

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

Running title: *Kullo et al.; Effect of Disclosure of CHD Genetic Risk on LDL-C*

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Abstract

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 old, at intermediate risk for CHD, and not on statins) were randomized 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 (⁺H-GRS) or average/low (⁺L-GRS) GRS. Risk was disclosed by a genetic counselor followed by shared decision-making regarding statin therapy with a physician. We compared the primary endpoint of LDL-C levels at 6 months and assessed whether any differences were due 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 vs. 105.9±33.3 mg/dL; *P*=0.04). ⁺H-GRS participants had lower LDL-C levels (92.3±32.9 mg/dL) than CRS participants (*P*=0.02) but not ⁺L-GRS participants (100.9±32.2 mg/dL; *P*=0.18). Statins were initiated more often in the ⁺GRS group than in the CRS group (39% vs. 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 Information—ClinicalTrials.gov. Identifier: NCT01936675.

Key words: Randomized clinical trial; coronary heart disease; genetic risk disclosure; genetic risk score; genomic medicine; prevention; single-nucleotide polymorphism; statins

As genetic testing becomes widely available, its use for estimating risk of common diseases is becoming of increasing scientific and public health interest.¹ Genome wide association studies (GWAS) 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 prevention of 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 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 due to changes in dietary fat intake, physical activity levels or statin initiation. We tested the following hypotheses: 1) in patients randomized to receive ⁺GRS, LDL-C levels at the end of the study period would be lower than in participants randomized 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 randomized 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 (CLIA)-certified laboratory and results were placed into the EHR. Additionally, 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) which recruits patients from the outpatient setting at Mayo.¹⁶ We identified 2026 participants who met the following eligibility criteria: age 45-65 years, 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 (**Supplemental Table 1**) that are not associated with blood pressure or lipid levels,³ in a random sample of 1000 participants who met eligibility criteria¹⁶ (**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 non-risk 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 , i.e., a 10% or greater 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 comprised the recruitment pool for the study are summarized in **Supplemental Table 2**. 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 CLIA-certified laboratory using the TaqMan[®] procedure (Roche Molecular Diagnostics, Branchburg, NJ). A GRS was calculated¹⁷ 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 6-10 weeks later (Visit 2) once CLIA genotyping and calculation of a GRS was completed (n=207). At this visit, patients were randomized (1:1) to receive a conventional risk score (CRS, n=103) vs. a combined conventional and genetic risk score (⁺GRS, n=104). Study participants then underwent a 30-min 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 three months after Visit 3. Apart from incorporating the GRS into the CRS in one arm of the study (⁺GRS), randomized 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 5-15% 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 randomized to receive ⁺GRS would have lower LDL-C levels than patients randomized 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 randomized to receive CRS alone.

Randomization

The second study visit was scheduled 6-10 weeks after the initial visit to allow for completion of genotyping and calculation of GRS. Patients were randomized (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-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. Fidelity of the scripts was assessed by analysis of video-recorded encounters. Having one 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 aid¹⁴ 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 (**Supplemental Figures 1-4**). 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 vs. genetics-informed CHD risk was deposited in the electronic health record 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 (PFat) screener²² was adapted to estimate changes in fat consumption and the telephonic assessment of physical activity (TAPA) questionnaire²³ was adapted to assess changes in physical activity. Anxiety level was measured at baseline and follow up using the validated State and Trait Anxiety Inventory for adults (STAI).²⁴ Further details are provided in the online-only Data Supplement (Methods – survey instruments).

Follow-up

Three and six months after disclosure of CHD risk, participants returned to undergo assessment of fasting plasma lipid levels and 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 (\pm SD) for continuous variables. Simple group comparisons were made using either the Chi-Square or Fisher's 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 pre-specified secondary analyses comparing 3 groups: CRS, ⁺H-GRS, and ⁺L-GRS. Since 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, since 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.

We included dietary fat intake, physical activity as well as statin use in models of the primary LDL-C endpoint 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 endpoints, 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 randomized (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 **Supplemental Table 3**.

At the end of the study period, the LDL-C in the ⁺GRS group was 9.4 mg/dL lower than the CRS group (96.5±32.7 vs. 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 to baseline values, the mean LDL-C change was -13.6±31.3 mg/dL in the CRS group vs. -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 (±SE) 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**). **Supplemental Table 4** summarizes results of expanded LDL-C comparisons between the study groups.

No significant differences in dietary fat intake, physical activity levels and anxiety levels six months after CHD risk disclosure were observed between CRS and ⁺GRS participants (**Figure 3** and **Supplemental Tables 5 and 6**). Statin use at the final visit was significantly higher in the ⁺GRS group than in the CRS group (39.2% vs. 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 vs.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. (OR: 1.92, 95% CI=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 disclosure of genetic risk of CHD influences LDL-C levels, lifestyle behavior as well as shared decision making regarding statin therapy. We included individuals at intermediate risk for CHD as 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 six 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. The differences in LDL-C levels were due to 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 due to a higher proportion starting statin therapy after shared decision making with a physician. Recent guidelines¹⁵ emphasize the need for shared decision making when considering statin medications for lowering CHD risk. We modified an existing decision aid¹⁴ 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 non-geneticist 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 due 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 in downgrading risk estimated based on conventional risk factors. However, the shared medical decision process that was utilized 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 genetic risk for cancer predisposition did not affect smoking cessation rates. Similarly, in volunteers who underwent direct-to-consumer genome-wide 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 prior 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 compared to the other study groups (**Supplemental Tables 5 and 6**).

To minimize potential confounding due to presence of family history of CHD, we randomized patients to study arms based on such history. The GRS tended to be higher in patients with family history but this difference was not statistically significant suggesting family history and GRS may provide additive information about CHD risk. Family history was not associated with post randomization 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 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 health care costs and utilization.

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 CLIA-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 i.e., they had a 10-year risk of $\geq 7.5\%$ (**Supplemental Table 7**). 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 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 conventional risk score alone. Shared decision making after CHD risk disclosure led to a greater proportion of patients who received CHD genetic risk 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 compared to participants who did

not receive GRS.

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Conflict of Interest Disclosures: None.

References:

1. Manolio TA. Bringing genome-wide association findings into clinical use. *Nat Rev Genet.* 2013;14:549-558.
2. The Coronary Artery Disease (C4D) 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.
3. Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, Goldstein BA, Stirrups K, Konig IR, Cazier JB, Johansson A, Hall AS, Lee JY, Willer CJ, Chambers JC, Esko T, Folkersen L, Goel A, Grundberg E, Havulinna AS, Ho WK, Hopewell JC, Eriksson N, Kleber ME, Kristiansson K, Lundmark P, Lyytikainen LP, Rafelt S, Shungin D, Strawbridge RJ, Thorleifsson G, Tikkanen E, Van Zuydam N, Voight BF, Waite LL, Zhang W, Ziegler A, Absher D, Altshuler D, Balmforth AJ, Barroso I, Braund PS, Burgdorf C, Claudi-Boehm S, Cox D, Dimitriou M, Do R, Doney AS, El Mokhtari N, Eriksson P, Fischer K, Fontanillas P, Franco-Cereceda A, Gigante B, Groop L, Gustafsson S, Hager J, Hallmans G, Han BG, Hunt SE, Kang HM, Illig T, Kessler T, Knowles JW, Kolovou G, Kuusisto J, Langenberg C, Langford C, Leander K, Lokki ML, Lundmark A, McCarthy MI, Meisinger C, Melander O, Mihailov E, Maouche S, Morris AD, Muller-Nurasyid M, Nikus K, Peden JF, Rayner NW, Rasheed A, Rosinger S, Rubin D, Rumpf MP, Schafer A, Sivananthan M, Song C, Stewart AF, Tan ST, Thorgeirsson G, van der Schoot CE, Wagner PJ, Wells GA, Wild PS, Yang TP, Amouyel P, Arveiler D, Basart H, Boehnke M, Boerwinkle E, Brambilla P, Cambien F,

- Cupples AL, de Faire U, Dehghan A, Diemert P, Epstein SE, Evans A, Ferrario MM, Ferrieres J, Gauguier D, Go AS, Goodall AH, Gudnason V, Hazen SL, Holm H, Iribarren C, Jang Y, Kahonen M, Kee F, Kim HS, Klopp N, Koenig W, Kratzer W, Kuulasmaa K, Laakso M, Laaksonen R, Lind L, Ouwehand WH, Parish S, Park JE, Pedersen NL, Peters A, Quertermous T, Rader DJ, Salomaa V, Schadt E, Shah SH, Sinisalo J, Stark K, Stefansson K, Tregouet DA, Virtamo J, Wallentin L, Wareham N, Zimmermann ME, Nieminen MS, Hengstenberg C, Sandhu MS, Pastinen T, Syvanen AC, Hovingh GK, Dedoussis G, Franks PW, Lehtimaki T, Metspalu A, Zalloua PA, Siegbahn A, Schreiber S, Ripatti S, Blankenberg SS, Perola M, Clarke R, Boehm BO, O'Donnell C, Reilly MP, Marz W, Collins R, Kathiresan S, Hamsten A, Kooner JS, Thorsteinsdottir U, Danesh J, Palmer CN, Roberts R, Watkins H, Schunkert H, Samani NJ. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet.* 2013;45:25-33.
4. Thanassoulis G, Peloso GM, Pencina MJ, Hoffmann U, Fox CS, Cupples LA, Levy D, D'Agostino RB, Hwang SJ, O'Donnell CJ. A genetic risk score is associated with incident cardiovascular disease and coronary artery calcium: the Framingham Heart Study. *Circ Cardiovasc Genet.* 2012;5:113-121.
5. 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.
6. Ganna A, Magnusson PK, Pedersen NL, de Faire U, Reilly M, Arnlov J, Sundstrom J, Hamsten A, Ingelsson E. Multilocus genetic risk scores for coronary heart disease prediction. *Arterioscler Thromb Vasc Biol.* 2013;33:2267-2272.
7. Tikkanen E, Havulinna AS, Palotie A, Salomaa V, Ripatti S. Genetic risk prediction and a 2-stage risk screening strategy for coronary heart disease. *Arterioscler Thromb Vasc Biol.* 2013;33:2261-2266.
8. Mega JL, Stitzel NO, Smith JG, Chasman DI, Caulfield MJ, Devlin JJ, Nordio F, Hyde CL, Cannon CP, Sacks FM, Poulter NR, Sever PS, Ridker PM, Braunwald E, Melander O, Kathiresan S, Sabatine MS. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials. *Lancet.* 2015;385:2264-2271.
9. Morrison AC, Bare LA, Chambless LE, Ellis SG, Malloy M, Kane JP, Pankow JS, Devlin JJ, Willerson JT, Boerwinkle E. Prediction of coronary heart disease risk using a genetic risk score: The Atherosclerosis Risk in Communities Study. *Am J Epidemiol.* 2007;166:28-35.
10. Ripatti S, Tikkanen E, Orho-Melander M, Havulinna AS, Silander K, Sharma A, Guiducci C, Perola M, Jula A, Sinisalo J, Lokki ML, Nieminen MS, Melander O, Salomaa V, Peltonen L, Kathiresan S. A multilocus genetic risk score for coronary heart disease: case-control and prospective cohort analyses. *Lancet.* 2010;376:1393-1400.
11. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med.* 2015;372:793-

795.

12. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837-1847.
13. Kullo IJ, Jarvik GP, Manolio TA, Williams MS, Roden DM. Leveraging the electronic health record to implement genomic medicine. *Genet Med*. 2013;15:270-271.
14. Weymiller AJ, Montori VM, Jones LA, Gafni A, Guyatt GH, Bryant SC, Christianson TJ, Mullan RJ, Smith SA. Helping patients with type 2 diabetes mellitus make treatment decisions: statin choice randomized trial. *Arch Intern Med*. 2007;167:1076-1082.
15. Goff DC, Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Sr., Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson J, Schwartz JS, Shero ST, Smith SC, Jr., Sorlie P, Stone NJ, Wilson PW. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:S49-73.
16. Olson JE, Ryu E, Johnson KJ, Koenig BA, Maschke KJ, Morrisette JA, Liebow M, Takahashi PY, Fredericksen ZS, Sharma RG, Anderson KS, Hathcock MA, Carnahan JA, Pathak J, Lindor NM, Beebe TJ, Thibodeau SN, Cerhan JR. The Mayo Clinic Biobank: a building block for individualized medicine. *Mayo Clin Proc*. 2013;88:952-962.
17. Ding K, Bailey KR, Kullo IJ. Genotype-informed calculation of risk of coronary heart disease based on genome-wide association data linked to the electronic medical record. *BMC Cardiovasc Disord*. 2011;11:66.
18. Kullo IJ, Jouni H, Olson JE, Montori VM, Bailey KR. Design of a randomized controlled trial of disclosing genomic risk of coronary heart disease: the Myocardial Infarction Genes (MI-GENES) study. *BMC Med Genomics*. 2015;8:51.
19. 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.
20. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM, Jr. 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.
21. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975;31:103-115.
22. Thompson FE, Midthune D, Subar AF, Kipnis V, Kahle LL, Schatzkin A. Development and evaluation of a short instrument to estimate usual dietary intake of percentage energy from fat. *J*

Am Diet Assoc. 2007;107:760-767.

23. Mayer CJ, Steinman L, Williams B, Topolski TD, LoGerfo J. Developing a Telephone Assessment of Physical Activity (TAPA) questionnaire for older adults. *Prev Chronic Dis.* 2008;5:A24.

24. Spielberger C. Spielberger C. Manual for the State-Trait Anxiety Inventory, STAI (Form Y). 1983.

25. Paulos JA. *Innumeracy: mathematical illiteracy and its consequences.* New York: Hill and Wang; 1988.

26. Robinson CL, Jouni H, Kruisselbrink TM, Austin EE, Christensen KD, Green RC, Kullo IJ. Disclosing genetic risk for coronary heart disease: effects on perceived personal control and genetic counseling satisfaction. *Clin Genet.* 2016;89:251-257.

27. McBride CM, Bepler G, Lipkus IM, Lyna P, Samsa G, Albright J, Datta S, Rimer BK. Incorporating genetic susceptibility feedback into a smoking cessation program for African-American smokers with low income. *Cancer Epidemiol Biomarkers Prev.* 2002;11:521-528.

28. 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.

29. Green RC, Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Brown T, Eckert SL, Butson M, Sadovnick AD, Quaid KA, Chen C, Cook-Deegan R, Farrer LA. Disclosure of APOE genotype for risk of Alzheimer's disease. *N Engl J Med.* 2009;361:245-254.

30. Lautenbach DM, Christensen KD, Sparks JA, Green RC. Communicating genetic risk information for common disorders in the era of genomic medicine. *Annu Rev Genomics Hum Genet.* 2013;14:491-513.

31. Jonathan E, Derrick B, Emma L, Sarah P, John D, Jane A, Rory C. C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20,536 patients in the Heart Protection Study. *Lancet.* 2011;377:469-476.

32. Nikpay M, Goel A, Won HH, Hall LM, Willenborg C, Kanoni S, Saleheen D, Kyriakou T, Nelson CP, Hopewell JC, Webb TR, Zeng L, Dehghan A, Alver M, Armasu SM, Auro K, Bjornes A, Chasman DI, Chen S, Ford I, Franceschini N, Gieger C, Grace C, Gustafsson S, Huang J, Hwang SJ, Kim YK, Kleber ME, Lau KW, Lu X, Lu Y, Lyttikainen LP, Mihailov E, Morrison AC, Pervjakova N, Qu L, Rose LM, Salfati E, Saxena R, Scholz M, Smith AV, Tikkanen E, Uitterlinden A, Yang X, Zhang W, Zhao W, de Andrade M, de Vries PS, van Zuydam NR, Anand SS, Bertram L, Beutner F, Dedoussis G, Frossard P, Gauguier D, Goodall AH, Gottesman O, Haber M, Han BG, Jalilzadeh S, Kessler T, Konig IR, Lannfelt L, Lieb W, Lind L, Lindgren CM, Lokki ML, Magnusson PK, Mallick NH, Mehra N, Meitinger T, Memon FU, Morris AP, Nieminen MS, Pedersen NL, Peters A, Rallidis LS, Rasheed A, Samuel M, Shah SH, Sinisalo J, Stirrups KE, Trompet S, Wang L, Zaman KS, Ardissino D, Boerwinkle E,

Borecki IB, Bottinger EP, Buring JE, Chambers JC, Collins R, Cupples LA, Danesh J, Demuth I, Elosua R, Epstein SE, Esko T, Feitosa MF, Franco OH, Franzosi MG, Granger CB, Gu D, Gudnason V, Hall AS, Hamsten A, Harris TB, Hazen SL, Hengstenberg C, Hofman A, Ingelsson E, Iribarren C, Jukema JW, Karhunen PJ, Kim BJ, Kooner JS, Kullo IJ, Lehtimaki T, Loos RJ, Melander O, Metspalu A, Marz W, Palmer CN, Perola M, Quertermous T, Rader DJ, Ridker PM, Ripatti S, Roberts R, Salomaa V, Sanghera DK, Schwartz SM, Seedorf U, Stewart AF, Stott DJ, Thiery J, Zalloua PA, O'Donnell CJ, Reilly MP, Assimes TL, Thompson JR, Erdmann J, Clarke R, Watkins H, Kathiresan S, McPherson R, Deloukas P, Schunkert H, Samani NJ, Farrall M. A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease. *Nat Genet.* 2015;47:1121-1130.



Circulation

Clinical Perspective

Genome wide 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 six months after disclosure of risk, compared to disclosure of a conventional risk estimate alone. The differences in LDL-C levels were due to 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 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.

Table 1. Participant characteristics (n=203).

	CRS n=100	+GRS n=103
Age, years	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, mmHg	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 year predictability 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 as percentage. * Dietary fat intake score is based on the percentage energy from fat (PFat) screener²²; † physical activity score based on assessment of physical activity (TAPA) questionnaire²³; ‡ anxiety scores based on the State and Trait Anxiety Inventory for adults (STAI).²⁴ 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 and HDL-cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, by 0.0113.

Table 2. Baseline and follow up LDL-C levels and statin use.

	Group	Baseline	3 months after CHD risk disclosure	6 months 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) ^A
	⁺ 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) ^B
Statin Use	CRS	0 (0%)	23 (23.7%)	21 (21.9%)
	⁺ GRS	0 (0%)	41 (40.2%)	40 (39.2%) ^A
	⁺ L-GRS	0 (0%)	14 (28.6%)	14 (28.6%)
	⁺ H-GRS	0 (0%)	27 (50.9%)	26 (49.1%) ^{B,C}

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 ; LDL-C: low-density lipoprotein cholesterol. LDL-C levels are presented as mean (SD). To convert LDL-C to mmol/L, multiply by 0.0259.

^A ⁺GRS \neq CRS at $P < 0.05$; ^B ⁺H-GRS \neq CRS at $P < 0.05$; ^C ⁺H-GRS \neq ⁺L-GRS at $P < 0.05$



Figure Legends:

Figure 1. Flow diagram of the 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 in order 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 approximately 10-20 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: atherosclerotic cardiovascular disease; CHD: coronary heart disease; GRS: genetic risk score).

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 post-disclosure were lower in ⁺GRS participants than 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 post-disclosure were lower in ⁺H-GRS participants than CRS participants. The downward trend in LDL-C was significantly greater in ⁺H-GRS participants than CRS participants. There was a trend towards a greater reduction in LDL-C levels in ⁺H-GRS vs. ⁺L-GRS. *denotes six month statistical significance at 0.05 level.

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 post-disclosure. 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).

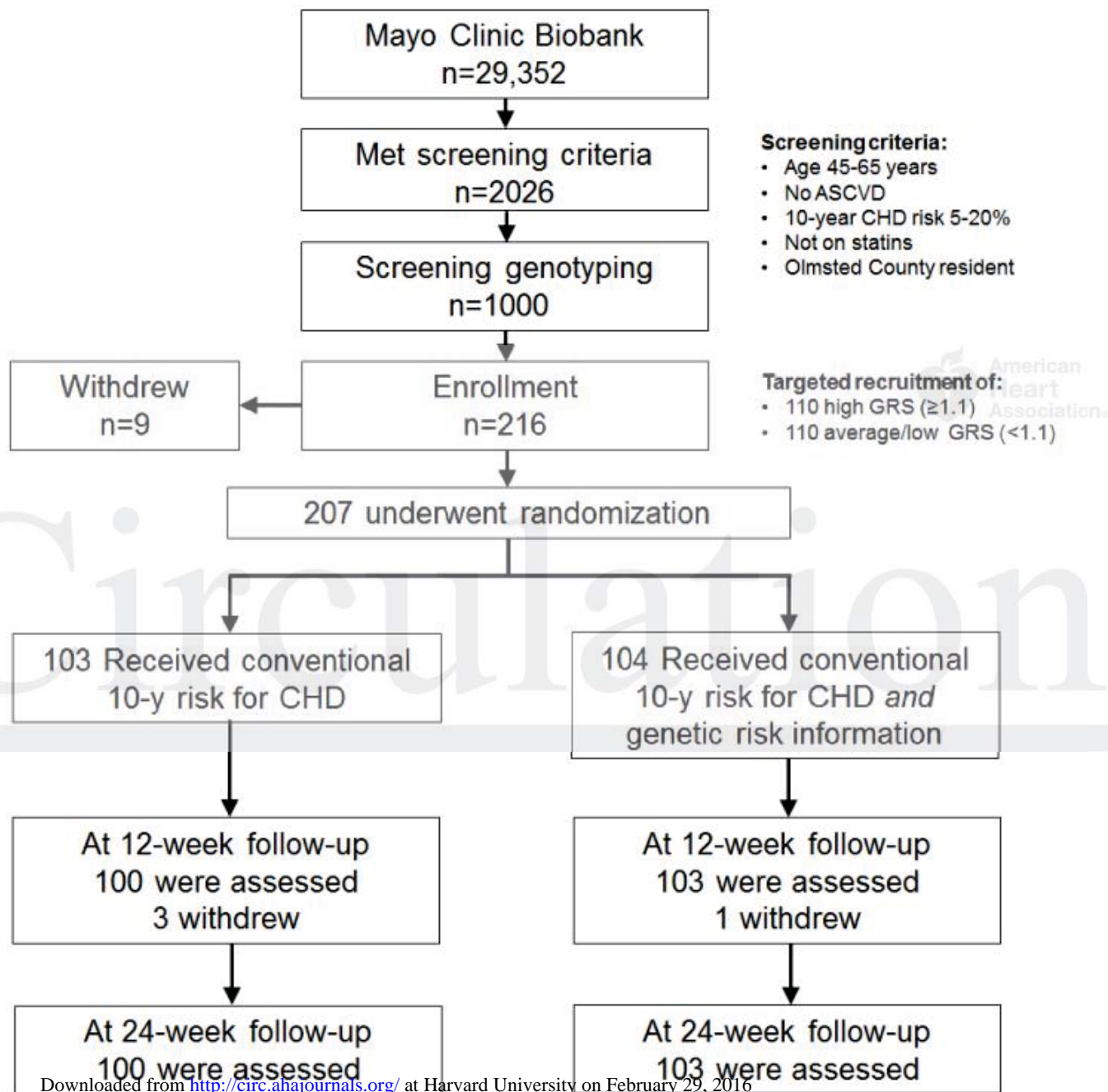


Figure 1

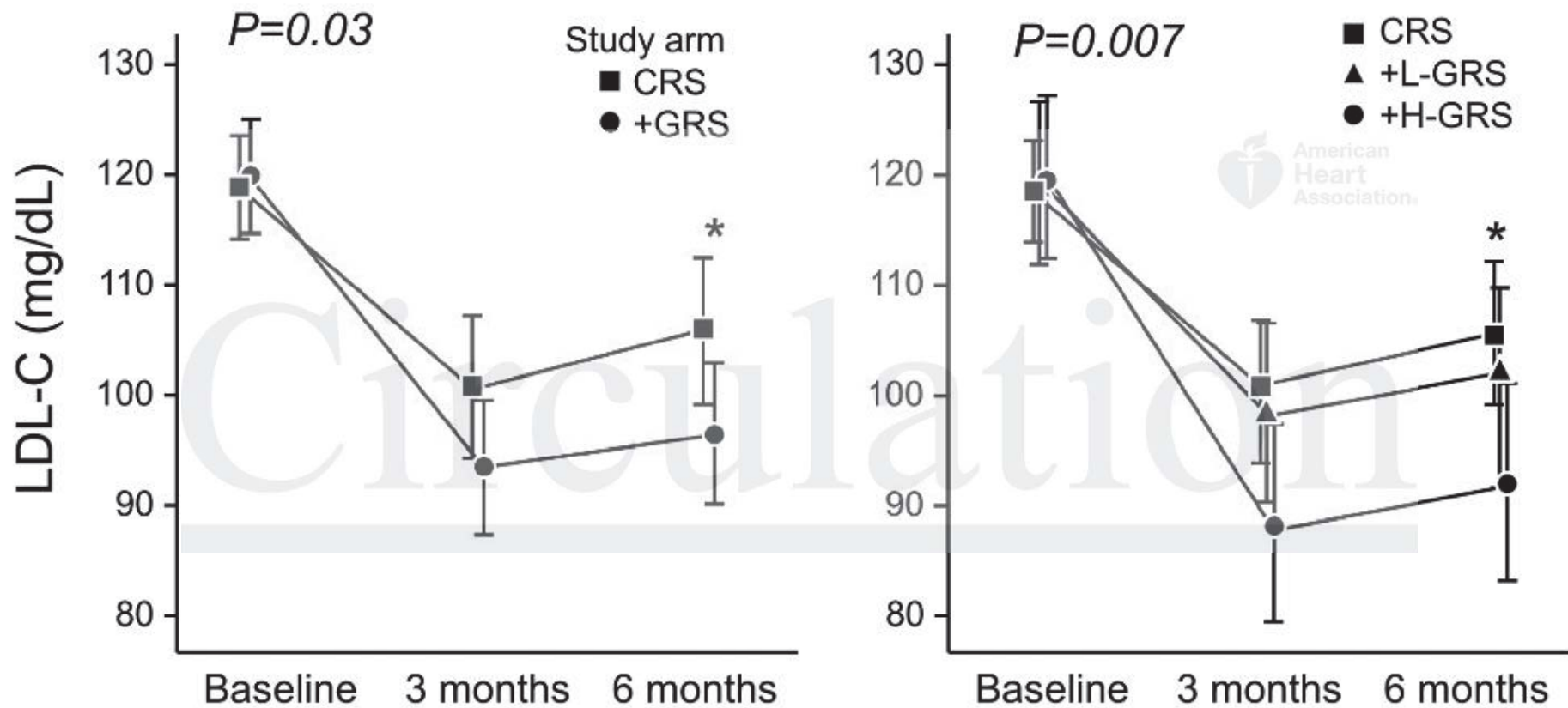


Figure 2

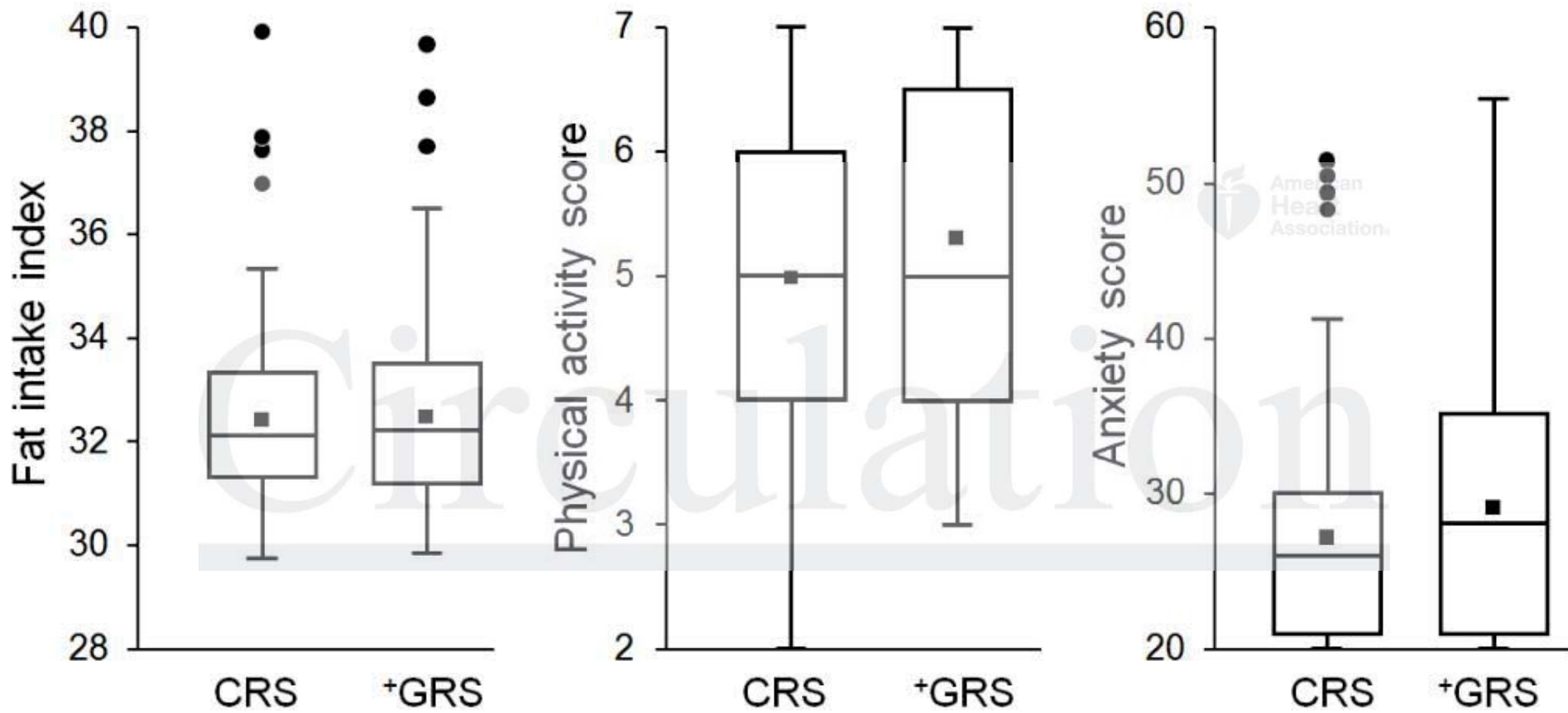


Figure 3

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

Iftikhar J. Kullo, Hayan Jouni, Erin E. Austin, Sherry-Ann Brown, Teresa M. Kruisselbrink, Iyad N. Isseh, Raad A. Haddad, Tariq S. Marroush, Khader Shameer, Janet E. Olson, Ulrich Broeckel, Robert C. Green, Daniel J. Schaid, Victor M. Montori and Kent R. Bailey

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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^R, 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 previously² 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	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇	<input type="checkbox"/> ₈	<input type="checkbox"/> ₉
2. Mayonnaise, regular	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇	<input type="checkbox"/> ₈	<input type="checkbox"/> ₉
3. Sausage or bacon, regular	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇	<input type="checkbox"/> ₈	<input type="checkbox"/> ₉
4. Cheese or cheese spread, regular	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇	<input type="checkbox"/> ₈	<input type="checkbox"/> ₉
5. Beef or pork hot dogs, regular	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇	<input type="checkbox"/> ₈	<input type="checkbox"/> 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	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
2. I feel secure	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
3. I am tense	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
4. I feel strained	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
5. I feel at ease	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
6. I feel upset	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
7. I am presently worrying over possible misfortunes	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
8. I feel satisfied	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
9. I feel tightened	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
10. I feel comfortable	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
11. I feel self-confident	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
12. I feel nervous	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
13. I am jittery	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
14. I feel indecisive	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
15. I am relaxed	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
16. I feel content	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
17. I am worried	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
18. I feel confused	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
19. I feel steady	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
20. I feel pleasant	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> 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	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
22. I feel nervous and restless	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
23. I feel satisfied with myself	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
24. I wish I could be as happy as others seem to be	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
25. I feel like a failure	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
26. I feel rested	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
27. I am "calm, cool, and collected"	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
28. I feel that difficulties are piling up so that I cannot overcome them	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
29. I worry too much over something that really doesn't matter	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
30. I am happy	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
31. I feel disturbing thoughts	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
32. I lack self confidence	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
33. I feel secure	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
34. I make decisions easily	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
35. I feel inadequate	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
36. I am content	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
37. Some unimportant thought runs through my mind and bothers me	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
38. I take disappointment so keenly that I can't put them out of my mind	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
39. I am a steady person	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4

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

Gene	SNP	CHR	Risk Allele	Risk Allele OR
<i>MIA3</i>	rs17465637	1	C	1.14
<i>PPAP2B</i>	rs17114036	1	A	1.11
<i>IL6R</i>	rs4845625	1	T	1.04
<i>WDR12</i>	rs6725887	2	C	1.12
<i>ZEB2-AC074093.1</i>	rs2252641	2	G	1.04
<i>VAMP5-VAMP8-GGCX</i>	rs1561198	2	A	1.05
<i>MRAS</i>	rs9818870	3	T	1.07
<i>EDNRA</i>	rs1878406	4	T	1.06
<i>SLC22A4-SLC22A5</i>	rs273909	5	C	1.09
<i>TCF21</i>	rs12190287	6	C	1.07
<i>PHACTR1</i>	rs9369640	6	A	1.09
<i>KCNK5</i>	rs10947789	6	T	1.06
<i>PLG</i>	rs4252120	6	T	1.06
<i>ANKS1A</i>	rs17609940	6	G	1.07
7q22 <i>BCAP29</i>	rs10953541	7	C	1.08
<i>HDAC9</i>	rs2023938	7	G	1.07
<i>CDKN2BAS1</i>	rs1333049	9	C	1.23
<i>CXCL12</i>	rs2047009	10	C	1.05
<i>KIAA1462</i>	rs2505083	10	C	1.06
<i>PDGFD</i>	rs974819	11	A	1.07
<i>COL4A1-COL4A2</i>	rs4773144	13	G	1.07
<i>COL4A1-COL4A2</i>	*rs9515203	13	T	1.08
<i>FLT1</i>	rs9319428	13	A	1.05
<i>HHIPL1</i>	rs2895811	14	C	1.06
<i>RAI1-PEMT-RASD1</i>	rs12936587	17	G	1.06
<i>SMG6</i>	rs216172	17	C	1.07
<i>UBE2Z</i>	rs46522	17	T	1.06
Gene desert (<i>KCNE2</i>)	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 \pm 5.41	57.6 \pm 5.37	57.5 \pm 5.43
Women	531 (55%)	169 (54%)	362 (55%)
CRS, %	7.98 \pm 3.16	7.89 \pm 3.13	8.02 \pm 3.18
GRS	1.00 \pm 0.28	1.33 \pm 0.20	0.85 \pm 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/m ²	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)	<i>P</i>
*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

Outcome	Group	*Visit 4		†Baseline to Visit 4	
		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 $\geq 10\%$	12 (57.1%)	24 (60%)	36 (59%)
ASCVD $\geq 7.5\%$	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

Welcome, Hayan Jouni | Logout Powered by VitaHealth Software 

Generic Disease Management System

Summary for diseases and preventive services

Birth date: 09/10/1967 | Age: 46 | Male | Female

Prim. Phys. []

Has: Congestive Heart Failure and Type 2 diabetes

Last blood pressure	126/83	Date	03/27/2014
Last height	162.8 cm	Date	02/18/2014
Last weight	76.9 kg	Date	03/27/2014
Last BMI	29	Date	03/27/2014
PHQ-9 score		Date	
Last Asthma Action Plan			
Current tobacco use	<input type="checkbox"/>	Last CVI	02/12/2014
Last advance directive			
Last echo			
Last ECG			03/21/2014
Last nuclearstudy			
ERA Score			
Ejection Fraction	65%		
Framingham score	10%	** Statin Decision Aid	
Major Fx 10 yr risk	2.4%		
Hip Fx 10 yr risk	0.1%		

Labs for past 5 years

	Normal value	Most recent value	mm/dd/yyyy
Hemoglobin	12.0 - 15.5	10.6 * g/dL	03/21/2014
Sodium	135 - 145	137 mmol/L	03/10/2014
Potassium	3.6 - 5.2	3.6 mmol/L	03/10/2014
Glucose	70 - 100	199 * mg/dL	02/12/2014
HbA1c	4.0-6.0	9.1 * %	02/12/2014
AST (SGOT)	8 - 43	31 U/L	02/12/2014
ALT (SGPT)			
Creatinine	0.6 - 1.1	0.6 mg/dL	03/10/2014
eGFR	>60	>60 mL/min/1.73m ²	03/10/2014
Total cholesterol	SeeComment	131 mg/dL	02/12/2014
Triglycerides	SeeComment	89 mg/dL	02/12/2014
HDL cholesterol	SeeComment	28 * mg/dL	02/12/2014
LDL cholesterol	SeeComment	85 mg/dL	02/12/2014
hsCRP			
Lipoprotein(a)			
INR	0.8-1.2	2.5	03/21/2014

Recommended actions

- Pap test due.
- HbA1c should be < 8. - Appt: 05/20/2014 12:00
- First dose of Hepatitis B vaccination recommended.

Rec. actions next 90 days

- HbA1c due by May 12, 2014 & recommended every 3 months if HbA1c >= 8. - Appt: 05/20/2014 12:00

Preventive services

Tdap vaccine	02/12/2014
Influenza vaccine	02/12/2014
Pneumococcal vaccine	02/12/2014
AAA screening	03/24/2014
Mammogram	02/11/2014
Eye exam	02/27/2014

AME, CPM's, Patient education and Decision aids

- [My Road to Better Health with Diabetes](#)
- [My Road to Better Health](#)
- [Daily Weight Diary](#)
- [Know Your Risk Factors for Coronary Artery Disease](#)
- [Pap Smear](#)
- ** Diabetes Decision Aid ****
- ** Statin Decision Aid ****

Alerts

- Recommend ACE or ARB.
- Advise lifestyle counseling as BMI > 25

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.

Current Risk

Framingham Risk Score

These figures are used to calculate my risk of having a heart attack in the next 10 years:

Input Clinical History

Age

Gender M F

Smoker Yes No

Diabetes Yes No

Treated SBP Yes No

Input Clinical History

Systolic Blood Pressure mmHg

Diastolic Blood Pressure mmHg

HDL Cholesterol mg/dL

Total Cholesterol mg/dL

High Sensitivity CRP mg/L


 GRS

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.

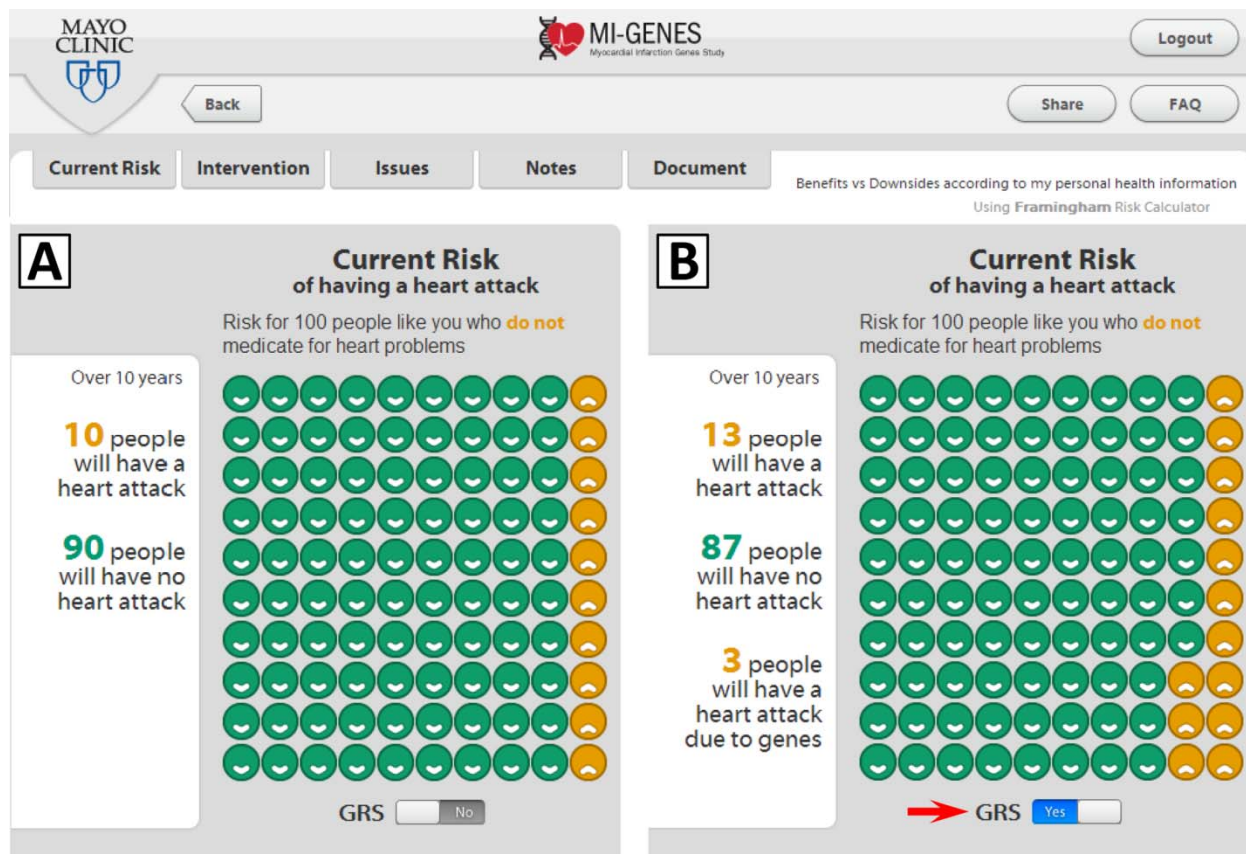


Figure 3. Disclosure of CHD risk

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.

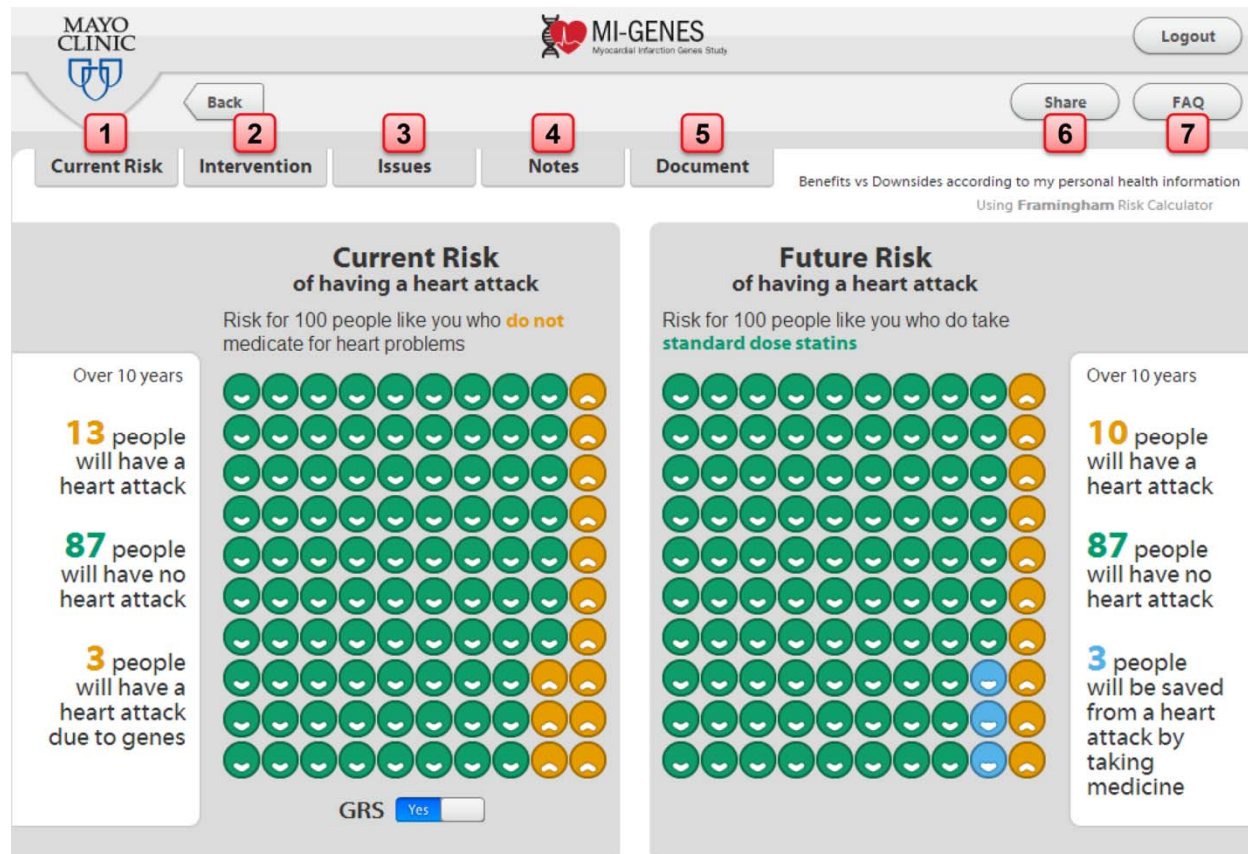


Figure 4. Summary of features included in the decision aid

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).

References

1. Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, Goldstein BA, Stirrups K, Konig IR, Cazier JB, Johansson A, Hall AS, Lee JY, Willer CJ, Chambers JC, Esko T, Folkersen L, Goel A, Grundberg E, Havulinna AS, Ho WK, Hopewell JC, Eriksson N, Kleber ME, Kristiansson K, Lundmark P, Lyytikainen LP, Rafelt S, Shungin D, Strawbridge RJ, Thorleifsson G, Tikkanen E, Van Zuydam N, Voight BF, Waite LL, Zhang W, Ziegler A, Absher D, Alshuler D, Balmforth AJ, Barroso I, Braund PS, Burgdorf C, Claudi-Boehm S, Cox D, Dimitriou M, Do R, Doney AS, El Mokhtari N, Eriksson P, Fischer K, Fontanillas P, Franco-Cereceda A, Gigante B, Groop L, Gustafsson S, Hager J, Hallmans G, Han BG, Hunt SE, Kang HM, Illig T, Kessler T, Knowles JW, Kolovou G, Kuusisto J, Langenberg C, Langford C, Leander K, Lokki ML, Lundmark A, McCarthy MI, Meisinger C, Melander O, Mihailov E, Maouche S, Morris AD, Muller-Nurasyid M, Nikus K, Peden JF, Rayner NW, Rasheed A, Rosinger S, Rubin D, Rumpf MP, Schafer A, Sivananthan M, Song C, Stewart AF, Tan ST, Thorgeirsson G, van der Schoot CE, Wagner PJ, Wells GA, Wild PS, Yang TP, Amouyel P, Arveiler D, Basart H, Boehnke M, Boerwinkle E, Brambilla P, Cambien F, Cupples AL, de Faire U, Dehghan A, Diemert P, Epstein SE, Evans A, Ferrario MM, Ferrieres J, Gauguier D, Go AS, Goodall AH, Gudnason V, Hazen SL, Holm H, Iribarren C, Jang Y, Kahonen M, Kee F, Kim HS, Klopp N, Koenig W, Kratzer W, Kuulasmaa K, Laakso M, Laaksonen R, Lind L, Ouwehand WH, Parish S, Park JE, Pedersen NL, Peters A, Quertermous T, Rader DJ, Salomaa V, Schadt E, Shah SH, Sinisalo J, Stark K, Stefansson K, Tregouet DA, Virtamo J, Wallentin L, Wareham N, Zimmermann ME, Nieminen MS, Hengstenberg C, Sandhu MS, Pastinen T, Syvanen AC, Hovingh GK, Dedoussis G, Franks PW, Lehtimaki T, Metspalu A, Zalloua PA, Siegbahn A, Schreiber S, Ripatti S, Blankenberg SS, Perola M, Clarke R, Boehm BO, O'Donnell C, Reilly MP, Marz W, Collins R, Kathiresan S, Hamsten A, Kooner JS, Thorsteinsdottir U, Danesh J, Palmer CN, Roberts R, Watkins H, Schunkert H, Samani NJ. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet.* 2013;45:25-33.
2. Ding K, Bailey KR, Kullo IJ. Genotype-informed estimation of risk of coronary heart disease based on genome-wide association data linked to the electronic medical record. *BMC cardiovascular disorders.* 2011;11:66.
3. Waghlikar KB, Hankey RA, Decker LK, Cha SS, Greenes RA, Liu H, Chaudhry R. Evaluation of the effect of decision support on the efficiency of primary care providers in the outpatient practice. *J Prim Care Community Health.* 2015;6:54-60.
4. Montori VM, Breslin M, Maleska M, Weymiller AJ. Creating a conversation: insights from the development of a decision aid. *PLoS Med.* 2007;4:e233.
5. Weymiller AJ, Montori VM, Jones LA, Gafni A, Guyatt GH, Bryant SC, Christianson TJ, Mullan RJ, Smith SA. Helping patients with type 2 diabetes mellitus make treatment decisions: statin choice randomized trial. *Arch Intern Med.* 2007;167:1076-1082.
6. Branda ME, LeBlanc A, Shah ND, Tiedje K, Ruud K, Van Houten H, Pencille L, Kurland M, Yawn B, Montori VM. Shared decision making for patients with type 2 diabetes: a randomized trial in primary care. *BMC Health Serv Res.* 2013;13:301.
7. Mann DM, Ponieman D, Montori VM, Arciniega J, McGinn T. The Statin Choice decision aid in primary care: a randomized trial. *Patient Educ Couns.* 2010;80:138-140.
8. Thompson FE, Midthune D, Subar AF, Kipnis V, Kahle LL, Schatzkin A. Development and evaluation of a short instrument to estimate usual dietary intake of percentage energy from fat. *J Am Diet Assoc.* 2007;107:760-767.
9. Tippet K, Cypel Y. Design and Operation: The Continuing Survey of Food Intakes by Individuals and the Diet and Health Knowledge Survey, 1994–96. *Agricultural Research Service NFS Report No. 96–1.* 1997

10. Mayer CJ, Steinman L, Williams B, Topolski TD, LoGerfo J. Developing a Telephone Assessment of Physical Activity (TAPA) questionnaire for older adults. *Prev Chronic Dis.* 2008;5:A24.
11. Spielberger C. *Manual for the State-Trait Anxiety Inventory, STAI (Form Y)*. . Palo Alto, California: Consulting Psychologists Press; 1983.

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^R, 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 previously² 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	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇	<input type="checkbox"/> ₈	<input type="checkbox"/> ₉
2. Mayonnaise, regular	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇	<input type="checkbox"/> ₈	<input type="checkbox"/> ₉
3. Sausage or bacon, regular	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇	<input type="checkbox"/> ₈	<input type="checkbox"/> ₉
4. Cheese or cheese spread, regular	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇	<input type="checkbox"/> ₈	<input type="checkbox"/> ₉
5. Beef or pork hot dogs, regular	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄	<input type="checkbox"/> ₅	<input type="checkbox"/> ₆	<input type="checkbox"/> ₇	<input type="checkbox"/> ₈	<input type="checkbox"/> 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	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
2. I feel secure	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
3. I am tense	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
4. I feel strained	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
5. I feel at ease	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
6. I feel upset	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
7. I am presently worrying over possible misfortunes	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
8. I feel satisfied	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
9. I feel tightened	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
10. I feel comfortable	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
11. I feel self-confident	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
12. I feel nervous	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
13. I am jittery	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
14. I feel indecisive	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
15. I am relaxed	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
16. I feel content	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
17. I am worried	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
18. I feel confused	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
19. I feel steady	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> ₄
20. I feel pleasant	<input type="checkbox"/> ₁	<input type="checkbox"/> ₂	<input type="checkbox"/> ₃	<input type="checkbox"/> 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	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
22. I feel nervous and restless	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
23. I feel satisfied with myself	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
24. I wish I could be as happy as others seem to be	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
25. I feel like a failure	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
26. I feel rested	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
27. I am "calm, cool, and collected"	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
28. I feel that difficulties are piling up so that I cannot overcome them	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
29. I worry too much over something that really doesn't matter	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
30. I am happy	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
31. I feel disturbing thoughts	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
32. I lack self confidence	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
33. I feel secure	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
34. I make decisions easily	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
35. I feel inadequate	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
36. I am content	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
37. Some unimportant thought runs through my mind and bothers me	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
38. I take disappointment so keenly that I can't put them out of my mind	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
39. I am a steady person	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4

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

Gene	SNP	CHR	Risk Allele	Risk Allele OR
<i>MIA3</i>	rs17465637	1	C	1.14
<i>PPAP2B</i>	rs17114036	1	A	1.11
<i>IL6R</i>	rs4845625	1	T	1.04
<i>WDR12</i>	rs6725887	2	C	1.12
<i>ZEB2-AC074093.1</i>	rs2252641	2	G	1.04
<i>VAMP5-VAMP8-GGCX</i>	rs1561198	2	A	1.05
<i>MRAS</i>	rs9818870	3	T	1.07
<i>EDNRA</i>	rs1878406	4	T	1.06
<i>SLC22A4-SLC22A5</i>	rs273909	5	C	1.09
<i>TCF21</i>	rs12190287	6	C	1.07
<i>PHACTR1</i>	rs9369640	6	A	1.09
<i>KCNK5</i>	rs10947789	6	T	1.06
<i>PLG</i>	rs4252120	6	T	1.06
<i>ANKS1A</i>	rs17609940	6	G	1.07
7q22 <i>BCAP29</i>	rs10953541	7	C	1.08
<i>HDAC9</i>	rs2023938	7	G	1.07
<i>CDKN2BAS1</i>	rs1333049	9	C	1.23
<i>CXCL12</i>	rs2047009	10	C	1.05
<i>KIAA1462</i>	rs2505083	10	C	1.06
<i>PDGFD</i>	rs974819	11	A	1.07
<i>COL4A1-COL4A2</i>	rs4773144	13	G	1.07
<i>COL4A1-COL4A2</i>	*rs9515203	13	T	1.08
<i>FLT1</i>	rs9319428	13	A	1.05
<i>HHIPL1</i>	rs2895811	14	C	1.06
<i>RAI1-PEMT-RASD1</i>	rs12936587	17	G	1.06
<i>SMG6</i>	rs216172	17	C	1.07
<i>UBE2Z</i>	rs46522	17	T	1.06
Gene desert (<i>KCNE2</i>)	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 \pm 5.41	57.6 \pm 5.37	57.5 \pm 5.43
Women	531 (55%)	169 (54%)	362 (55%)
CRS, %	7.98 \pm 3.16	7.89 \pm 3.13	8.02 \pm 3.18
GRS	1.00 \pm 0.28	1.33 \pm 0.20	0.85 \pm 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/m ²	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)	<i>P</i>
*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

Outcome	Group	*Visit 4		†Baseline to Visit 4	
		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 $\geq 10\%$	12 (57.1%)	24 (60%)	36 (59%)
ASCVD $\geq 7.5\%$	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

Welcome, Hayan Jouni | Logout Powered by VitaHealth Software 

Generic Disease Management System

Summary for diseases and preventive services

Birth date: 09/10/1967 | Age: 46 | Male | Female

Prim. Phys. []

Has: Congestive Heart Failure and Type 2 diabetes

Last blood pressure	126/83	Date	03/27/2014
Last height	162.8 cm	Date	02/18/2014
Last weight	76.9 kg	Date	03/27/2014
Last BMI	29	Date	03/27/2014
PHQ-9 score		Date	
Last Asthma Action Plan			
Current tobacco use	<input type="checkbox"/>	Last CVI	02/12/2014
Last advance directive			
Last echo			
Last ECG			03/21/2014
Last nuclearstudy			
ERA Score			
Ejection Fraction	65%		
Framingham score	10%	** Statin Decision Aid	
Major Fx 10 yr risk	2.4%		
Hip Fx 10 yr risk	0.1%		

Labs for past 5 years

	Normal value	Most recent value	mm/dd/yyyy
Hemoglobin	12.0 - 15.5	10.6 * g/dL	03/21/2014
Sodium	135 - 145	137 mmol/L	03/10/2014
Potassium	3.6 - 5.2	3.6 mmol/L	03/10/2014
Glucose	70 - 100	199 * mg/dL	02/12/2014
HbA1c	4.0-6.0	9.1 * %	02/12/2014
AST (SGOT)	8 - 43	31 U/L	02/12/2014
ALT (SGPT)			
Creatinine	0.6 - 1.1	0.6 mg/dL	03/10/2014
eGFR	>60	>60 mL/min/B	03/10/2014
Total cholesterol	SeeComment	131 mg/dL	02/12/2014
Triglycerides	SeeComment	89 mg/dL	02/12/2014
HDL cholesterol	SeeComment	28 * mg/dL	02/12/2014
LDL cholesterol	SeeComment	85 mg/dL	02/12/2014
hsCRP			
Lipoprotein(a)			
INR	0.8-1.2	2.5	03/21/2014

Recommended actions

- Pap test due.
- HbA1c should be < 8. - Appt: 05/20/2014 12:00
- First dose of Hepatitis B vaccination recommended.

Rec. actions next 90 days

- HbA1c due by May 12, 2014 & recommended every 3 months if HbA1c >= 8. - Appt: 05/20/2014 12:00

Preventive services

Tdap vaccine	02/12/2014
Influenza vaccine	02/12/2014
Pneumococcal vaccine	02/12/2014
AAA screening	03/24/2014
Mammogram	02/11/2014
Eye exam	02/27/2014

AME, CPM's, Patient education and Decision aids

- [My Road to Better Health with Diabetes](#)
- [My Road to Better Health](#)
- [Daily Weight Diary](#)
- [Know Your Risk Factors for Coronary Artery Disease](#)
- [Pap Smear](#)
- ** Diabetes Decision Aid ****
- ** Statin Decision Aid ****

Alerts

- Recommend ACE or ARB.
- Advise lifestyle counseling as BMI > 25

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.

Current Risk

Framingham Risk Score

These figures are used to calculate my risk of having a heart attack in the next 10 years:

Input Clinical History

Age

Gender M F

Smoker Yes No

Diabetes Yes No

Treated SBP Yes No

Input Clinical History

Systolic Blood Pressure mmHg

Diastolic Blood Pressure mmHg

HDL Cholesterol mg/dL

Total Cholesterol mg/dL

High Sensitivity CRP mg/L


 GRS

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.

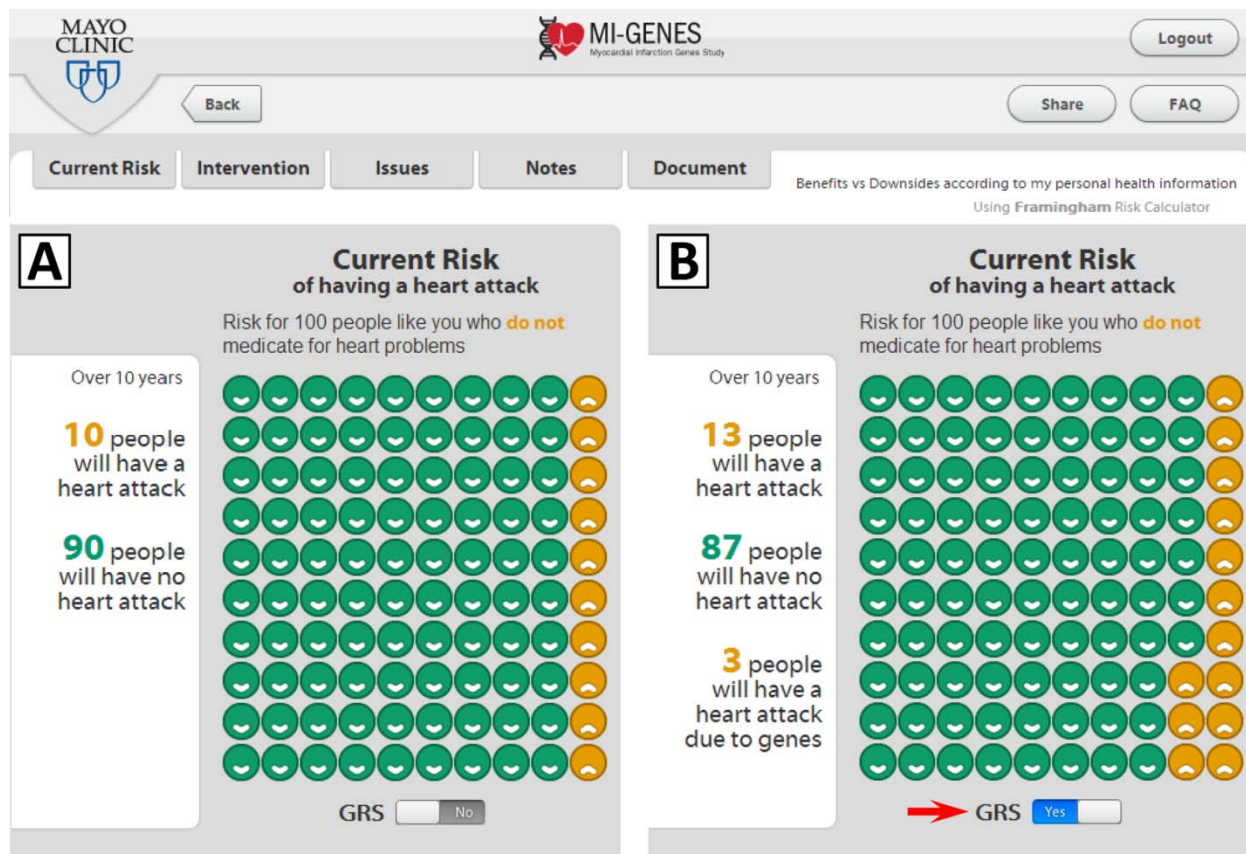


Figure 3. Disclosure of CHD risk

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.

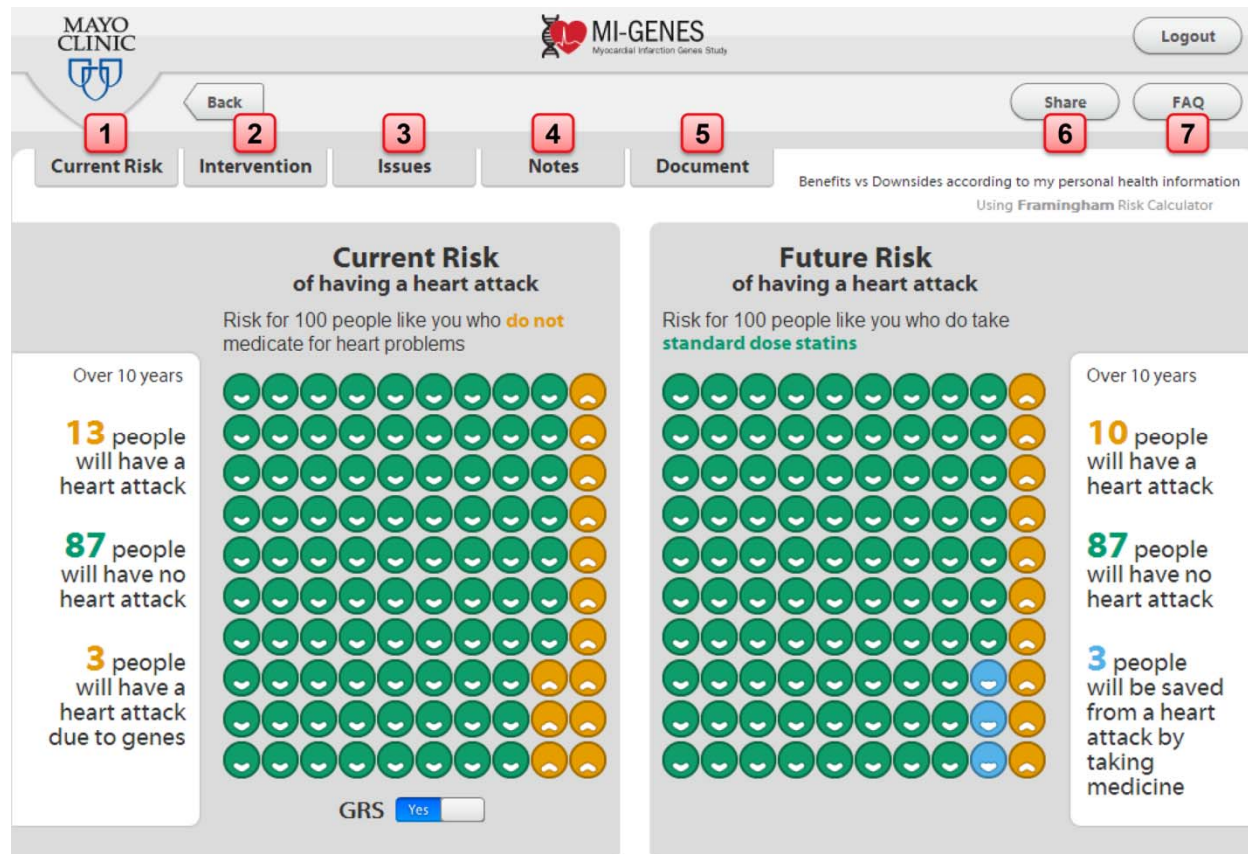


Figure 4. Summary of features included in the decision aid

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).

References

1. Deloukas P, Kanoni S, Willenborg C, Farrall M, Assimes TL, Thompson JR, Ingelsson E, Saleheen D, Erdmann J, Goldstein BA, Stirrups K, Konig IR, Cazier JB, Johansson A, Hall AS, Lee JY, Willer CJ, Chambers JC, Esko T, Folkersen L, Goel A, Grundberg E, Havulinna AS, Ho WK, Hopewell JC, Eriksson N, Kleber ME, Kristiansson K, Lundmark P, Lyytikainen LP, Rafelt S, Shungin D, Strawbridge RJ, Thorleifsson G, Tikkanen E, Van Zuydam N, Voight BF, Waite LL, Zhang W, Ziegler A, Absher D, Alshuler D, Balmforth AJ, Barroso I, Braund PS, Burgdorf C, Claudi-Boehm S, Cox D, Dimitriou M, Do R, Doney AS, El Mokhtari N, Eriksson P, Fischer K, Fontanillas P, Franco-Cereceda A, Gigante B, Groop L, Gustafsson S, Hager J, Hallmans G, Han BG, Hunt SE, Kang HM, Illig T, Kessler T, Knowles JW, Kolovou G, Kuusisto J, Langenberg C, Langford C, Leander K, Lokki ML, Lundmark A, McCarthy MI, Meisinger C, Melander O, Mihailov E, Maouche S, Morris AD, Muller-Nurasyid M, Nikus K, Peden JF, Rayner NW, Rasheed A, Rosinger S, Rubin D, Rumpf MP, Schafer A, Sivananthan M, Song C, Stewart AF, Tan ST, Thorgeirsson G, van der Schoot CE, Wagner PJ, Wells GA, Wild PS, Yang TP, Amouyel P, Arveiler D, Basart H, Boehnke M, Boerwinkle E, Brambilla P, Cambien F, Cupples AL, de Faire U, Dehghan A, Diemert P, Epstein SE, Evans A, Ferrario MM, Ferrieres J, Gauguier D, Go AS, Goodall AH, Gudnason V, Hazen SL, Holm H, Iribarren C, Jang Y, Kahonen M, Kee F, Kim HS, Klopp N, Koenig W, Kratzer W, Kuulasmaa K, Laakso M, Laaksonen R, Lind L, Ouwehand WH, Parish S, Park JE, Pedersen NL, Peters A, Quertermous T, Rader DJ, Salomaa V, Schadt E, Shah SH, Sinisalo J, Stark K, Stefansson K, Tregouet DA, Virtamo J, Wallentin L, Wareham N, Zimmermann ME, Nieminen MS, Hengstenberg C, Sandhu MS, Pastinen T, Syvanen AC, Hovingh GK, Dedoussis G, Franks PW, Lehtimaki T, Metspalu A, Zalloua PA, Siegbahn A, Schreiber S, Ripatti S, Blankenberg SS, Perola M, Clarke R, Boehm BO, O'Donnell C, Reilly MP, Marz W, Collins R, Kathiresan S, Hamsten A, Kooner JS, Thorsteinsdottir U, Danesh J, Palmer CN, Roberts R, Watkins H, Schunkert H, Samani NJ. Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet.* 2013;45:25-33.
2. Ding K, Bailey KR, Kullo IJ. Genotype-informed estimation of risk of coronary heart disease based on genome-wide association data linked to the electronic medical record. *BMC cardiovascular disorders.* 2011;11:66.
3. Waghlikar KB, Hankey RA, Decker LK, Cha SS, Greenes RA, Liu H, Chaudhry R. Evaluation of the effect of decision support on the efficiency of primary care providers in the outpatient practice. *J Prim Care Community Health.* 2015;6:54-60.
4. Montori VM, Breslin M, Maleska M, Weymiller AJ. Creating a conversation: insights from the development of a decision aid. *PLoS Med.* 2007;4:e233.
5. Weymiller AJ, Montori VM, Jones LA, Gafni A, Guyatt GH, Bryant SC, Christianson TJ, Mullan RJ, Smith SA. Helping patients with type 2 diabetes mellitus make treatment decisions: statin choice randomized trial. *Arch Intern Med.* 2007;167:1076-1082.
6. Branda ME, LeBlanc A, Shah ND, Tiedje K, Ruud K, Van Houten H, Pencille L, Kurland M, Yawn B, Montori VM. Shared decision making for patients with type 2 diabetes: a randomized trial in primary care. *BMC Health Serv Res.* 2013;13:301.
7. Mann DM, Ponieman D, Montori VM, Arciniega J, McGinn T. The Statin Choice decision aid in primary care: a randomized trial. *Patient Educ Couns.* 2010;80:138-140.
8. Thompson FE, Midthune D, Subar AF, Kipnis V, Kahle LL, Schatzkin A. Development and evaluation of a short instrument to estimate usual dietary intake of percentage energy from fat. *J Am Diet Assoc.* 2007;107:760-767.
9. Tippet K, Cypel Y. Design and Operation: The Continuing Survey of Food Intakes by Individuals and the Diet and Health Knowledge Survey, 1994–96. *Agricultural Research Service NFS Report No. 96–1.* 1997

10. Mayer CJ, Steinman L, Williams B, Topolski TD, LoGerfo J. Developing a Telephone Assessment of Physical Activity (TAPA) questionnaire for older adults. *Prev Chronic Dis.* 2008;5:A24.
11. Spielberger C. *Manual for the State-Trait Anxiety Inventory, STAI (Form Y)*. . Palo Alto, California: Consulting Psychologists Press; 1983.