Incorporating a Genetic Risk Score Into Coronary Heart Disease Risk Estimates

Effect on Low-Density Lipoprotein Cholesterol Levels (the MI-GENES Clinical Trial)

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Background—Whether knowledge of genetic risk for coronary heart disease (CHD) affects health-related outcomes is unknown. We investigated whether incorporating a genetic risk score (GRS) in CHD risk estimates lowers low-density lipoprotein cholesterol (LDL-C) levels.

Methods and Results—Participants (n=203, 45–65 years of age, at intermediate risk for CHD, and not on statins) were randomly assigned to receive their 10-year probability of CHD based either on a conventional risk score (CRS) or CRS + GRS ($^{+}$GRS). Participants in the $^{+}$GRS group were stratified as having high or average/low GRS. Risk was disclosed by a genetic counselor followed by shared decision making regarding statin therapy with a physician. We compared the primary end point of LDL-C levels at 6 months and assessed whether any differences were attributable to changes in dietary fat intake, physical activity levels, or statin use. Participants (mean age, 59.4±5 years; 48% men; mean 10-year CHD risk, 8.5±4.1%) were allocated to receive either CRS (n=100) or $^{+}$GRS (n=103). At the end of the study period, the $^{+}$GRS group had a lower LDL-C than the CRS group (96.5±32.7 versus 105.9±33.3 mg/dL; P=0.04). Participants with high GRS had lower LDL-C levels (92.3±32.9 mg/dL) than CRS participants (P=0.02) but not participants with low GRS (100.9±32.2 mg/dL; P=0.18). Statins were initiated more often in the $^{+}$GRS group than in the CRS group (39% versus 22%, P<0.01). No significant differences in dietary fat intake and physical activity levels were noted.

Conclusions—Disclosure of CHD risk estimates that incorporated genetic risk information led to lower LDL-C levels than disclosure of CHD risk based on conventional risk factors alone.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01936675.

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As genetic testing becomes widely available, its use for estimating the risk of common diseases is becoming of increasing scientific and public health interest.[1] Genomewide association studies have identified multiple loci associated with coronary heart disease (CHD).[2,3] The majority of these loci are associated with CHD independent of conventional risk factors and could potentially improve the accuracy of CHD risk estimates. Several studies have investigated the association of a genetic risk score (GRS) based on multiple CHD susceptibility single-nucleotide polymorphisms (SNPs) with incident CHD events.[4–10] Most of the studies reported that a GRS is associated with adverse CHD events.[4,6–10] Incorporating CHD genetic risk information in clinical practice may refine risk estimates and aid in the prevention of

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CHD, concordant with recent calls to promote the practice of precision medicine.[11]

Whether knowledge of genetic risk for CHD influences health-related outcomes remains unknown. We conducted a clinical trial (Myocardial Infarction Genes [MI-GENES] Study) to investigate whether disclosing a GRS for CHD leads to lowering of low-density lipoprotein cholesterol (LDL-C) levels. The GRS was incorporated into the CHD risk estimates in combination with a conventional risk score (CRS) yielding a genetically informed risk score (+GRS).[12] We assessed whether disclosure of genetic risk for CHD affects LDL-C levels, and whether any differences were attributable to changes in dietary fat intake, physical activity levels, or statin initiation. We tested the following hypotheses: (1) in patients randomly assigned to receive +GRS, LDL-C levels at the end of the study period would be lower than in participants randomly assigned to receive CRS alone; (2) +GRS participants with a high GRS would have lower LDL-C levels than +GRS participants with average/low GRS and those randomly assigned to receive CRS alone.

A major challenge in implementing genomic medicine is the integration of genomic information into the electronic health record (EHR).[13] Genotyping was performed in a Clinical Laboratory Improvement Amendments–certified laboratory and results were placed into the EHR. In addition, a decision aid was modified to include genetic risk information and allow integration of such information into the EHR to facilitate shared decision making regarding statin therapy.[14,15]

Methods

Study Design

Study participants were drawn from the Mayo Clinic Biobank (n=29 352 at the time of study initiation) that recruits patients from the outpatient setting at Mayo Clinic.[16] We identified 2026 participants who met the following eligibility criteria: 45 to 65 years of age, non-Hispanic white ethnicity, no history of atherosclerotic cardiovascular disease, not on statins, at intermediate risk for CHD (10-year CHD risk, 5%–20%), and residents of Olmsted County, Minnesota. To maximize the information yield from the study, we performed an initial screening genotyping of 28 CHD-susceptibility SNPs (Table I in the online-only Data Supplement) that are not associated with blood pressure or lipid levels,[3] in a random sample of 1000 participants who met eligibility criteria[16] (Figure 1).

A GRS for each individual was calculated as previously described, taking into account the average genetic risk in the population.[17] In brief, we assumed an additive genetic model in which the genotypes are coded 0 for nonrisk allele homozygotes, 1 for heterozygotes, and 2 for risk-allele homozygotes. A weighted GRS was calculated by multiplying the logarithm of the odds ratio for a particular SNP by 0, 1, or 2 according to the number of risk alleles carried by each person. We used a GRS of ≥1.1, ie, a ≥10% increase in risk for CHD than would be predicted by a CRS, to classify individuals as having high GRS. Those with a GRS of <1.1 were classified as having average/low GRS.

Characteristics of the individuals who composed the recruitment pool for the study are summarized in Table II in the online-only Data Supplement. The initial screening genotyping allowed us to perform a targeted enrollment of equal numbers of high GRS and average/low GRS individuals. We were able to enroll 216 of a target of 220 participants for the study. A study coordinator invited these patients by phone to participate in the study and subsequently confirmed eligibility and obtained written informed consent. Individuals who agreed to participate underwent a blood draw for genotyping of 28 CHD susceptibility SNPs in a Clinical Laboratory Improvement Amendments–certified laboratory using the TaqMan procedure (Roche Molecular Diagnostics, Branchburg, NJ). A GRS was calculated,[17] and the CRS was then multiplied by the GRS to generate a genotype-informed probability of adverse CHD events over the next 10 years (+GRS). The 10-year probability of CHD was calculated at the first study visit as previously described.[12] Additional information about the screening genotyping and GRS calculation can be found in the online-only Data Supplement.

Risk factors for CHD including family history were assessed at the first study visit. Participants returned 6 to 10 weeks later (visit 2) once Clinical Laboratory Improvement Amendments genotyping and calculation of a GRS was completed (n=207). At this visit, patients were randomly assigned (1:1) to receive a CRS (n=103) versus a combined conventional and genetic risk score (+GRS, n=104). Study participants then underwent a 30-minute CHD risk-counseling session, followed by a visit with a physician for shared decision making regarding statin use. Three months following the disclosure of CHD risk, participants returned (visit 3) for measurement of fasting lipid levels and assessment of dietary fat intake and physical activity levels. The final study visit (visit 4) occurred 3 months after visit 3. Apart from incorporating the GRS into the CRS in 1 arm of the study (+GRS), randomly assigned patients received identical exposure to education about CHD risk reduction and preventive measures. The study was approved by the Mayo Clinic institutional review board and was registered at ClinicalTrials.gov (NCT01936675). Study methods and protocol have been previously described.[18]

Outcome Measures

The primary outcome was change in LDL-C level 6 months after disclosure of CHD risk (for ease of interpretation, we present comparison of the actual LDL-C levels at the 6-month time point, the inferences being the same). Behaviors related to cardiovascular health including dietary fat intake and physical activity levels were assessed at baseline and subsequent study visits. Differences in the study arms as a result of disclosing CHD risk were assessed at 6 months after disclosure. To assess whether disclosure of genetic risk led to an increase in anxiety, anxiety levels were assessed at baseline and subsequent study visits.

Sample Size and Power

In general, studies have shown a 5% to 15% decrease in LDL-C with diet and lifestyle changes and a ≈30% decrease in LDL-C with statin therapy.[19,20] Assuming the standard deviation of LDL-C change in the entire group to be 25 mg/dL, we had sufficient power to detect an LDL-C change of 15 mg/dL and to test the hypotheses that: (1) patients randomly assigned to receive +GRS would have lower LDL-C levels than patients randomly assigned to CRS; and (2) +GRS participants with a high GRS (≥1.1) would have lower LDL-C levels than +GRS participants with average/low GRS (<1.1) and those randomly assigned to receive CRS alone.

Randomization

The second study visit was scheduled 6 to 10 weeks after the initial visit to allow for completion of genotyping and calculation of GRS. Patients were randomly assigned (1:1) by means of a computer-generated random sequence stratifying for age, sex, and family history for CHD.[21] The +GRS arm received genetically informed 10-year CHD risk and the CRS arm received conventional risk factor information alone.

Disclosure of CHD Risk

The CHD risk estimate was disclosed by the genetic counselor during a 30-minute semiscripted session. Patients randomly assigned to +GRS were shown a pictograph that incorporated the revised 10-year CHD risk based on the genotypes of the 28 CHD-susceptibility SNPs. The control group was shown a pictograph based on the CRS. The pictograph depicted 100 people like the participant and indicated how many in the next 10 years could be expected to experience an adverse CHD event and how many would not. The genetic counselor helped participants interpret and understand their results, highlighting the

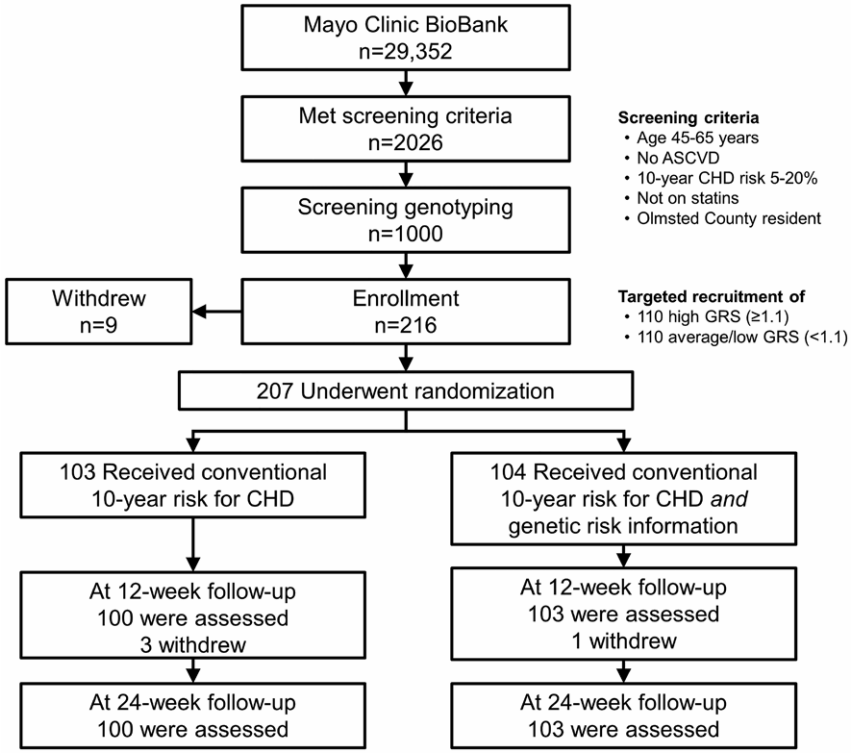

Figure 1. Flow diagram of the Myocardial Infarction Genes (MI-GENES) clinical trial. Of the 2026 individuals from the Mayo Biobank who met the eligibility criteria, a random subset of 1000 was genotyped. Genotyping results passed quality control measures in 968 individuals. Recruitment was based on screening genotyping results to achieve the targeted enrollment goals of ≈110 individuals with high GRS (≥1.1) and ≈110 with average/low GRS (<1.1) with the expectation that ≈10 to 20 study participants may withdraw from the study or be lost to follow-up. Participants who withdrew from the study stated that they could not fit the study visits into their schedule. ASCVD indicates atherosclerotic cardiovascular disease; CHD, coronary heart disease; and GRS, genetic risk score.

probabilistic nature of the genetic testing and that lifestyle factors such as diet, exercise, and smoking are major risk factors for developing CHD. The counselor encouraged participants to sign an action plan for behavioral change that included increased physical activity, reduced dietary fat intake and smoking cessation if the participant was a smoker. Participants were provided with a Frequently Asked Questions sheet that reiterated the key points conveyed by the genetic counselor at the visit. Fidelity of the scripts was assessed by analysis of video-recorded encounters. Having 1 genetic counselor (T.M.K) disclose CHD risk estimates to all study participants helped ensure that risk was disclosed similarly to all study participants (in their respective randomization groups).

Shared Decision Making Regarding Statin Therapy

Following the visit with the genetic counselor, each patient saw a physician in the Mayo Cardiovascular Health Clinic. During the patient-physician encounter the focus was on shared decision making regarding the need for statin therapy. The physicians (n=6) underwent a training session in the use of a Statin Choice decision aid[14] modified to include the GRS (migenesstudy.mayoclinic.org) to disclose CHD risk and help patients understand the benefits and downsides of taking a statin medication to reduce CHD risk (Figures I through IV in the online-only Data Supplement). The participant and clinician navigated through pictograms that display the 10-year probability of CHD, as well as the potential benefit of using statin medications. Consistency of the disclosure process was assured by following a checklist maintained by the study coordinator for both study arms and by review of videotaped encounters. A risk report describing conventional versus genetics-informed CHD risk was deposited in the EHR according to the participant's randomization group. New statin prescriptions were recorded by review of the EHRs. The online-only Data Supplement includes further details regarding the genomic decision aid, integration into the EHR, and the disclosure process of CHD risk estimates.

Dietary Fat Intake, Physical Activity, and Anxiety Levels

We used validated surveys to assess whether disclosure of CHD risk led to changes in dietary fat intake, physical activity, and anxiety levels. The percentage energy from fat screener[22] was adapted to estimate changes in fat consumption and the telephonic assessment of physical activity questionnaire[23] was adapted to assess changes in physical activity. Anxiety level was measured at baseline and follow-up by using the validated State and Trait Anxiety Inventory for adults.[24] Further details are provided in the online-only Data Supplement (Methods – survey instruments).

Follow-Up

Three and 6 months after disclosure of CHD risk, participants returned to undergo assessment of fasting plasma lipid levels and to fill out study questionnaires. Recruitment started in October 2013 and ended in May 2014. Acquisition of visit 4 data was completed in December 2014.

Statistical Methods

All study data were analyzed using R software (version 3.1.2). Data analysts were blinded to allocation. Descriptive data were provided for all measures, using frequencies (%) for categorical variables and mean (±standard deviation) for continuous variables. Simple group comparisons were made using either the χ^2 or Fisher exact test as appropriate for binary variables and *t* tests for continuous outcomes such as LDL-C levels.

We analyzed the primary outcome – LDL-C levels at 6 months after CHD risk disclosure – in the randomized treatment groups, CRS and $^{+}$GRS. We conducted prespecified secondary analyses comparing 3 groups: CRS, participants randomly assigned to $^{+}$GRS with a GRS ≥1.1 (high GRS, $^{+}$H-GRS), and participants randomly assigned to $^{+}$GRS with a GRS <1.1 (average/low GRS, $^{+}$L-GRS). Because overall hypothesis testing was based on the original 2 randomized groups, these secondary between-group analyses were each conducted at the nominal 0.05 level of significance without correction for multiple comparisons. We also compared change in LDL-C levels from baseline in the study groups. Finally, because LDL-C levels were measured at 3 and 6 months, we assessed the between-group difference in the slope of LDL-C after randomization, in a mixed-effects model with uncorrelated random effects for sample intercepts and the effect of time.

Table 1. Participant Characteristics (n=203).

	CRS n=100	+GRS n=103
Age, y	59.4±5.3	59.4±4.9
Male sex, n (%)	49 (49.0)	48 (46.6)
Ever smoker, n (%)	41 (41.0)	32 (31.1)
Family history of CHD, n (%)	30 (30.0)	25 (24.3)
Body mass index, kg/m^2	30.5±7.0	30.2±6.1
Systolic blood pressure, mm Hg	130.1±14.2	131.9±17.6
Total cholesterol, mg/dL	200.8±30.2	203.3±27.6
LDL-C, mg/dL	118.8±23.9	119.8±26.4
HDL-C, mg/dL	55.0±15.6	56.4±16.8
Triglycerides, mg/dL	134.1±70.2	132.7±78.8
College education or higher, n (%)	67 (67.0)	58 (56.3)
GRS	1.11±0.31	1.14±0.29
CRS, 10-y probability of CHD, %	8.48±3.76	8.56±4.47
Dietary fat intake score*	34±2.6	33.6±2.4
Physical activity score†	4.68±1.43	4.87±1.57
Anxiety trait score‡	31.1±7.8	30.9±7.6
Anxiety state score	27.9±7.5	28.8±9

Continuous traits are presented as mean±standard deviation and categorical variables are presented as percentage. CHD indicates coronary heart disease; CRS, conventional risk score; GRS, genetic risk score; +GRS, combined conventional and genetic risk score; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. To convert total, LDL-C, and HDL-C to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113.

*Dietary fat intake score is based on the percentage energy from fat (PFat) screener.[22]

† Physical activity score is based on the assessment of physical activity (TAPA) questionnaire.[23]

‡ Anxiety scores are based on the State and Trait Anxiety Inventory for adults (STAI).[24]

We included dietary fat intake, physical activity, and statin use, as well, in models of the primary LDL-C end point to determine their influence on LDL-C levels. We also assessed whether incorporation of a GRS into conventional risk estimates led to an increase in anxiety levels. Family history of CHD was also analyzed as a predictor of LDL-C levels at follow-up and the secondary end points, independent of randomized group status.

Results

The study flow from initial screening of Mayo BioBank participants through recruitment and the final study cohort is summarized in Figure 1. Characteristics of the participants randomly assigned (n=203) are summarized in Table 1. No significant differences were present between the study groups for any of the characteristics listed. Baseline characteristics of +H-GRS and +L-GRS participants are provided in Table III in the online-only Data Supplement.

At the end of the study period, the LDL-C in the +GRS group was 9.4 mg/dL lower than in the CRS group (96.5±32.7 versus 105.9±33.3 mg/dL; P=0.04). +H-GRS participants had a 13.6 mg/dL lower LDL-C level (92.3±32.9 mg/dL) than CRS participants (P=0.02) and a 8.6 mg/dL lower LDL-C than +L-GRS participants (100.9±32.2 mg/dL; P=0.18; Table 2 and Figure 2). When the values at 6 months after CHD disclosure were compared with baseline values, the mean LDL-C change was –13.6±31.3 mg/dL in the CRS group versus –23.3±33.6 mg/dL in the +GRS group (P=0.03). The overall downward longitudinal trend in LDL-C was significantly greater in +GRS participants than in CRS participants (P=0.04). The downward trend in LDL-C in +H-GRS participants was significantly greater than in CRS participants (P=0.007) and tended to be greater than in the +L-GRS participants (P=0.07). The estimated slopes (±standard error) representative of LDL-C change per 30 days were –1.8±0.4 mg/dL and –3.0±0.4 mg/dL in the CRS and +GRS groups, respectively (Figure 2). Table IV in the online-only Data Supplement summarizes results of expanded LDL-C comparisons between the study groups.

No significant differences in dietary fat intake, physical activity levels, and anxiety levels were observed between CRS and +GRS participants, 6 months after CHD risk disclosure (Figure 3 and Tables V and VI in the online-only Data Supplement). Statin use at the final visit was significantly higher in the +GRS group than in the CRS group (39.2% versus 21.9%; P<0.01; Table 2). A higher proportion of +H-GRS participants (49.1%) were on statins than CRS (21.9%, P<0.01) and +L-GRS (28.6%, P=0.03) participants. After adjustment for statin initiation, group randomization was not significantly associated with the end-of-study LDL-C levels (P=0.74).

Family history of CHD was considered as a potential predictor variable of LDL-C levels. The mean GRS tended to be higher in patients with a family history of CHD than those without such history (1.19 versus 1.10, P=0.09). Family history was not associated with the 6-month LDL-C by itself (P=0.48) nor in combination with group randomization (P=0.40). However, family history was a borderline significant predictor of statin use at 6 months, independent of allocation to +GRS or CRS (odds ratio, 1.92; 95% confidence interval, 0.97–3.79; P=0.06). An interaction term between family history and group allocation was not significant (P=0.40).

Discussion

Our goal in this study was to investigate whether the disclosure of genetic risk of CHD influences LDL-C levels, as well as lifestyle behavior and shared decision making regarding statin. We included individuals at intermediate risk for CHD because decisions regarding statin initiation are often complex and motivating patients to change diet and lifestyle can be challenging. Disclosing CHD risk estimates that included genetic risk information in addition to conventional risk factors led to lower LDL-C levels 6 months after disclosure of risk. +H-GRS participants had significantly lower LDL-C levels than CRS participants and tended to have lower LDL-C levels than +L-GRS participants. The differences in LDL-C levels were attributable to a higher proportion of participants in the +GRS arm being started on a statin medication. Disclosure of a GRS for CHD did not lead to significant differences in dietary fat intake, physical activity, or anxiety levels at the end of the study.

The lower LDL-C level in patients allocated to receive +GRS was attributable to a higher proportion starting statin therapy after shared decision making with a physician. Recent guidelines[15] emphasize the need for shared decision making

Table 2. Baseline and Follow-Up LDL-C Levels and Statin Use

Group	Baseline	3 mo After CHD Risk Disclosure	6 mo After CHD Risk Disclosure
LDL-C, mg/dL			
CRS	118.79 (23.94)	100.75 (32.69)	105.86 (33.31)
+GRS	119.77 (26.39)	93.52 (31.10)	96.48 (32.71)*
+L-GRS	119.54 (25.75)	98.68 (28.65)	100.92 (32.24)
+H-GRS	119.98 (27.23)	88.66 (32.78)	92.28 (32.90)†
Statin use, n (%)			
CRS	0 (0)	23 (23.7)	21 (21.9)
+GRS	0 (0)	41 (40.2)	40 (39.2)*
+L-GRS	0 (0)	14 (28.6)	14 (28.6)
+H-GRS	0 (0)	27 (50.9)	26 (49.1)†,‡

LDL-C levels are presented as mean (SD). To convert LDL-C to mmol/L, multiply by 0.0259. CHD indicates coronary heart disease; CRS, conventional risk score; +GRS, combined conventional and genetic risk score; +H-GRS, participants randomly assigned to +GRS with a GRS ≥1.1; +L-GRS, participants randomly assigned to +GRS with a GRS <1.1; and LDL-C: low-density lipoprotein cholesterol.

*+GRS≠CRS at $P<0.05$.

†+H-GRS≠CRS at $P<0.05$.

‡+H-GRS≠+L-GRS at $P<0.05$.

when considering statin medications for lowering CHD risk. We modified an existing decision aid[14] to incorporate genetic risk information and facilitate shared decision making in the setting of disclosure of CHD genetic risk. Such visual depictions help patients, as well as physicians, to better comprehend statistical probabilities related to risk of disease.[25] Armed with appropriate resources and a genomic decision aid embedded in the EHR, study participants and nongeneticist physicians were able to use genetic risk information in the shared decision-making process.

Participants in the +GRS group were more likely to receive statins than the CRS group. Increased statin prescription in the +H-GRS group was likely attributable to the increase in overall estimated CHD risk by at least 10% after including the GRS. Although in the +L-GRS subset the estimated CHD risk was lower, statin initiation was not significantly different than in the CRS group. One possibility is that clinicians may not be comfortable with downgrading risk estimated based on conventional risk factors. However, the shared medical decision process that was used in the trial ensured that the decision to start statins was made taking both physician and participant preferences into account.

We previously reported that +GRS participants in this trial had higher perceived personal control and genetic counseling satisfaction than those who received conventional risk factor information.[26] However, disclosure of CHD genetic risk did not lead to changes in dietary fat intake and physical activity levels. McBride et al[27] demonstrated that disclosure of

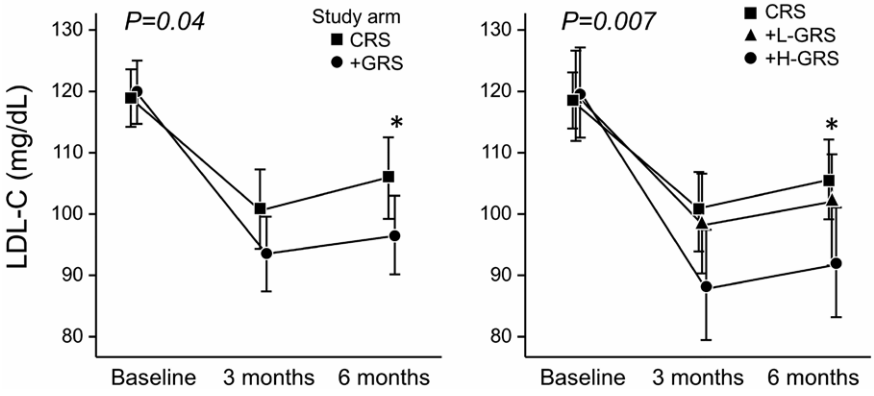

Figure 2. Change in LDL-C levels from baseline over the follow-up period overall and in categories of GRS. LDL-C levels at 6 months postdisclosure were lower in +GRS participants than in CRS participants. The overall downward longitudinal trend in LDL-C was significantly greater in +GRS participants than CRS participants. LDL-C levels at 6 months postdisclosure were lower in +H-GRS participants than in CRS participants. The downward trend in LDL-C was significantly greater in +H-GRS participants than in CRS participants. There was a trend toward a greater reduction in LDL-C levels in +H-GRS versus +L-GRS. *denotes 6-month statistical significance at 0.05 level. CRS indicates conventional risk score; GRS, genetic risk score; +GRS, combined conventional and genetic risk score; +H-GRS, high genetic risk score; +L-GRS, average/low genetic risk score; and LDL-C, low-density lipoprotein cholesterol.

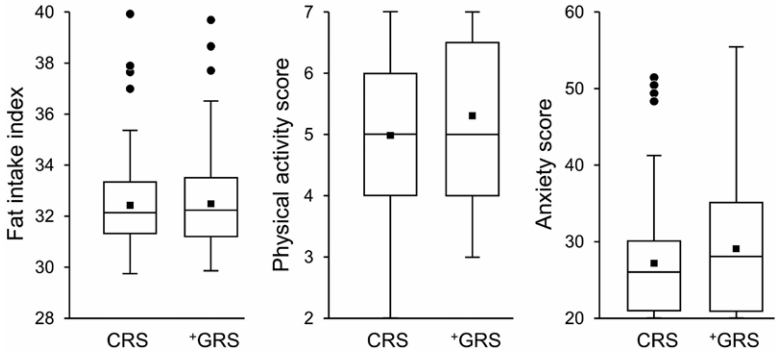

Figure 3. Dietary fat intake, physical activity, and anxiety levels in the study groups. There was no difference between CRS and +GRS group in either dietary fat intake, physical activity, or anxiety levels 6 months postdisclosure. Dietary fat intake scores ranged between 0 (no fat intake) to 110 (indicative of very high dietary fat intake). Physical activity scores ranged between 7 (active) and 1 (sedentary). Anxiety scores ranged between 20 (least anxious) up to 80 (highly anxious). CRS indicates conventional risk score; and +GRS, combined conventional and genetic risk score.

genetic risk for cancer predisposition did not affect smoking cessation rates. Similarly, in volunteers who underwent direct-to-consumer genomewide testing for various medical conditions, there were no significant changes in participants' dietary or physical activity behaviors.[28] Our results highlight that prompting patients to adopt and sustain lifestyle changes remains challenging despite the provision of personalized disease risk estimates.

There is concern that disclosure of genetic risk for a disease may increase anxiety levels in patients with high genetic risk and induce a sense of invulnerability in those at low genetic risk. We found that disclosure of CHD genetic risk was not associated with greater anxiety levels consistent with previous studies of disclosing genetic risk of common disorders.[29,30] Also, we did not observe increased dietary fat intake or decreased physical activity levels in those at low genetic risk in comparison with the other study groups (Tables V and VI in the online-only Data Supplement).

To minimize potential confounding attributable to the presence of a family history of CHD, we randomly assigned patients to study arms based on such history. The GRS tended to be higher in patients with a family history, but this difference was not statistically significant, suggesting that family history and GRS may provide additive information about CHD risk. Family history was not associated with postrandomization LDL-C levels, although it tended to be associated with greater statin use at the end of the study period.

Our study has implications for the prevention of CHD, which often manifests as sudden death or myocardial infarction. Several circulating biomarkers have been proposed for improving risk stratification for adverse CHD events, but most are associated to a varying degree with known risk factors.[31] Although the genetic susceptibility variants measured in this study have modest effects, these were not associated with established factors (GRS and CRS were not correlated in our study) and therefore provide an orthogonal means of risk assessment. As genome sequencing becomes more common, it will be possible to estimate a GRS for common diseases such as CHD and further refine risk estimates and inform targeted therapy. However, large clinical trials will be needed to investigate the effects of such an approach on reducing adverse CHD outcomes and on healthcare costs and use.

Our study demonstrates that genetic risk information for a common disease can be incorporated into the EHR to enable shared decision making regarding drug therapy. Blood draws and genotyping were done in a Clinical Laboratory Improvement Amendments environment and results were placed in the EHR. Several limitations deserve mention. We did not prospectively validate the GRS; however, in a recent study,[8] a GRS based on 27 genetic variants was independently associated with adverse cardiovascular outcomes and response to statin therapy.[8] CHD risk scores are not static, and newly discovered variants may need to be included.[32] The study sample size was relatively small and the intervention was not blinded. We were not able to use the risk calculator and categories recommended in the latest ACC/AHA guidelines which appeared after the study began. Of note, the majority (82%) of participants were appropriately initiated on statins based on these guidelines, ie, they had a 10-year risk of ≥7.5% (Table VII in the online-only Data Supplement). The short-term and modest reduction in LDL-C levels observed in this study may not ultimately translate to improved outcomes, and large clinical trials will be needed to prove the clinical utility of a GRS for CHD. Additional studies are needed to study the effects of disclosure of genetic risk for CHD in various ethnic groups and in the real-world setting of primary care.

Conclusions

We demonstrate that genetic risk information for a common disease can be effectively incorporated into the EHR and used at the point of care to guide therapy. Individuals who received a GRS in addition to a conventional risk estimate for CHD had lower LDL-C levels 6 months after disclosure than participants who received a CRS alone. Shared decision making after CHD risk disclosure led to a greater proportion of patients who received a GRS being initiated on a statin medication. Disclosure of a GRS did not lead to significant changes in dietary fat intake, physical activity levels, or anxiety. The lowering of LDL-C was greatest in individuals with a high GRS for CHD in comparison with participants who did not receive a GRS.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Genomewide association studies have identified multiple genetic susceptibility loci for coronary heart disease (CHD), and several studies have reported that a genetic risk score (GRS) based on such loci is associated with adverse CHD events. However, no prospective studies have investigated whether knowledge of genetic risk for CHD influences health-related outcomes. We conducted a randomized clinical trial to assess the effect of disclosure of a GRS for CHD on low-density lipoprotein cholesterol (LDL-C) levels. Risk disclosure (by a genetic counselor) and shared decision making regarding statin therapy (with a physician) were facilitated by a decision aid that was integrated in the electronic health record and modified to include genetic risk information. Disclosure of a CHD risk estimate that included GRS in addition to conventional risk factors led to lower LDL-C levels 6 months after disclosure of risk, in comparison with the disclosure of a conventional risk estimate alone. The differences in LDL-C levels were attributable to a higher proportion of participants in the GRS arm being started on a statin medication. Disclosure of a GRS did not lead to significant differences in dietary fat intake, physical activity, or anxiety levels. Our study demonstrates that genetic risk information for CHD can be used at the point of care to enable shared decision making regarding statin therapy with a subsequent change in LDL-C levels. The reduction in LDL-C levels observed in this study was modest, and large clinical trials will be needed to prove the clinical utility of a GRS for CHD.

Incorporating a Genetic Risk Score Into Coronary Heart Disease Risk Estimates: Effect on Low-Density Lipoprotein Cholesterol Levels (the MI-GENES Clinical Trial)

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Supplemental Material

Incorporating a Genetic Risk Score into Coronary Heart Disease Risk Estimates: Effect on LDL Cholesterol Levels (the MIGENES Clinical Trial)

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Methods

Screening Genotyping

Of the 46 single-nucleotide polymorphisms (SNPs) associated with coronary heart disease (CHD) in genome-wide association studies, 29 are not associated with BP or lipid levels.[1] DNA from eligible Mayo Clinic BioBank participants was genotyped for 28 of the 29 CHD susceptibility SNPs on the Veracode Bead Express (Illumina®, San Diego, CA); one SNP (rs3825807) could not be genotyped for technical reasons. Genotype calls were made with Illumina's GenomeStudio software (http://www.illumina.com), and samples with >98% call rates across all SNPs on the array were considered for analysis. Samples with lower call rates were rerun as necessary. A genetic risk score (GRS) for each individual was calculated as previously described, taking into account the average genetic risk in the population.[2] In brief, we assumed an additive genetic model in which the genotypes are coded '0' for non-risk allele homozygotes, '1' for heterozygotes, and '2' for risk-allele homozygotes. A weighted GRS was calculated by multiplying the logarithm of odds ratio for a particular SNP by 0, 1, or 2 according to the number of risk alleles carried by each person. We used a GRS of ≥1.1, i.e., a 10% or greater increase in risk for CHD, to classify individuals as having 'high' GRS. Those with a GRS of <1.1 were classified as having average/low GRS. SNPs genotyped for GRS are listed in Table 1 in the online-only data supplement. Characteristics of the 968 individuals who comprised the recruitment pool for the study are summarized in Table 2 in the online-only data supplement. Screening genotyping was performed to facilitate goal recruitment of 100 participants with high GRS and 100 others with average/low GRS.

CLIA Genotyping and Calculation of GRS

After informed consent and enrollment in the study, study participants underwent baseline blood lipid testing as well as DNA testing in a CLIA-approved laboratory. Twenty mL of blood were drawn by venipuncture and DNA was extracted in a CLIA-certified laboratory using standard procedures. All patients underwent genotyping of the 28 CHD susceptibility SNPs using the TaqMan® procedure (Roche Molecular Diagnostics, Branchburg, NJ). The list of the 28 susceptibility SNPs and the associated genes, if known, is summarized in Table 1 in the online-only data supplement and is the same list that was used for screening genotyping. A GRS was calculated as described previously[2] and the conventional risk score was then multiplied by the genetic risk score to generate a genotype-informed probability of adverse CHD events over the next 10 years ($^{+}$GRS).

Methods

Genomic Decision Aid and Integration into the Electronic Health Record

The generic disease management system (GDMS), developed by the Mayo Clinic in collaboration with VitalHealth software, is a web-based guideline reminder system used at the point-of-care at Mayo Clinic Rochester. GDMS is integrated into the Mayo EHR by means of a web viewer system named "Synthesis", and assists with guideline-compliance and improvement of quality metrics.[3] GDMS pulls relevant medical information from the EHR such as age, sex, and other CHD risk factors in an automated fashion to estimate the patient's 10-year probability of CHD based on CRS.[3] In order to incorporate GRS into CRS for the genetics-informed CHD risk ($^{+}$GRS), GDMS was modified to deliver a web link to the genomic decision aid tool. When the link is clicked, GDMS transmits pertinent risk factors and the GRS to the online tool via a secure link without any patient identifiers (online-only data supplement Figure 1).

The Statin Choice decision aid was originally developed to disclose CHD risk and help patients as well as clinicians review the benefits and downsides of taking a statin medication to reduce CHD risk.[4, 5] The tool displays the 10-year probability of CHD based on CRS in addition to the absolute risk reduction with use of statin drugs, and the associated costs/ side effects. The patient and clinician navigate through pictograms that display the 10-year probability of CHD as well as the potential benefit of using statin medications. These pictograms display the number affected by CHD among 100 people with a risk profile similar to that of the patient. The original Statin Choice decision aid has been evaluated previously in three randomized controlled trials,[5-7] and is used at time of statin initiation at Mayo Clinic. It can be freely accessed online at http://statindecisionaid.mayoclinic.org.

In order to implement the GRS into CRS for the genetics-informed risk ($^{+}$GRS), the Statin Choice decision aid was modified to include a variable for GRS for incorporation into the 10-year conventional risk score (online-only data supplement Figure 2). A feature was added to the tool enabling the physician as well as the patient to visualize the effect of implementing GRS into CRS (online-only data supplement Figure 3). Afterwards, the provider can discuss the benefits of starting standard vs. high dose statins as well as potential side effects (online-only data supplement Figure 4). The tool was also equipped with a report generating function and a frequently asked questions page that includes additional information about GRS. The genomic decision aid can be accessed freely online but use is restricted to research purposes: http://migenesstudy.mayoclinic.org; password: "migenes".

Methods

Disclosure of CHD Risk and Shared Decision Making Regarding Statin Therapy

The CHD risk estimate was disclosed by the genetic counselor during a 30-min semi-scripted session. Patients randomized to $^{+}$GRS were shown a pictograph that incorporated the revised 10-year CHD risk based on the genotypes of the 28 CHD susceptibility SNPs. The control group was shown a pictograph based on the CRS. The pictograph depicted 100 people "like the participant" and indicated how many in the next 10 years could be expected to experience an adverse CHD event and how many would not. The genetic counselor helped participants interpret and understand their results, highlighting the probabilistic nature of the genetic testing and that lifestyle factors such as diet, exercise, and smoking are major risk factors for developing CHD. The counselor encouraged participants to sign an action plan for behavioral change that included increased physical activity and reduced dietary fat intake and smoking cessation if the participant was a smoker. Participants were provided with a *Frequently Asked Questions* sheet that reiterated the key points conveyed by the genetic counselor at the visit.

Following the visit with the genetic counselor, each patient saw a physician in the preventive cardiology clinic. The physicians had undergone a training session in the use of the Statin Choice decision aid that was modified to incorporate genotype-informed estimate of CHD risk (migenesstudy.mayoclinic.org). During the patient-physician encounter the focus was on shared decision making regarding the need for statin therapy. Consistency of the disclosure process was assured by following a checklist maintained by the study coordinator for both study arms and by review of videotaped encounters.

Survey instruments

Dietary fat intake

The validated percentage energy from fat (PFat) screener was adapted to estimate changes in fat consumption following CHD risk disclosure.[8] Intake proportions of age- and gender-specific portion sizes for fatty foods were determined in order to estimate individuals' percentage energy from fat. Five types of fatty foods were assessed in five questions each with 9 options ranging from "never" to "2 or more times per day". Participant responses were scored by first converting the reported categorical frequency (e.g., "1 time per day") to the number of times each type of fatty food was consumed per day. This frequency was then multiplied by the participant's age- and gender-specific portion size for each type of fatty food, estimated from the US Department of Agriculture's 1994-96 Continuing Survey of Food Intakes by Individuals.[9] Regression coefficients were then applied to the multiplication product for each food item, using estimated regression coefficients for fatty foods (the dependent variables) as predictors of sex-specific percentage energy gained from fat. Thus, the five reported average proportions per day were then combined as a type of average weighted by the fat estimated within each type of food. The resulting formula (essentially a linear equation) included more than five questions and a sex-dependent constant with maximum and minimum possible scores of 0-110, respectively. The average proportions for the ten additional unused types of intake of fatty foods from the validated survey were given a score of 0, without applying the corresponding constant for unused questions. The survey used to estimate fat intake is listed on page 7 of this online-only data supplement.

Physical activity and exercise

The validated telephonic assessment of physical activity (TAPA) questionnaire was adapted to assess changes in physical activity.[10] Patients' report of light, moderate, and vigorous activity over the course of one week were collated. Ten questions with "Yes" or "No" responses corresponding to eight levels of exercise produced maximum and minimum scores of 7 "active" and 0 "sedentary", respectively. A higher score indicated a greater level of physical activity. The survey used to estimate fat intake is listed on page 8 of this online-only data supplement.

Anxiety

Anxiety was measured at baseline and follow up using the validated State and Trait Anxiety Inventory for adults (STAI).[11] STAI uses two sets of twenty questions each (for a total of forty questions with four options each) subcategorized according to current symptoms "right now" and a general propensity towards anxiety "generally". A higher score (out of 80) for either subcategory indicated greater levels of anxiety, with the minimum possible score of 20 for each subcategory and a maximum score of 80 representative of highest anxiety levels. The 2 subset scores were then averaged to a single score ranges from 20-80 and was used for analyses. The survey used to estimate fat intake is listed on pages 9 and 10 of this online-only data supplement.

Diet: Fat intake

Think about your eating habits over the past 3 months. About how often did you eat or drink each of the following foods? Remember breakfast, lunch, dinner, snacks, and eating out.

	Never	Less than once per month	1-2 times per month	3-4 times per month	1-2 times per week	3-4 times per week	5-6 times per week	1 time per day	2 or more times per day
1. Margarine or butter	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9
2. Mayonnaise, regular	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9
3. Sausage or bacon, regular	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9
4. Cheese or cheese spread, regular	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9
5. Beef or pork hot dogs, regular	☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9

Physical activity

Read the following statement about activities in the last 3 months and indicate whether they describe you. Do the best you can do answer using the yes/no format.

1. I rarely or never do any physical activities. ☐ Yes ☐ No

The next statements are about three types of activities: light, moderate, and vigorous. Light activities are activities when your heart beats only slightly faster than normal and you can still talk and sing during them. Some examples of light activities are walking leisurely, light vacuuming, light yard work, or light exercise such as stretching.

2. I do some light physical activities, but not every week. ☐ Yes ☐ No

3. I do some light physical activity every week. ☐ Yes ☐ No

Next are moderate activities. Moderate activities are activities when your heart beats faster than normal. You can still talk but not sing during such activities. Some examples of moderate activities are fast walking, aerobics class, strength training, or swimming gently.

4. I do some moderate physical activities, but not every week. ☐ Yes ☐ No

5. I do some moderate physical activities every week, but less than 30 minutes per day. ☐ Yes ☐ No

6. I do some moderate physical activities every week, but less than 5 days per week. ☐ Yes ☐ No

7. I do 30 minutes or more per day of moderate physical activities, 5 or more days per week. ☐ Yes ☐ No

The next three statements are about vigorous activities. Vigorous activities are activities when your heart rate increases a lot. You typically can't talk or your talking is broken up by large breaths. Some examples of vigorous activities are jogging, running, using a stair machine, or playing tennis, racquetball, or badminton.

8. I do some vigorous physical activities every week, but less than 20 minutes per day. ☐ Yes ☐ No

9. I do some vigorous physical activities every week, but less than 3 days per week. ☐ Yes ☐ No

10. I do 20 minutes or more per day of vigorous physical activities, 3 or more days per week. ☐ Yes ☐ No

State-Trait Anxiety Inventory

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel ***right now, that is, at this moment.*** There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

Y1	Not at all	Somewhat	Moderately so	Very much so
1. I feel calm	☐1	☐2	☐3	☐4
2. I feel secure	☐1	☐2	☐3	☐4
3. I am tense	☐1	☐2	☐3	☐4
4. I feel strained	☐1	☐2	☐3	☐4
5. I feel at ease	☐1	☐2	☐3	☐4
6. I feel upset	☐1	☐2	☐3	☐4
7. I am presently worrying over possible misfortunes	☐1	☐2	☐3	☐4
8. I feel satisfied	☐1	☐2	☐3	☐4
9. I feel tightened	☐1	☐2	☐3	☐4
10. I feel comfortable	☐1	☐2	☐3	☐4
11. I feel self-confident	☐1	☐2	☐3	☐4
12. I feel nervous	☐1	☐2	☐3	☐4
13. I am jittery	☐1	☐2	☐3	☐4
14. I feel indecisive	☐1	☐2	☐3	☐4
15. I am relaxed	☐1	☐2	☐3	☐4
16. I feel content	☐1	☐2	☐3	☐4
17. I am worried	☐1	☐2	☐3	☐4
18. I feel confused	☐1	☐2	☐3	☐4
19. I feel steady	☐1	☐2	☐3	☐4
20. I feel pleasant	☐1	☐2	☐3	☐4

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you ***generally*** feel.

Y2	Not at all	Somewhat	Moderately so	Very much so
21. I feel pleasant	☐1	☐2	☐3	☐4
22. I feel nervous and restless	☐1	☐2	☐3	☐4
23. I feel satisfied with myself	☐1	☐2	☐3	☐4
24. I wish I could be as happy as others seem to be	☐1	☐2	☐3	☐4
25. I feel like a failure	☐1	☐2	☐3	☐4
26. I feel rested	☐1	☐2	☐3	☐4
27. I am "calm, cool, and collected"	☐1	☐2	☐3	☐4
28. I feel that difficulties are piling up so that I cannot overcome them	☐1	☐2	☐3	☐4
29. I worry too much over something that really doesn't matter	☐1	☐2	☐3	☐4
30. I am happy	☐1	☐2	☐3	☐4
31. I feel disturbing thoughts	☐1	☐2	☐3	☐4
32. I lack self confidence	☐1	☐2	☐3	☐4
33. I feel secure	☐1	☐2	☐3	☐4
34. I make decisions easily	☐1	☐2	☐3	☐4
35. I feel inadequate	☐1	☐2	☐3	☐4
36. I am content	☐1	☐2	☐3	☐4
37. Some unimportant thought runs through my mind and bothers me	☐1	☐2	☐3	☐4
38. I take disappointment so keenly that I can't put them out of my mind	☐1	☐2	☐3	☐4
39. I am a steady person	☐1	☐2	☐3	☐4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	☐1	☐2	☐3	☐4

Table 1. Genetic loci associated with coronary heart disease used in genetic risk score calculation

Gene	SNP	CHR	Risk Allele	Risk Allele OR
MIA3	rs17465637	1	C	1.14
PPAP2B	rs17114036	1	A	1.11
IL6R	rs4845625	1	T	1.04
WDR12	rs6725887	2	C	1.12
ZEB2-AC074093.1	rs2252641	2	G	1.04
VAMP5-VAMP8-GGCX	rs1561198	2	A	1.05
MRAS	rs9818870	3	T	1.07
EDNRA	rs1878406	4	T	1.06
SLC22A4-SLC22A5	rs273909	5	C	1.09
TCF21	rs12190287	6	C	1.07
PHACTR1	rs9369640	6	A	1.09
KCNK5	rs10947789	6	T	1.06
PLG	rs4252120	6	T	1.06
ANKS1A	rs17609940	6	G	1.07
7q22 *BCAP29*	rs10953541	7	C	1.08
HDAC9	rs2023938	7	G	1.07
CDKN2BAS1	rs1333049	9	C	1.23
CXCL12	rs2047009	10	C	1.05
KIAA1462	rs2505083	10	C	1.06
PDGFD	rs974819	11	A	1.07
COL4A1-COL4A2	rs4773144	13	G	1.07
COL4A1-COL4A2	*rs9515203	13	T	1.08
FLT1	rs9319428	13	A	1.05
HHIPL1	rs2895811	14	C	1.06
RAI1-PEMT-RASD1	rs12936587	17	G	1.06
SMG6	rs216172	17	C	1.07
UBE2Z	rs46522	17	T	1.06
Gene desert (*KCNE2*)	rs9982601	21	T	1.13

CHR: Chromosome; OR: odds ratio; SNP: single-nucleotide polymorphism; *rs9515203 had an r^2 of 0.01 with rs4773144.

Table 2. Characteristics of Mayo biobank individuals comprising the recruitment pool*

	Overall	GRS ≥1.1	GRS <1.1
N	968	311	657
Age, years	57.6±5.41	57.6±5.37	57.5±5.43
Women	531 (55%)	169 (54%)	362 (55%)
CRS, %	7.98±3.16	7.89±3.13	8.02±3.18
GRS	1.00±0.28	1.33±0.20	0.85±0.16

* A total of 2026 individuals met the eligibility criteria. A random sample of 1000 individuals underwent screening genotyping of whom 968 passed quality control measures for genotyping.
CRS: conventional risk score; GRS: genetic risk score

Table 3. Baseline characteristics of $^{+}$H-GRS and $^{+}$L-GRS participants

	$^{+}$L-GRS n=50	$^{+}$H-GRS n=53
Age, years	59.7±4.9	59.1±4.9
Male sex, n (%)	24 (48.0%)	24 (45.3%)
Ever smoker, n (%)	15 (30.0%)	17 (32.1%)
Family history of CHD, n (%)	8 (16.0%)	17 (32.1%)
BMI, kg/m2	29.3±5.5	31.0±6.5
SBP, mmHg	129.5±14.0	134.1±20.3
*Total cholesterol, mg/dL	203.5±27.5	203.0±27.9
LDL-C, mg/dL	119.5±25.8	120.0±27.2
HDL-C, mg/dL	56.9±19.5	56.0±13.9
Triglycerides, mg/dL	135.5±80.6	130.1±77.6
College education or higher, n (%)	30 (60.0%)	28 (52.8%)
Physical activity score	4.96±1.67	4.79±1.49
Dietary fat intake score	33.7±2.4	33.5±2.4
Anxiety state score	27.5±8.6	30.0±9.3
Anxiety trait score	31.1±8.0	30.7±7.3
GRS	0.89±0.13	1.37±0.20
CRS	8.50±4.17	8.62±4.77

BMI: body mass index; CHD: coronary heart disease; CRS: conventional risk score; GRS: genetic risk score; $^{+}$GRS: combined conventional and genetic risk score arm; HDL-C: high-density lipoprotein cholesterol; $^{+}$H-GRS: participants randomized to $^{+}$GRS with a GRS ≥1.1; $^{+}$L-GRS: participants randomized to $^{+}$GRS with a GRS <1.1; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure

* To convert LDL and HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, by 0.0113.

Table 4. A comparison of changes in LDL-C levels from baseline to end of study period (6 months after CHD risk disclosure) in the study groups

Outcome	Group	Mean (95% CI)	*P*
***ΔLDL-C** mg/dL	$^{+}$GRS vs. CRS	-9.74 (-18.76,-0.71)	0.03
	$^{+}$H-GRS vs. CRS	-14.14 (-25.12,-3.16)	0.01
	$^{+}$L-GRS vs. CRS	-5.06 (-15.86,5.73)	0.36
	$^{+}$H-GRS vs. $^{+}$L-GRS	-9.08 (-22.17,4.02)	0.17

CRS: conventional risk score; $^{+}$GRS: combined conventional and genetic risk score; $^{+}$H-GRS: participants randomized to $^{+}$GRS with a GRS ≥1.1; $^{+}$L-GRS: participants randomized to $^{+}$GRS with a GRS <1.1; LDL-C: low-density lipoprotein cholesterol

***** To convert LDL-C to mmol/L, multiply by 0.0259.

Table 5. Longitudinal changes in fat intake, physical activity and anxiety levels

Outcome	Group	Baseline	3 Months after CHD risk disclosure	6 Months later after CHD risk disclosure
Dietary Fat Intake	CRS	33.99 (2.63)	32.97 (1.84)	32.57 (1.69)
	$^{+}$GRS	33.60 (2.42)	32.53 (1.88)	32.56 (1.83)
	$^{+}$L-GRS	33.69 (2.44)	32.96 (2.22)	32.86 (2.01)
	$^{+}$H-GRS	33.51 (2.42)	32.12 (1.40)	32.27 (1.61)
Physical Activity Score	CRS	4.68 (1.43)	5.08 (1.27)	4.99 (1.34)
	$^{+}$GRS	4.87 (1.57)	5.31 (1.44)	5.28 (1.34)
	$^{+}$L-GRS	4.96 (1.67)	5.64 (1.45)	5.36 (1.32)
	$^{+}$H-GRS	4.79 (1.49)	5.00 (1.37)	5.21 (1.36)
Anxiety Trait	CRS	31.11 (7.81)	31.55 (8.63)	30.28 (7.82)
	$^{+}$GRS	30.89 (7.62)	30.57 (8.41)	30.63 (7.84)
	$^{+}$L-GRS	31.08 (7.97)	30.22 (8.01)	31.40 (8.83)
	$^{+}$H-GRS	30.72 (7.35)	30.90 (8.85)	29.91 (6.78)
Anxiety State	CRS	27.94 (7.51)	27.40 (7.72)	26.97 (7.08)
	$^{+}$GRS	28.78 (9.02)	27.51 (8.27)	28.56 (8.26)
	$^{+}$L-GRS	27.48 (8.58)	26.50 (6.04)	29.10 (9.19)
	$^{+}$H-GRS	30.00 (9.33)	28.48 (9.91)	28.06 (7.33)

CHD: coronary heart disease; CRS: conventional risk score; $^{+}$GRS: combined conventional and genetic risk score; $^{+}$H-GRS: participants randomized to $^{+}$GRS with a GRS ≥1.1; $^{+}$L-GRS: participants randomized to $^{+}$GRS with a GRS <1.1. Data presented as mean (SD).

Table 6. Visit 4 and study period change comparisons in dietary fat intake, physical activity score and anxiety levels following CHD risk disclosure

		*Visit 4		†Baseline to Visit 4	
Outcome	**Group**	**Mean (95% CI)**	***P***	**Mean (95% CI)**	***P***
Dietary Fat Intake	[+]GRS vs. CRS	-0.01 (-0.50,0.48)	0.96	0.39 (-0.27,1.05)	0.25
	[+]H-GRS vs. CRS	-0.30 (-0.86,0.26)	0.29	0.19 (-0.65,1.02)	0.66
	[+]L-GRS vs. CRS	0.29 (-0.33,0.91)	0.36	0.60 (-0.23,1.43)	0.16
	[+]H-GRS vs. [+]L-GRS	-0.59 (-1.30,0.12)	0.10	-0.41 (-1.25,0.42)	0.33
Physical Activity Score	[+]GRS vs. CRS	0.29 (-0.08,0.66)	0.12	0.08 (-0.30,0.46)	0.66
	[+]H-GRS vs. CRS	0.22 (-0.23,0.67)	0.35	0.09 (-0.36,0.54)	0.69
	[+]L-GRS vs. CRS	0.37 (-0.09,0.83)	0.11	0.08 (-0.39,0.54)	0.75
	[+]H-GRS vs. [+]L-GRS	-0.15 (-0.68,0.37)	0.57	0.02 (-0.54,0.57)	0.96
Anxiety Trait	[+]GRS vs. CRS	0.35 (-1.82,2.52)	0.75	0.56 (-1.04,2.17)	0.49
	[+]H-GRS vs. CRS	-0.38 (-2.89,2.14)	0.77	0.02 (-1.83,1.86)	0.99
	[+]L-GRS vs. CRS	1.12 (-1.68,3.92)	0.43	1.15 (-0.89,3.18)	0.27
	[+]H-GRS vs. [+]L-GRS	-1.49 (-4.56,1.57)	0.34	-1.13 (-3.48,1.22)	0.34
Anxiety State	[+]GRS vs. CRS	1.59 (-0.55,3.74)	0.14	0.68 (-1.52,2.89)	0.54
	[+]H-GRS vs. CRS	1.09 (-1.33,3.50)	0.37	-1.05 (-3.55,1.45)	0.41
	[+]L-GRS vs. CRS	2.13 (-0.57,4.83)	0.12	2.52 (-0.02,5.05)	0.05
	[+]H-GRS vs. [+]L-GRS	-1.04 (-4.28,2.20)	0.52	-3.56 (-7.07,-0.06)	0.05

***** Data represent mean difference (SD) of absolute scores at visit 4. † Data represent mean difference (SD) of baseline to visit 4 change. CHD: coronary heart disease; CRS: conventional risk score; [+]GRS: combined conventional and genetic risk score; [+]H-GRS: participants randomized to [+]GRS with a GRS ≥1.1; [+]L-GRS: participants randomized to [+]GRS with a GRS <1.1.

Table 7. Statin initiation stratified by CHD risk scores and study groups

	*CRS Group n=21	+GRS Group n=40	Overall n=61
CRS ≥10%	12 (57.1%)	24 (60%)	36 (59%)
ASCVD ≥7.5%	16 (76.2%)	34 (85%)	50 (82%)

*Numbers depict those who were started on statins in each study group
ASCVD: atherosclerotic vascular disease pooled cohort risk; CHD: coronary heart disease; CRS: conventional risk score based on Framingham risk score; +GRS: combined conventional and genetic risk score group

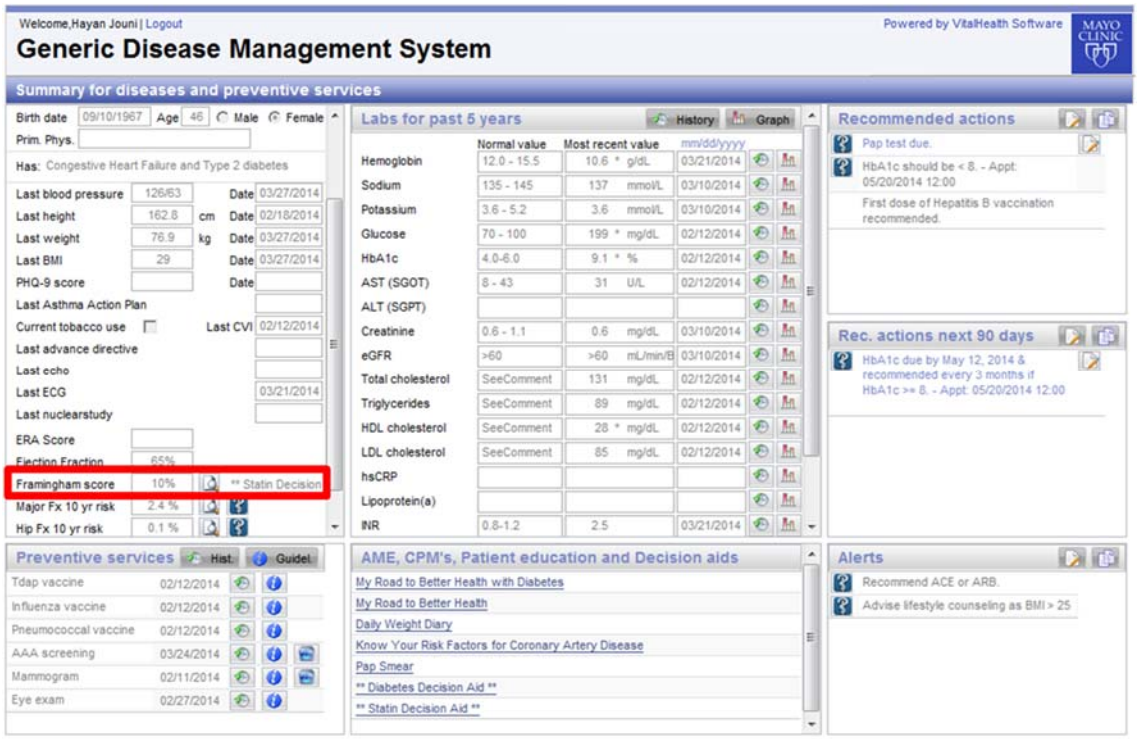

Figure 1. Generic disease management interface in the electronic health record
A sample of how the generic disease management interface appears in the electronic health record. GDMS summarizes pertinent information such as the most recent vitals, laboratory studies, Framingham risk score, and preventive measures. It also provides alerts regarding recommended actions as well as links to resources and guidelines. The box above highlights the 10-year Framingham risk score and associated link that takes the provider to the statin decision aid tool simultaneously transmitting the relevant risk factors and laboratory values.

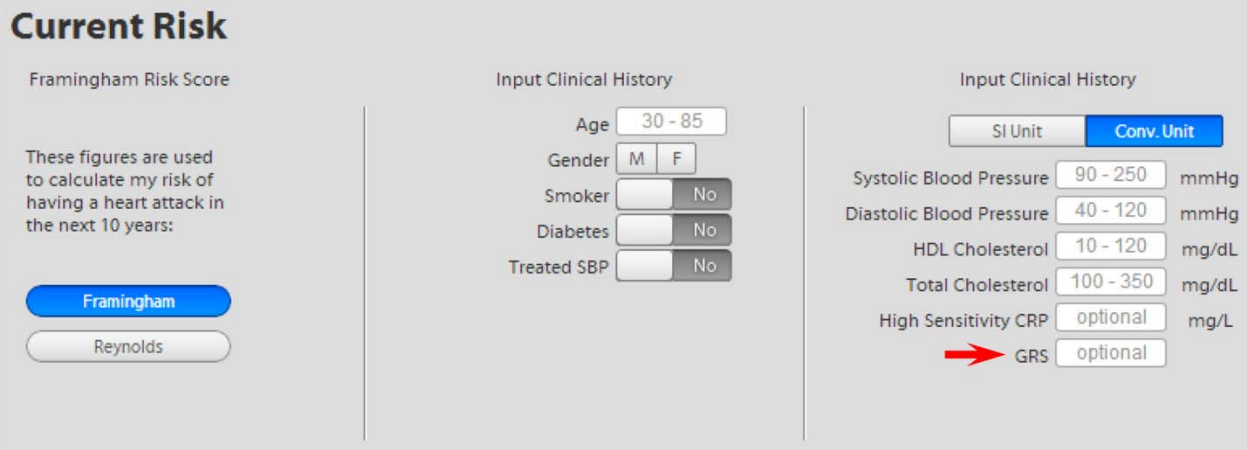

Figure 2. Data entry screen for the decision aid
The risk factor entry screen of the decision aid was modified to implement the genetic risk score (GRS) as highlighted in the figure. Implementation of GRS into the conventional risk score was embedded into the coding of the decision aid application.

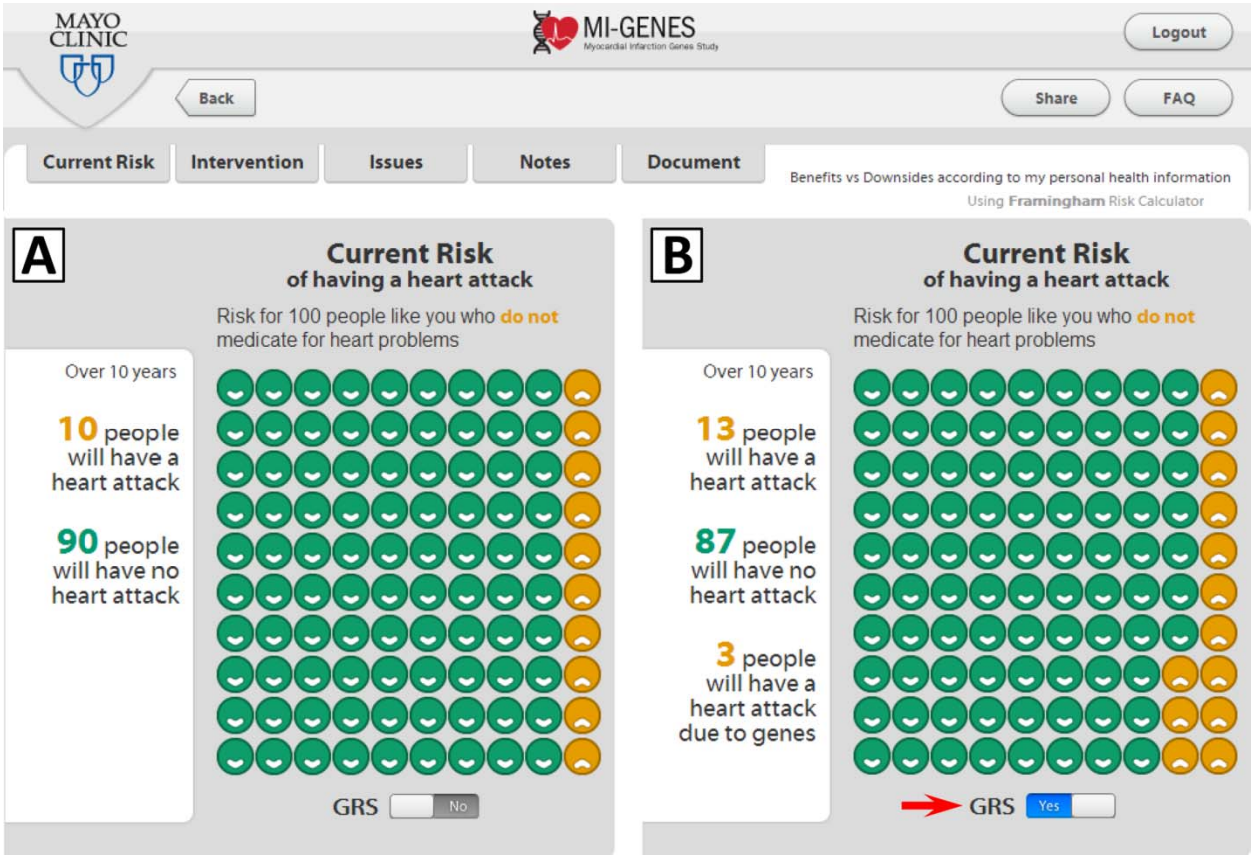

Figure 3. Disclosure of CHD risk
Disclosure of CHD risk estimates based on the conventional risk score (CRS, panel A) and after implementing the genetic risk score ($^{+}$GRS, panel B) by clicking the GRS button (arrow). In this example, the patient's 10-year CHD risk based on CRS is displayed as 10% (panel A). With a GRS of 1.3, the overall risk $^{+}$GRS increases to 13% as shown in panel B.

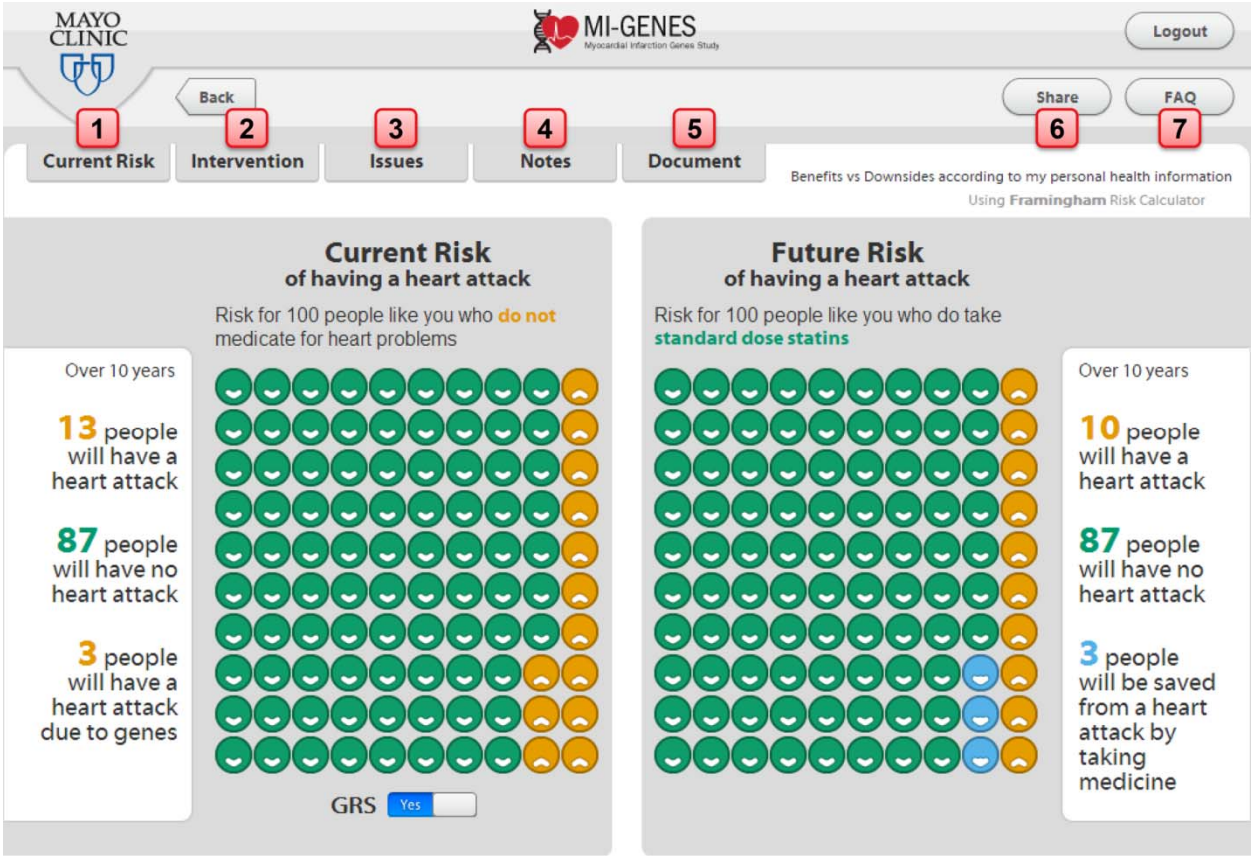

Figure 4. Summary of features included in the decision aid
Features included in this tool are: (1) CHD risk estimates which can be modified to show patients how risk can change according to their risk factors. (2) The healthcare provider can select an intervention such as standard dose versus high dose statins. (3) Statin side effects can be discussed with the patient. (4) There is also a section where the healthcare provider and patient can input notes regarding CHD risk assessment and associated interventions. (5) A complete risk assessment statement can be generated and includes the patient's estimated 10-year CHD risk. This statement can be copied and pasted into an electronic medical note if desired. (6) The displayed risk report can be exported as an e-mail or printed as a PDF document. The exported data includes the patient's CHD estimate risk and impact of using statins, without any patient identifiers. (7) A page dedicated to frequently asked questions (including questions regarding the genetic risk score for CHD and how it was calculated).

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