRS reported by Mega et al. 2015 (Appendix 22)in each race/ethnicity using typed (e.g. Affy 6, Metabochip, or exome chip) or, if unavailable, 1000 genomes imputed data as the sum of the dosage (or genotype for typed data) for each SNP in Appendix 22 weighted by the log of the odds ratio reported with the SNP in the table, as shown in Appendix 1.[16] The SNPs, risk alleles and associated odds ratios used in the cGRS were selected from a literature review of GWAS- CHD outcomes studies completed by Mega et al. We excluded SNPs with poor imputation quality (oevar_imp <0.3) or with minor allele counts <10. We used race-specific quintiles to assign ordinal categories for the cGRS; quintile 1 was defined as low risk, quintiles 2-4 were defined to be intermediate risk and quintile 5 was high risk, in accordance with Mega et al. (2015).

Covariates: traditional cardiovascular risk factors

We used age, gender, race, baseline total cholesterol, HDL cholesterol, systolic blood pressure, current smoking status and anti-hypertensive medication use in the statistical models as covariates to adjust for the independent effect of these variables on ASCVD outcomes.

2.2.4. Analysis

We calculated summary statistics to describe baseline ASCVD risk factors. We used the Framingham risk equations to calculate 10-year CHD risk and the Pooled Cohort Equations to

calculate 10-year ASCVD risk (Chambless 2003; Goff 2013). We calculated the total number of events, average time-to-event and observed event rate separately for each cGRS category.

We used Cox proportional hazards regression to investigate the association between cGRS and both incident CHD and ASCVD outcomes, after adjusting for the effects of traditional ASCVD risk factors.

Model development and performance

We used the Grambsch & Therneau test for non-zero slope of Schoenfeld residuals over time to test the proportional hazards assumption for each model; a chi-square with p-value less than 0.05 indicates violation of the proportional hazards assumption (Hosmer and Lemeshow 2008). We also visually examined plots of -ln(ln(survival plot)) vs ln(time) across each cGRS category; convergence, divergence or crossing of lines indicates violation of proportional hazards assumption. The proportional hazards assumption was satisfied for a follow-up of 10 years.

We used the Wald test to determine whether the effect of cGRS on model outcomes was statistically significant at $p<0.05$. Using the Wald test, we tested the hypothesis that the beta coefficients associated with intermediate cGRS and high cGRS were significantly different than 0, and we did this for both the pooled ASCVD model and the incident CHD model. Next, for each of the models described above, we tested a pre-specified interaction between race and the cGRS in predicting events by testing whether the addition of an interaction term between the 27-SNP cGRS and race resulted in a statistically significant increase in predictive power using a likelihood ratio test.

We tested model discrimination by evaluating the change in Harrell's C-statistic. We used likelihood ratio tests to assess if the addition of cGRS to each of the Cox models resulted in a statistically significant increase in the Harrell's C-statistic at $p<0.05$.

All statistical analyses were performed using Stata 14 (Stata, College Station, TX).

2.3. Results

2.3.1. Baseline ASCVD risk factors

There were 8,884 participants included in the final analytic dataset: 8,884, 6,937 (79%) were white and 1,889 (21%) were black. The average age for all participants was 53.7 ± 5.7 years; the average total cholesterol was 210 ± 38 mg/dL and the average LDL cholesterol was 133 ± 37 mg/dL. Table 1 shows the baseline risk factors stratified by gender and race. The average cGRS differed by race; for white participants, the cGRS was 0.87 ± 0.10, while the average cGRS for black participants was 0.79 ± 0.08. Average 10-year CHD risk and 10-year ASCVD risk also varied by race, as well as gender (Table 1). Baseline ASCVD risk factors, 10-year CHD risk and 10-year ASCVD risk did not vary by cGRS category, apart from LDL cholesterol (Table 2). LDL cholesterol was statistically significantly higher for the intermediate cGRS and high cGRS categories, compared to low cGRS, but the magnitude of the difference was small (low cGRS: 131 ± 37 mg/dL; intermediate cGRS: 133 ± 37 m/dL; high cGRS: 135 ± 36 mg/dL; p=0.01).

2.3.2. Pooled ASCVD events and incident CHD events during 10 years of follow-up

The observed event rates for both pooled ASCVD events and incident CHD events are shown in Table 3. When we separated the outcomes by GRS, we observed higher event rates corresponding with higher cGRS for both pooled ASCVD events and incident CHD events.

Table 1: Summary statistics of baseline ASCVD risk factors and global risk scores, by gender and race

Variable of interest	White (n=6,937)		Black (n=1,889)	
	Male (n=3,143)	Female (n=3,794)	Male (n=740)	Female (n=1,149)
Cardiovascular genetic risk				
Mean overall cGRS	0.89 ± 0.10	0.89 ± 0.10	0.79 ± 0.08	0.79 ± 0.08
Cardiovascular disease risk factors				
Age at baseline (years)	54.3 ± 5.7	53.6 ± 5.7	53.1 ± 5.9	52.5 ± 5.6
Total cholesterol at baseline (mg/dL)	206 ± 36	212 ± 39	209 ± 41	213 ± 42
HDL cholesterol at baseline (mg/dL)	34 ± 10	42 ± 10	39 ± 12	41 ± 11
LDL cholesterol at baseline (mg/dL)	136 ± 34	130 ± 37	136 ± 40	133 ± 41
Systolic Blood Pressure at baseline (mmHg)	119 ± 15	116 ± 17	129 ± 21	126 ± 20
Diastolic Blood Pressure at baseline (mmHg)	74 ± 10	70 ± 10	83 ± 13	78 ± 12
Current smokers (%) at baseline	24%	25%	37%	26%
Anti-hypertensive medication (%) at baseline	16%	20%	29%	39%
BMI at baseline (kg/m2)	27.2 ± 3.4	26.0 ± 5.1	27.4 ± 4.5	30.1 ± 6.3
Global cardiovascular risk scores				
10-year ASCVD risk (%)	9.9 ± 6.5 %	3.8 ± 3.2	8.7 ± 7.5 %	7.3 ± 7.7
10-year CHD risk (%)	10.9 ± 6.5 %	2.9 ± 3.5	5.5 ± 5.8%	3.8 ± 5.3

2.3.3. Association between cGRS, pooled ASCVD outcomes and incident CHD at 10 years of follow-up

Compared to individuals with low cGRS, intermediate cGRS and high cGRS were associated with 10-year pooled ASCVD and 10-year incident CHD outcomes; an intermediate cGRS was associated with a 1.32-fold increase in risk of ASCVD events (95% CI: 0.97-1.79), and a high cGRS was associated with a 1.47-fold higher risk (95% CI: 1.03-2.10) of ASCVD events (Table

4, Figure 2). However, when we examined the association between cGRS and incident ischemic stroke alone, the cGRS was not a statistically significant predictor of increased risk of ischemic stroke. Finally, having an intermediate cGRS was associated with a 1.69-fold higher risk of incident CHD (95% CI: 1.15-2.49) and having a high cGRS was associated with a 1.89-fold increase in risk of incident CHD events (95% CI: 1.22-2.92) (Figure 2).

Table 2: Baseline ASCVD risk factors, stratified by cGRS category

Variable of interest	Low cGRS	Intermediate cGRS	High cGRS
Cardiovascular disease risk factors			
Age at baseline (years)	53.6 ± 5.7	53.7 ± 5.7	53.4 ± 5.7
Total cholesterol at baseline (mg/dL)	208 ± 38	210 ± 39	211 ± 38
HDL cholesterol at baseline (mg/dL)	38 ± 11	39 ± 11	38 ± 10
LDL cholesterol at baseline (mg/dL)	131 ± 37*	133 ± 37*	135 ± 36*
Systolic Blood Pressure at baseline (mmHg)	119 ± 18	119 ± 18	119 ± 18
Diastolic Blood Pressure at baseline (mmHg)	74 ± 11	73 ± 11	73 ± 11
Current smokers (%) at baseline	26%	25%	25%
Anti-hypertensive medication (%) at baseline	20%	22%	23%
BMI at baseline (kg/m2)	27.1 ± 4.9	27.1 ± 5.0	27.1 ± 5.0
Global cardiovascular risk scores			
10-year ASCVD risk (%)	7.0 ± 6.8 %	7.0 ± 6.2 %	6.9 ± 6.2%
10-year CHD risk (%)	6.3± 6.6 %	6.3 ± 6.2 %	6.4 ± 6.5 %

*Baseline LDL varies significantly by cGRS category; p=0.01

For each of the models described above, we tested whether the addition of an interaction term between the 27-SNP cGRS and race resulted in a statistically significant increase in predictive power using the likelihood ratio test. Pre-specified testing for interaction with race were negative in both the 10-year pooled ASCVD model and the 10-year incident CHD model,

thus, the final overall models did not include an interaction term between cGRS and race. For pooled ASCVD outcomes, baseline LDL did not significantly improve model performance and was not included in the final model. For incident CHD outcomes, the addition of baseline LDL to the model resulted in a statistically significant improvement ($p<0.01$); thus, we added baseline LDL to the final 10-year incident CHD model.

Table 3: Fatal CHD and non-fatal MI events cGRS category: Number of events and average follow-up time for 10-year follow-up

Time-to-incident CHD				
cGRS category	# of fatal CHD and non-fatal MI events	Average follow-up time for events (years)	Average follow-up time for events & non-events (years)	Average event rate per 1000 people per year
Low risk (n=1,766)	31	5.99 ± 2.55	9.76 ± 1.05	1.8
Intermediate risk (n=5,296)	157	5.97 ± 2.83	9.68 ± 1.29	3.1
High risk (n=1,764)	60	6.17 ± 2.72	9.72 ± 1.19	3.5
All (n=8,826)	248	6.02 ± 2.76	9.70 ± 1.22	2.9
Time-to-pooled ASCVD				
cGRS category	# of fatal CHD, non-fatal MI, ischemic stroke events	Average follow-up time for events (years)	Average follow-up time for events & non-events (years)	Average event rate per 1000 people per year
Low risk (n=1,766)	51	5.96 ± 2.53	9.72 ± 1.16	3.0
Intermediate risk (n=5,296)	198	5.90 ± 2.83	9.64 ± 1.37	3.9
High risk (n=1,764)	75	6.11 ± 2.75	9.68 ± 1.26	4.4
All (n=8,826)	324	5.96 ± 2.78	9.66 ± 1.30	3.8

2.3.4. Improvement in discrimination for 10-year pooled ASCVD and 10-year incident CHD models

The improvement in discrimination when adding cGRS to the pooled ASCVD model was not statistically significant (ΔC-statistic= 0.0025; p=0.08) and the improvement in discrimination when adding cGRS to the incident CHD model was statistically significant but small ((ΔC-statistic= 0.0077; p<0.01) (Table 5).

Table 4: Hazard ratios for cGRS and pooled ASCVD and incident CHD

Time to first pooled ASCVD event ~ established risk factors[a]				Time to first CHD event ~ established risk factors[b]			
	HR	95% CI	P value[c]	Model	HR	95% CI	P value[c]
Low cGRS	1.0 (ref)	---		Low cGRS	1.0 (ref)	---	
Intermediate cGRS	1.32	0.97-1.79		Intermediate cGRS	1.69	1.15-2.49	
High cGRS	1.47	1.03-2.10	P=0.034	High cGRS	1.89	1.22-2.92	P=0.003

Table 5: Improvement in discrimination for pooled ASCVD and incident CHD models

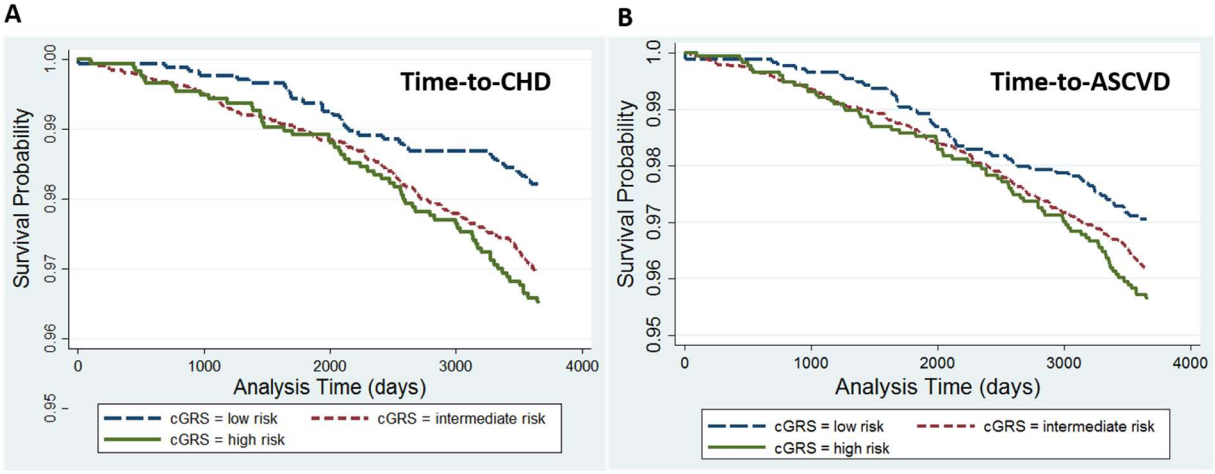
Time to first pooled ASCVD event ~ established risk factors[a]				Time to first CHD event ~ established risk factors[b]			
Model	C statistic	Delta	P value[c]	Model	C statistic	Delta	P value[c]
Reference	0.7629	--	--	Reference	0.7694	--	--
+ cGRS	0.7654	0.0025	P=0.087	+ cGRS	0.7771	0.0077	P=0.004

[a]Adjusted for traditional risk factors: age, gender, SBP, treatment for hypertension, smoking, TC, HDL-C, race

[b]LDL-C is an additional covariate in the incident CHD model

[c]P-value is from Likelihood Ratio test comparing nested vs. non-nested models

Figure 2: Kaplan-Meier survival curves for time-to-CHD (A)
and time-to-ASCVD (B), stratified by cGRS category



2.4. Discussion

Overall, the 27-SNP cGRS was significantly associated with incident CHD and pooled ASCVD outcomes at 10 years in a diverse, population-based cohort. Furthermore, the 27-SNP cGRS offered a statistically significant, albeit very small, improvement in discrimination for the 10-year incident CHD model; however, addition of cGRS did not significantly improve discrimination of the 10-year pooled ASCVD model.

Pooled ASCVD outcomes, as opposed to CHD outcomes alone, are commonly used to assess global cardiovascular disease risk, because atherosclerosis contributes to higher risk of ischemic stroke as well as CHD. We have shown that there is a significant association between the 27-SNP cGRS and pooled 10-year ASCVD outcomes; this relationship is important when considering how we can integrate the information provided by cGRS into existing risk prediction models, such as the Pooled Cohort Equations, which provide predicted risk estimates for pooled 10-year ASCVD outcomes (Goff 2013).

Although the association between cGRS and pooled 10-year ASCVD outcomes was significant, when we looked at ischemic stroke alone as an outcome, we did not observe any association between cGRS and incident ischemic stroke at 10 years. This finding is not surprising, given that Mega et al. developed the cGRS based on SNPs that had been shown to be related to incident CHD in prior GWAS studies (Mega 2015). Some of the SNPs included in Mega et al's risk score likely have a marginal effect on ischemic stroke, but that may reflect their effect on vessel wall pathology and/or thrombosis factors (Vasan 2006). GWAS studies to date have been largely unsuccessful at identifying loci significantly associated with stroke; this may be due to the inclusion of both ischemic and hemorrhagic stroke as outcomes, which may have slightly different underlying pathophysiology and predisposing risk factors (Sierra 2011). However, one analysis of shared genetic susceptibility found substantial overlap in the genetic risk associated with ischemic stroke and coronary artery disease (Dichgans 2014), which may partly explain our observation that cGRS was significantly associated with pooled ASCVD outcomes. To further improve the 27-SNP cGRS' ability to predict pooled ASCVD beyond traditional risk factors, future research is necessary to identify loci that may have pleiotropic, as well as independent, effects on both CHD outcomes and ischemic stroke, potentially through a GWAS of both combined ischemic stroke and CHD outcomes.

Last, in the overall model that included white and black participants, cGRS was associated with incident CHD at 10-years follow-up and the magnitude of association between cGRS and incident CHD was similar to what was observed by Mega et al. This was an unexpected result given that we hypothesized a priori that Mega et al's cGRS would perform poorly in black Americans due to race/ethnicity specific linkage disequilibrium patterns and population-specific

variants (Franchescini 2014). However, it is possible that Mega e al. identified causal variants versus markers that are simply close to the causal variants, which could explain why the association between the cGRS and incident CHD was also significant in a biracial population.

One limitation of our analysis is that we used a cGRS that only includes 27 SNPs; some other analyses have used as many as 152 SNPs to help further increase the effect of the cGRS at improving overall risk prediction (de Vries 2015; Deghan 2016). However, these risk scores have generally not offered substantial improvements in risk prediction compared to the 27-SNP cGRS (Tada 2015). Another limitation of the 27-SNP cGRS is that there are no SNPs included that have been shown to be associated with incident ischemic stroke. We considered adding additional SNPs to the cGRS to expand prediction potential to ischemic stroke, but recent GWAS consortia were unable to identify any loci that were significantly associated with incident ischemic stroke (Traylor 2012). Another limitation was that we excluded all individuals who reported statin use at visits 1-4, which eliminated the participants at highest risk of CHD and ASCVD events. While this limitation should be considered for determining generalizability of our findings, we believe excluding statin users was appropriate because we are most interested in considering cGRS testing for targeting statin therapy in the primary prevention of ASCVD.

2.5. Conclusions

We have demonstrated that a 27-SNP cGRS is associated with incident CHD and pooled ASCVD events in a biracial, population-based study cohort free of diabetes at study baseline. While this association was significant, the improvement in discrimination, when compared to models that did not include cGRS, was very small. However, even small improvements in risk prediction may be valuable enough to warrant measurement, depending on the overall balance

of benefits, harms and costs (Pletcher 2011). Further research, such as decision-analytic modeling, is necessary to achieve the overall goal of demonstrating the clinical utility of cGRS testing in diverse populations.

CHAPTER 3: INTERPRETING A 27-SNP CGRS IN COMBINATION WITH TRADITIONAL RISK FACTORS FOR PREDICTION OF ASCVD

3.1. Background

Inclusion of novel cardiovascular disease risk factors to improve prediction of ASCVD risk is controversial and the subject of much ongoing research (Cainzos-Achirica 2015; Goff 2013; Yeboah 2015; Yeboah 2016; Zamarano 2016). For example, one area of intense research is the use of cardiovascular genetic risk information in clinical decision-making (Kullo 2016; Paynter 2016; Tikkanen 2013; Krarup 2015; Shah 2016). Genetic factors may reflect genetic susceptibility to accelerated atherosclerosis, related potentially to errors in cholesterol metabolism, thrombosis and/or other endothelium-related factors (Vasan et al. 2006), and measuring these factors may improve ASCVD risk prediction beyond traditional risk factors (Antiochos 2016; Kullo 2016; Paynter 2016; Tikkanen 2013; Krarup 2015).

Genetic risk scores that aggregate information about the effect of many genetic variants (SNPs) on disease outcomes (Smith 2015) may be particularly useful for ASCVD risk prediction. In 2015, Mega et al. demonstrated a significant association between a 27-SNP cGRS and cardiovascular disease outcomes that was independent of traditional risk factors. Specifically, compared to individuals with low cGRS, those with intermediate and high cGRS had a1.34-fold and 1.72-fold increase in risk of incident coronary heart disease events for intermediate and high cGRS, respectively, over an average follow-up time of 3.6 years (Mega 2015). Yet, it remains unclear how to integrate information from the cGRS with a 10-year ASCVD risk estimate using

the current guideline-recommended absolute risk assessment algorithm, the Pooled Cohort Equations, to produce clinical actionable information (Goff 2013).

In order to use novel risk factors, such as the 27-SNP cGRS developed by Mega et al., in combination with existing ASCVD risk prediction estimates, we need to know the expected distribution of the cGRS, conditional on traditional ASCVD risk factors. For example, race/ethnicity, which is known to affect underlying population frequency of risk alleles, may modify the expected distribution of the cGRS (Franchescini 2014). Once we know the expected distribution of cGRS, we can integrate information about the cGRS into existing risk prediction models, using previously developed methods, to produce expected post-test risk estimates for individual patients (Kooter 2011; Pletcher 2011; Pletcher 2013; Jarmul 2015). These analyses and methods are necessary to successfully translate improved risk prediction offered by novel risk factors, such as the 27-SNP cGRS, into actionable information that physicians can use to guide clinical decision-making around preventive therapies, such as statins or aspirin.

In the current study, we derived the expected distribution of cGRS using genome-wide genotype data and traditional ASCVD risk factors collected by the National Longitudinal Study of Adolescent to Adult Health (Add Health) in non-diabetic, ASCVD-free individuals. We then demonstrate, using previously described methods, how different cGRS scores would modify pretest 10-year ASCVD risk estimates in different clinical scenarios (Pletcher 2013; Jarmul 2015).

3.2. Methods

3.2.1. Data Source and Sample

Data Source

Add Health is a nationally representative, longitudinal school-based study of a nationally of US adolescents who were in grades 7 to 12 during the 1994-1995 school year (Harris 2013). The sample of 80 high schools and 52 middle schools was representative of US schools with respect to region of the country, degree to which the location was urbanized, school size, school type, and students' race/ethnicity. The baseline sample (Wave I) included 20,745 adolescents selected from student rosters; Add Health oversampled of adolescents with disabilities and racial/ethnic minorities (Chinese, Cuban, Puerto Rican, and Black adolescents) to ensure adequate representation of these groups. Wave IV data collection was completed between 2008 and 2009.

Sample

We included all participants with complete phenotype data and who gave their consent to collect genotype data (n= 7,387). We excluded participants who were pregnant at Wave IV (n = 240), self-reported a diagnosis of heart disease (n=62), for diabetes (n=201), lacked valid sample weights (n= 290), and those missing covariate data for a final sample of 4,116 (Appendix 7).

3.2.2. Measures

Data collection included in-home interviews, anthropometric measurements and biologic specimens. Medication use during the preceding four weeks was determined through self-report during the in-home interview. Three blood pressure measurements were obtained at 30-second intervals after a 5-minute seated rest; the latter two readings were averaged to calculate resting SBP. For measurement of lipids and whole genome sequencing during Wave IV, trained and certified field interviewers collected samples of capillary whole blood via finger prick, which were then shipped, assayed and archived as dried blood spots (Whitsel 2013). TC and HDL cholesterol concentrations (mg/dL) were rank ordered and reported as deciles (Whitsel 2013).

We calculated the 27-SNP cGRS (Mega et al., 2015) using imputed data from the Illumina Omni 1.0 or 2.5 arrays imputed to 1000 genomes phase three reference panes and estimated as the sum of the dosage for each SNP (Appendix 2) weighted by the log of the odds ratio reported with the SNP in the table (Appendix 1). The SNPs, risk alleles and associated odds ratios used in the cGRS were selected from a literature review of GWAS- CHD outcomes studies completed by Mega et al. We excluded SNPs with poor imputation quality (oevar_imp <0.3) or with minor allele counts <10.

Gender, age, SBP, use of antihypertensive medications, smoking status and diabetes were determined from interview data, anthropometric measurements, and biological specimens taken at Wave IV. We defined current smoking status as self-reported cigarette use in the 30 days preceding the interview. We defined diabetes as self-report of diabetes diagnosis by a health provider (except during pregnancy). Anti-hypertension medication use was based on self-reported use of an anti-hypertensive agent in the past year. Race/ethnicity was reported at

Wave I; participants were asked if they were Hispanic and to select a racial category (White, Black/African American, American Indian/Native American, Asian/Pacific Islander, or other). The final race/ethnicity categories were "Non-Hispanic White/ Other", "Non-Hispanic Black", and "Hispanic". The final sample contained only 1 individual who identified as Asian, therefore we included that individual in the Non-Hispanic White/Other category. TC and HDL cholesterol concentrations (mg/dL) were reported as deciles in the Add Health data, (Whitsel 2013).

3.2.3. Analysis

We used a cross-sectional study design to analyze data from individuals with valid sample weights at Wave IV. We calculated means +/- standard deviations and proportions +/- linearized standard errors to describe the sample.

We developed a prediction model for the expected distribution of cGRS, as a function of traditional ASCVD risk factors using linear regression analysis (Equation 1). Predictor variables included gender, race/ethnicity, age, SBP, TC, HDL cholesterol, use of antihypertensive medication, and smoking. For the regression analysis, we divided continuous variables (age and SBP) by 10 and centered the TC and HDL cholesterol values to decile 5 (e.g. individuals in decile 1 would be assigned a value of -4 and individuals in decile 9 would be assigned a value of 4).

Equation 1: cGRS prediction model

$$cGRS = \alpha_0 + \beta_{age} * age + \beta_{gender} * gender + \beta_{race} * race + \beta_{TC} * TC + \beta_{HDL} * HDL + \beta_{SBP} * SBP + \beta_{smoker} * smoker + \beta_{ant\ HTN} * anti_{HTN} + interaction\ terms + \varepsilon_0$$

Given the large number of potential interaction terms and functional forms of our candidate predictor variables, we used an unbiased model selection process with 10-fold cross-validation that we previously developed (Jarmul 2015; Pletcher 2011; Hastie 2009). The unbiased model selection algorithm tests models with all possible combinations of predictors, with up to 2 pairwise interactions (0, 1, or 2) and up to 1 quadratic term (0 or 1) for each continuous variable. We assessed model performance using the cross-validated R^2.

The cross-validated R^2 is preferable to the unadjusted R^2 because adding predictor variables will not automatically increase in the value of the statistic; this allows us to compare the performance of models with different total numbers of predictor variables (Hastie 2009). Furthermore, the cross-validation process uses subsets of the data as training sets to calculate many sets of coefficient estimates (in this case, 10 sets) and then compares each set of predicted cGRS values (from the 10 sets of coefficient estimates) to actual cGRS values in an unused subset of the data (validation set). The cross-validated R^2 will increase as the correlation between average predicted cGRS values and the actual cGRS values increases, but will be subject to a penalty if the variation in predicted cGRS values across the training sets is large. We have previously used these methods to describe the distribution of expected coronary artery calcium (CAC) and expected hemoglobin A1C (Pletcher 2013; Jarmul 2015).

To integrate the cGRS into existing ASCVD risk prediction models, we need to know the relationship between different thresholds of the cGRS and ASCVD events, as well as how those specific thresholds are tied to absolute values of the cGRS in a target population. In Mega et al.'s analysis, low risk is defined as quintile 1, intermediate risk is defined as quintiles 2-4 and high risk is defined as quintile 5; corresponding hazard ratios for low, intermediate and high cGRS were

1.0 (reference), 1.34 and 1.72, respectively (Mega 2015). These hazard ratios do not include any relationship between the 27-SNP cGRS and ischemic stroke, because Mega et al. only looked at coronary heart disease (CHD) outcomes (fatal CHD and nonfatal MI). For our analysis, we assumed that the 27-SNP cGRS was not significantly associated with ischemic stroke so that we could to integrate into the PCEs, which predict pooled ASCVD outcomes.

In addition, because Mega et al.'s analyses were conducted in predominantly non-Hispanic white individuals, we used race-specific thresholds; i.e. we created separate quintiles for non-Hispanic white, non-Hispanic black, non-Hispanic Asian and Hispanic participants based on the distribution of cGRS within those populations. We used example clinical scenarios to demonstrate the effect of integrating cGRS into existing 10-year predicted risk equations, using methods described in detail elsewhere (Appendix 8; Kooter 2011; Pletcher 2011; Jarmul 2015; Pletcher 2013). We created an Excel-based calculator to calculate pretest 10-year ASCVD risk, expected cGRS distribution and post-test 10-year ASCVD risk for patients with a set of user-defined inputs, including age, sex, race/ethnicity, systolic blood pressure, total cholesterol, HDL-cholesterol, current smoking, and hypertension treatment status. For the sensitivity analysis, we replaced the deciles reported for TC and HDL cholesterol variables with absolute values calculated from non-diabetic, ASCVD-free individuals aged 25-35 years in the 2013-2014 NHANES sample, a nationally representative sample of U.S. individuals. The specific values used in place of the deciles are reported in the supplementary materials (Appendix 9). We found no differences in the overall cross-validated r2 after this change.

All statistical analyses were performed using Stata 14 (Stata, College Station, TX). We accounted for the complex design by using sampling weights, clustering by the primary sampling unit (schools) and the U.S. region.

3.3. Results

3.3.1. Summary statistics

Of the 4,116 participants in the final sample, 48% were women, 4% were Hispanic, 76% non-Hispanic white/other, 20% non-Hispanic black, and <1% were non-Hispanic Asian. The average age of participants was 29.0 +/- 1.7 years. Both cGRS values and other risk factor levels differed across race/ethnicity and sex (Table 6).

Table 6: Summary statistics for Add Health participants

Characteristics	Hispanic (n=158)	NH White/ Other (n=3.131)	NH Black (n=827)
Age (years)	29.5 ± 1.8	29.3 ± 1.8	29.4 ± 1.7
Male (%)	58% ± 6%	51% ± 1%	49% ± 2%
SBP (mmHg)*	124 ± 14	125± 13	127± 15
DBP (mmHg)*	80 ± 11	80 ± 10	81 ± 11
BMI (kg/m^2)	30.3 ± 6.8	28.5 ± 7.1	31.1 ± 8.4
Daily smoker (%)‡	15 ± 3	29 ± SE	21 ±
HTN dx (%)‡	10 ± 2	12 ± 1	13 ± 1
HLD dx (%)‡	7 ± 2	9 ± 1	5 ± 1
Anti-HTN meds (%)‡	0.5 ± 0.5 %	0.9 ± 0.1%	1.3 ± 0.4 %
Mean HbA1C (%)	5.7 ± 0.6	5.5 ± 0.5	5.9 ± 0.7
Mean cGRS	0.84 ± 0.11	0.86 ± 0.10	0.73 ± 0.09

Values are means ± standard deviation (except where otherwise noted)
*NH, Non-Hispanic; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; HTN, hypertension diagnosis; HLD, hyperlipidemia diagnosis; HbA1C, hemoglobin A1C; cGRS, cardiovascular genetic risk score
‡ prevalence estimates ± linearized standard errors

3.3.2. Main analyses

We examined the top 20 models (ranked by cross-validated R^2) chosen through the unbiased model selection process. For comparison purposes, Model 1 only includes race/ethnicity and Model 2 includes all traditional ASCVD risk factors, without any interaction terms (Table 7). The cross-validation selector, or the top performing model, included the predictor variables race/ethnicity, HDL, TC, HDL*race/ethnicity, smoking status, smoking status*race/ethnicity, and TC*TC; the beta coefficients and 95% CI are shown in Appendix 9 (cross-validated R2 of 0.180). Race/ethnicity alone was a significant predictor of cGRS and explained a fair amount of the variation in cGRS (Table 7; Model 1: cross-validated R2 of 0.177). In comparison, the model that included all traditional ASCVD risk factors (Table 7; Model 2) had a cross-validated R2 of 0.172, indicating worse performance than the model that included race/ethnicity alone. After evaluating all options, we chose to use Model 1 as the final model for the sake of parsimony and because, apart from race/ethnicity, the beta coefficients for the remaining covariates were extremely small and unlikely to change the actual expected cGRS distribution.

Table 7: Comparison of prediction models for expected cGRS distribution

Model Predictors	Race/ ethn only	Quintile-based TC/HDL	Absolute TC/HDL	Unbiased model selector
	B (95% CI)*	B (95% CI)*	B (95% CI)*	B (95% CI)*
Hispanic‡	-0.024 (-0.053, 0.006)	-0.024 (-0.054, -0.005)	-0.024 (-0.054, 0.005)	-0.016 (-0.048, 0.016)
Non-Hispanic black‡	-0.138 (-0.147, -0.129)	-0.137 (-0.146, -0.128)	-0.137 (-0.146, -0.128)	-0.139 (-0.148, -0.129)
Male (1=Yes)		0.001 (-0.009, 0.010)	0.001 (-0.009,0.010)	
SBP, per 10 mmHg		0.0002 (-0.003, 0.003)	0.0001 (-0.003, 0.003)	
TC, per quintile		0.001 (-0.0003, 0.003)	--	0.001 (-0.003, 0.001)
HDL, per quintile		-0.001 (-0.003, 0.001)	--	0.001 (-0.0001, 0.003)
TC, per 10 mg/dL		--	0.001 (-0.0002, 0.003)	
HDL, per 10 mg/dL		--	-0.002 (-0.007, 0.002)	
Anti-HTN medication		0.001 (-0.042, 0.045)	0.001 (-0.042, 0.044)	
Age, per 10 years		-0.002 (-0.025, 0.021)	-0.002 (-0.0002, 0.003)	
Daily Smoker		0.001 (-0.008, 0.010)	0.001 (-0.008, 0.01)	0.001 (-0.008, 0.011)
HDL*NHB				0.002 (-0.001, 0.006)
HDL * Hispanic				-0.008 (-0.021, 0.005)
Daily Smoker (yes) * NHB				0.006 (-0.016, 0.027)
Daily smoker (yes) * Hispanic				-0.070 (-0.134, -0.005)
TC * TC				0.001 (-0.000, 0.001)
Constant	0.863 (0.858, 0.868)	0.866 (0.797, 0.934)	0.855 (0.782, 0.928)	0.869 (0.851, 0.866)
Cross-validated R^2	0.177	0.172	0.172	0.180

The standard deviation of the residuals for the final cGRS model is 0.056

*Standard errors and 95% confidence intervals (CI) calculated using Taylor series linearization method

‡ vs. non-Hispanic white/other (reference category)

We investigated the effect of integrating information from cGRS with information from other ASCVD risk factors for several example clinical scenarios to help understand the implications of using cGRS for risk prediction. Incorporating cGRS post-test risk increase from having a high cGRS tends to approximate the risk increase from being 5 years older (Table 8). For example, a 50-year old non-Hispanic black non-smoker with TC/HDL of 190/50 mg/dL and untreated SBP of 125 mmHg has 10-year pretest ASCVD risk of 5.0%. If they have a high cGRS, the expected post-test 10-year ASCVD risk estimate increases to 6.4%. In comparison, the same individual would have a pretest 10-year ASCVD risk of 6.3% at age 55 years old.

We also examined the effect of race/ethnicity on integration of cGRS with other ASCVD risk factors (Table 9). Integrating cGRS with traditional risk factors did not result in clinically significant differences in post-test predicted risk between the different race/ethnicities. The clinical scenarios show that regardless of race/ethnicity, the difference between pretest and post-test risk is, at most, 1.6 percentage points (Table 9).

Table 8: Example clinical scenarios showing the effect of cGRS and age on expected proportion and post-test ASCVD risk

Clinical scenario	Age (yrs)	Race / ethnicity	Gender	Smoker?	TC/ HDL (mg/ dL)	SBP (mmHg)	Pretest ASCVD risk	cGRS category	Race-specific thresholds	
									Proportion in cGRS category	Post-test ASCVD risk
1	40	*NHB*	Male	Non-Smoker	190/ 50	125 mmHg (untreated)	2.9 %	Low	0.11	2.2 %
								Intermediate	0.77	2.9 %
								High	0.12	3.7 %
2	45	*NHB*	Male	Non-Smoker	190/ 50	125 mmHg (untreated)	3.9 %	Low	0.11	2.9 %
								Intermediate	0.77	3.9 %
								High	0.12	5.0 %
3	50	*NHB*	Male	Non-Smoker	190/ 50	125 mmHg (untreated)	5.0 %	Low	0.11	3.7 %
								Intermediate	0.77	5.0 %
								High	0.12	6.4 %
4	55	*NHB*	Male	Non-Smoker	190/ 50	125 mmHg (untreated)	6.3 %	Low	0.11	4.7 %
								Intermediate	0.77	6.3 %
								High	0.12	8.0 %
5	60	*NHB*	Male	Non-Smoker	190/ 50	125 mmHg (untreated)	7.8 %	Low	0.11	5.8 %
								Intermediate	0.77	7.7 %
								High	0.12	9.9 %
6	65	*NHB*	Male	Non-Smoker	190/ 50	125 mmHg (untreated)	9.4 %	Low	0.11	7.0 %
								Intermediate	0.77	9.3 %
								High	0.12	12.0 %
7	70	*NHB*	Male	Non-Smoker	190/ 50	125 mmHg (untreated)	11.1 %	Low	0.11	8.3 %
								Intermediate	0.77	11.1 %
								High	0.12	14.2 %
8	75	*NHB*	Male	Non-Smoker	190/ 50	125 mmHg (untreated)	13.1 %	Low	0.11	9.7 %
								Intermediate	0.77	13.0 %
								High	0.12	16.7 %

Table 9: The effect of race/ethnicity on the proportion of individuals in each cGRS category and expected post-test ASCVD risk

Clinical scenario	Age (yrs)	Race/ethnicity	Gender	Smoker?	TC/HDL (mg/dL)	SBP (mmHg)	Pretest ASCVD risk	cGRS category	Proportion in cGRS category	Post-test ASCVD risk
1	40	*NHW / other*	Male	Smoker	200/45	135 mmHg (treated)	5.5 %	Low	0.08	4.1 %
								Intermediate	0.86	5.5 %
								High	0.06	7.1 %
2	40	*NHB*	Male	Non-Smoker	200/45	130 mmHg (treated)	5.5 %	Low	0.11	4.1 %
								Intermediate	0.77	5.4 %
								High	0.12	7.0 %
3	40	*Hispanic*	Male	Non-smoker	200/45	135 mmHg (treated)	5.5 %	Low	0.07	4.1 %
								Intermediate	0.89	5.6 %
								High	0.04	7.1 %

3.4. Discussion

We have shown that the expected cGRS distribution varies based on race/ethnicity, but not on traditional ASCVD risk factors, as expected. When modeled separated for each race/ethnicity, expected cGRS was orthogonal to the remaining traditional ASCVD risk factors. Integrating information from cGRS with information from other ASCVD risk factors has modest effects on post-test predicted ASCVD risk; the post-test risk increase from having a high cGRS tends to approximate the risk increase from being 5 years older. Furthermore, while race/ethnicity was a statistically significant predictor of cGRS, integrating cGRS with traditional risk factors did not result in clinically significant differences in post-test predicted risk between the different race/ethnicities.

Other nontraditional risk factors, such as CAC and hemoglobin A1C, have been shown to improve ASCVD risk prediction (McClelland 2015; Danesh 2014). One potential advantage of using a cGRS is that the value will not change throughout an individual's lifetime. For example, if 60-year old individual found out they had a high cGRS, but the overall risk was still relatively low, future risk calculations would still be able to account for the extra information from the cGRS. For example, if the individual shown in Appendix 10 was found to have a high cGRS, they might not act on that information at age 50, where the post-test risk is 6.4%; however, they may decide to start statin therapy at age 60, when their post-test risk, conditional on the high cGRS, is 9.9%. Risk factors, such as CAC or HbA1C, may have changed substantially over the course of 10 years.

Previous work has shown that cardiovascular genetic risk varies between white and black populations (Morrison 2007; Franceschini 2014;), but to our knowledge, no other work has shown the expected cGRS distributions for Mega et al.'s 27-SNP cGRS in non-Hispanic black or Hispanic populations. Given that the 27-SNP cGRS was developed in a primarily non-Hispanic white population, its use, in combination with traditional ASCVD risk factors, in a diverse population may lead to less accurate ASCVD risk prediction for individuals of race/ethnicities other than non-Hispanic white.

Our analysis is an intermediate step toward the larger goal of evaluating the clinical utility of cGRS measurement for ASCVD risk assessment. We found that incorporating cGRS with traditional risk factors had only modest effects on predicted risk; previous studies have found that adding cGRS does little to improve discrimination and reclassification (de Vries 2015; Morrison 2007; Tada 2015). However, even measures of improved risk prediction, such as

discrimination and reclassification, are unable to fully evaluate the clinical utility of cGRS. Such an evaluation will require the use of decision modeling to assess the costs, risks, and benefits, while considering the cost of cGRS testing, health impact (e.g., incidence and severity of the disease or quality of life), and clinical decisions that might change with measurement of the risk factor (e.g., preventative therapies or treatments) (Pletcher 2011). While the effects of cGRS on expected post-test risk were small, even small changes in risk prediction may be valuable enough to warrant measurement if the cost and harms are low; our next step is to perform evaluate the clinical utility of cGRS testing using decision modeling, as we have done previously for coronary artery calcium scanning (Pletcher 2014). Cost-effectiveness analyses are often sensitive to changes in the population prevalence of biomarkers or conditions, especially when evaluating primary prevention or screening strategies (Kooter 2011; Pletcher 2014). Furthermore, genetic markers of risk can vary substantially between race/ethnicities; thus, it is important for modelers to build in these differences to obtain valid model outputs.

Finally, it is important to consider that implementation of genetic risk testing (or any other novel risk factor) in a clinical setting has many barriers; one such barrier is clinicians' ability to easily interpret test results in combination with traditional clinical risk factors. The included online Excel calculator, provide an example of how to give clinicians the ability to calculate the expected post-test risk prior to ordering genetic risk testing, as well as for interpreting results from genetic risk testing.

One limitation of our analysis is that participants in the Add Health study are generally younger than individuals for whom ASCVD risk prediction is indicated (40-79 years old). However, given that there were no significant age interaction effects and that race/ethnicity

does not vary by age, we would expect our findings to replicate in older individuals. Another limitation is the low number of Hispanic participants in our analytic sample. Although we adjusted point estimates and regression models using sample weights, the low number of participants with genetic data limits our ability to fully understand and describe the distribution of cardiovascular genetic risk in this population. Finally, another limitation is the use of quintiles for reporting TC and HDL values. However, in our sensitivity analyses, the substitution of absolute TC and HDL values from the 2013-2014 NHANES sample did not substantially improve performance of the prediction model for expected cGRS.

3.5. Conclusions

Our analysis is an intermediate step toward the larger goal of evaluating the clinical utility of cardiovascular genetic risk testing for ASCVD risk assessment. We developed a prediction equation for expected cGRS distribution conditional on traditional ASCVD risk characteristics; using this prediction equation, we demonstrate how an individual patient's expected cGRS distribution can be incorporated into predicted 10-year ASCVD risk by calculating post-test ASCVD risk estimates for a selection of clinical scenarios. Our study is a necessary intermediate step before conducting more comprehensive cost–effectiveness analyses that will assess the utility of cGRS testing in ASCVD primary prevention and the larger question of the utility of precision medicine for improving population health.

CHAPTER 4: CARDIOVASCULAR GENETIC RISK TESTING FOR TARGETING STATIN THERAPY IN THE PRIMARY PREVENTION OF ASCVD: A COST-EFFECTIVENESS ANALYSIS

4.1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) affects around 11.2% of Americans and, in 2010, accounted for nearly $64 billion in health care costs (Heidenreich 2013). Statins, a group of highly efficacious lipid-lowering agents, significantly reduce the risk of MI, stroke and all-cause mortality, and are recommended as preventive therapy in non-diabetic, ASCVD-free individuals who have a 10-year predicted ASCVD risk (calculated using the Pooled Cohort Equations, or PCEs) greater than or equal to 7.5% (Goff 2013; Stone 2013).

However, the PCEs 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 (McEvoy 2014; Amin 2014; Yeboah 2015; Hutchins 2015). Furthermore, the 7.5% threshold is based on expert opinion, rather than evidence from cost-effectiveness analyses (Goff 2013). Apart from the threshold, the 2013 ACC/AHA 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 (Stone 2013). 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, as has been previously done for CAC scanning (Pletcher 2014; Roberts 2015).

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 (O'Donnell 2016; Kullo 2016; Paynter 2016; Goldstein 2014; Tikkanen 2013; Krarup 2015; Shah 2016; Morrison 2007; de Vries 2016). An individual's cGRS may reflect genetic susceptibility to accelerated atherosclerosis, related potentially to errors in cholesterol metabolism, thrombosis and/or other endothelium-related factors (Vasan 2006). In 2015, Mega et al. demonstrated a significant association between a 27-SNP cGRS and cardiovascular disease outcomes (Mega 2015); this 27-SNP cGRS, as well as other cGRSs, have been shown to be associated with ASCVD outcomes and to marginally improve ASCVD risk prediction over traditional ASCVD risk factors; however, whether their impact on predicted risk produces important differences in clinical decision-making regarding statin initiation is unclear (Tada 2015; Kullo 2016; Paynter 2016; Goldstein 2014; Tikkanen 2013; Krarup 2015; Shah 2016; Morrison 2007; de Vries 2016).

In the absence of large, generalizable randomized controlled trials comparing clinical management with and without additional testing for novel risk factors, clinical decision analysis is a method used to explicitly compare alternative clinical options regarding their relative downstream risks, benefits and costs (Pletcher 2013; Hlatky 2014; Cook 2007). Here, we have used decision analysis and a state transition model to evaluate the clinical utility and cost-effectiveness of cGRS testing for targeting statin therapy in the primary prevention of ASCVD.

4.2. Methods

4.2.1. 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, mortality, quality of life, and costs with and without a prevention intervention, for specific clinical scenarios (Pletcher 2014). In the model, a specific clinical scenario is defined by age, sex, and ASCVD risk factors, including SBP, TC, HDL cholesterol, smoking status and anti-hypertensive medication use. A cohort of 10,000 individuals with these characteristics begins in the healthy state and then may transition every 12 months (Figure 3). Myopathy, angina, MI, and stroke are modeled as separate health states; costs, quality of life, and mortality rates differ in each state. The probability of transitioning from healthy to angina, myocardial infarction and stroke is determined by the Framingham risk models for each of those health states (Anderson 1991). We chose to include angina as an outcome (even though angina is not a part of the 10-year ASCVD risk calculation) because of the clinical relevance of angina and the significant reductions in quality of life as well as utilization that can be incurred when individuals experience angina.

Figure 3: Model health states and transitions

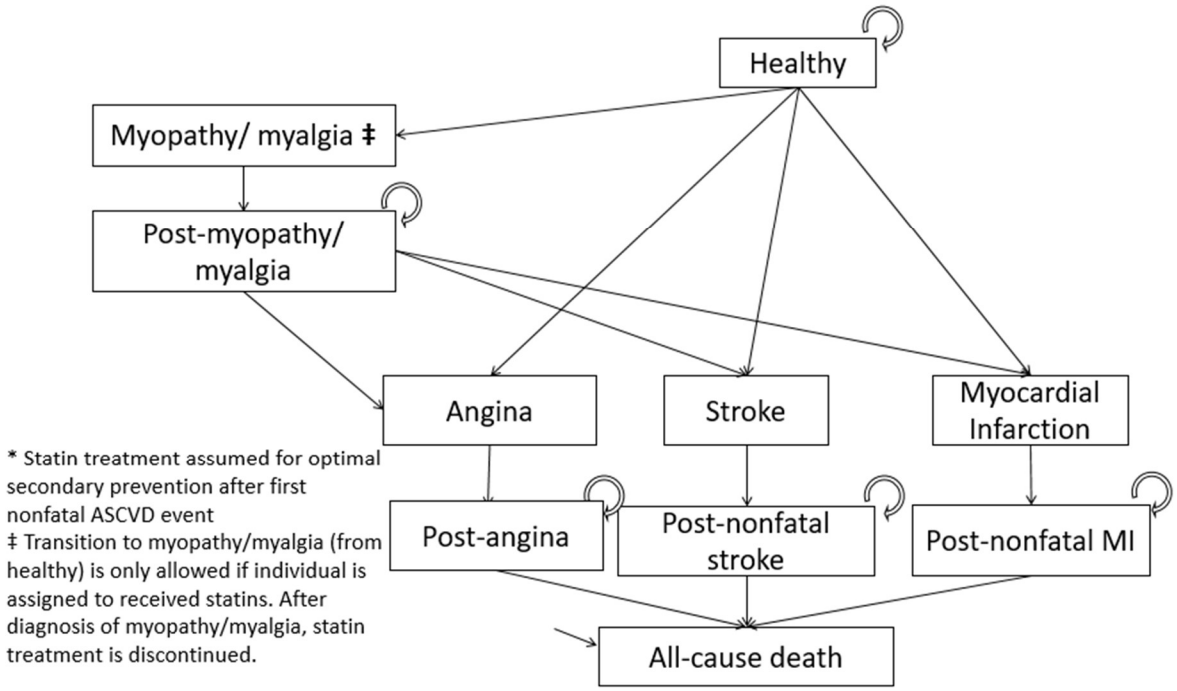


Figure 4: Decision tree for test/treat strategies

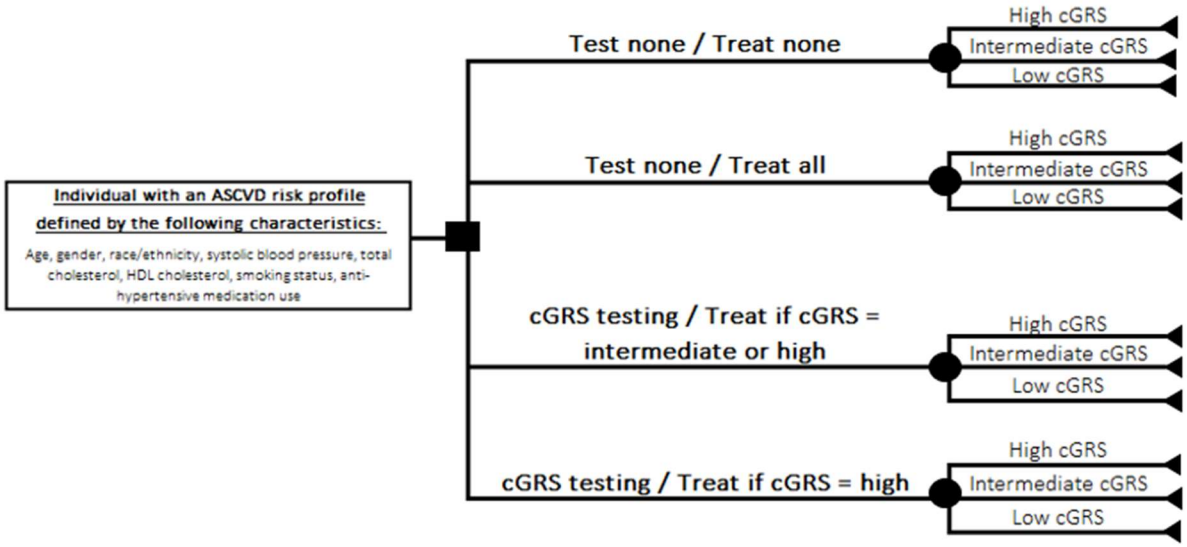


Table 10: Base case model parameters

Parameters	Base Case	Range	Source
Costs for incident events:			
Myocardial infarction	$41,797	+/- 20%	Pletcher 2014
Stroke	$54,847	+/- 20%	Pletcher 2014
Myalgia/myopathy	$398	+/- 20%	Pletcher 2014
Angina	$16,777	+/- 20%	Pletcher 2014
Ongoing costs for post-event health states:			
Post-myocardial infarction	$5,091	+/- 20%	Pletcher 2014
Post-stroke	$14,607	+/- 20%	Pletcher 2014
Post-angina	$7,323	+/- 20%	Pletcher 2014
Testing costs:			
Cardiovascular genetic risk test	$100	$1-$100	Expert opinion
Cost of one physician visit (to discuss cGRS test results)	$70.46	+/- 20%	Pletcher 2014
Treatment costs:			
Statin therapy, generic	$0.1333/day	$0.05/day - $7/day	Pandya 2015; Pletcher 2014
One physician visit	$70.46	+/- 20%	Pletcher 2014
Lipid panel	$23.49	+/- 20%	Pletcher 2014
Health state utilities:			
Healthy	1.0	Not varied in SA	Assumed
MI	0.859	±0.0311	Dehmer 2015; Pletcher 2014
Post-MI	1.0	Not varied in SA	Dehmer 2015;Pletcher 2014
Stroke	0.771	±0.1505	Dehmer 2015;Pletcher 2014
Post-stroke	0.771	±0.1542	Dehmer 2015; Pletcher 2014
Angina	0.929	0.40-1.0	Pletcher 2014
Post-angina	0.997	0.68-1.0	Pletcher 2014
Statin treatment-related disutilities:			
Daily statin therapy	0.001	0-0.02	Pletcher 2014; Hutchins 2015
Myalgia/myopathy	0.017	0-0.1^	Pletcher 2014
Effects of statin treatment:			
RR: CHD death	0.64	0.49-0.84	CTT 2012
RR: Stroke	0.85	0.80-0.89	CTT 2012
RR: Angina	0.74	0.71-0.77	CTT 2012
RR: Myocardial infarction	0.74	0.71-0.77	CTT 2012
IR: Myalgia/myopathy	0.001	0-0.05^	Graham 2004; Pignone 2006

*Costs from Pletcher 2014 updated to USD 2016 (not shown)

^range is based on expert opinion

Our primary outcome measure was the incremental cost-effectiveness ratio (ICER), measured in cost per QALY. We identified preferred strategies under the assumption that society is willing to pay ≤$50 000 per QALY gained. Our secondary outcome measure was net benefit (in QALYs), which is the balance of benefits and harms for a strategy over the lifetime horizon at a willingness to pay threshold of <$50,000 per QALY, as well as incremental net benefit (in QALYs), which we defined as the difference in net benefit between two strategies.

The model was used to compare 4 different interventions: 2 strategies where statin prescribing does not depend on results of cGRS testing (treat none and treat all), and 2 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, treat if cGRS is high) (Figure 4). Statin prescribing was assumed to be differential for 10 years, but cumulative costs and 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.

Total costs (in 2016 US dollars) and quality-adjusted life-years (QALYs) were calculated (discounting at 3%/year for costs and utilities) over a lifetime horizon using a US health care system payer perspective.

4.2.2. cGRS testing parameters

Costs for genetic risk testing vary based on the number of SNPs genotyped and the lab at which the genotyping is performed (https://ghr.nlm.nih.gov/primer/testing/costresults). We assumed a base case cost of $100, but varied the cost between $1 and $2,500 in sensitivity analyses. We also added the cost of one physician visit to discuss cGRS test results with patients.

The expected distribution of cGRS depends on race/ethnicity; for each of our base case clinical scenarios, we used the results from Chapter 3 to account for differences in expected distribution of cGRS by race/ethnicity, and to estimate the proportion of scores falling into categories of low risk, intermediate risk and high risk (Chapter 3). We then estimated post-test risk for angina, MI, and CHD death in these categories using cGRS-specific relative risks and previously described methods (Mega 2015; Kooter 2011; Pletcher 2013). We assumed that the risk of stroke did not vary with cGRS.

4.2.3. Statin disutility, costs and efficacy parameters

In our base case scenario, we assumed that statins can be obtained at a daily cost of $0.13 per pill (based on $4/month prescribing programs at some large discount retailers) and that taking a statin pill every day is associated with a small reduction in quality of life (disutility of 0.001) (Table 12). 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 (Hutchins 2015).

We also assumed that statin therapy triggers 1 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%) (Mihaylova 2012), as well as increased risk of myopathy (absolute rate of 0.001 cases per year; associated cost, mortality, and disutility applied for 1 year, after which statins are discontinued). We assumed immediate discontinuation of statins in 31% of individuals to simulate the effect of non-adherence to treatment (Lemstra 2012).

While there is evidence that statin initiation is associated with a small, but statistically significant increase in hemoglobin A1C and new diagnoses of diabetes mellitus (Sattar 2011) with high dose therapy, the short-term cardiovascular risks are accounted for in the statin efficacy estimates from clinical trials (Mihaylova 2011). Furthermore, the long-term cardiovascular risks associated with this small increase in hemoglobin A1C are not well-understood (Sattar 2011). Thus, in this model, we ignored the long-term risk of diabetes that may be associated with the slight increase in HbA1C due to statin initiation.

4.2.4. ASCVD risk factor profiles

We created five 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; 2) a 65 year old woman at 7.5% risk; 3) a 45 year old woman at 2.5% risk; 4) a 45 year-old woman at 5% risk; and 5) a 45 year old woman at 7.5% risk (Table 11).

Table 11: Description of scenario analyses

Scenario	Statin cost	Statin disutility	cGRS cost	RR for cGRS*	Interpretation
Base case	$4/ month	0.001	$100	1.31; 1.72	Base case assumptions
1	$4/ month	0.001	$1	1.31; 1.72	Less expensive cGRS test
2	$4/ month	0.011	$100	1.31; 1.72	Strong preference against daily statin therapy
3	$15/ month	0.011	$100	1.31; 1.72	Strong preference against daily statin therapy; more expensive statin therapy
4	$15/ month	0.011	$1	1.31; 1.72	Strong preference against daily statin, expensive statin therapy, but less expensive cGRS test
5	$4/ month	0.001	$100	3.93; 5.16	Hypothetical cGRS test with improved prediction of CHD outcomes
6	$4/ month	0.001	$1	3.93; 5.16	Hypothetical cGRS test with improved prediction of CHD; less expensive cGRS

*compared to low cGRS (reference)

4.2.5. Sensitivity analyses

We varied incidence of myopathy, disutility for myopathy, and statin effect modification in a one-way deterministic sensitivity analysis. To investigate statin effect 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 performed a two-way sensitivity analysis of statin disutility and statin cost by varying the cost of statins from $2/month to $200/month and the disutility of daily statin use from 0 to 0.10 (Pandya 2015; Hutchins 2015). For context, a disutility of 0.02 is equivalent to 10 weeks of perfect health traded away to avoid 10 years on statins (Hutchins 2015). We completed the same two-way sensitivity analysis for both the 45-year-old woman (Profile 3) and 65-year-old woman (Profile 4) 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. 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 as well as the strength of the relationship between the 27-SNP cGRS and cardiovascular disease outcomes (Table 11). Last, we conducted a global probabilistic sensitivity analysis using first-order Monte Carlo simulation (n=1000 trials) to determine the effect of parameter uncertainty on the probability of cost-effectiveness for the scenario analyses presented in Table 11. Parameter ranges and distributions are reported in the Appendix 10.

4.3. Results

4.3.1. 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 (Profile 1) over a lifetime horizon. Compared to treat none, the cohort of 10,000 men experienced 24 fewer MIs, 19 fewer strokes, 80 fewer cases of angina, and 65 more cases of myopathy over a lifetime horizon (Table 12).

Table 12: Model outcomes for 10,000 65-year-old women at 7.5% ASCVD risk (Profile 4)

	Treat none	Treat if cGRS = intermediate or high	Treat if cGRS = high	Treat all
Total cost of cGRS testing	0	$1,704,600	$1,704,600	0
Number on statins at baseline	0	9230	615	10,000
Total lifetime cost of statin therapy (per patient)	$81	$765.80	$126.16	$824
Other healthcare costs (per patient)	$81035	$80,180	$80,970	$80119
Total costs per patient	$81116	$80,946	$81,096	$80943
Total Life-Years	17.237	17.332	17.244	17.338
Total QALYs	12.976	13.034	12.981	13.038
Total number of events				
Angina	680	606	674	600
Myocardial infarction	272	249	270	248
Stroke	631	614	630	612
Statin-induced myopathy	0	60	4	65

Table 13: Preferred strategy, incremental net benefit and probability of cost-effectiveness for ASCVD risk profiles

	45-year-old woman			65-year-old woman
	2.5%	5%	7.5%	7.5%
Base case scenario: Statin disutility = 0.001; statin cost = $4/month; cGRS test cost = $100				
Preferred	Treat all (SD)	Treat all (SD)	Treat all (SD)	Treat all (SD)
INB	0.0429	0.0770	0.0840	0.0612
Pr(CE)	100%	100%	100%	100%
Scenario analysis #1: Statin disutility = 0.001; statin cost = $4/month; cGRS test cost = $1				
Preferred	Treat all (SD)	Treat all (SD)	Treat all (SD)	Treat all (SD)
INB	0.0429	0.0770	0.0840	0.0612
Pr(CE)	100%	100%	100%	100%
Scenario analysis #2: Statin disutility = 0.011; statin cost = $4/month; cGRS test cost = $100				
Preferred	Treat none ($26,045/QALY)	Treat all	Treat all	Treat all
INB	-	0.0037	0.0104	0.0040
Pr(CE)	55%	70%	85%	83%
Scenario analysis #3: Statin disutility = 0.011; statin cost = $15/month; cGRS test cost = $100				
Preferred	Treat none (SD)	Treat if cGRS = high (SD)	Treat if cGRS = int/ high (SD)	Treat none
INB	-	0.0042	0.0105	-
Pr(CE)	79%	43%	40%	71%
Scenario analysis #4: Statin disutility = 0.011; statin cost = $15/month; cGRS test cost = $1				
Preferred	Treat none (SD)	Treat if cGRS = int/high (SD)	Treat if cGRS = int/ high (SD)	Treat none
INB	-	0.0043	0.0105	-
Pr(CE)	82%	43%	36%	75%
Scenario analysis #5: Statin disutility = 0.001; statin cost = $4/month; cGRS test cost = $100; RR_cGRS= 3x				
Preferred	Treat all ($26,158/QALY)	Treat all ($6,555/QALY)	Treat all ($4,838/QALY)	Treat all (SD)
INB	0.0426	0.0760	0.0829	0.0610
Pr(CE)	91%	100%	100%	100%
Scenario analysis #6: Statin disutility = 0.001; statin cost = $4/month; cGRS test cost = $1; RR_cGRS = 3x				
Preferred	Treat all ($27,328/QALY)	Treat all ($6,614/QALY)	Treat all ($4,870/QALY)	Treat all (SD)
INB	0.0426	0.0760	0.0829	0.0610
Pr(CE)	90%	100%	100%	100%

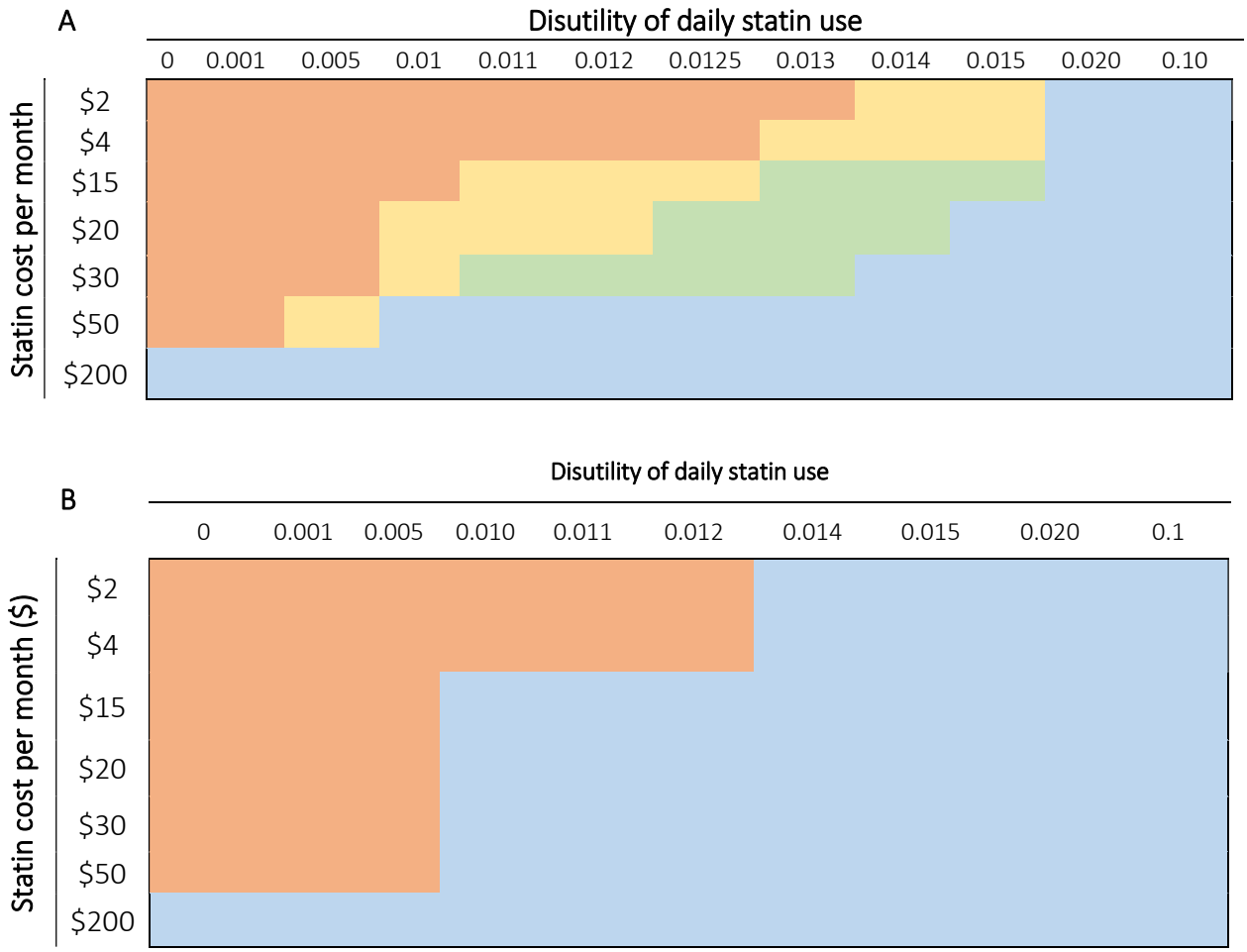
*INB (incremental net benefit) = difference in QALYs between preferred strategy and treat none

Treat 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 (Profile 2). For the 45-year-old women at 2.5%, 5%, and 7.5% 10-year ASCVD risk was to treat all with no cGRS testing, and the incremental net benefit (INB) associated with that strategy (compared to treat none) increased with increasing 10-year ASCVD risk (base case scenario; Table 13). Furthermore, the INB associated with treating all 65-year-old women at 7.5% 10-year ASCVD risk is lower than the INB associated with treating all 45-year-old women at 7.5% 10-year ASCVD risk. For all profiles, under base case assumptions, the probability of cost-effectiveness of treat all with no cGRS testing compared to treat none with no cGRS testing was 100%.

4.3.2. Two-way sensitivity analysis: statin disutility vs. statin cost

The specific combinations of statin disutility and statin cost that lead to cGRS testing as a preferred strategy were dependent on the ASCVD risk factors for the specific profile considered (Appendix 20). For example, we found that none of the tested statin disutility/statin cost combinations led to a preferred strategy of cGRS testing for the 65-year-old woman with 7.5% 10-year ASCVD risk (Profile 4; Figure 5) while cGRS testing was preferred for many statin disutility/statin cost combinations for the 45-year-old woman with 7.5% 10-year ASCVD risk (Profile 3; Figure 5).

Figure 5: Two-way sensitivity analysis of statin cost and disutility of daily statin use for A) 45 year old woman wiht 7.5% ASCVD risk (profile 3) and B) 65 year old woman with 7.5% ASCVD risk (profile 4)



*red = treat all; yellow = treat if cGRS is interm

4.3.3. Scenario analyses: cGRS testing cost, statin disutility, statin cost, RR associated with CHD outcomes

Through our scenario analyses (Table 13), we found that changing the cGRS testing cost alone did not affect the preferred strategy for the clinical profiles considered (scenario #1 vs. 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 either cGRS testing cost was decreased (scenario #4 vs. scenario #2) or statin cost was increased (scenario #3 vs.

scenario #2). If both statin disutility and statin cost were increased compared to 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 very inexpensive (scenarios #5 and #6 vs. base case).

4.3.4. Probabilistic sensitivity analysis

The probability of cost-effectiveness for the preferred strategies vary considerably across profiles and scenarios (Table 13). 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 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 was much lower (36%-43%). In general, the probability of cost-effectiveness for the preferred strategy was also lower in scenarios #2, #3, and #4, indicating that parameter uncertainty plays an important role in determining the preferred strategy when statin disutility and cost are increased.

4.4. 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 prevent some patients from being prescribed a statin was not a cost-effective strategy. Instead, our results indicate that the preferred strategy is to treat all patients with statins under base case assumptions for statin disutility and cost. Furthermore, the magnitude of incremental net benefit varied depending on both 10-year ASCVD risk and

specific ASCVD risk factors, indicating the importance of considering individualized net benefit as a part of the statin initiation decision.

Under base case assumptions for statin cost and disutility, cGRS testing is not the preferred strategy for the four clinical scenarios shown; however, cGRS testing can be cost-effective under a small set of assumptions related to statin cost and statin disutility. For example, when the cost of obtaining a cGRS test is $100, statin cost is $15/month, and statin disutility is 0.011, the preferred strategy (using a WTP of $50,000/QALY gained) for the 45-year-old woman with 7.5% 10-year ASCVD risk (Profile #3) is to obtain a cGRS test and treat if cGRS is intermediate or high (scenario #3). However, even though a cGRS testing strategy was preferred for this profile and specific combination of model parameters, the probability of cost-effectiveness at any WTP of $50,000/QALY gained was only 40%.

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 (Pandya 2015; Pletcher 2014). A recent study found that the prevalence of statin disutility greater than 0.01 (trading away 5 weeks of perfect health to avoid 10 years on statins) was approximately 7.4%, with most individuals being unwilling to trade any length of time to avoid statin therapy (87% with statin disutility = 0) (Hutchins 2015). 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 daily preventive medication use, we can assume that the conditions under which cGRS testing is the preferred strategy are uncommon during routine clinical practice.

When we examined the two-way sensitivity analysis (statin disutility vs. 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, there were many combinations of statin disutility and statin cost that led to a cGRS testing strategy being preferred for the 45-year-old woman at 7.5% 10-year ASCVD risk. 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 45-year-old has more years to accumulate benefit from cGRS testing compared to a 65-year-old; furthermore, a 45-year-old woman with 7.5% 10-year ASCVD risk will have more risk factors (high cholesterol, smoking, etc.) compared to a 65-year-old woman with 7.5% 10-year ASCVD risk. Thus, it is important to be able to make individualized 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.

Although the 27-SNP cGRS test is an independent predictor of ASCVD outcomes, the strength of the association is small (Mega 2015). Other approaches to targeting statin therapy, such as the selective use of imaging (CAC scanning), are substantially better at improving risk prediction in intermediate risk patients (Yeboah 2016). Furthermore, CAC scanning has been shown to be cost-effective under more reasonable set of assumptions than those needed to make cGRS testing cost-effective (Pletcher 2014; Roberts 2015). 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, or those that have been associated with ischemic stroke outcomes (Vasan 2006; O'Donnell 2016;

Paynter 2016). However, GWAS studies to date have been largely unsuccessful at identifying loci significantly associated with stroke; this may be due to the inclusion of both ischemic and hemorrhagic stroke as outcomes, which may have slightly different underlying pathophysiology and predisposing risk factors (Sierra 2011). To further improve the 27-SNP cGRS' ability to predict pooled ASCVD beyond traditional risk factors, future research is necessary to identify loci that may have pleiotropic, as well as independent, effects on both CHD outcomes and ischemic stroke, potentially through a GWAS of both combined ischemic stroke and CHD outcomes.

Over $200 million has been invested in the Presidential Precision Medicine Initiative, which seeks to advance our knowledge and ability to incorporate individuals' genetic information into clinical decision-making to improve health outcomes (Paynter 2016; Shah 2016; Ma 2016). However, little attention has been given to the methods that are needed to assess the clinical utility of precision medicine. Clinical decision analysis and cost-effectiveness modeling are methods used to explicitly compare alternative clinical options regarding their relative downstream risks, benefits and costs. The work presented here is an example of the type of analysis that can help identify conditions under which genetic 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 (Palomaki 2010; Thanassoulis 2010). 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 plays a limited role in determining the overall clinical utility of cGRS testing. Another potential application of this type of cost-effectiveness analysis is to develop evidence against overuse of routine testing, such as routine EKGs, stress testing, or point-of-care ultrasounds.

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 due to limited evidence supporting this assumption. Furthermore, we did not explicitly account for new-onset diabetes in the model. However, as previously stated, while there is evidence that statin initiation is associated with a small, but statistically significant increase in hemoglobin A1C and new diagnoses of diabetes mellitus (Sattar 2012), the cardiovascular benefits outweigh the risks, at least in the short-term, and it is unclear whether there are long-term microvascular implications associated with the small increase in HbA1C or slightly earlier diagnosis of diabetes.

4.5. 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 between 2.5% and 7.5%. While 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. Unless better makers of genetic risk are determined, future efforts to improve upon the cGRS may not be worthwhile, given its limited clinical utility for targeting statin therapy for primary prevention of ASCVD.

CHAPTER 5: CONCLUSIONS AND RECOMMENDATIONS

5.1. Summary of research questions and findings

Cardiovascular genetic risk testing theoretically provides the opportunity to more precisely identify individuals at high risk for developing ASCVD for whom preventive therapy, such as statins, can be directed (O'Donnell 2016; Kullo 2016; Paynter 2016; Goldstein 2014; Tikkanen 2013; Krarup 2015; Shah 2016; Morrison 2007; de Vries 2016). An individual's cardiovascular genetic risk score (cGRS) may reflect genetic susceptibility to accelerated atherosclerosis, related potentially to errors in cholesterol metabolism, thrombosis and/or other endothelium-related factors (Vasan 2006). In 2015, Mega et al. demonstrated a significant association between a 27-SNP cGRS and CHD outcomes, after adjusting for traditional ASCVD risk factors (Mega 2015); however, the impact of obtaining cardiovascular genetic risk information on clinical decision-making regarding statin initiation is unclear.

The 27-SNP cGRS developed by Mega et al was constructed using only risk alleles associated with CHD outcomes, and validated in individuals primarily of European ancestry; thus, it was unclear whether this association would extend to pooled ASCVD outcomes in diverse populations. In Aim 1, I examined the association between the 27-SNP cGRS and pooled ASCVD outcomes in white and black non-diabetic, ASCVD-free participants from the prospective, population-based ARIC study. In a model that included traditional ASCVD risk factors as covariates, having an intermediate and high cGRS was associated with a 1.32-fold (95% CI: 0.97-1.79) and 1.47-fold (95% CI: 1.03-2.10) higher risk of 10-year pooled ASCVD events, respectively.

Higher cGRS was also associated with increased risk of 10-year incident CHD (intermediate cGRS HR (vs. low cGRS): 1.69; 95% CI: 1.15-2.49; high cGRS HR: 1.89; 95% CI: 1.22-2.92). Adding cGRS to the incident CHD model resulted in a statistically significant but small improvement in discrimination (ΔC-statistic= 0.0077; $p<0.01$). Overall, my findings from Aim #1 showed that the 27-SNP cGRS was associated with both incident CHD and pooled ASCVD events in a diverse population, but the magnitude of improvement in risk prediction was small.

Translation of improved risk prediction offered by novel risk factors, such as the 27-SNP cGRS, into actionable information to guide clinical decision-making can be achieved by integrating the 27-SNP cGRS with existing ASCVD risk prediction estimates (Pletcher 2011; Kooter 2011). To do this, we needed to know the expected distribution of the cGRS, conditional on traditional ASCVD risk factors (Pletcher 2013; Jarmul 2015). In Aim #2, I used an unbiased model selection algorithm with 10-fold cross-validation to examine the distribution of the 27-SNP cGRS in a multi-ethnic, nationally representative sample of individuals living in the United States, the Add Health study, as a function of traditional ASCVD risk factors (age, race, gender, total cholesterol, HDL cholesterol, systolic blood pressure, current smoking status, and anti-hypertensive medication use). I found that race/ethnicity was the only statistically significant predictor of cGRS and explained a fair amount of the variation (cross-validated $r2= 0.177$); however, the risk increase associated with having a high expected cGRS was modest (approximately 30% increase in 10-year predicted ASCVD risk, comparable to the risk increase associated with being 5 years older).

In Aims #1 and #2, I established that the 27-SNP cGRS is associated with 10-year ASCVD outcomes beyond traditional risk factors, and demonstrated that integration of the 27-SNP cGRS

into existing risk prediction estimates produces modest changes in 10-year ASCVD predicted risk estimates. In Aim #3, I addressed the question of whether obtaining the additional information provided by the 27-SNP cGRS is a cost-effective strategy for targeting statin therapy in the primary prevention of ASCVD. Using the previously developed UNC-RTI CHD Prevention Model (Pignone 2007; Pignone 2006; Pletcher 2014), I found that obtaining a cGRS test to prevent some patients from being prescribed a statin was not a cost-effective strategy for a set of clinical scenarios of individuals with 10-year predicted ASCVD risk ranging from 2.5% to 7.5%. In sensitivity analyses, I found that for certain clinical scenarios, such as a 65-year-old man with a 10-year predicted risk of 7.5%, cGRS testing can be cost-effective under a very limited set of assumptions; for example, when the cost of obtaining a cGRS test is $100, daily statin cost is $0.50, and statin disutility is 0.013, the preferred strategy (using a WTP of $50,000/QALY) is to obtain a cGRS test and treat if cGRS is intermediate or high.

5.2. Limitations

One limitation of this dissertation was that I focused on a specific cGRS that only includes 27 SNPs; some other analyses have used as many as 152 SNPs to help further increase the effect of the cGRS at improving overall risk prediction (de Vries 2015; Deghan 2016). However, these risk scores have generally not offered substantial improvements in risk prediction compared to the 27-SNP cGRS (Tada 2015). Another limitation of the 27-SNP cGRS is that there are no SNPs included that have been shown to be associated with incident ischemic stroke. We considered adding additional SNPs to the cGRS to expand prediction potential to ischemic stroke, but recent GWAS consortia were unable to identify any loci that were significantly associated with incident ischemic stroke (Traylor 2012).

I was unable to test the association between the 27-SNP cGRS and ASCVD outcomes over the extended follow-up period available in the ARIC study (~22 years), because of violation of the proportional hazards assumption. Future analyses could utilize more complex modeling techniques, such as Cox models that include time-dependent variables or non-parametric survival models, in order to understand the relationship between the 27-SNP cGRS and long-term ASCVD outcomes.

Last, there were two main limitations in the cost-effectiveness analysis: 1) I did not incorporate a potential interaction effect between the 27-SNP cGRS and statin treatment efficacy (Mega 2015) and 2) I did not include "new-onset diabetes" as a health state in the Markov model. Although the potential for an interaction between genetic risk and statin treatment efficacy could change the balance of benefit, risk and costs for cGRS testing, the evidence for this interaction effect is not entirely convincing (Mega 2015). Also, while there is evidence that statin initiation is associated with a small, but statistically significant increase in hemoglobin A1C and new diagnoses of diabetes mellitus (Sattar 2012), the cardiovascular benefits outweigh the risks, at least in the short-term, and it is unclear whether there are long-term microvascular implications associated with the small increase in HbA1C or slightly earlier diagnosis of diabetes.

5.3. Contribution to literature

This is the first analysis to examine the cost-effectiveness of a cardiovascular genetic risk testing for targeting statin therapy in primary prevention of ASCVD. Furthermore, this is the first analysis to investigate the value of genetic testing for additional predictive risk information for targeting primary prevention interventions. These findings are relevant to researchers

investigating new biomarkers and tests, clinicians and patients who may need to decide whether to test for novel risk factors, and policy makers who make decisions about whether to pay for novel risk factor testing. For the case of cardiovascular genetic risk testing, my work has shown that testing for a 27-SNP cGRS is not a cost-effective strategy for targeting statin therapy in the primary prevention of cardiovascular disease. For genetic risk testing generally, my findings demonstrate the importance of assessing clinical utility and cost-effectiveness prior to extensive commercialization, use in clinical practice, or reimbursement decisions.

Over the past 25 years, there have been substantial advancements in both the methods and applications of decision modeling. However, decision modeling is still not routinely used to inform clinical guidelines; although recently the US Preventative Services Task Force (USPSTF) has included modeling results in justification for its recommendations on primary prevention of CVD and CRC using aspirin, breast cancer screening, colorectal cancer screening and lung cancer screening (Zauber 2015; Mandelblatt 2015; de Konig 2014). While past work has examined the clinical utility of screening or diagnostic testing, the work done in this dissertation provides a conceptual framework for modeling the clinical utility and cost-effectiveness of tests that offer predictive information. As we continue to accumulate data on the long-term effects of risk factors on health outcomes, our goal, as health services researchers and clinicians, will be to use this information to identify at-risk individuals earlier and implement interventions to avoid adverse health outcomes. It will be increasingly important that we utilize decision modeling to understand the incremental value of predictive information, such as cardiovascular genetic risk information, in enhancing clinical decision-making and ultimately improving patient outcomes.

5.4. Recommendations for future research

In Chapter 5, I presented evidence that, under base case assumptions, testing for this 27-SNP cGRS is generally not cost-effective for individuals with 10-year predicted ASCVD risk between 2.5% and 7.5%. Future research in this area could examine the cost-effectiveness of improving upon the current 27-SNP cGRS to include risk alleles that are more strongly associated with CHD and/or ischemic stroke outcomes, if discovered. However, unless genetic variants are discovered that are significantly more associated with CHD and/or ischemic stroke, this may not be a fruitful endeavor. Additionally, future research could examine the base case assumptions for the cost-effectiveness model, including uncertainty with respect to model structure. For example, I could continue to update the UNC-RTI CHD Prevention Model to include the cGRS*statin efficacy interaction effect, as well as add the new-onset diabetes health state. If the addition of the cGRS*statin interaction effect led to cGRS testing being a preferred strategy, one could consider doing a value of information analysis to investigate the amount of money that a decision-maker might want to spend to determine whether the cGRS*statin interaction effect could be replicated in a prospective, randomized controlled trial (Barton 2008; Briggs 2012).

5.5. Conclusions

In conclusion, I found that a 27-SNP cGRS is independently associated with 10-year ASCVD outcomes in a diverse population; however, the magnitude of change in updated 10-year ASCVD predicted risk is small. More importantly, through the work done in this dissertation, I can conclude that, when compared to no genetic risk testing, obtaining cardiovascular genetic risk information by testing for a 27-SNP cGRS is generally not a cost-effective strategy for targeting statin therapy in the primary prevention of ASCVD.

APPENDIX 1: CALCULATION OF 27-SNP CGRS

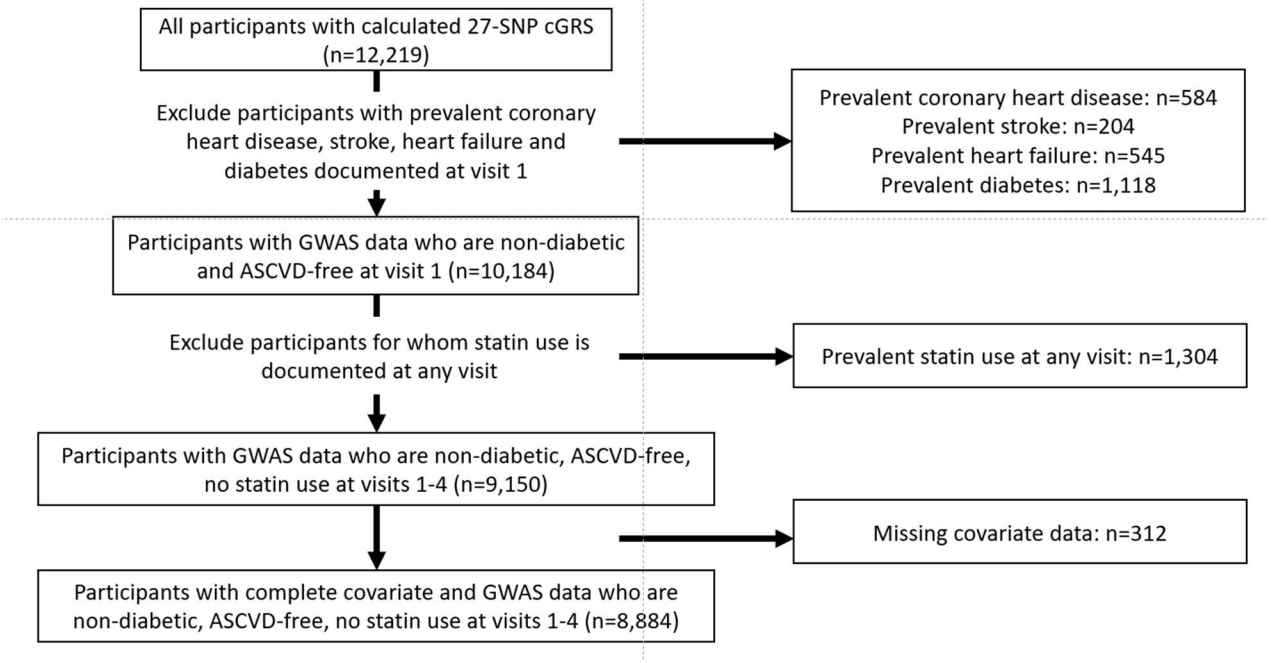
$$\text{27-SNP cGRS} = \sum_i \frac{1}{Odds\ Ratio_{SNPi}} (SNP_i\ dosage)$$

where i is the index of SNPs included in Appendix A.

APPENDIX 2: LEAD SNPS AND ORS FOR CHD USED TO CALCULATE THE CGRS (MEGA 2015)

Gene	Lead SNP	Odds Ratio for coronary heart disease	Risk allele	Build 38
1p13.3 (*SORT1*)	rs646776	1.19	T	1:109275908
1p32.3 (*PPAP2B*)	rs17114036	1.17	A	1:56497149
1p32.3 (*PCSK9*)	rs11206510	1.15	T	1:55030366
1q41 (*MIA3*)	rs17465637	1.14	C	1:222650187
2q33.1 (*WDR12*)	rs6725887	1.17	C	2:202881162
3q22.3 (*MRAS*)	rs9818870	1.15	T	3:138403280
6p21.31 (*ANKS1A*)	rs17609940	1.07	G	6:35067023
6p24.1 (*PHACTR1*)	rs9349379	1.12	G	6:12903725
6q23.2 (*TCF21*)	rs12190287	1.08	C	6:133893387
6q25.3 (*LPA*)	rs3798220	1.47	C	6:160540105
6q25.3 (*LPA*)	rs10455872	1.70	G	6:160589086
7q32.3 (*ZC3HC1*)	rs11556924	1.09	C	7:130023656
9p21.3 (*CDKN2A*)	rs4977574	1.29	G	9:22098575
9q34.2 (*ABO*)	rs9411489	1.10	T	9:133279427
10q11.21 (*CXCL12*)	rs1746048	1.17	C	10:44280376
10q24.32 (*CYP17A1*)	rs12413409	1.12	G	10:102959339
11q23.3 (*APOA5*)	rs964184	1.13	G	11:116778201
12q2.4 (*HNF1A*)	rs2259816	1.08	T	12:120997784
12q24.12 (*SH2B3*)	rs3184504	1.13	T	12:111446804
13q3.4 (*COL4A1*)	rs4773144	1.07	G	13:110308365
14q32.2 (*HHPL1*)	rs2895811	1.07	C	14:99667605
15q25.1 (*ADAMTS7*)	rs3825807	1.08	T	15:78796769
17p11.2 (*RASD1*)	rs12936587	1.07	G	17:17640408
17p13.3 (*SMG6*)	rs216172	1.07	C	17:2223210
17q21.32 (*UBE2Z*)	rs46522	1.06	T	17:48911235
19p13.2 (*LDLR*)	rs1122608	1.15	G	19:11052925
21q22.11 (*KCNE2*)	rs9982601	1.20	T	21:34226827

APPENDIX 3: CREATION OF ARIC ANALYTIC DATA SET



APPENDIX 4: FATAL CHD AND NON-FATAL MI EVENTS BY RACE AND CGRS CATEGORY: # OF EVENTS AND AVERAGE FOLLOW-UP TIME FOR NON-HISPANIC WHITE PARTICIPANTS

White participants (n=6,937)					
cGRS category	# of fatal CHD and non-fatal MI events	Median follow-up time for events (years)	Average follow-up time for events & non-events (years)	Average event rate per 1000 people per year	Risk of events over 10 years
Low risk (n=1,388)	95 (%)	14.9	21.9	3.1	3.1%
Intermediate risk (n=4,162)	393 (%)	14.0	21.7	4.3	4.2%
High risk (n=1,387)	177 (%)	14.4	21.6	5.9	5.7%
All (n=6,937)	665 (%)	14.3	21.8	4.4	4.3%
Black participants (n=1,889)					
cGRS category	# of fatal CHD and non-fatal MI events	Average follow-up time for events (years)	Average follow-up time for events & non-events (years)	Average event rate per 1000 people per year	Risk of events over 10 years
Low risk (n=378)	26 (%)	11.6	22.2	3.1	3.1%
Intermediate risk (n=1,134)	149 (%)	14.0	21.1	6.2	6.0%
High risk (n=377)	42 (%)	14.4	21.7	5.1	5.0%
N=1,889	217 (%)	13.8	21.4	5.4	5.2%

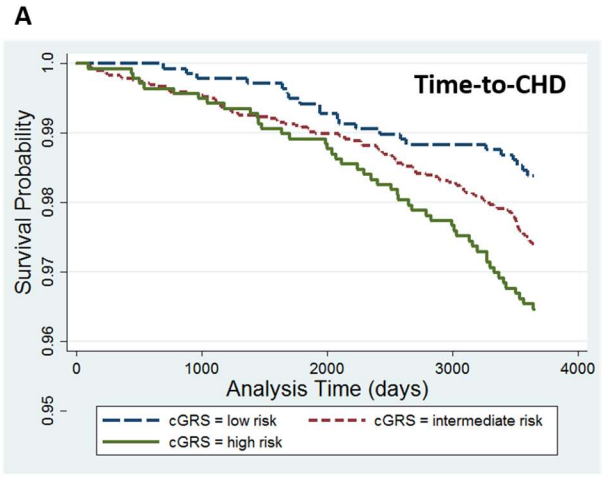
APPENDIX 5: FATAL CHD, NON-FATAL MI, AND ISCHEMIC STROKE EVENTS BY RACE AND CGRS CATEGORY: # OF EVENTS AND AVERAGE FOLLOW-UP TIME FOR NON-HISPANIC WHITE PARTCIPANTS

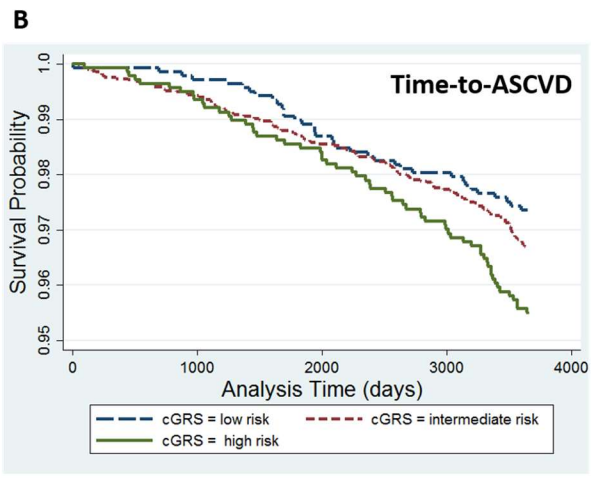
White participants (n= 6,937)					
cGRS category	# of fatal CHD, non-fatal MI, ischemic stroke events	Median follow-up time for events (years)	Average follow-up time for events & non-events (years)	Average event rate per 1000 people per year	Risk of events over 10 years
Low risk (n=1,388)	143 (%)	15.7	21.7	4.7	4.6 %
Intermediate risk (n=4,162)	499 (%)	14.0	21.5	5.6	5.4 %
High risk (n=1,387)	213 (%)	13.5	21.4	7.2	6.9 %
All (n=6,937)	855 (%)	14.1	21.6	5.7	6.0 %

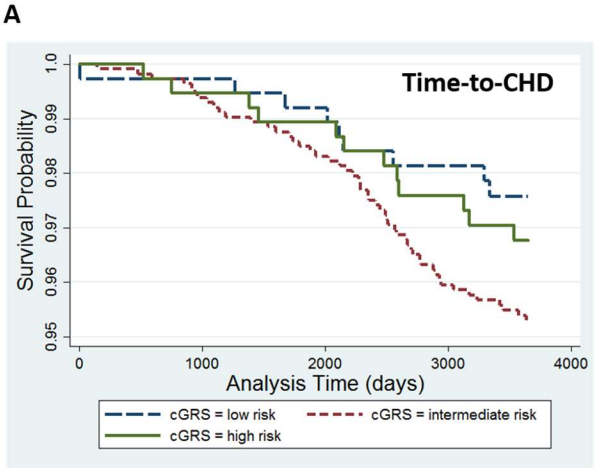
Table 3. B) Fatal CHD, non-fatal MI, and ischemic stroke events by race and cGRS category: # of events and average follow-up time for black participants

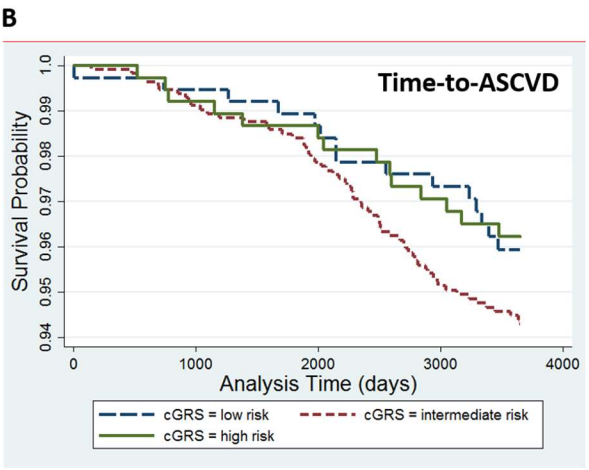
Black participants (n=1,889)					
cGRS category	# of fatal CHD, non-fatal MI, ischemic events	Median follow-up time for events (years)	Average follow-up time for events & non-events (years)	Average event rate per 1000 people per year	Risk of events over 10 years
Low risk (n=378)	50 (%)	13.7	21.9	6.0	5.9 %
Intermediate risk (n=1,134)	217 (%)	13.8	20.8	9.2	8.8 %
High risk (n=377)	63 (%)	13.4	21.5	7.8	7.5 %
N=1,889	330 (%)	13.7	21.2	8.3	7.9 %

APPENDIX 6: KAPLAN MEIER SURVIVAL CURVES FOR WHITE PARTICPANTS (TOP TWO PANELS) AND BLACK PARTICIPANTS (BOTTOM TWO PANELS)

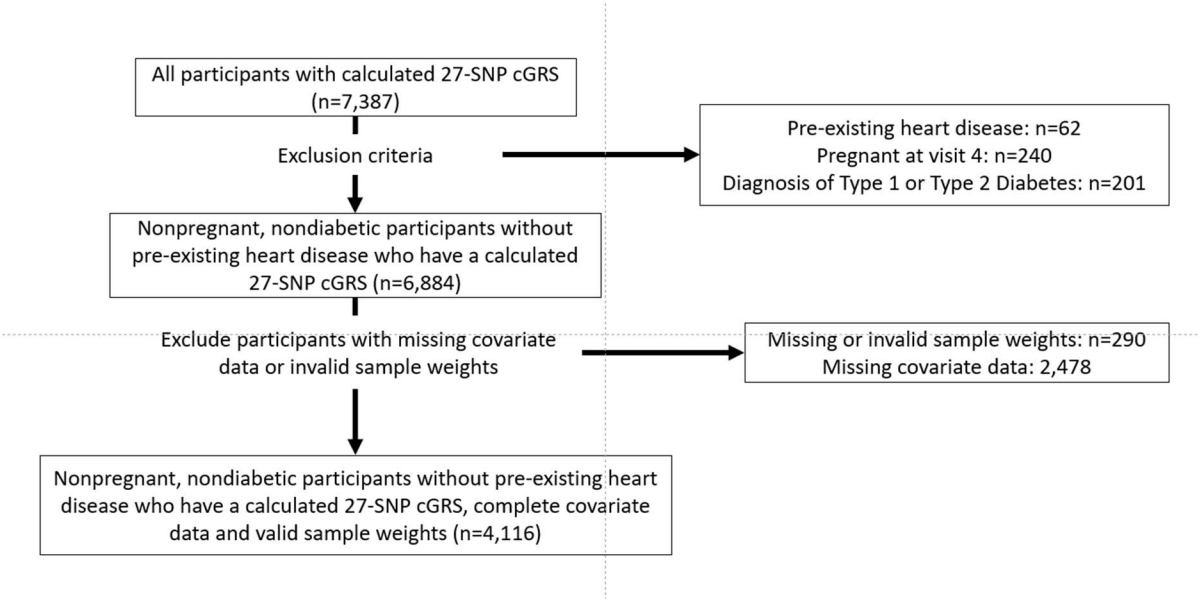








APPENDIX 7: CREATION OF ADD HEALTH ANALYTIC DATA SET



APPENDIX 8: EXAMPLE CALCULATION USING EXPECTED DISTRIBUTION OF CGRS

$[r] = 0.06 * RR_{cGRS=low} + 0.86 * RR_{cGRS=intermediate} + 0.08 * RR_{cGRS=high}$

if $RR_{cGRS=low} = 1.0$, $RR_{cGRS=intermediate} = 1.31$ and $RR_{cGRS=high} = 1.72$,
$[r] = 1.324$

$MF_{cGRS=low} = 1.0 / 1.324 = 0.755$

$MF_{cGRS=intermediate} = 1.31 / 1.324 = 0.989$
$MF_{cGRS=high} = 1.72 / 1.324 = 1.299$

F(post-test ASCVD risk | cGRS = low) = 7.5% * 0.755 = 5.7%

APPENDIX 9: 2013-2014 TOTAL CHOLESTEROL AND HDL CHOLESTEROL DECILES

	Values used for total cholesterol (mg/dL)	Values used for HDL cholesterol (mg/dL)
Quintile 1	136	34
Quintile 2	150	38
Quintile 3	161	42
Quintile 4	170	45
Quintile 5	179	49
Quintile 6	188	53
Quintile 7	199	58
Quintile 8	212	63
Quintile 9	232	71

APPENDIX 10: DISTRIBUTIONAL ASSUMPTIONS FOR PARAMETERS INCLUDED IN THE PROBABALISTIC SENSITIVITY ANALYSIS

Parameter	Included in PSA?	Base case	Standard Error	Distribution	a	b
Cost of cGRS Testing	N	$100.00	---	---	---	---
Cost Adherence Rates: Statin	Y	69.00%	0.001020	Beta	141,745.71	63,682.85
Efficacy Adherence Rates: Statin	Y	69.00%	0.001020	Beta	141,745.71	63,682.85
Drug Costs: Statin	N	$48.67	9.73	Gamma	25.00	1.95
HS Cost Healthy	Y	$70.46	14.09	Gamma	25.00	2.82
Added Cost of Taking a Statin	Y	$93.94	18.79	Gamma	25.00	3.76
HS Cost Angina	Y	$16,777.67	3355.53	Gamma	25.00	671.11
HS Cost Post Angina	Y	$7,323.20	1464.64	Gamma	25.00	292.93
HS Cost Stroke	Y	$54,847.38	10969.48	Gamma	25.00	2,193.90
HS Cost Post Stroke	Y	$14,607.18	2921.44	Gamma	25.00	584.29
HS Cost Myocardial Infarction	Y	$41,797.60	8359.52	Gamma	25.00	1,671.90
HS Cost Post Myocardial Infarction	Y	$5,091.17	1018.23	Gamma	25.00	203.65
HS Cost Myopathy	Y	$398.77	79.75	Gamma	25.00	15.95
Relative Risks Statin: Angina	Y	0.7400	0.0153	Normal	2,337.40	0.00
Relative Risks Statin: Stroke	Y	0.8500	0.0255	Normal	1,110.22	0.00
Relative Risks Statin: Myocardial Infarction	Y	0.7400	0.0153	Normal	2,337.40	0.00
Mortality Risks: No Treatment CHD Death	N	1.0000	0.2000	Gamma	25.00	0.04

Mortality Risks: Statin CHD Death	Y	0.8000	0.0255	Normal	983.45	0.00
Mortality Risks: Statin Myopathy	N	0.0016	0.0003	Gamma	25.00	0.00
Rhabdo Incidence	Y	0.0160	0.00002	Normal	646,580.93	0.00
Rhabdo fatality	Y	0.1000		Beta	96.00	839.00
Mortality Post Myocardial Infarction	Y	3.7000	0.5102	Gamma	52.59	0.07
Mortality Post Angina	Y	3.0000	0.6122	Gamma	24.01	0.12
Mortality Post Stroke	Y	2.3000	1.1735	Gamma	3.84	0.60
Utilities: Healthy	N	1.00	0.2000	Beta	-1.00	0.00
Utilities: Angina	Y	0.93	0.2699	Truncated Normal		
Utilities: Post Angina	Y	0.997	0.1617	Truncated Normal		
Utilities: Stroke	Y	0.77	0.1505	Beta	5.24	1.56
Utilities: Post Stroke	Y	0.77	0.1542	Beta	4.95	1.47
Utilities: Myocardial Infarction	Y	0.86	0.0311	Beta	106.55	17.49
Utilities: Post Myocardial Infarction	N	1.00	0.0714	Beta	-1.00	0.00
Utilities: No Treatment	N	1.000	0.2000	Beta	-1.00	0.00
Utilities: Myopathy	Y	0.983	0.1966	Truncated Normal		
Utilities: Disutility due to taking a pill	N	0.999	0.1998	Beta	-0.97	0.00
Relative Risk of Events: low cGRS	N	1.00	0.2000	Gamma	25.00	0.04
Relative Risk of Events: intermediate cGRS	Y	1.31	0.2620	Gamma	25.00	0.05
Relative Risk of Events: high cGRS	Y	1.72	0.3440	Gamma	25.00	0.07

General Healthcare Costs for 35 - 44	Y	$4,552.11	910.42	Gamma	25.00	182.08
General Healthcare Costs for 45 - 54	Y	$6,687.27	1337.45	Gamma	25.00	267.49
General Healthcare Costs for 55 - 64	Y	$9,375.97	1875.19	Gamma	25.00	375.04
General Healthcare Costs for 65 - 69	Y	$14,396.15	2879.23	Gamma	25.00	575.85
General Healthcare Costs for 70+	Y	$20,102.47	4020.49	Gamma	25.00	804.10
Proportion of Strokes that are Fatal	Y	14.4%	0.0287	Beta	21.26	126.72

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