

## Expert Review of Precision Medicine and Drug **Development**

Personalized medicine in drug development and clinical practice

ISSN: (Print) 2380-8993 (Online) Journal homepage: http://www.tandfonline.com/loi/tepm20

# Coronary Artery Disease Genetic Risk Awareness Motivates Heart Health Behaviors in the Coriell Personalized Medicine Collaborative

Laura B. Scheinfeldt, Tara J. Schmidlen, Neda Gharani, Matthew MacKnight, Joseph P. Jarvis, Susan K. Delaney, Erynn S. Gordon, Courtney J. Kronenthal, Norman P. Gerry & Michael F. Christman

To cite this article: Laura B. Scheinfeldt, Tara J. Schmidlen, Neda Gharani, Matthew MacKnight, Joseph P. Jarvis, Susan K. Delaney, Erynn S. Gordon, Courtney J. Kronenthal, Norman P. Gerry & Michael F. Christman (2016): Coronary Artery Disease Genetic Risk Awareness Motivates Heart Health Behaviors in the Coriell Personalized Medicine Collaborative, Expert Review of Precision Medicine and Drug Development

To link to this article: http://dx.doi.org/10.1080/23808993.2016.1197039



© 2016 The Author(s). Published by Taylor & Francis

Accepted author version posted online: 09 lun 2016. Published online: 09 Jun 2016.



🖉 Submit your article to this journal 🗹



View related articles 🗹



View Crossmark data 🗹

Full Terms & Conditions of access and use can be found at http://www.tandfonline.com/action/journalInformation?journalCode=tepm20

#### Publisher: Taylor & Francis

#### Journal: Expert Review of Precision Medicine and Drug Development

DOI: 10.1080/23808993.2016.1197039

Coronary Artery Disease Genetic Risk Awareness Motivates Heart Health Behaviors in the Coriell Personalized Medicine Collaborative

Laura B. Scheinfeldt<sup>1,2,3\*</sup>, Tara J. Schmidlen<sup>1</sup>, Neda Gharani<sup>1</sup>, Matthew MacKnight<sup>1</sup>, Joseph P. Jarvis<sup>1</sup>, Susan K. Delaney<sup>1</sup>, Erynn S. Gordon<sup>4</sup>, Courtney J. Kronenthal<sup>1</sup>, Norman P. Gerry<sup>1</sup>, Michael F. Christman<sup>1</sup>

<sup>1</sup>Coriell Institute for Medical Research, 403 Haddon Ave, Camden NJ, 08103, USA

<sup>2</sup> Department of Biology, Temple University, 1900 N 12<sup>th</sup> St, Philadelphia, PA, 19122, USA

<sup>3</sup> Institute for Genomics and Evolutionary Medicine, Temple University, 1900 N 12<sup>th</sup> St, Philadelphia, PA, 19122, USA

<sup>4</sup>23andMe, Inc., 1390 Shorebird Way, Mountain View, CA, 94043, USA

\* Correspondence to: Laura Scheinfeldt, Institute for Genomics and Evolutionary Medicine, Temple University, 1900 N 12<sup>th</sup> St, Philadelphia, PA, 19122, USA. Email: laura.scheinfeldt@temple.edu. Phone: 215-204-1814.

#### Abstract

#### Objective:

The Coriell Personalized Medicine Collaborative (CPMC) research study is designed to evaluate the potential contributions of common genetic risk factors to complex disease prevention, screening, and management. Here we have focused on the impact of personalized risk reports including genetic and non-genetic risk factors for coronary artery disease (CAD) on heart health behaviors.

#### Methods:

We analyzed self-reported behavioral outcome data from 683 CPMC participants who received personalized CAD risk reports including: genetic risk, family history risk, and self-reported non-genetic risks based on smoking and diabetes status.

#### Results:

Participants with awareness of increased genetic risk for CAD were significantly more likely to report increases in heart health behaviors after viewing their personalized risk report (F-value=14.11, p-value=9.92 x  $10^{-7}$ ). This result remained significant after controlling for BMI and gender (eta=0.58, p-value = 6.91 x  $10^{-7}$ ).

#### Conclusion:

Our study indicates that individuals who are aware of their genetic risk for CAD may have higher motivation to increase heart health behaviors.

### Keywords

Disease prevention, healthy behavior, personalized disease risk

#### 1 Introduction

Coronary artery disease (CAD) is a leading cause of death in the United States and is responsible for hundreds of thousands of deaths each year [1,2]. CAD decreases quality of life and contributes to comorbidities. Additionally, the cost of treating CAD exceeds \$100 billion dollars each year [2,3]. There is currently no cure for CAD; however, there are several ways to reduce the risk of developing heart disease and improve prognosis once diagnosed [4-8], including regular exercise, healthy dietary choices, and smoking cessation.

Motivating patients to adopt or increase heart health behaviors is a major public health challenge [8] that may benefit from a precision medicine approach: identifying individuals that are at increased risk for developing CAD and/or would most likely benefit from preventive behavior change. CAD is a complex disease driven by inherited genetic risk factors, co-morbidities, lifestyle factors, such as diets high in added sugar and saturated fats, smoking, and physical inactivity [1,9-12]; therefore it is difficult to predict with any certainty who is likely to develop heart disease over time. However, individuals with increased risk due to genetic factors, co-morbidities or family history may be particularly motivated to mitigate this risk with heart health behaviors.

Previous work investigating the potential of genetic risk information to motivate preventive behavior change provides mixed results depending on the types of diseases and range of outcomes that have been investigated [13,14]. There is, however, some cause for optimism in a subset of cases. For example, Hartz et al. [15] documented a significant increase (p=0.003) in attempts to stop smoking after the delivery of genetic risk information for five complex diseases despite a modest sample size (n=50).

Likewise, Diseati et al. [16] demonstrated a significant increase in sun protective behaviors in the Coriell Personalized Medicine Collaborative (CPMC) after the delivery of personalized genetic and family history risk information for melanoma in participants with increased risk awareness. Here, we extend that work to study the impact of personalized genetic and non-genetic risk estimates for CAD on participant motivation to increase heart health behavior.

## 2 Results

The CPMC is an ongoing prospective research study that focuses on the potential clinical utility of common genetic risk factors in complex disease prevention and management [17-21]. Participants in the CPMC research study received personalized risk information for CAD. In particular, the CPMC CAD risk report includes relative risk estimates for genetic risk (based on rs1333049), self-reported family history risk (based on parental disease status), self-reported diabetes status, and self-reported smoking status (also see Figure S1 for example personalized risk report, and see experimental section for more detail on personalized risk factors). Table 1 displays a summary of participant demographics for the subset of participants that viewed their personalized risk report for CAD and chose to participate in an optional online outcome survey of self-reported heart health behavior change. In general, participants tended to be older (mean age of 50), primarily Caucasian (88%), and majority female

## (60%).

We used ANOVA to compare heart health behavior change across risk groups. We defined heart health behavior change as no or yes, where yes indicated that a participant reported at least one of the following: an increase in exercise or healthier diet choices, or a decrease in alcohol or smoking consumption. With respect to behavior change, we did not find significant differences between current smokers and non-smokers (F-value=2.51, p-value=0.11) or between participants reporting that they have either type 1 or type 2 diabetes and participants reporting that they do not have diabetes (F-value=1.31, p-value=0.25); although our sample sizes for the two variables were not well powered for these comparisons (35/683 and 51/683, respectively; Table 1). We did, however, find a significant difference in behavior change between participants reporting family history and those that did not (F-value=15.35, p-value=9.84 x  $10^{-5}$ ), as well as across the three genetic risk categories (F-value=14.11, p-value=9.92 x  $10^{-7}$ ). These differences across family history and genetic risk categories for the two most common behaviors, increased exercise and healthy dietary choices after viewing their personalized risk report, individually (Figures S2 and S3, respectively).

To further explore the relationship between reported risk categories and behavior change, we used multivariate binomial regression with behavior change as the outcome variable and controlled for gender and BMI. We used stepAIC to evaluate the predictive power of all of the reported risk factors (genetic risk, family history risk, smoking risk, and diabetes risk), and retained family history risk and genetic risk in our model (see Table 2 for descriptive variable summaries). In this model family history risk is significant (eta=0.37, p-value = 0.03), and genetic risk is highly significant (eta=0.58, p-value =  $6.91 \times 10^{-7}$ ), also see Table 3 for model results.

We evaluated three additional predictor variables for potential contributions to behavior change: whether participants shared their CAD risk report with a healthcare provider, whether participants reported feeling any anxiety after first viewing their CAD risk report, and participants' self-rated perceived lifetime risk of developing CAD (see Table 4 for descriptive variable summaries). In this expanded model, after controlling for gender and BMI, in addition to genetic risk (eta=0.41, p-value=9.11 x  $10^{-4}$ ), whether participants chose to share their CAD risk report with a healthcare provider or plan to share their CAD risk report with a healthcare provider in the future is significantly associated with behavior change (eta=0.22, p-value = 0.02), and reported anxiety level is highly significant (eta=0.33, p-value=8.96 x  $10^{-4}$ ), also see Table 5 for model results.

Given the highly significant association between anxiety and behavior change, we applied a more formal mediation model to examine the relationship among anxiety, genetic risk, and behavior change. As Figure S4 shows, the variation in behavior change that is explained by genetic risk directly (ADE=0.1155, p-value < 0.01) is larger than the variation explained by anxiety that is generated by genetic risk (ACME=0.0261, p-value=0.01). Both predictors are significant, and genetic risk remains significant after taking anxiety into account consistent with a model in which anxiety only partially explains the impact of genetic risk on behavior change; indeed the proportion of the total effect (0.1416) that is explained by anxiety is 18%.

In addition, we asked participants that reported healthy behavior change to self-report what motivated them to change their behavior (Appendix A). The most common answer was "My CPMC genetic

variant result for coronary artery disease"; indeed 44% of participants that reported making a healthy behavior change self-reported that it was due to genetic risk. Following genetic risk, family history risk (31%) and an HCP recommendation (27%) were the next two most common answers. The remaining answers combined comprised less than 8% of the answers.

## 3 Discussion

The CPMC is designed to evaluate the clinical utility of genetic information. One component of this goal is focused on the potential for personalized risk information to support patients in their decision making and health behavior choices. Here we have analyzed participant responses to personalized risk information for CAD to ascertain how genetic risk information might enhance motivation to increase heart healthy behaviors and mitigate risk for cardiovascular disease.

There are several behavioral factors that can increase or decrease the risk of developing cardiovascular disease in general, and CAD in particular. Healthy dietary choices and exercise have been shown to reduce the risk of heart disease in previous studies [8,22-24]. Here we found that a greater proportion of participants reporting an increased risk of CAD due to genetic risk have increased exercise and healthy dietary choices after viewing their personalized risk report. More generally, we found that participants reporting an increased risk of CAD due to family history or genetic risk are significantly more likely to increase at least one heart health behavior, but that the impact of genetic risk was stronger and more significant (Table 3). We additionally found that anxiety levels partially explain the significant association between increased genetic risk for CAD and behavior change, but genetic risk remains significant after taking into account anxiety. Consistent with previous work [16], we found that very few participants reported high (11/683 or 1.6%) or very high levels (1/683, 0.1%) of anxiety after viewing their CAD risk report. These results suggest that low or moderate anxiety may be sufficient to motivate behavior change in conjunction with additional genetic risk.

We have found that sharing personalized genetic information with a healthcare provider is another significant predictor of positive behavior change (Table 5). This result suggests that the communication of personalized risk information and subsequent discussion with clinicians should be further investigated as a preventive behavior motivational model for heart disease. Indeed, previous work has highlighted the potential for healthcare providers to leverage their patient visits to contribute to behavior change interventions [25]. More recently, Spring et al. published a science advisory [8] highlighting the expanded role that clinicians could play in supporting and encouraging healthy behavior in line with American Heart Association goals [26].

While our sample size of participants that shared personalized risk results with a healthcare provider was not statistically powered to formally test, we observed some intriguing descriptive trends. Based on the CPMC CAD surveys, 113 participants reported that they have already shared their personalized risk reports with a healthcare provider. Fifty four (48%) of these participants reported that they were advised by their healthcare providers to make a lifestyle change, and 49 of the 54 (91%) reported that they made at least one lifestyle change. In particular, 29 out of 39 participants (74%) advised to exercise more told us they did so, 32 out of 38 participants (84%) advised to eat healthier told us they did so, 19 out of 39 participants (49%) advised to lose weight told us they did so, and 1/1 participant advised to quit smoking told us they did so.

Contrary to our results, a previous study that evaluated the impact of direct to consumer testing did not find a significant change in diet or exercise after genetic testing [13]. However, the approach taken in

the personalized risk assessment in Bloss et al. [13] focused on genetic risk only, and provided absolute risk values for 23 health conditions at the same time, including risk for obesity and heart attack. Alternatively, the CPMC provides personalized genetic relative risk values for complex disease within the larger context of family history and other non-genetic risk factors [18,20]. Moreover, in the case of obesity risk, Bloss et al. [13] found that there was a significant association between genetic risk and reduction in fat intake after genetic testing (OR = 0.89, p-value=0.004) consistent with the possibility that some disease conditions may be better suited for personalized risk assessment than others (two other conditions had significant findings, breast cancer and rheumatoid arthritis).

There are several limitations to the current study that should be considered alongside interpretations of the results presented here. Participants were not demographically representative of the US population at large (Table 1). In particular, participants in the current study tended to be older (mean age of 50), primarily Caucasian (88%), and majority female (60%). In addition, the largest recruitment cohort represented is the United States Air Force cohort, all of whom had the means and access to healthcare, healthy foods, and physical activity on base. Communities that do not have access to these resources either due to economic or time-based constraints would need access before considering whether personalized risk information would encourage additional motivation to adopt healthy behavior choices [27-30].

The results presented here may be subjected to social desirability bias <sup>e.g.,</sup>[31] and/or by self-selection bias due to the voluntary nature of CPMC recruitment [18]. The current study also uses self-reported data that may be introducing reporting bias. The CPMC CAD personalized risk report calculated genetic risk using only a single genetic variant that does not capture the entire inherited risk component of the disease, and non-genetic risk factors are limited to smoking and diabetes. In addition, we had a very small number of smokers/diabetics in the study and therefore limited ability to assess the impact of these risk factors. Furthermore, we did not assess risk comprehension, baseline anxiety, or baseline heart health, and recognize that participants are likely to be over interpreting the importance of their personalized genetic risk [19]. Online survey completion rate was 37%, and we were not able to incorporate data from participants that did not complete the survey. Our study design also does not permit a case/control comparison of behavior change.

In summary, our study demonstrates the motivational potential of personalized genetic risk information to increasing heart health behaviors. We anticipate that as genetic and genomic studies continue to improve our understanding of the inherited component of CAD <sup>e.g.,[11,32,33]</sup>, the accuracy of personalized genetic risk estimates for CAD will also improve. Future work is also needed to evaluate the sustainability of heart health behavior motivation over longer time periods, and if consistent with the current study, whether this motivation results in improvements in clinical health measures such as BMI and lipids, and ultimately in a decrease in CAD. Moreover, we agree with Spring et al.'s [8] emphasis on providing multilevel (e.g. healthcare access, policy, coverage, education) support for clinicians and patients to work together toward heart health behavior change.

## 4 Materials and Methods

## 4.1 Study Population

CPMC inclusion criteria consist of an age of at least 18 years, access to a valid email address, written informed consent, and willingness to provide a saliva sample for DNA analysis. The study was

reviewed and approved by the Coriell Institute for Medical Research's Institutional Review Board (IRB) as well as the IRBs of collaborating institutions, including: The Ohio State University, Fox Chase Cancer Center, and the United States Air Force.

#### 4.2 Study Infrastructure

Once participants agree to join the study, they set up a secure online portal account and complete several required questionnaires that focus on demographics, lifestyle, medical history, medication history, family medical history and baseline disease risk perception [18]. When these questionnaires are complete, DNA from participant saliva samples is extracted and genotyped in Coriell's CLIA-certified genotyping facility with the Affymetrix 6.0 genotyping array. After the genetic data are validated and approved by CPMC's medical geneticist, each participant receives periodic emails letting them know that their personalized risk reports for potentially actionable complex genetic health conditions, including CAD, are available. Then participants choose which if any personalized risk reports they would like to view through a secure online web portal.

The CPMC CAD report includes personalized risk for four risk factors: genetic risk, family history risk, smoking status, and diabetes (see Figure S1 for example report). Genetic relative risk (RR) is based on the presence or absence of the rs1333049 C risk allele [34,35] (based on the forward strand in versions 32 and 33 of Affymetrix's 6.0 annotation file) (RR=1.7 for participants carrying two copies of the C risk allele, RR=1.3 for participants carrying one copy of the C risk allele, and RR=1 for participants carrying no copies of the C risk allele), self-reported family history [36] (RR=1.2 for female participants or RR=1.4 for male participants reporting that they have at least one parent that has been diagnosed with CAD, and RR=1 for participants reporting that they do not have any parents that have been diagnosed with CAD), self-reported diabetes [10] (RR=2 for participants reporting that they have been diagnosed with either type 1 or type 2 diabetes and RR=1 for participants reporting that they do not have diabetes), and self-reported current smoking status [10] (ranging from RR=1.3-2.8 for current smokers depending on ethnicity and gender and RR=1 for non-smokers). Sample reports can be found on the CPMC website (https://cpmc.coriell.org/v/Report/Demo/CAD/DemoNat). Participants that choose to view their personalized CAD risk report can also request telephone-based genetic counseling at no charge to discuss results [18,19].

#### 4.3 Data Collection

A minimum of three months after participants first view their personalized CAD risk report, they become eligible to complete an online survey focused on what they did with the information in their risk report. The CAD outcome surveys included in the current analysis were first offered on 4/27/2011. As of 9/30/2014, 4630 CAD personalized risk reports were released, 4160 participants viewed their CAD personalized risk reports and were eligible for a CAD outcome survey, 784 participants completed an older, incomplete version of the outcome survey that was not used for analysis in the current report, and 743 CPMC participants completed the updated CAD outcome survey that was used for analysis in the current report. Taken together, 37% of participants that were eligible for any CAD outcome survey completed a CAD outcome survey. We further excluded 22 participants reporting that they have already been diagnosed with CAD. We also excluded 38 participants that reported they were motivated to make a preventive behavior change due to risk for a different complex disease, and retained outcome survey data from 683 participants for all of the data analyses included in the current study.

## 4.4 Data Analysis

We used the glm function in R [37] to implement binomial logistic regression to better understand which variables contributed to an increase in heart health behaviors. We coded the behavior change outcome variable as a binary trait of "no" or "yes"; participants were coded as "yes" if they reported at least one of the following increases in heart health behaviors: an increase in the "the amount I exercise", an increase in "my frequency of healthier diet choices", a decrease in "the amount of alcohol I drink", or a decrease in "the number of cigarettes I smoke" (also see Appendix A).

In order to reduce the chance that we were over-parameterizing our regression model [38], we used the stepAIC function in the R MASS package [37,39] to evaluate the following set of demographic (Table 1) and predictor variables: recruitment cohort, age, gender, BMI, and ethnicity, and retained gender and BMI in our final model. We also examined each demographic covariate individually, and the results were not significant (p>0.2) for recruitment cohort, age, or ethnicity, consistent with the model recommended based on Akaike information criterion (AIC). We also included several predictor variables for our behavior change outcome variable: whether participants had an increased risk of CAD due to self-reported family history, whether participants had an increased risk of CAD due to selfreported smoking status, whether participants had an increased risk of CAD due to self-reported diabetes status, the number of copies participants report having of the genetic risk variant for CAD, whether participants did not share, shared, or plan to share their personalized CAD risk report with a healthcare provider, the self-reported level of anxiety participants reported feeling after viewing their CPMC risk report (Likert scale: none, low, moderate, high, very high)[16,18], and the self-reported perceived risk of developing CAD (Likert scale: where 1 is certain not to happen and 5 is certain to happen)[16,18] (also see Appendix A). Four participants chose not to report an anxiety level, and seven participants chose not to provide a self-reported perceived risk of developing CAD. The best model produced by stepAIC (lowest AIC) retained HCP sharing, family history risk, genetic risk, and anxiety level. In addition, we independently tested the correlation between behavior change and the cumulative number of reported CAD risk factors (ranging from 0-4 for family history risk, genetic risk, smoking risk, diabetes risk), and found no significant association.

We additionally used the R mediation package [40] to execute a mediation model involving behavior change, anxiety and genetic risk. More specifically, behavior change was the outcome variable, genetic risk was the treatment variable, and anxiety was the mediator. We included gender and BMI as covariates, and used the sandwich [41] method to estimate p-values with 1000 simulations.

## 5 Acknowledgments

We would like express our great appreciation to the CPMC participants as well as the CPMC team at Coriell. We would also like to offer thanks to the United States Air Force and the RNR Foundation for funding this work.

## 6 Author Contributions

MFC, NPG, CJK, ERS, SKD, NG, and TJS designed the overall CPMC study and collected the data used here. LBS conducted the analysis and wrote the manuscript. TJS, MM and JPG assisted in the

manuscript preparation. All authors read and approved the final manuscript.

7 Conflicts of Interest

The authors declare that there are no conflicts of interest.

## References

1. Mozaffarian, D.; Benjamin, E.J.; Go, A.S.; Arnett, D.K.; Blaha, M.J.; Cushman, M.; de Ferranti, S.; Despres, J.P.; Fullerton, H.J.; Howard, V.J., *et al.* Heart disease and stroke statistics--2015 update: A report from the american heart association. *Circulation* **2015**, *131*, e29-322.

2. Benjamin, R.M. The million hearts initiative: Progress in preventing heart attacks and strokes. *Public health reports* **2012**, *127*, 558-560.

3. Heidenreich, P.A.; Trogdon, J.G.; Khavjou, O.A.; Butler, J.; Dracup, K.; Ezekowitz, M.D.; Finkelstein, E.A.; Hong, Y.; Johnston, S.C.; Khera, A., *et al.* Forecasting the future of cardiovascular disease in the united states: A policy statement from the american heart association. *Circulation* **2011**, *123*, 933-944.

4. Stampfer, M.J.; Hu, F.B.; Manson, J.E.; Rimm, E.B.; Willett, W.C. Primary prevention of coronary heart disease in women through diet and lifestyle. *The New England journal of medicine* **2000**, *343*, 16-22.

5. Dong, J.Y.; Zhang, Y.H.; Wang, P.; Qin, L.Q. Meta-analysis of dietary glycemic load and glycemic index in relation to risk of coronary heart disease. *The American journal of cardiology* **2012**, *109*, 1608-1613.

6. Dauchet, L.; Amouyel, P.; Hercberg, S.; Dallongeville, J. Fruit and vegetable consumption and risk of coronary heart disease: A meta-analysis of cohort studies. *The Journal of nutrition* **2006**, *136*, 2588-2593.

7. (US)., C.f.D.C.a.P.U.N.C.f.C.D.P.a.H.P.U.O.o.S.a.H. *How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the surgeon general.* Centers for Disease Control and Prevention (US): Atlanta, GA, 2010.

8. Spring, B.; Ockene, J.K.; Gidding, S.S.; Mozaffarian, D.; Moore, S.; Rosal, M.C.; Brown, M.D.; Vafiadis, D.K.; Cohen, D.L.; Burke, L.E., *et al.* Better population health through behavior change in adults: A call to action. *Circulation* **2013**, *128*, 2169-2176.

9. Wilson, P.W.; D'Agostino, R.B.; Levy, D.; Belanger, A.M.; Silbershatz, H.; Kannel, W.B. Prediction of coronary heart disease using risk factor categories. *Circulation* **1998**, *97*, 1837-1847.

10. D'Agostino, R.B., Sr.; Grundy, S.; Sullivan, L.M.; Wilson, P.; Group, C.H.D.R.P. Validation of the framingham coronary heart disease prediction scores: Results of a multiple ethnic groups investigation. *Jama* **2001**, *286*, 180-187.

11. Angelakopoulou, A.; Shah, T.; Sofat, R.; Shah, S.; Berry, D.J.; Cooper, J.; Palmen, J.; Tzoulaki, I.; Wong, A.; Jefferis, B.J., *et al.* Comparative analysis of genome-wide association studies signals for lipids, diabetes, and coronary heart disease: Cardiovascular biomarker genetics collaboration. *European heart journal* **2012**, *33*, 393-407.

12. Yang, Q.; Zhang, Z.; Gregg, E.W.; Flanders, W.D.; Merritt, R.; Hu, F.B. Added sugar

intake and cardiovascular diseases mortality among us adults. *JAMA internal medicine* **2014**, *174*, 516-524.

13. Bloss, C.S.; Schork, N.J.; Topol, E.J. Effect of direct-to-consumer genomewide profiling to assess disease risk. *The New England journal of medicine* **2011**, *364*, 524-534.

14. Marteau, T.M.; French, D.P.; Griffin, S.J.; Prevost, A.T.; Sutton, S.; Watkinson, C.; Attwood, S.; Hollands, G.J. Effects of communicating DNA-based disease risk estimates on risk-reducing behaviours. *The Cochrane database of systematic reviews* **2010**, CD007275.

15. Hartz, S.M.; Olfson, E.; Culverhouse, R.; Cavazos-Rehg, P.; Chen, L.S.; DuBois, J.; Fisher, S.; Kaphingst, K.; Kaufman, D.; Plunk, A., *et al.* Return of individual genetic results in a high-risk sample: Enthusiasm and positive behavioral change. *Genetics in medicine : official journal of the American College of Medical Genetics* **2015**, *17*, 374-379.

16. Diseati, L.; Scheinfeldt, L.B.; Kasper, R.S.; Zhaoyang, R.; Gharani, N.; Schmidlen, T.J.; Gordon, E.S.; Sessions, C.K.; Delaney, S.K.; Jarvis, J.P., *et al.* Common genetic risk for melanoma encourages preventive behavior change. *Journal of personalized medicine* **2015**, *5*, 36-49.

 Gharani, N.; Keller, M.A.; Stack, C.B.; Hodges, L.M.; Schmidlen, T.J.; Lynch, D.E.; Gordon, E.S.; Christman, M.F. The coriell personalized medicine collaborative pharmacogenomics appraisal, evidence scoring and interpretation system. *Genome medicine* 2013, *5*, 93.

18. Keller, M.A.; Gordon, E.S.; Stack, C.B.; Gharani, N.; Sill, C.J.; Schmidlen, T.J.; Joseph, M.; Pallies, J.; Gerry, N.P.; Christman, M.F. Coriell personalized medicine collaborative®: A prospective study of the utility of personalized medicine. *Personalized Medicine* **2010**, *7*, 301-317.

19. Schmidlen, T.J.; Wawak, L.; Kasper, R.; Garcia-Espana, J.F.; Christman, M.F.; Gordon, E.S. Personalized genomic results: Analysis of informational needs. *Journal of genetic counseling* **2014**.

 Stack, C.B.; Gharani, N.; Gordon, E.S.; Schmidlen, T.; Christman, M.F.; Keller, M.A. Genetic risk estimation in the coriell personalized medicine collaborative. *Genetics in medicine : official journal of the American College of Medical Genetics* 2011, *13*, 131-139.
 Schmidlen, T.J.; Scheinfeldt, L.; Zhaoyang, R.; Kasper, R.; Sweet, K.; Gordon, E.S.; Keller, M.; Stack, C.; Gharani, N.; Daly, M.B., *et al.* Genetic knowledge among participants in

the coriell personalized medicine collaborative. *Journal of genetic counseling* 2015.
22. Fung, T.T.; Rexrode, K.M.; Mantzoros, C.S.; Manson, J.E.; Willett, W.C.; Hu, F.B.

Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation* **2009**, *119*, 1093-1100.

23. Manson, J.E.; Greenland, P.; LaCroix, A.Z.; Stefanick, M.L.; Mouton, C.P.; Oberman, A.; Perri, M.G.; Sheps, D.S.; Pettinger, M.B.; Siscovick, D.S. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *The New England journal of medicine* **2002**, *347*, 716-725.

24. Mora, S.; Cook, N.; Buring, J.E.; Ridker, P.M.; Lee, I.M. Physical activity and reduced risk of cardiovascular events: Potential mediating mechanisms. *Circulation* **2007**, *116*, 2110-2118.

25. Franklin, B.A.; Vanhecke, T.E. Counseling patients to make cardioprotective lifestyle changes: Strategies for success. *Preventive cardiology* **2008**, *11*, 50-55.

26. Lloyd-Jones, D.M.; Hong, Y.; Labarthe, D.; Mozaffarian, D.; Appel, L.J.; Van Horn, L.; Greenlund, K.; Daniels, S.; Nichol, G.; Tomaselli, G.F., *et al.* Defining and setting national goals for cardiovascular health promotion and disease reduction: The american heart association's strategic impact goal through 2020 and beyond. *Circulation* **2010**, *121*, 586-613.

27. Gordon-Larsen, P.; Nelson, M.C.; Page, P.; Popkin, B.M. Inequality in the built environment underlies key health disparities in physical activity and obesity. *Pediatrics* **2006**, *117*, 417-424.

28. Lurie, N.; Dubowitz, T. Health disparities and access to health. *Jama* **2007**, *297*, 1118-1121.

29. Walker, R.E.; Keane, C.R.; Burke, J.G. Disparities and access to healthy food in the united states: A review of food deserts literature. *Health & place* **2010**, *16*, 876-884.

30. Larson, N.I.; Story, M.T.; Nelson, M.C. Neighborhood environments: Disparities in access to healthy foods in the u.S. *American journal of preventive medicine* **2009**, *36*, 74-81.

31. Hebert, J.R.; Clemow, L.; Pbert, L.; Ockene, I.S.; Ockene, J.K. Social desirability bias in dietary self-report may compromise the validity of dietary intake measures. *International journal of epidemiology* **1995**, *24*, 389-398.

32. International Consortium for Blood Pressure Genome-Wide Association, S.; Ehret, G.B.; Munroe, P.B.; Rice, K.M.; Bochud, M.; Johnson, A.D.; Chasman, D.I.; Smith, A.V.; Tobin, M.D.; Verwoert, G.C., *et al.* Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature* **2011**, *478*, 103-109.

33. Teslovich, T.M.; Musunuru, K.; Smith, A.V.; Edmondson, A.C.; Stylianou, I.M.; Koseki, M.; Pirruccello, J.P.; Ripatti, S.; Chasman, D.I.; Willer, C.J., *et al.* Biological, clinical and population relevance of 95 loci for blood lipids. *Nature* **2010**, *466*, 707-713.

34. Hinohara, K.; Nakajima, T.; Takahashi, M.; Hohda, S.; Sasaoka, T.; Nakahara, K.; Chida, K.; Sawabe, M.; Arimura, T.; Sato, A., *et al.* Replication of the association between a chromosome 9p21 polymorphism and coronary artery disease in japanese and korean populations. *Journal of human genetics* **2008**, *53*, 357-359.

35. Schunkert, H.; Gotz, A.; Braund, P.; McGinnis, R.; Tregouet, D.A.; Mangino, M.; Linsel-Nitschke, P.; Cambien, F.; Hengstenberg, C.; Stark, K., *et al.* Repeated replication and a prospective meta-analysis of the association between chromosome 9p21.3 and coronary artery disease. *Circulation* **2008**, *117*, 1675-1684.

36. Myers, R.H.; Kiely, D.K.; Cupples, L.A.; Kannel, W.B. Parental history is an independent risk factor for coronary artery disease: The framingham study. *American heart journal* **1990**, *120*, 963-969.

37. Team, R.C. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing: Vienna, Austria, 2014.

38. Scheinfeldt, L.B.; Gharani, N.; Kasper, R.S.; Schmidlen, T.J.; Gordon, E.S.; Jarvis, J.P.; Delaney, S.; Kronenthal, C.J.; Gerry, N.P.; Christman, M.F. Using the coriell personalized medicine collaborative data to conduct a genome-wide association study of sleep duration. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics* **2015**.

39. Ripley, W.N.V.a.B.D. *Modern applied statistics with s*. Fourth ed.; Springer: New York, 2002.

40. Tingley D, Y.T., Hirose K, Keele L, Imai K. Mediation: R package for causal mediation analysis. *Journal of Statistical Software* **2014**, *59*, 1-38.

41. Zeileis, A. Object-oriented computation of sandwich estimators. 2006.

 Table 1. Participant Information.

n	683
male, n (%)	276 (40.41)
female, n (%)	407 (59.59)
age, mean (range)	50.36 (23-95)
Caucasian, n (%)	604 (88.4)
African American, n (%)	17 (2.5)
Asian, n (%)	12 (1.8)
Hispanic, n (%)	23 (3.4)
other ethnicity, n (%)	27 (4.0)
Air Force recruitment cohort, n (%)	283 (41.4)
CPMC community recruitment cohort, n (%)	214 (31.3)
Fox Chase Cancer Center recruitment cohort, n (%)	21 (3.1)
OSU community recruitment cohort, n (%)	103 (15.1)
OSU chronic disease recruitment cohort, n (%)	62 (9.1)
Smokers, n (%)	35 (5.1)
Diabetes, n (%)	51 (7.5)
BMI, mean (range)	26.68 (18.0-52.6)
Fable 2. CAD risk factors	
n	683
participants with no FH, n (%)	395 (57.83)
participants with FH, n (%)	288 (42.17)
participants with no GR, n (%)	301 (44.07)
participants with 1 copy GR, n (%)	267 (39.09)
participants with 2 copies GR, n (%)	115 (16.84)

FH = family history, GR = genetic risk variant

	eta	SE	z-value	p-value
Intercept	-2.81	0.459	-6.13	8.97e-10
gender	-0.346	0.161	-2.14	0.0321
BMI	0.0802	0.0161	4.99	6.17e-07
family history	0.336	0.164	2.04	0.0413
genetic risk	0.571	0.114	5.02	5.22e-07

Table 3. Logistic regression modeling results for preventive behavior change and CAD risk.

**T** 11 ALICO 1 1

n	683
did not share with HCP, n (%)	366 (53.59)
shared with HCP, n (%)	113 (16.54)
plan to share with HCP, n (%)	204 (29.87)
participant anxiety none, n (%)	339 (49.63)
participant anxiety low, n (%)	239 (34.99)
participant anxiety moderate, n (%)	89 (13.03)
participant anxiety high, n (%)	11 (1.61)
participant anxiety very high, n (%)	1 (0.15)
participants not reporting anxiety, n (%)	4 (0.59)
participant rated risk of CAD is 1, n (%)	33 (4.83)
participant rated risk of CAD is 2, n (%)	216 (31.63)
participant rated risk of CAD is 3, n (%)	244 (35.74)
participant rated risk of CAD is 4, n (%)	153 (22.25)
participant rated risk of CAD is 5, n (%)	31 (4.54)
participant not reporting rated risk of CAD, n (%)	7 (1.02)

HCP = healthcare provider

eta	SE	z-value	p-value
-3.66	0.511	-7.17	7.25e-13
-0.24	0.166	-1.45	0.148
0.0729	0.0164	4.44	9.18e-06
0.27	0.0921	2.94	0.00332
0.387	0.121	3.19	0.00143
0.262	0.172	1.53	0.126
0.344	0.0997	3.45	0.00055
0.122	0.0778	1.56	0.118
	-3.66 -0.24 0.0729 0.27 0.387 0.262 0.344	-3.660.511-0.240.1660.07290.01640.270.09210.3870.1210.2620.1720.3440.0997	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

**Table 5.** Logistic regression modeling results for preventive behavior change, CAD risk, sharing, anxiety, and self-rated risk.

HCP = healthcare provider

Figure 1. Family history risk and behavior change. The y-axis displays the proportion of participants that did (shown in orange) and did not (shown in blue) increase heart health preventive behaviors (prev beh) after viewing their personalized CAD risk reports. The x-axis displays results for participants with (left) and without (right) family history for CAD.

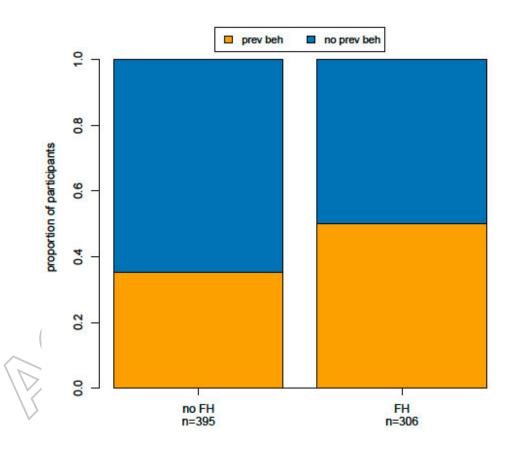


Figure 2. Genetic risk and behavior change. The y-axis displays the proportion of participants that did (shown in orange) and did not (shown in blue) increase heart health preventive behaviors (prev beh) after viewing their personalized CAD risk reports. The x-axis displays results for participants carrying no (left), one (middle) and two (right) genetic risk variants for CAD.

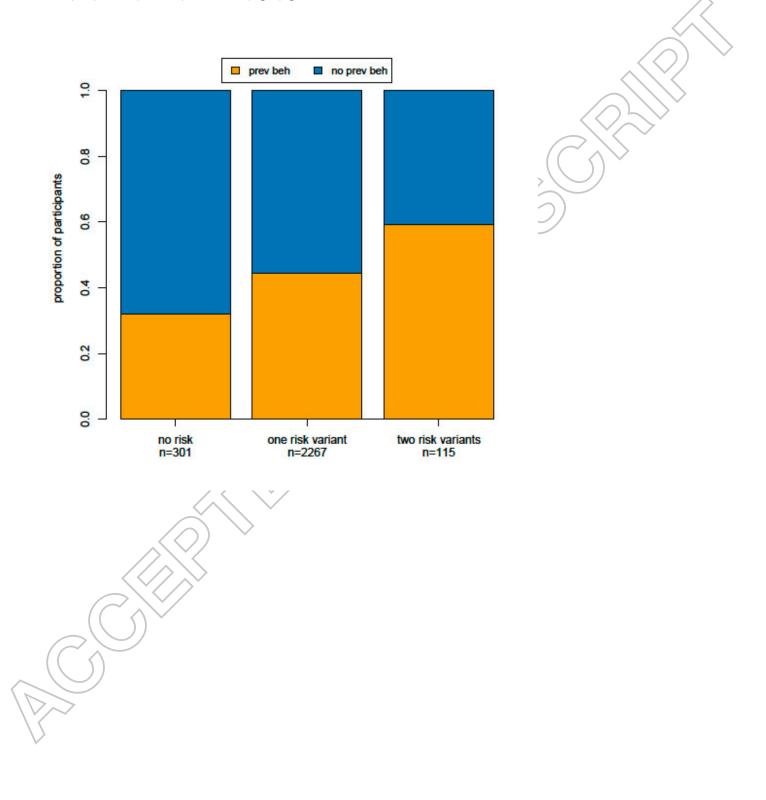


Figure S1. Example CAD personalized risk report. The y-axis displays the example personalized relative risk for each of the four risk factors. Each cylinder displays relative risk as well as the range of relative risk that is possible for a given risk factor. Genetic risk, family history risk, co-morbidity risk due to diabetes, and smoking risk are included.

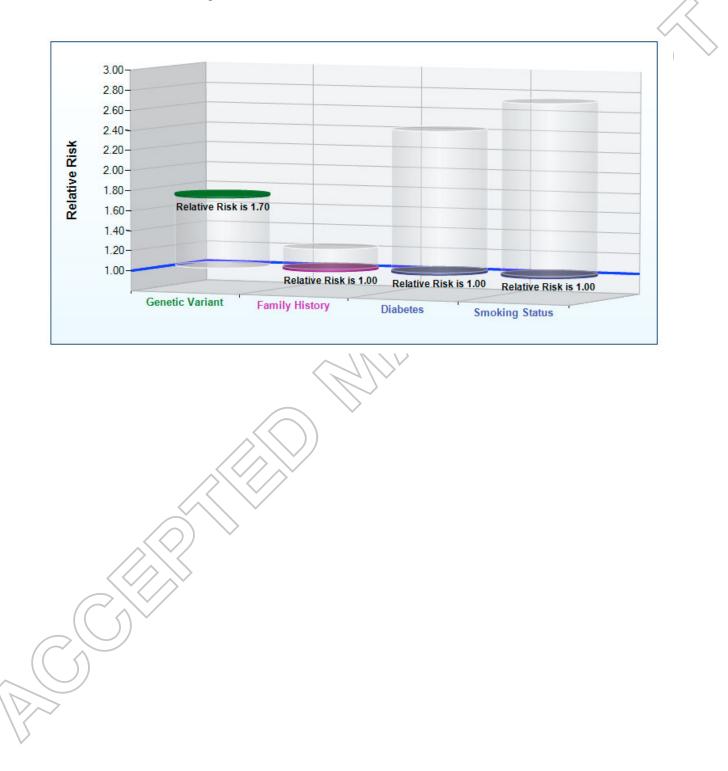


Figure S2. Genetic risk and exercise. The y-axis displays the proportion of participants that did (shown in orange) and did not (shown in blue) increase the amount they exercise after viewing their personalized CAD risk reports. The x-axis displays results for participants carrying no (left), one (middle) and two (right) genetic risk variants for CAD.

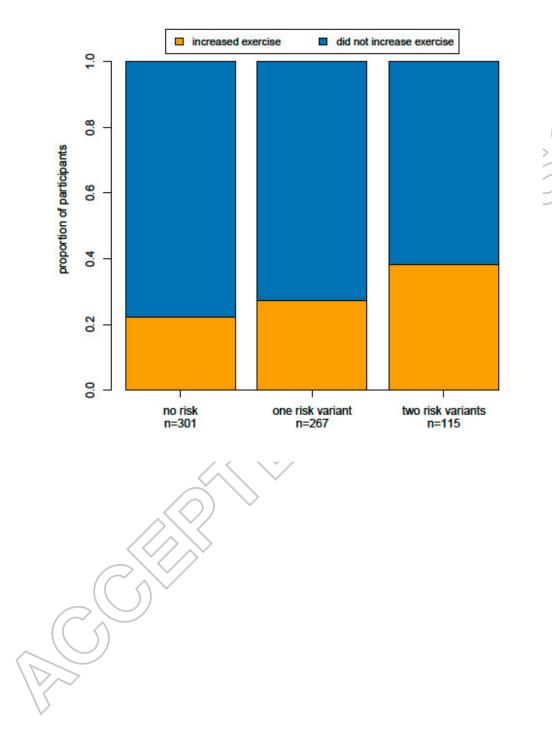
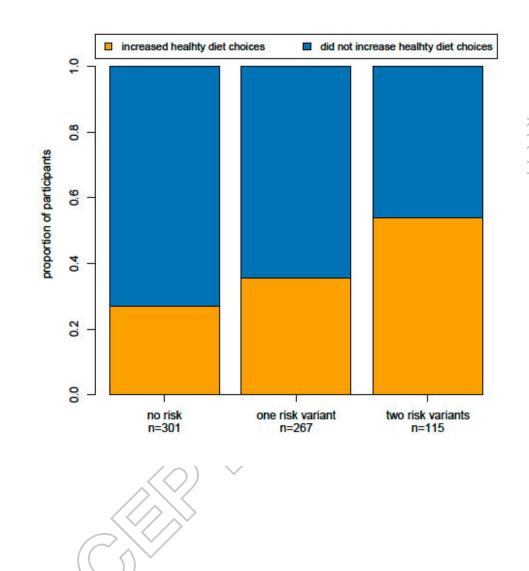
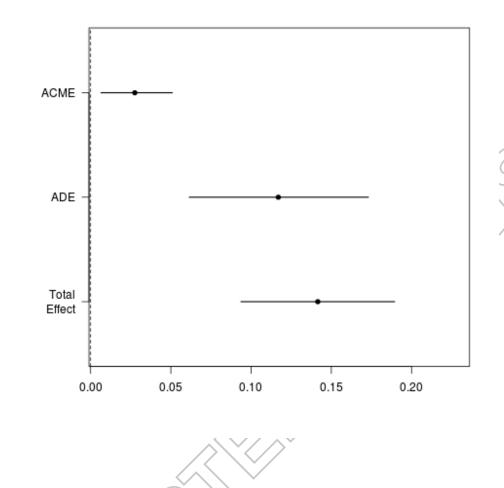


Figure S3. Genetic risk and dietary choices. The y-axis displays the proportion of participants that did (shown in orange) and did not (shown in blue) increase healthy dietary choices after viewing their personalized CAD risk reports. The x-axis displays results for participants carrying no (left), one (middle) and two (right) genetic risk variants for CAD.



17

Figure S4. Mediation model results. The y-axis displays the variation in behavior change explained by anxiety that is generated by genetic risk, average ACME (top), the variation in behavior change explained by genetic risk directly, average ADE (middle), and the total effect (bottom). The x-axis displays the estimates generated by the mediation model within the 95% confidence intervals.



Appendix A

On a scale of 1 to 5, where 1 is certain NOT to happen and 5 is certain TO happen, what do you think is your chance of developing coronary artery disease in your lifetime?

1	
2	
3	
4	
5	
Do not want to answe	r

Did your CPMC result show that you have a genetic risk variant for coronary artery disease? Yes, 1 copy Yes, 2 copies No Do not know

Do not want to answer

Did your CPMC result show that you have an increased risk for coronary artery disease based on your family history? Yes No Do not know Do not want to answer

Did your CPMC result show that you have an increased risk for coronary artery disease based on your smoking status? Yes

No

Do not know Do not want to answer

Did your CPMC result show that you have an increased risk for coronary artery disease based on whether or not you have diabetes?

Yes No Do not know Do not want to answer

Have you shared your CPMC result for coronary artery disease with a health care provider? Yes

No

Not yet, but I am planning to Do not want to answer

Please answer the following questions about your lifestyle since viewing your CPMC results for coronary artery disease.

If you have never in the past engaged in a behavior (e.g. smoking cigarettes) and you do not currently engage in the behavior, please mark "Did not Change".

Did you make any lifestyle changes after viewing your CPMC result for coronary artery disease?

	Increased	Did not change	Decreased	Do not want to answer
The amount I exercise				
My frequency of healthier diet choices				
The amount of alcohol I drink				
The number of cigarettes I smoke				

What motivated you to change the amount you exercise? My CPMC genetic variant result for coronary artery disease My CPMC family history result for coronary artery disease My CPMC risk due to smoking for coronary artery disease My CPMC risk due to having diabetes for coronary artery disease I had symptoms of coronary artery disease My CPMC results for other conditions My health care provider's recommendations Do not want to answer Other

What motivated you to change how frequently you make healthier diet choices? My CPMC genetic variant result for coronary artery disease My CPMC family history result for coronary artery disease My CPMC risk due to smoking for coronary artery disease My CPMC risk due to having diabetes for coronary artery disease I had symptoms of coronary artery disease My CPMC results for other conditions My health care provider's recommendations Do not want to answer Other

What motivated you to change the amount of alcohol you drink? My CPMC genetic variant result for coronary artery disease My CPMC family history result for coronary artery disease My CPMC risk due to smoking for coronary artery disease My CPMC risk due to having diabetes for coronary artery disease I had symptoms of coronary artery disease My CPMC results for other conditions My health care provider's recommendations Do not want to answer Other What motivated you to change the number of cigarettes you smoke? My CPMC genetic variant result for coronary artery disease My CPMC family history result for coronary artery disease My CPMC risk due to smoking for coronary artery disease My CPMC risk due to having diabetes for coronary artery disease I had symptoms of coronary artery disease My CPMC results for other conditions My health care provider's recommendations Do not want to answer Other

Please indicate on the following scale the level of anxiety, if any, you felt immediately after viewing your CPMC result report for coronary artery disease:

None Low Moderate High Very High Do not want to answer