

Randomized Trial of Personal Genomics for Preventive Cardiology Design and Challenges

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Background

Genome-wide association studies (GWAS) have identified more than 1500 disease-associated single nucleotide polymorphisms (SNPs), including many related to atherosclerotic cardiovascular disease (CVD). Associations have been found for most traditional risk factors (TRFs), including lipids,^{1,2} blood pressure/hypertension,^{3,4} weight/body mass index,^{5,6} smoking behavior,⁷ and diabetes.^{8–13} GWAS have also identified susceptibility variants for coronary heart disease (CHD). The first and, so far, strongest of these signals was found in the 9p21.3 locus, where common variants in this region increase the relative risk of CVD by 15% to 30% per risk allele in most race/ethnic groups.^{13–20} Subsequent large-scale GWAS meta-analyses and replication studies in largely white/European populations have led to the reliable identification of an additional 26 loci conferring susceptibility to CHD,^{2,20–23} all with substantially lower effects sizes compared with the 9p21 locus. Many of these CVD susceptibility loci appear to be conferring risk independent of TRFs and thus cannot currently be assessed by surrogate clinical measures (Table 1). Among the 27 independent loci identified in the most recent large meta-analyses of CVD, 21 were reported not to be associated with any of the TRFs.^{20,21}

Several studies have explored whether initial CVD-related genetic markers can improve risk prediction over standard models restricted to TRFs using a genetic risk score (GRS) constructed on the basis of the number of risk alleles inherited.^{24–26} Results to date have been mixed. Although all have shown that a GRS is strongly associated with the outcome of interest independent of TRFs, none were able to demonstrate a significant improvement in the c-statistic. Two of the 3 studies showed some modest improvement in newly defined discrimination indices, including the integrated dis-

crimination index, the net reclassification index, and the clinical net reclassification index (net reclassification index in the intermediate-risk subjects). Thus, the use of these markers has not yet been shown to convincingly outperform models that include TRFs and family history alone.

One important reason for the failure of these markers to demonstrate clinically meaningful improvement of risk prediction relates to the small proportion of the genetic variance explained by these markers, a phenomenon commonly referred to as the heritability gap. The basis for this heritability gap is the focus of intense investigation. Despite this gap, it is still possible that knowledge of genetic risk may improve patient outcomes through means other than enhanced risk reclassification. For instance, genetic testing may improve patient adherence and CVD risk factor reduction for Mendelian disorders related to CHD, such as familial hypercholesterolemia.²⁷ This effect may be owing to an increase in patient motivation (eg, people who recognize and accept their high risk are more encouraged to reduce it); however, no clinical trial to date has demonstrated that newly discovered genetic markers improve risk factor profiles by improving adherence to prescribed therapy for complex (garden variety) CVD.

Here, we describe the design of an ongoing randomized trial to investigate whether CVD risk factor profiles can be improved by providing participants with knowledge related to their inherited risk of CVD in addition to information on their risk related to measured TRFs. We also discuss some of the challenges that arise in the design and conduct of such a trial and how they were addressed.

Methods

Clinical Trial Registration

This trial is registered at ClinicalTrials.gov (NCT01406808).

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Table 1. SNPs Related to CVD That Are Independent of Traditional Risk Factors

SNP Tested	Risk Allele	Risk Allele Frequency	Chrom.	Nearby Genes	Odds Ratio*	Ref.
rs17465637	C	0.74	1	<i>MIA3</i>	1.14	14, 21, 23
rs9970807†	T	0.91	1	<i>PPAP2B</i>	1.17	21
rs6725887	C	0.15	2	<i>WDR12</i>	1.17	21, 23
rs2306374	C	0.18	3	<i>MRAS</i>	1.15	21, 22
rs12190287	G	0.76	6	<i>TCF21</i>	1.08	21
rs12204265‡	C	0.67	6	<i>ANKS1A</i>	1.07	21
rs12526453	C	0.62	6	<i>PHACTR1</i>	1.12	21, 23
rs11556924	C	0.62	7	<i>ZC3HC1</i>	1.09	21
rs4977574	G	0.46	9	<i>CDKN2A, CDKN2B</i>	1.28	13, 15, 21, 23
rs1746048	C	0.87	10	<i>CXCL12</i>	1.17	14, 21, 23
rs2246833	C	0.42	10	<i>LIPA</i>	1.09	20
rs2505083	T	0.37	10	<i>KIAA1462</i>	1.07	20
rs974819	T	0.29	11	<i>PDGFD</i>	1.07	20
rs4773144	G	0.44	13	<i>COL4A1, COL4A2</i>	1.07	21
rs2895811	C	0.43	14	<i>HHIPL1</i>	1.07	21
rs7177699§	T	0.56	15	<i>ADAMTS7</i>	1.08	21
rs12449964	C	0.56	17	<i>RASD1, SMCR3, PEMT</i>	1.07	21
rs143499¶	C	0.36	17	<i>SMG6, SRR</i>	1.07	21
rs9305545#	A	0.16	21	<i>SLC5A3, MRPS6, KCNE2</i>	1.2	21, 23

SNP indicates single nucleotide polymorphism; CVD, cardiovascular disease; Chrom., chromosome; Ref, reference.

*Odds ratio based on that reported for lead SNP reported by large-scale meta-analyses.^(20,21)

†Proxy for lead CARDIOGRAM SNP rs17114036 ($r^2=0.90$).

‡Proxy for lead CARDIOGRAM SNP rs17609940 ($r^2=0.91$).

§Proxy for lead CARDIOGRAM SNP rs3825807 ($r^2=1$).

||Proxy for lead CARDIOGRAM SNP rs12936587 ($r^2=1$).

¶Proxy for lead CARDIOGRAM SNP rs216172 ($r^2=1$).

#Proxy for lead CARDIOGRAM SNP rs9982601 ($r^2=0.87$).

Trial Flow

Patient Eligibility and Recruitment

The study population consists of new or continuing patients seen at the Stanford Preventive Cardiology Clinic (PCC), including patients who were referred to the clinic by other providers or patients that self-referred to the clinic. The PCC staff includes 3 attending physicians, a clinical nurse specialist, and a dietician. Flyers describing the trial were sent to cardiologists, general internists, and family physicians at Stanford University Medical Center and in the surrounding area. Inclusion and exclusion criteria are summarized in Table 2. Participants do not receive financial remuneration (or any form of payment) for their participation in the trial.

Patients are eligible if they have a $\geq 6\%$ risk over the next 10 years or a $\geq 20\%$ risk over the next 30 years of atherosclerotic CVD as determined by respective Framingham risk scores.^{28,29} These criteria will result in the inclusion of some individuals who would be classified as low-risk based on current National Cholesterol Education Program/Adult Treatment Panel III guidelines, which define risk as low, moderate, and high, based on cutoffs of $<10\%$, 10% to 20% , and $>20\%$ over 10 years.³⁰ We chose these eligibility criteria for several reasons. First, we wanted to have fairly broad entry criteria to be able to ascertain whether there is a differential effect of receiving genetic information depending on CVD risk. We chose not to include individuals at very low risk ($<6\%$ over 10 years or $<20\%$ over 30 years) because it would be difficult to see the effect of the genetic score intervention in these patients, as these patients would be largely left untreated. Interestingly, low risk was defined as $<6\%$ risk over 10 years until the current National Cholesterol Education Program/Adult Treatment Panel III guidelines were published, and this cut-off is still used as defining the boundary between low and moderate risk in some settings.^{31–34} Second, we wanted to include low-risk individuals who will not qualify for statin-based therapy

built on our treatment algorithm derived from National Cholesterol Education Program/Adult Treatment Panel III guidelines, so that we will be able to capture whether genetic information is sufficient to motivate changes in diet and lifestyle that are sufficient to affect our

Table 2. Eligibility Criteria

Inclusion criteria
Adults age >18 y
White/European, South Asian, or Hispanic/Latino race/ethnicity*
Patient seeking cardiovascular risk evaluation
At intermediate (6% to 20%) or high risk ($>20\%$) over 10 y of CVD, as defined by Framingham 10-y risk score AND/OR at $\geq 20\%$ risk of CVD over 30 y using the Framingham 30-y risk calculator
Exclusion criteria
History of myocardial infarction, angina, stroke, peripheral arterial disease, PCI, or CABG
Already on lipid-lowering therapy
Anticipated survival <1 y (eg, metastatic cancer)
Serious conditions that would limit ability to adhere to recommendations (inability to take statins, exercise)
Already had genetic testing

*The 19 genetic loci that comprise our risk score have been evaluated predominantly in white/European subjects; however, there is considerable overlap in genetic architecture between white/European populations and South Asian or Hispanic/Latino populations. Therefore, we have limited our study population to these 3 race/ethnicity groups.

Y indicates years; CVD, cardiovascular disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

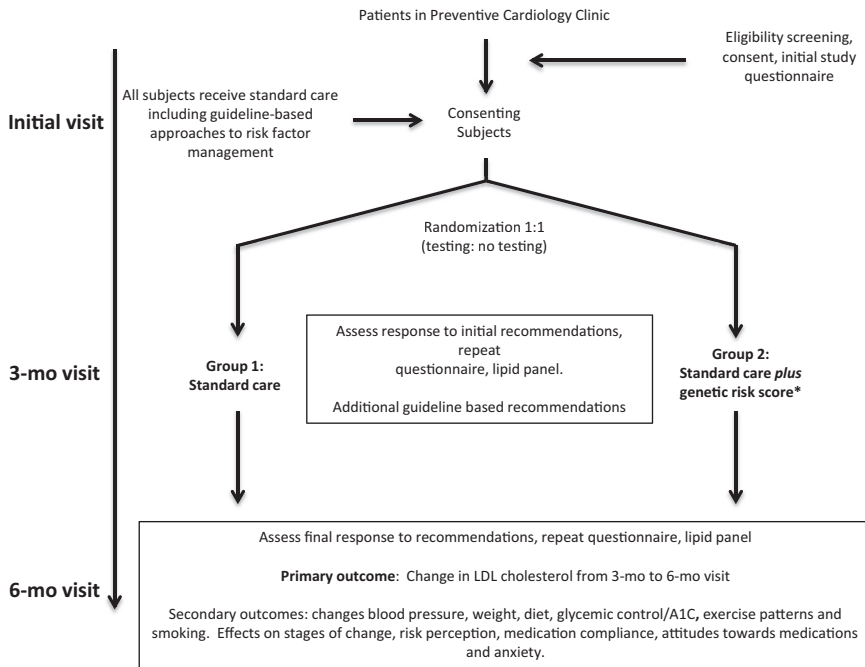


Figure 1. Study Schema.

* Genetic risk score given at the end of the 3 mo clinic visit, after all therapeutic decisions have been made and guideline based recommendations have been given. Altering therapy based on genetic test results is not permitted.

primary outcome (change in low-density lipoprotein [LDL] cholesterol). Third, there are persuasive arguments that assessing 30-year or lifetime risk of CVD should be a standard part of risk assessment.^{35–37} This strategy identifies a significant number of individuals (particularly younger individuals) who have a low 10-year risk but a substantial lifetime risk. Targeting these individuals with early, preventive measures to reduce long-term risk could potentially result in substantial public health benefit.^{29,35–38}

Participants are not eligible if they have already had an atherosclerotic-related cardiovascular event, including myocardial infarction, stroke, coronary revascularization of any type, or if they had a CVD risk-equivalent condition such as documented peripheral arterial disease or carotid stenosis. For these participants, we cannot stratify future risk of recurrent events easily, although we know it is high. We also concluded that the life experience related to the initial CVD event(s) experienced by these individuals is likely to serve as a far stronger motivator than any genetic risk score. Patients are excluded if they were already on lipid-lowering therapy, as the inclusion of participants on different statins at various doses with a range of LDL targets introduces considerable heterogeneity into the analyses. In addition, inclusion of people already adherent to therapy and at goal for risk factor reduction strategies would limit our ability to detect relevant outcomes.

Finally, the SNPs included in the genetic score have been evaluated predominantly in white/European subjects. Because there is considerable overlap in the genetic architecture between white/European populations and South Asian or Hispanic/Latino populations, we thought it reasonable to include these latter race/ethnic groups. In particular the recent publication from the Coronary Artery Disease (C4D) Genetics Consortium demonstrated “little evidence for ancestry-specific effects”²⁰ of the known CHD/myocardial infarction variants in South Asians versus white/European populations. We are limited by the paucity of published findings in Hispanic populations; however, given the high degree of white/European ancestry in these populations, we would expect these markers to perform well. Furthermore, one of us (J.P.A.I.) has also recently published a manuscript demonstrating that, although the effect sizes for single variants may differ between white/European and Asian populations, they are, on average, larger in 1 or the other ancestry group, thus a multigene signature is likely to carry similar predictive

ability, although this is not true for white/European (or Asian) versus African descent.³⁹ Therefore, we are limiting the trial population to these 3 race/ethnicity groups as based on self-identification, while excluding blacks, East Asians, and Pacific Islanders. We are careful to acknowledge that these SNPs may not convey the exact same risk in South Asian or Hispanic populations in the information we give to patients. (See online-only Data Supplement Appendix.) We evaluated the risk score in blacks and in whites/Europeans from the Atherosclerosis Risk in Communities (ARIC) cohort. In blacks, the relative risk for a standard deviation increase in the Risk Score of CHD over 10 years (controlled for age and sex) is 1.04 (0.93, 1.16), while in whites/Europeans, the equivalent relative risk is 1.18 (1.12, 1.25). This indicates that the SNPs that are used in the risk score are not valid in blacks.

Initial Clinic Visit: Eligibility and Consent and Guideline-Based Standard Care

At the initial clinic visit (time=0), eligibility screening and consent are completed (Figure 1). After consent is obtained, participants complete a comprehensive baseline questionnaire. (See online-only Data Supplement Appendix for details.) Participants are then randomized to 1 of the 2 arms using a permuted block algorithm (block size 8) implemented in StudyTrax. A saliva sample is collected for DNA preparation using kits from Oragene, and a medical history and physical examination are also performed. All patients receive standard care including: assessment of personal medical history, social history, and family history; measurements of height, weight, and blood pressure; laboratory testing, such as fasting lipids and blood chemistries; and calculation of 10- and 30-year risk using Framingham models.^{28,29} Most importantly, the patient’s target LDL based on National Cholesterol Education Program/Adult Treatment Panel III guidelines is determined and documented at this initial visit.^{30,40} Based on the same guidelines, recommendations how to optimize one’s diet and physical activity levels are also made. If applicable, medications are prescribed according to guidelines (see Figure 1).

Second Clinic Visit: Guideline-Based Standard Care and Discussion of Genetic Testing Results With Intervention Patients Only

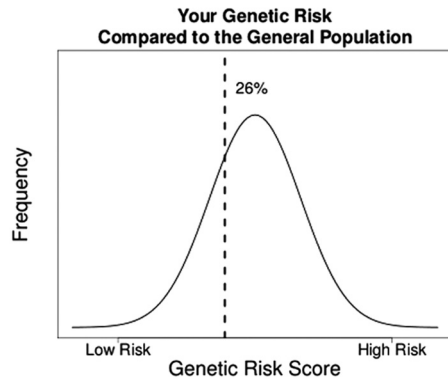
The second clinic visit is scheduled 3 months after the initial visit. This schedule follows the usual practice at PCC and was chosen for

Your Risk Score

Based on the traditional Framingham risk score, your risk of coronary heart disease over the next 10 years is approximately 9.7%.

We tested for a total of 38 possible risk variants or alleles. Out of these 38, you carry 15 variants that are associated with higher risk.

Your genetic profile puts you in the 26 percentile for risk. This means 26% of the general population have a genetic risk score more favorable than you and 74% have a genetic risk score less favorable than you.



Based on the traditional Framingham risk score plus the genetic risk score, your risk of coronary heart disease over the next 10 years is approximately 8.7%.

Figure 2. Genetic risk score report: This score was derived for a hypothetical patient.

several reasons. First, it allows sufficient time to gauge the effectiveness of the initial diet and lifestyle interventions and, when applicable, pharmacological therapy. Second, the interval allows for the completion of genetic testing, which currently takes ~2 months. Immediately before the second clinic visit, participants fill out another study questionnaire and undergo a fasting measurement of lipids. A reassessment of risk factors such as weight, blood pressure, and smoking behavior are performed, to measure progress with initial recommendations. If additional evaluations were completed, such as noninvasive imaging studies of atherosclerotic plaque development (eg, coronary artery calcium scan), these studies are reviewed, as this additional information may change therapeutic recommendations.⁴¹ Guideline-based therapeutic recommendations are discussed with the patient.

At the conclusion of the second clinic visit, the clinician opens a sealed envelope that contains either the genetic risk score or a note indicating that the patient was randomized to the nonintervention arm and will receive his or her genetic risk score at the conclusion of the trial (6-month visit). Importantly, before this point, the clinician is blinded to the results of the genetic testing.

The genetic test results are discussed with the patient by guiding him or her through an individualized genetic risk report (Figure 2). A standard script was developed to help clinicians discuss these results (online-only Data Supplement Appendix). This risk report includes (1) a traditional estimate of both 10-year risks based on the Framingham model; (2) the absolute number of risk alleles carried by the patient (out of a possible 38 alleles); (3) an estimate of the participant's percentile of genetic risk based on the absolute number of risk alleles in relation to the frequency distribution of risk alleles observed in the ARIC cohort of whites; (4) an estimate of the participant's 10-year risk of CHD before and after the addition of the genetic data to the standard Framingham 10-year risk model; and (5) a list of SNPs tested annotated with the nearest genes. We also provide participants with a take-home *Frequently Asked Questions* sheet that reiterates much of the message conveyed by the clinician at the visit (online-only Data Supplement Appendix). We aimed for

a very short session (10 minutes) to convey the genetic information. This mode of information delivery does entail the risk that participants may not fully comprehend this information, and this may affect their response to it; however, it would have been difficult to advocate adoption of a genomic information intervention in the everyday busy clinical practice, if this were to take a lot of time to deliver. Moreover, a lengthy delivery of the information may have seriously unbalanced the 2 arms in regards to the attention they received and may have introduced a spurious effect due to greater attention alone. Furthermore, providing more time and detailed emphasis might have given the wrong impression that this information is as important as major genetic risks conferred by major mutations in monogenic disease that require careful and in-depth genetic counseling. This mode of information delivery does entail the risk that participants may not fully comprehend this information, and this may affect their response to it. We do not involve a genetic counselor in the interpretation and discussion of the results of the genetic testing with the participant. Involvement of a genetic counselor would be a different type of intervention, and it would add to the complexity and cost of care. Moreover, it was felt that a genetic counselor would be unnecessary for conveying information for modest multigenetic risks, as opposed to large risks conferred by Mendelian monogenic inheritance. Furthermore, we do not perform a time-matched intervention in the nonintervention arm, since the time required to convey the genetic information is relatively minimal, and time-matching would add an extra layer of complexity to the design.

Third Clinical Visit: Final Outcome Assessment

The third clinical visit is scheduled for 3 months after the second clinic visit (6 months after enrollment at the initial clinic visit). This schedule is typical for PCC and allows adequate assessment of the success of diet, lifestyle, and pharmacological interventions. Participants once again fill out a questionnaire and undergo testing to determine serum lipid levels immediately before this visit. At the clinic visit, the participant's cardiovascular risk factors are reassessed, and progress in relation to original therapeutic recommendations is documented and discussed. At this visit, participants in the nonintervention arm also receive their genetic testing results, which are reviewed in the same manner as they were reviewed for the intervention arm at the 3-month visit.

Pharmacological Algorithm for Lowering LDL

A rigid LDL-lowering algorithm is implemented to minimize the possibility of a channeling bias introduced by a treating physician's knowledge of the genetic testing results. Both the LDL target and the therapeutic regimen are established before the genetic results are disclosed, and no change in the lipid-lowering algorithm is permitted for the duration of the trial except in the case of drug intolerance. If a statin is needed, the initial choice is either simvastatin 20 mg per day for the vast majority of the cases, where mild to moderate (<35%) LDL lowering is required, or atorvastatin 40 mg per day, if more potent LDL lowering (>35%) is required or if there is a previously documented intolerance to simvastatin.³⁰

Genotyping Strategy

We encountered several challenges in establishing an efficient method to perform and deliver the genetic testing for this trial. Despite decreasing costs, genetic testing remains relatively expensive if a limited set of SNPs is queried in a small number of individuals (several hundred dollars per participant). In addition, US Food and Drug Administration (FDA)-approved commercial genotyping assays for testing variants associated with complex diseases are not available. Furthermore, we were unable to identify an academic laboratory that offers Clinical Laboratory Improvement Amendments-certified genotyping for these markers, and the cost for developing such an assay at Stanford University Medical Center in 2011 was estimated to be >\$25,000. Thus, this trial would have not have been possible if it were not for a waiver granted by the Stanford Institutional Review Board allowing us to deliver genetic testing

results to our participants from a non-Clinical Laboratory Improvement Amendments certified laboratory.

We elected to genotype participants in this trial using Illumina's custom iSelect Cardio-MetaboChip (CM), a 200-k array designed by academic investigators in 2009. SNPs included in this array allow for wet-laboratory replication of the top $\approx 2\%$ signals emanating from several large-scale GWAS meta-analyses of cardiovascular-related traits, including body mass index, lipids, blood pressure, and CHD phenotypes and an opportunity to fine map a majority of the currently published validated GWAS loci for CHD.²¹ Because many investigators around the world were willing to purchase large volumes of the CM array, Illumina made the array available to the scientific community for only $\approx \$40$ /sample. DNA is purified from saliva samples using standard protocols (PrepIt L2P, Oragene). Genotyping is performed at the HudsonAlpha Institute for Biotechnology using 250 ng of genomic DNA combined with standard Illumina reagents and protocols. Genotype calls are made with Illumina's GenomeStudio software (<http://www.illumina.com>), and samples with $>98\%$ call rates across all SNPs on the array are considered for analysis. Samples with lower call rates are rerun as necessary.

Assessment of CHD Risk Using a Genetic Risk Score

At the time this trial was implemented, the published lead SNPs at 21 out of 27 known CHD loci did not appear to be associated with TRFs in the CARDIoGRAM study.^{20,21} One may debate whether genetic variants that relate to TRFs should also have been considered in the polygenic score. We opted to exclude them, since these variants in theory do not provide information that is beyond what can be gleaned already by measurements of TRFs. An evaluation of the ARIC data showed that consideration of these 6 variants, as well as the 3 variants that were not present in the panel that we chose for genotyping, did not alter the Appropriate Use Criteria. Among these 21 loci, 19 are represented on the CM and were considered in this study. Two loci (located at 17q21.32 and 7q22) identified by the C4D consortium did not meet the prespecified threshold for significance in the CARDIoGRAM study and were thus not included on the CM, which was exclusively populated with the top hits from the CARDIoGRAM meta-analysis.

Individual level genotype (including imputation up to ≈ 2.5 million HapMap SNPs) and phenotype data from the ARIC cohort were acquired through an application to the National Institutes of Health-controlled access database of Genotypes and Phenotypes (dbGaP) by 1 of the coinvestigators of this study (T.L.A.).^{4,42,43} The ARIC data were then used to calculate 10-year risks of CHD for participants before and after incorporating their genotyping results at the 19 loci of interest. Owing to pruning algorithms implemented during the design of the CM array and limitations in imputation quality in ARIC for some SNPs, only 11 out of the 19 lead SNPs were found to be present both on the CM and available in the ARIC imputation file secured from dbGaP. For 3 loci, the lead SNP was not present on the CM and a proxy with $r^2 > 0.9$ on the array was chosen to represent these loci. For 5 loci, the ARIC imputation file did not have genotype information for the lead SNP, and thus a proxy-imputed SNP was chosen to represent these loci in ARIC (the $r^2 = 1$ for 4 of these proxies, $r^2 = 0.97$ for 1, and the $r^2 = 0.87$ for the last) (Table 1).

The 19 identified risk SNPs were abstracted from the ARIC imputation file. Using the estimated log odds ratios from the CARDIoGRAM study as weights, a normalized risk score was derived for all whites ($n = 8734$) in ARIC. This distribution of scores served as the population-based comparison for the participant's genetic risk score. To assess the 10-year risk of CVD based on an individual's genetic risk score, a relative risk regression was estimated within the ARIC cohort, adjusting for sex and age. Within the ARIC sample, 13% were identified as having CHD within 10 years, and the relative risk for a 1-standard deviation increase in genetic risk was found to be 1.18 (95% confidence intervals: 1.12, 1.25). For participants in this study, a genetic risk score was calculated in the same manner as it was calculated for ARIC cohort members, with the

caveat that genotype information for each locus was derived from the SNPs at each locus on the CM array. Each individual's 10-year risk of CHD based on the Framingham risk calculator was computed. This 10-year risk was then multiplied by the individual's estimated genetic relative risk to generate an updated risk.

Outcomes

Primary Outcome

The primary outcome is the change in LDL cholesterol between the 3-month and 6-month visits. We chose this as the primary outcome for several reasons. First, a strong relationship exists between LDL cholesterol and CVD, and LDL cholesterol reduction is a major therapeutic goal in both primary and secondary prevention of CVD. Second, it is easy to measure and accurately quantify LDL cholesterol. Finally, repeated measures of LDL cholesterol are standard of care.

Secondary Outcomes

Providing participants information on genetic risk may affect other outcomes of interest in the context of the goal of this trial. Thus, we are assessing 4 sets of secondary outcomes. As in the primary outcome, the main comparison for each of these sets of outcomes is the difference in these measures between the 3-month and 6-month visits.

The first set of secondary outcomes includes changes in traditional cardiovascular risk factors other than LDL, such as high-density lipoprotein cholesterol, blood pressure, weight, smoking status, glycemic control (as assessed by hemoglobin A1C), as well as physical activity and dietary patterns. We assess usual leisure time physical activity in the past month with a single self-report item consisting of 6 descriptive categories ranging from inactive to very active.⁴⁴ This item, the Stanford Leisure-Time Activity Categorical Item (L-Cat), has strong psychometrics in a sample of obese women in a randomized behavioral weight management trial, including excellent test-retest reliability; concurrent criterion validity with pedometer steps and weight loss; and sensitivity to change. To assess usual dietary patterns in the past month, we revised a previously validated brief dietary questionnaire.⁴⁵ Revisions included updating item content to reflect current CVD-related dietary guidelines and simplifying response categories. The revised questionnaire consists of 11 self-report items, with 10 response categories ranging from *one time or less in the last month* to *5 plus times a day*. We will examine the internal consistency of the dietary items in this sample.

The second set of secondary outcomes involves measures of adherence to, and attitudes toward, taking medications. Medication adherence to cholesterol-lowering drugs and antihypertensive medications are each assessed with a single item using a visual analog scale. These items have adequate validity, with unannounced phone-based pill counts in similar clinical samples.⁴⁶ Medication attitudes are assessed with 12 self-report items from the Beliefs About Medicines Questionnaire,⁴⁷ which examine perceived necessity of medications and concerns taking medications as validated against the Illness Perception Questionnaire, the Reported Adherence to Medication scale, and the Sensitive Soma Scale. We will examine the internal consistency of the items in this sample.

The third set of secondary outcomes focuses on perceptions of risk. Relative and absolute perception of risk is each assessed by a single item measured on a 5-point Likert scale ranging from *not at all* to *extremely*. The items included, "Over the next 10 years, compared to others your age and sex, how would you rate your risk of having a heart attack or dying due to blocked coronary arteries?" and "Over the next 10 years, how likely do you think it is that you personally will have a heart attack or die due to blocked coronary arteries?"⁴⁸ These items have validity in other clinical samples.⁴⁹ We also assess whether patients discuss their risk of CVD with others and encourage others to be screened; each are assessed by a single item measured on a 5-point Likert scale with response options ranging from *not at all* to *extremely*. Informed by the transtheoretical stages of change model,⁵⁰ we assess stages of change with 5 questions adapted from a questionnaire previously validated in a preventive cardiology

setting.⁵¹ These questions focused on stages later than the first (precontemplation) stage, as we reasoned that patients coming to the PCC would have already advanced past the precontemplation stage. We will examine the internal consistency of the items in this sample.

The final set of outcomes focuses on psychological outcomes, given the potential of genetic risk information to have negative psychological impact. Informed by previous literature on the potential psychological impacts of genetic screening for pregnancy and mammogram screening,⁵² we assess 5 constructs with single- or 2-question items adapted from previously published reports.^{53,54} To minimize participant burden, we standardize the items using 5-point Likert scales with response options ranging from *not at all* to *extremely*. The constructs include anxiety associated with testing, fatalism, depression, stress, and mood. These items have adequate validity in similar clinical samples.

Subgroup Analyses

The size of this trial limits the ability to examine subgroups robustly. We will nevertheless examine trends of association in 2 important subgroups to help plan future intervention trials that build off this pilot study. The first is the subgroup with participants whose 10-year risk of CHD is increased when genetic information is incorporated into the ARIC cohort modeling compared with those who have a lower updated risk. The second is the subgroup that demonstrates a clear reluctance to taking or initiating medications at the 3-month visit based on their responses to the Beliefs about Medicines Questionnaire.

Statistical Methods and Power Calculations

For the primary outcome and all the secondary continuous end points, the mean changes between 3- and 6-month visits will be compared between the 2 arms, adjusting for baseline values. Scales will be analyzed assuming interval scaling. With 50 patients per arm, the trial has $\approx 85\%$ power to detect a difference of 8 mg/dL of LDL cholesterol at $\alpha=0.05$ (assuming post-treatment LDL values of 108 and 100 mg/dL in the 2 arms and a standard deviation of 15 mg/dL). These LDL values are representative of typical patients in the PCC, with pretreatment LDL cholesterol values ≈ 130 to 160 mg/dL. In general, studies have confirmed a 5% to 15% decrease in LDL with diet and lifestyle changes and a 30% to 40% decrease in LDL with statin therapy.^{55,56} Thus, the trial is well-powered to identify an effect of genetic testing that is in the same range as that of diet and exercise.

Human Subject Protection

The Stanford Institutional Review Board approved this protocol. A research exception was made to allow the return of non-Clinical Laboratory Improvement Amendments certified genotypic information to patients.

Discussion

Genome-wide association studies continue to identify a growing number of susceptibility variants for various complex diseases, offering hope that this information may allow for improved risk prediction and a reduction of risk through the more efficient application of proven primary and secondary prevention strategies; however, the use of these markers in clinical practice has not yet been shown to improve patient outcomes or risk factor profiles in CVD. The National Institutes of Health and the US Preventive Services Task Force has indicated that genetic screening will be highly scrutinized until randomized trials demonstrate clinical benefit.⁵⁷ Currently, both the Evaluation of Genomic Applications in Practice and Prevention Working Group and the American College of Cardiology/American Heart Association Taskforce on Practice Guidelines recommend against genetic testing for cardiovascular disease, citing lack of

clinical trial data supporting its use.^{41,58} Despite these recommendations and lack of efficacy data, there is growing enthusiasm for personalized medicine approaches, fueled also by direct-to-consumer genetic testing companies. In this context, an important opportunity exists to develop well-designed clinical trials that objectively examine the population effect of providing information on complex trait susceptibility variants to individuals at risk. We seek to help answer some of these questions by determining if genetic testing plus standard care improves cardiovascular risk profiles in the short term compared with standard care alone.

Although there are no published clinical trials using genetic testing specifically for complex CVD, we note the recently reported results of Bloss et al involving over 2000 research volunteers participating in the Scripps Genomic Health Initiative.⁵⁹ In this nonrandomized survey, participants reported on changes in levels of anxiety, fat intake, and exercise after being provided the genotyping results of a genome-wide array. The genetic risk score for a number of common conditions was provided to the participants along with genetic counseling services. The investigators found that this information had no effect on exercise and dietary habits. Furthermore, they observed no short-term adverse negative psychological impacts. Importantly, these participants were not enrolled based on a prior existing condition or set of risk factors and so may not represent the effect genetic testing would have on individuals with a specific disease or risk for disease.

Recently, Grant et al published a description of the methods of a randomized trial of genetic risk testing to evaluate risk of diabetes and motivate behavioral change to reduce that risk.⁶⁰ The trial design of that study and ours has several similarities, including the creation of a genetic risk score based on the latest set of validated susceptibility variants; enrollment of patients with a baseline elevated risk of a condition; and assessment of secondary outcomes measures, such as changes in weight, exercise, and diet, as well as psychological stages of change, and levels of anxiety. The trials also have important differences. The primary outcome for the Grant et al trial is attendance at 12-week diabetes prevention classes rather than change in a quantitative risk variable (eg, LDL). In addition, the investigators used a novel allocation scheme based on the application of Mendelian randomization to exclude individuals at average genetic risk of diabetes, with the hypothesis that there would be a differential effect of the genetic testing on the behaviors of people at higher versus lower genetic risk. Conversely, we have opted to enroll participants regardless of their genetic profile, but we plan to examine effects between participants whose CVD risk increases because of their genetic profile versus participants whose risk decreases.

Although the CM contains more than 200 000 SNPs related to many cardiometabolic risk factors, participants in this study are receiving genetic risk information restricted to the 19 loci that have been unequivocally associated with CVD and appear to be mediating risk independent of TRFs. We opted for this strategy for several reasons. Although many true susceptibility loci likely exist among the top signals included on the CM, a GRS incorporating many of these loci

for CVD has not been shown to be superior to a GRS restricted to validated loci. Similarly, the addition of information from either validated or promising susceptibility loci for risk factors of CVD such as LDL, body mass index, or blood pressure to a GRS based on CVD variants alone has also not been shown to improve risk prediction substantially.²⁶ Furthermore, we thought it best to focus on a discrete number of susceptibility variants for a single phenotype, given the complexities of conveying the genetic information in a standard clinical visit. Thus, we chose focus on the single phenotype that would be most directly relevant from a clinical perspective and would conceivably have the largest impact on behavior.

Although several trials assessing the efficacy of genetic testing have employed genetic counselors,⁵⁹ we made a conscious decision to avoid that paradigm because we wanted to mimic what might happen in real world scenarios where access to genetic counselors is often limited. Involvement of a genetic counselor would change the purpose of the trial from ascertaining usefulness of genetic testing alone to ascertaining the usefulness of genetic testing combined with genetic counseling. In contrast to Mendelian disorders, where counseling is usually limited to a few family members at risk, counseling for complex genetic disease would involve a much larger population. This approach currently appears neither efficient nor practical, given the number of individuals at intermediate or high risk of CVD.⁶¹ Optimal ways of conveying complex genetic information to people without necessarily involving genetics experts need to be explored in depth.

We do not perform a time-matched alternate intervention in control patients who do not receive their genetic data at the second visit. Time-matched alternate interventions may be necessary when testing more complex interventions, where considerably more time is spent interacting with volunteers and where there is a danger that this interaction in of itself will result in a benefit that is independent of the intervention being tested. Thus, a time-matched alternate intervention was not deemed necessary, given that the genetic score information can be generally conveyed in 10 minutes and the pharmacological algorithm for lowering LDL is locked for the duration of the trial.

Potential strengths of our trial include the development of a comprehensive risk score based on 19 validated loci associated with CVD independent of TRFs. This risk score was designed to present a fair and balanced view of the genetic risk by showing not only the effect on overall risk but also the patient-specific risk relative to the general population. Another strength is use of change in LDL cholesterol as the primary outcome, which is a quantitative measure that has a direct effect on the risk of CVD and is a widely accepted major target for therapeutic intervention. Many of the secondary outcome measures have also been shown to markedly impact CVD risk, including changes in blood pressure, weight, and diet. We are also capturing information about more subtle but important ways in which genetic testing may have a positive impact, such as moving patients along the spectrum of the stages of change, giving them a more realistic appraisal of their absolute and relative risk of cardiovascular

disease. We tried to remove the impact of genetic testing on physician prescriptions, since there is no evidence that physicians should react to such genetic information and allowing such reaction might have added an uncontrolled source of variance (eg, the response might have been better in the genetic information group simply because physicians prescribed higher doses of medication); however, future trials may need to try to address also the impact of such information on physician behavior. Finally, 1 of the key issues we are assessing is whether genetic testing for CVD will result in increased anxiety, depression, or other psychological harm. We chose to address this issue because discussions of the potential for psychological harm are prominent in the screening literature regarding other conditions. For example, the US Preventive Services Task Force has explicitly sought and commented on evidence regarding psychological harms in its evidence reviews of the use of mammography for cancer screening.⁶²

The limitations of the trial include the relatively small sample size and short duration, but these were considered appropriate for a proof of concept trial designed to demonstrate feasibility. We hope that successful completion of the trial will demonstrate that such experimental designs can be adapted to larger, multicenter trials, with long term follow-up that includes hard clinical outcomes. Another potential limitation relates to the generalizability of results, given the patient population being tested. Patients who present to the PCC are likely to be more motivated than the general population and more likely to undertake recommended beneficial lifestyle changes. They also may be more highly educated and more willing to embrace new technologies (as early adopters) compared with the general population. Although we recognize this latter limitation, we also believe that this could be beneficial. If the trial fails to show benefit in a highly motivated population such as this one, it may be more difficult to show benefit in the general population for people who have less interest in seeking expert help and intervention for their cardiovascular health. Furthermore, we will be able to gauge the motivation level within this group in the time between the first and second clinical visits. This should provide us greater insight into the impact of the genetic testing, as we will be able to also use each individual as his or her own control. Lastly, while we have some understanding of the genetic basis for CVD based on large GWAS studies, a large fraction of the inherited risk remains unexplained. In the future, the magnitude of changes in risk imparted by a genetic score may be much greater, and this could significantly affect the patient response and outcome. We are unable to assess whether an enhanced risk score based on additional markers would substantially change the outcome. As more risk variants are discovered, a challenge will be to keep the genetic score up to date. Maintaining an updated genetic risk score is less of a concern for our relatively short-term trial, but it may become an issue for larger long-term trials, where the list of validated or relevant genetic variants may grow substantially during the trial. One option in this situation may be to build an analytic pipeline that can quickly adapt the genetic risk score to include newly validated variants in the risk calculations.

There are similar challenges in the adoption of information also from other cardiovascular biomarkers, including, but not limited to, coronary artery calcium, intima-media thickness, and blood protein biomarkers.^{63,64} Ideally, similar pilot trials should be performed also for other biomarkers that are contemplated for use in clinical practice. Until such trials are available, it is difficult to discern the relative merits of different types of genetic versus nongenetic markers, other than their discriminating ability, which generally seems to be modest for all available proposed markers.

In conclusion, we have designed a trial to assess whether we can reduce risk in patients through providing them with information about CVD susceptibility loci. Trials such as this are necessary before we can advocate for widespread application of genetic testing for common, complex disease phenotypes. This type of trial may be adopted for prevention settings for other chronic diseases in which there are good treatments available but suboptimal risk discrimination that could potentially be improved by consideration of genetic information.

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Disclosures

Dr Ashley is a founder and consultant for Personalis. The other authors report no conflicts.

References

1. Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, et al. Biological, clinical and population relevance of 95 loci for blood lipids. *Nature*. 2010;466:707–713.
2. Kathiresan S, Willer CJ, Peloso GM, Demissie S, Musunuru K, Schadt EE, et al. Common variants at 30 loci contribute to polygenic dyslipidemia. *Nat Genet*. 2009;41:56–65.
3. Newton-Cheh C, Johnson T, Gateva V, Tobin MD, Bochud M, Coin L, et al. Genome-wide association study identifies eight loci associated with blood pressure. *Nat Genet*. 2009;41:666–676.
4. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, et al. Genome-wide association study of blood pressure and hypertension. *Nat Genet*. 2009;41:677–687.
5. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*. 2007;316:889–894.
6. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analyses of 249 796 individuals reveal 18 new loci associated with body mass index. *Nat Genet*. 2010;42:937–948.
7. Tobacco and Genetics Consortium. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. *Nat Genet*. 42:441–447.
8. Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature*. 2007;445:881–885.
9. Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research, Saxena R, Voight BF, Lyssenko V, Burt NP, de Bakker PI, Chen H, et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science*. 2007;316:1331–1336.
10. Scott LJ, Mohlke KL, Bonnycastle LL, Willer CJ, Li Y, Duren WL, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science*. 2007;316:1341–1345.
11. Steinthorsdottir V, Thorleifsson G, Reynisdottir I, Benediktsson R, Jonsson T, Walters GB, et al. A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. *Nat Genet*. 2007;39:770–775.
12. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, et al. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat Genet*. 2008;40:638–645.
13. Wellcome Trust Case Control Consortium. Genome-wide association study of 14 000 cases of seven common diseases and 3000 shared controls. *Nature*. 2007;447:661–678.
14. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, et al; WTCCC and the Cardiogenics Consortium. Genomewide association analysis of coronary artery disease. *N Engl J Med*. 2007;357:443–453.
15. McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, et al. A common allele on chromosome 9 associated with coronary heart disease. *Science*. 2007;316:1488–1491.
16. Helgadóttir A, Thorleifsson G, Manolescu A, Gretarsdóttir S, Blondal T, Jonasdóttir A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science*. 2007;316:1491–1493.
17. Saleheen D, Alexander M, Rasheed A, Wormser D, Soranzo N, Hammond N, et al. Association of the 9p21.3 locus with risk of first-ever myocardial infarction in Pakistanis: case-control study in South Asia and updated meta-analysis of Europeans. *Arterioscler Thromb Vasc Biol*. 2010;30:1467–1473.
18. Shen GQ, Li L, Rao S, Abdullah KG, Ban JM, Lee BS, et al. Four SNPs on chromosome 9p21 in a South Korean population implicate a genetic locus that confers high cross-race risk for development of coronary artery disease. *Arterioscler Thromb Vasc Biol*. 2008;28:360–365.
19. Lettre G, Palmer CD, Young T, Ejebe KG, Allayee H, Benjamin EJ, et al. Genome-wide association study of coronary heart disease and its risk factors in 8090 African Americans: the NHLBI care project. *PLoS Gen*. 2011;7:e1001300.
20. Coronary Artery Disease (CAD) Genetics Consortium. A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease. *Nat Genet*. 2011;43:339–344.
21. Schunkert H, König IR, Kathiresan S, Reilly MP, Assimes TL, Holm H, et al. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. *Nat Genet*. 2011;43:333–338.
22. Erdmann J, Grosshennig A, Braund PS, König IR, Hengstenberg C, Hall AS, et al. New susceptibility locus for coronary artery disease on chromosome 3q22.3. *Nat Genet*. 2009;41:280–282.
23. Myocardial Infarction Genetics Consortium, Kathiresan S, Voight BF, Purcell S, Musunuru K, Ardissono D, et al. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. *Nat Genet*. 2009;41:334–341.
24. Kathiresan S, Melander O, Anevski D, Guiducci C, Burt NP, Roos C, et al. Polymorphisms associated with cholesterol and risk of cardiovascular events. *N Engl J Med*. 2008;358:1240–1249.
25. Ripatti S, Tikkanen E, Orho-Melander M, Havulinna AS, Silander K, Sharma A, et al. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. *Lancet*. 2010;376:1393–1400.
26. Paynter NP, Chasman DI, Pare G, Buring JE, Cook NR, Miletich JP, Ridker PM. Association between a literature-based genetic risk score and cardiovascular events in women. *JAMA*. 2010;303:631–637.
27. Umans-Eckenhausen MA, Defesche JC, van Dam MJ, Kastelein JJ. Long-term compliance with lipid-lowering medication after genetic screening for familial hypercholesterolemia. *Arch Intern Med*. 2003;163:65–68.
28. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.
29. Pencina MJ, D'Agostino RB Sr, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the Framingham Heart Study. *Circulation*. 2009;119:3078–3084.
30. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–3421.
31. Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyörälä K. Prevention of coronary heart disease in clinical practice: recommen-

- dations of the Second Joint Task Force of European and Other Societies on Coronary Prevention. *Atherosclerosis*. 1998;140:199–270.
32. U.S. Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med*. 2002;136:157–160.
 33. Erbel R, Mohlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, et al; Heinz Nixdorf Recall Study Investigative Group. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: the Heinz Nixdorf Recall study. *J Am Coll Cardiol*. 2010;56:1397–1406.
 34. Greenland P, Smith SC Jr, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. *Circulation*. 2001;104:1863–1867.
 35. Forrester JS. Redefining normal low-density lipoprotein cholesterol: a strategy to unseat coronary disease as the nation's leading killer. *J Am Coll Cardiol*. 2010;56:630–636.
 36. Steinberg D. Earlier intervention in the management of hypercholesterolemia: what are we waiting for? *J Am Coll Cardiol*. 2010;56:627–629.
 37. Lloyd-Jones DM. Cardiovascular risk prediction: basic concepts, current status, and future directions. *Circulation*. 2010;121:1768–1777.
 38. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, Wolf PA, Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113:791–798.
 39. Ntzani EE, Liberopoulos G, Manolio TA, Ioannidis JP. Consistency of genome-wide associations across major ancestral groups. *Hum Genet*. 2011 Dec 20. [Epub ahead of print]
 40. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227–239.
 41. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al; American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. *Circulation*. 2010;122:2748–2764.
 42. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol*. 1989;129:687–702.
 43. Psaty BM, O'Donnell CJ, Gudnason V, Lunetta KL, Folsom AR, Rotter JI, et al; CHARGE Consortium. Cohorts for heart and aging research in genomic epidemiology (charge) consortium: design of prospective meta-analyses of genome-wide association studies from 5 cohorts. *Circ Cardiovasc Genet*. 2009;2:73–80.
 44. Kiernan M, Schoffman DE, Lee K, Moore S, Fair J, Taylor-Piliae R, et al. Using the Stanford Leisure-Time Activity Categorical Item (L-CAT) to assess changes in leisure-time activity among obese women. *Ann Behav Med*. 2011;41:S187.
 45. Paxton AE, Strycker LA, Toobert DJ, Ammerman AS, Glasgow RE. Starting the conversation performance of a brief dietary assessment and intervention tool for health professionals. *Am J Prev Med*. 2011;40:67–71.
 46. Kalichman SC, Amaral CM, Swetzes C, Jones M, Macy R, Kalichman MO, et al. A simple single-item rating scale to measure medication adherence: further evidence for convergent validity. *J Int Assoc Physicians AIDS Care (Chic)*. 2009;8:367–374.
 47. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res*. 1999;47:555–567.
 48. Kreuter MW, Strecher VJ. Changing inaccurate perceptions of health risk: results from a randomized trial. *Health Psychol*. 1995;14:56–63.
 49. Strecher VJ, Kreuter MW, Kobrin SC. Do cigarette smokers have unrealistic perceptions of their heart attack, cancer, and stroke risks? *J Behav Med*. 1995;18:45–54.
 50. Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. *J Consult Clin Psychol*. 1983;51:390–395.
 51. Miller ANR. The CaReS battery: measuring stages of change in cardiac rehabilitation through the development of a targeted instrument. Kent State. Master's Thesis. Psychology. 2010.
 52. Watson EK, Henderson BJ, Brett J, Bankhead C, Austoker J. The psychological impact of mammographic screening on women with a family history of breast cancer – a systematic review. *Psychooncology*. 2005;14:939–948.
 53. Meisel SF, Walker C, Wardle J. Psychological responses to genetic testing for weight gain: a vignette study. *Obesity (Silver Spring)*. 2012;20:540–546.
 54. Cameron LD, Sherman KA, Marteau TM, Brown PM. Impact of genetic risk information and type of disease on perceived risk, anticipated affect, and expected consequences of genetic tests. *Health Psychol*. 2009;28:307–316.
 55. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301–1307.
 56. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Gotto AM. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615–1622.
 57. Ioannidis JP. Prediction of cardiovascular disease outcomes and established cardiovascular risk factors by genome-wide association markers. *Circ Cardiovasc Genet*. 2009;2:7–15.
 58. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP working group: genomic profiling to assess cardiovascular risk to improve cardiovascular health. *Genet Med*. 2010;12:839–843.
 59. Bloss CS, Schork NJ, Topol EJ. Effect of direct-to-consumer genomewide profiling to assess disease risk. *N Engl J Med*. 2011;364:524–534.
 60. Grant RW, Meigs JB, Florez JC, Park ER, Green RC, Waxler JL, et al. Design of a randomized trial of diabetes genetic risk testing to motivate behavior change: the Genetic Counseling/Lifestyle Change (GC/LC) Study for Diabetes Prevention. *Clin Trials*. 2011;8:609–615.
 61. Rosamond W, Flegal K, Friday G, Furie K, Go A, Greenlund K, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2007;115:e69.
 62. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;151:727–737, W237–W742.
 63. Korcarz CE, DeCara JM, Hirsch AT, Mohler ER, Pogue B, Postley J, et al. Ultrasound detection of increased carotid intima-media thickness and carotid plaque in an office practice setting: does it affect physician behavior or patient motivation? *J Am Soc Echocardiogr*. 2008;21:1156–1162.
 64. Kalia NK, Miller LG, Nasir K, Blumenthal RS, Agrawal N, Budoff MJ. Visualizing coronary calcium is associated with improvements in adherence to statin therapy. *Atherosclerosis*. 2006;185:394–399.

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Randomized Trial of Personal Genomics for Preventive Cardiology: Design and Challenges

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