1.a. **Full Title**: Interpretation of a novel cardiovascular genetic risk score in combination with conventional risk factors for cardiovascular risk prediction

b. **Abbreviated Title (Length 26 characters)**: Combining cGRS with traditional risk factors

2. **Writing Group**:
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**3. Timeline:** Analysis will begin in mid-2016, upon approval. We aim to submit the manuscript for P&P review by late summer, 2016.
4. **Rationale:**

As many as 40% of Americans are expected to have cardiovascular disease (CVD) by 2030, contributing to a projected 100% increase in expected CVD medical costs between 2013 and 2030 (Mozaffarian 2015). Thus, emphasis on primary prevention of atherosclerotic cardiovascular disease (ASCVD), which includes non-fatal ischemic stroke, fatal stroke, non-fatal myocardial infarction (MI) and fatal MI, is critical for improving overall population health. The most recent ASCVD primary prevention guidelines, published in 2013 by the American College of Cardiology (ACC) and American Heart Association (AHA), recommend that clinicians use 10-year predicted ASCVD risk estimates, calculated using the Pooled Cohort Equations (PCE), to guide initiation of statin therapy (Goff et al., 2013). Using the currently suggested ASCVD risk threshold for statin initiation of 7.5% of greater, approximately 33.0 million Americans without pre-existing ASCVD or diabetes eligible for statin therapy (Goff et al., 2013; Pencina et al., 2014).

Clinicians may not feel confident using population-level estimates of risk to guide statin treatment decisions in individuals close to the 7.5% treatment threshold, simply because of the wide variance inherent in individual-level ASCVD predicted risk estimates (McEvoy et al., 2014; Amin et al., 2014; Yeboah et al., 2015). The 2013 ACC/AHA guidelines suggest that additional nontraditional risk factors, such as coronary artery calcium (CAC), ankle-brachial index (ABI), high-sensitivity C-reactive protein, and family history of premature cardiovascular disease, may be useful during shared decision-making (Stone et al. 2013). Of these, only CAC has been shown to modestly improve discrimination between individuals who do and those who don’t go on to experience ASCVD events within 10 years (Yeboah et al., 2016). However, presence of CAC indicates relatively advanced vascular disease and significantly increased short-term ASCVD risk; this limits the extent to which we can utilize CAC as a risk stratification tool in younger adults, who are far less likely to have accumulated enough vascular damage to have measurable CAC, but still may have significant predicted lifetime ASCVD risk (Sniderman et al., 2014; Detrano et al., 2008; Zamarano and del Val, 2016).

Using a cardiovascular genetic risk score (cGRS), such as Mega et al.’s 27-SNP cGRS or the 49-SNP CARDIOGRAMplusC4D cGRS, to improve ASCVD risk prediction is a promising approach because genetic markers of increased ASCVD risk are present from birth and have also been shown to be significant predictors of subclinical atherosclerotic disease (Mega et al., 2015; Thanassoulis et al., 2013; Salfati et al., 2015). Ideally, we would identify individuals with increased cGRS before there is any significant vascular remodeling or damage, and initiate lifestyle interventions or statin therapy to prevent or slow progression of atherosclerosis.

In a recent JAMA editorial, Sniderman et al. emphasized that clinicians must understand the differences between group risk and individual risk, and be able to incorporate additional nontraditional risk factors into their clinical decisions when faced with patients that do not necessarily resemble clinical trial populations (Sniderman et al., 2015). Their argument is logical but shows little appreciation for the decision complexity involved in determining which additional risk factor would provide the most useful information for the patient at hand (e.g. cGRS vs. CAC vs. hemoglobin A1C). First, the positive and negative likelihood ratios for cGRS, CAC and hemoglobin A1C (HbA1C) depend on expected distribution of cGRS, CAC and HbA1C, respectively, conditional on the patient’s ASCVD risk factor profile (Kooter et al. 2011). In order to incorporate these “risk profile-adjusted” likelihood ratios into decision-
making, clinicians would need risk calculators for the expected distribution of the cGRS, CAC and HbA1C, that use the patient’s traditional ASCVD risk factors as input variables (see Supplementary material- Excel calculator). Second, the risks and costs associated with each nontraditional risk factor test are not equivalent and thus should be balanced against the expected benefits as a part of the clinical decision-making process.

In order to facilitate implementation of Sniderman et al.’s advice into clinical practice, we aim to develop a prediction model for expected cGRS, conditional on traditional ASCVD risk factors, and present a framework for identifying subpopulations of individuals in whom testing for a specific nontraditional risk factor will most likely result in statin treatment re-classification. We will use this framework in future cost-effectiveness analyses to fully assess and compare the benefits, risks and costs of each of the identified population-level testing strategies.

5. Main Hypothesis/Study Questions:

For this manuscript, we propose using ARIC data to develop race/ethnicity-specific prediction models for cGRS, as a function of traditional cardiovascular risk factors, in order to integrate cGRS into baseline 10-year ASCVD risk predictions, as described in the Design and Analysis section briefly, and in more detail in Appendix B. We will then use the 2013-2014 National Health and Nutrition Examination Survey (NHANES) sample and calculate the predicted cGRS for all nondiabetic, ASCVD-free individuals in order to describe the subpopulation of individuals who: 1) have the potential to be re-classified over the 7.5% statin treatment threshold based on cGRS test results and 2) the likelihood of re-classification (ie the proportion of individuals with a specific risk factor profile that would be expected to have a high cGRS). For comparison, we will calculate predicted CAC and predicted HbA1C (using previously developed prediction models) for the same individuals in the NHANES sample (Pletcher et al., 2013; Jarmul et al., 2015). First, we will describe the distribution of baseline 10-year ASCVD risk in the nondiabetic, ASCVD-free NHANES sample; then, we will calculate the proportion and characteristics of individuals who have the potential to be re-classified by each of the risk factors.

Our main hypothesis is that individuals who only have the potential to be re-classified through cGRS testing will have a distinct ASCVD risk factor profile that will enable targeted recommendations for cardiovascular genetic risk testing in that subpopulation. Identifying the profile of individuals in this subpopulation, as well as individuals who are only re-classified using HbA1C or CAC, will help inform the set of population-level testing strategies for which we will compare the balance of benefits, risks and costs in future cost-effectiveness analyses.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design: Cross-sectional linear regression analysis at ARIC study baseline

Inclusion criteria: Non-pregnant individuals with visit 1 data who have consented to allow use of genetic data for research.

Exclusion criteria: participants with congestive heart failure defined using the Gothenburg criteria, prevalent coronary heart disease (CHD), diabetes, or prevalent stroke. Prevalent diabetes, CHD, and stroke is classified using ARIC investigator definitions.
**Data elements requested:** Visit 1 measured age, sex, race/ethnicity, systolic blood pressure, fasting status, total cholesterol, LDL cholesterol, HDL cholesterol, smoking history, current medications, derived stroke, CHD, diabetes, and heart failure variables, and GWAS data.

**Outcome variable:** The “cardiovascular genetic risk score” (cGRS) will be calculated as the sum of the number of risk alleles for each SNP in Appendix A, Table 1 weighted by the log of the odds ratio reported with the SNP in the table, as shown in Equation 2 (Mega et al., 2015).

**Equation 1**

\[
\text{Cardiovascular genetic risk score} = \sum_{i} \frac{1}{\text{odds Ratio}_{SNP_i}} (\# \text{ of risk alleles present for SNP}_i)
\]

where \(i\) is the index of SNPs included in Appendix A, Table 1.

**Explanatory/predictor variables:** The explanatory/predictor variables for the linear regression analysis are age, sex, race/ethnicity, systolic blood pressure, total cholesterol, HDL cholesterol, current smoking status, and current anti-hypertension medication.

**Summary of planned data analyses:**

For this analysis, we propose using ARIC data to develop race/ethnicity-specific models for expected cardiovascular genetic risk score (cGRS), adjusting for age, sex, systolic blood pressure, total cholesterol, HDL cholesterol, smoking status, diabetes and anti-hypertension treatment (Equation 2; detailed statistical methods in Appendix B). We plan to use the cGRS published by Mega et al., who developed a 27-SNP risk score and used pooled individual-level data from randomized controlled trials evaluating statin efficacy to demonstrate that intermediate and high cGRS risk scores were associated with increased hazard ratio for ASCVD events (Mega et al., 2015).

We will use previously developed prediction models for CAC and HbA1C (Table 1), as well as the race/ethnicity-specific prediction models for cGRS, to predict expected values and distributions of cGRS, HbA1C and CAC for all nondiabetic, ASCVD-free individuals aged 40-79 years old in the 2013-2014 National Health and Nutrition Examination Survey (NHANES) sample. First, we will use the Pooled Cohort Equations from the 2013 ACC/AHA guidelines to calculate population-level estimates of baseline ASCVD risk (Goff et al., 2013). Second, for each individual, we will calculate the likelihood of re-classification using cGRS testing, CAC testing and HbA1C testing. Third, we will use comparative analysis to identify individuals for whom only one of the three tests produce a large enough shift in ASCVD risk to re-classify that individual across the statin treatment threshold (Figure 1). Once these individuals are identified, we will present summary statistics of their risk factor profiles and create suggestions for potential population-level test/treat strategies based on the subpopulations identified (Table 2). In subsequent analyses, these population-level test/treat strategies will be compared in a cost-effectiveness analysis using individual-level simulation model.

We would like to make it clear that the genetic risk score and hazard ratios associated with ASCVD were derived in an overwhelmingly white sample of individuals enrolled in the statin efficacy trials (Mega et al., 2015). Thus, Mega et al.’s risk score is unlikely to be valid in African American participants (Franceschini et al., 2014). Therefore, we will present all summary statistics and regression analyses by race/ethnicity, and remain abreast of the literature, if and when a genetic risk score for African Americans becomes available. In its absence, we will consider restricting our results to Caucasians, making sure to discuss the potential of our findings to exacerbate health disparities.
Equation #2

Cardiovascular GRS

\[ \text{Cardiovascular GRS} = \alpha_0 + \beta_{age} \times age + \beta_{gender} \times gender + \beta_{race} \times race + \beta_{TC} \times TC + \beta_{HDL} \times HDL + \beta_{SBP} \times SBP + \beta_{smoker} \times smoker + \beta_{antiHTN} \times antiHTN \]

+ interaction terms + \( \varepsilon_0 \)

Table 1: Final prediction models for HbA1C, CAC and cGRS

<table>
<thead>
<tr>
<th>Model Predictors</th>
<th>Expected HbA1C</th>
<th>Likelihood of any CAC</th>
<th>Expected ln(CAC)</th>
<th>Expected cGRS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient (95% CI)*</td>
<td>Odds Ratios (95% CI)*</td>
<td>Coefficient (95% CI)*</td>
<td>Coefficient (95% CI)*</td>
</tr>
<tr>
<td>Age, per 10 years</td>
<td>0.102 (0.072, 0.132)</td>
<td>2.48 (2.33, 2.65)</td>
<td>0.61 (0.54, 0.67)</td>
<td></td>
</tr>
<tr>
<td>Hispanic‡</td>
<td>0.186 (0.072, 0.300)</td>
<td>Hispanic female*</td>
<td>0.55 (0.44, 0.68)</td>
<td>-0.37 (-0.62, -0.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hispanic male#</td>
<td>1.65 (1.33, 2.06)</td>
<td>0.53 (0.30, 0.75)</td>
</tr>
<tr>
<td>Non-Hispanic black‡</td>
<td>0.223 (0.112, 0.334)</td>
<td>Black female*</td>
<td>0.56 (0.46, 0.68)</td>
<td>-0.18 (-0.40, -0.036)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Black male#</td>
<td>1.16 (0.95, 1.43)</td>
<td>0.30 (0.081, 0.51)</td>
</tr>
<tr>
<td>Non-Hispanic Asian‡</td>
<td>0.226 (0.007, 0.380)</td>
<td>Asian female*</td>
<td>0.87 (0.67, 1.13)</td>
<td>-0.19 (-0.48, 0.10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asian male#</td>
<td>1.92 (1.47, 2.51)</td>
<td>0.33 (0.067, 0.59)</td>
</tr>
<tr>
<td>Male (1=Yes)</td>
<td>-0.043 (-0.112, 0.026)</td>
<td>White male*</td>
<td>3.31 (2.73, 4.01)</td>
<td>0.88 (0.70, 1.06)</td>
</tr>
<tr>
<td>Current Smoker (1=Yes)</td>
<td>0.112 (-0.010, 0.235)</td>
<td></td>
<td>1.57 (1.33, 1.86)</td>
<td>0.22 (0.045, 0.40)</td>
</tr>
<tr>
<td>SBP, per 10 mmHg</td>
<td>0.022 (0.001, 0.043)</td>
<td></td>
<td>1.112 (1.071, 1.155)</td>
<td>0.078 (0.039, 0.117)</td>
</tr>
<tr>
<td>TC, per 10 mg/dL</td>
<td>0.016 (0.009, 0.023)</td>
<td></td>
<td>1.057 (1.039, 1.075)</td>
<td>0.0088 (-0.008, 0.026)</td>
</tr>
<tr>
<td>HDL, per 10 mg/dL</td>
<td>-0.076 (-0.106, -0.047)</td>
<td></td>
<td>0.892 (0.854, 0.931)</td>
<td>0.006 (-0.038, 0.050)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.50 (1.25, 1.78)</td>
<td></td>
<td>0.44 (0.28, 0.61)</td>
<td></td>
</tr>
<tr>
<td>Anti-HTN meds</td>
<td>4.9 (2.4, 10)</td>
<td></td>
<td>1.15 (0.43, 1.87)</td>
<td></td>
</tr>
<tr>
<td>SBP* anti-HTN meds</td>
<td>0.912 (0.863, 0.964)</td>
<td></td>
<td>-0.065 (-0.119, -0.011)</td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>4.76 (4.54, 4.98)</td>
<td></td>
<td>-7.900618</td>
<td>-1.411425</td>
</tr>
<tr>
<td>Cross-validated R²</td>
<td>0.0735</td>
<td></td>
<td>0.789</td>
<td>0.160</td>
</tr>
</tbody>
</table>
The standard deviation of the residuals for the final HbA1C model is 0.63995; for ln(CAC), it is 1.67148.

*Standard errors and 95% confidence intervals (CI) calculated using Taylor series linearization method
‡ vs. non-Hispanic white/other (reference category)
# vs. white females (reference category)

Table 2: Summary statistics of characteristics associated with re-classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Pretest ASCVD risk (Mean ± SD)</th>
<th>Post-test ASCVD risk (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals with ASCVD pretest risk &lt; 7.5% (n= XXX)</td>
<td>Only re-classified if cGRS = high risk (n=xx)</td>
<td>Only re-classified if CAC &gt; 0 (n= XX)</td>
</tr>
<tr>
<td></td>
<td>Only re-classified if HbA1C is &gt;= 6.5% (n= XX)</td>
<td></td>
</tr>
<tr>
<td>Individuals with ASCVD pretest risk &gt;= 7.5% (n= XXX)</td>
<td>Only re-classified if cGRS = low (n=XX)</td>
<td>Only re-classified if CAC = 0 (n= XX)</td>
</tr>
<tr>
<td></td>
<td>Only re-classified if HbA1C &lt; 5.7%(n= XX)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Venn diagrams that show planned comparative analyses of individuals who are only re-classified across treatment threshold by one of the three risk factors

A. For individuals with ASCVD pretest risk < 7.5%  
B. For individuals with ASCVD pretest risk > 7.5%
7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ____ No

   b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used?  ____ Yes  ____ No
   (This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript?  
   ___X___ Yes  ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____X____ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at:  http://www.cscc.unc.edu/ARIC/search.php

   ___X___ Yes  ______ No

Per Christy Avery: The majority of approved ARIC manuscript proposals examining genetic risk scores for CHD and related outcomes were proposed five-eight years ago. We also have engaged ARIC colleagues (e.g. Alanna Morrison) who were involved in these early proposals to ensure the least amount of overlap possible.

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

   See above

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____ Yes  ____X____ No

11.b. If yes, is the proposal
   ___  A. primarily the result of an ancillary study (list number* _________)
      ___  B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/
12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.
References:


Appendix A:
Table 1: Lead SNPs and ORs for CHD used to calculate the cardiovascular genetic risk score (cGRS) (Mega et al., 2015).

<table>
<thead>
<tr>
<th>Gene</th>
<th>Lead SNP</th>
<th>Odds Ratio for coronary heart disease</th>
<th>Risk allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>1p13.3 (SORT1)</td>
<td>Rs646776</td>
<td>1.19</td>
<td>T</td>
</tr>
<tr>
<td>1p32.3 (PPAP2B)</td>
<td>Rs17114036</td>
<td>1.17</td>
<td>A</td>
</tr>
<tr>
<td>1p32.3 (PCSK9)</td>
<td>Rs11206510</td>
<td>1.15</td>
<td>T</td>
</tr>
<tr>
<td>1q41 (MIA3)</td>
<td>Rs17465637</td>
<td>1.14</td>
<td>C</td>
</tr>
<tr>
<td>2q33.1 (WDR12)</td>
<td>Rs6725887</td>
<td>1.17</td>
<td>C</td>
</tr>
<tr>
<td>6p21.31 (ANKS1A)</td>
<td>Rs17609940</td>
<td>1.07</td>
<td>G</td>
</tr>
</tbody>
</table>
Appendix B: Detailed statistical methods that will be used for cGRS prediction model selection

Development of cGRS prediction model

We will use linear regression analysis to model the expected distribution of the cGRS within the analytic population (Equation 2). We have specified a set of candidate predictor variables based on information that is used to calculate predicted 10-year ASCVD risk; the set of candidate predictor variables includes age, sex, race/ethnicity, total cholesterol, HDL-cholesterol, systolic blood pressure, smoking status, and hypertension treatment status. Given the large number of potential interaction terms and functional forms of our candidate predictor variables, we will use an unbiased model selection process with 10-fold cross-validation that we have 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 will assess 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 result in increase in the value of the statistic; this allows me 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 cardiovascular GRS values (from the 10 sets of coefficient estimates) to actual cardiovascular GRS values in an unused subset of the data (the validation set). The cross-validated R^2 will increase as the correlation between average predicted cardiovascular GRS...
values and the actual cardiovascular GRS values increases, but will be subject to a penalty if the variation in predicted cardiovascular GRS values across the training sets is large.

Calculate pretest and post-test ASCVD risk:

In order to calculate the post-test ASCVD risk, we will first calculate 10-year ASCVD risk for all individuals in 2013-2014 NHANES sample using the 2013 ACC/AHA Pooled Cohort Risk Equations; this will be defined as the pretest risk. We will use then use the coefficient estimates from the cGRS unbiased model selection process to create a prediction model, which allows calculation of the expected cardiovascular GRS distribution based on an individual patient’s characteristics. Low, intermediate and high risk categories will be based on absolute cardiovascular GRS cut-offs in Mega et al.; a cardiovascular GRS of less than 1.00 will be considered “low risk”, a GRS greater than or equal to 1.00 and less than 1.50 will be “intermediate risk”, and a GRS greater than or equal to 1.50 will be considered “high risk.” The relative risks in each cardiovascular GRS category are assumed to differ according to adjusted hazard ratio estimates from Mega et al: low GRS: 1.0 (reference category), intermediate genetic risk: 1.31 (95% CI: 1.19-1.45), and high genetic risk: 1.72 (95% CI: 1.53- 1.92). These hazard ratios were adjusted for age, sex, race, smoking status, systolic blood pressure, total cholesterol, HDL-cholesterol, diabetes status, hypertension, and family history of coronary heart disease. We will obtain post-test ASCVD risk, conditional on testing into the low, intermediate or high genetic risk categories, we will multiply the pretest ASCVD by a “multiplication factor” (MF) for each category. The multiplication factor can be calculated using Equations 4-6. Equation 7 shows the calculation of posttest risk using the pretest risk and appropriate multiplication factor.

<table>
<thead>
<tr>
<th>Equations (from Kooter et al., 2011)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
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<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

*Where \([r]\) is the weighted mean relative risk; \(p_1\) is the prevalence of “low genetic risk” in the population of interest, \(p_2\) is the prevalence of “intermediate genetic risk” and \(p_3\) is the prevalence of “high genetic risk” (Kooter et al. 2011). \(RR_1\) is the relative risk of the lowest level of risk (= 1), \(RR_2\) is the relative risk of “intermediate genetic risk” (HR = 1.31), and \(RR_3\) is the relative risk of “high genetic risk” (HR = 1.72).