Supplemental Material

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

Table of Contents: **Page**

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Methods

Screening Genotyping

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

CLIA Genotyping and Calculation of GRS

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

Methods

Genomic Decision Aid and Integration into the Electronic Health Record

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

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

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

Methods

Disclosure of CHD Risk and Shared Decision Making Regarding Statin Therapy

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

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

Survey instruments

Dietary fat intake

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

Physical activity and exercise

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

Anxiety

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

Diet: Fat intake

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

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

Physical activity

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

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

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

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

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

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

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

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

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

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

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

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

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

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

State-Trait Anxiety Inventory

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

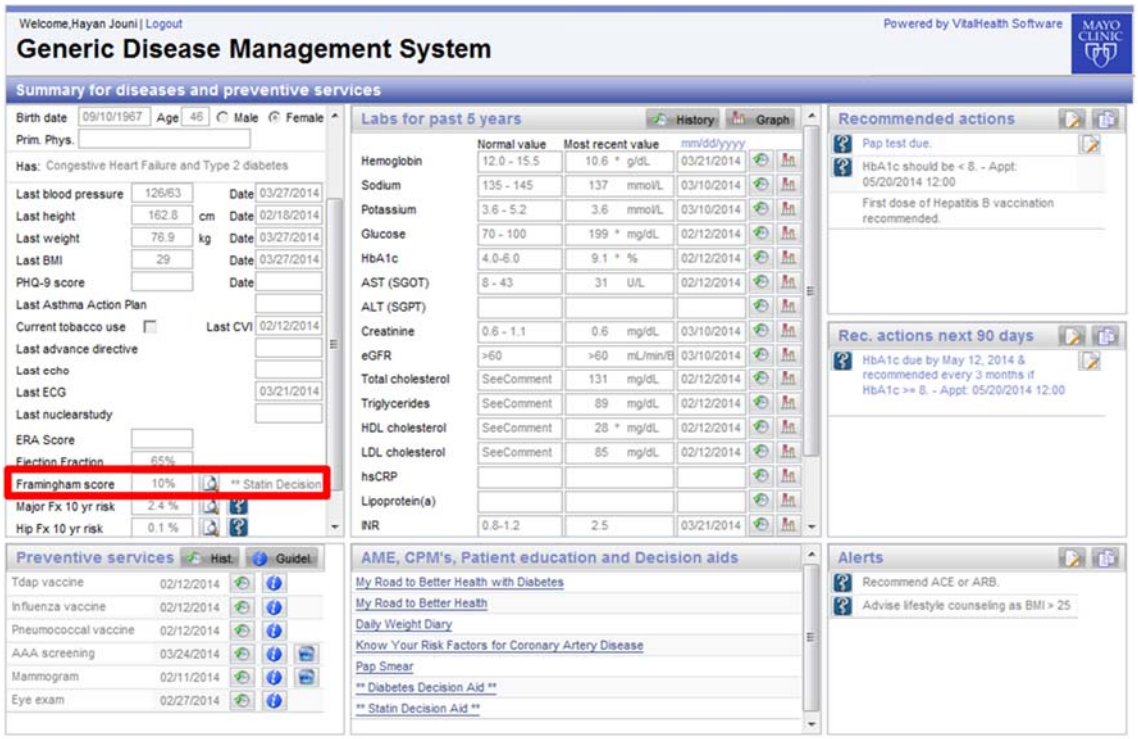

Figure 1. Generic disease management interface in the electronic health record
A sample of how the generic disease management interface appears in the electronic health record. GDMS summarizes pertinent information such as the most recent vitals, laboratory studies, Framingham risk score, and preventive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

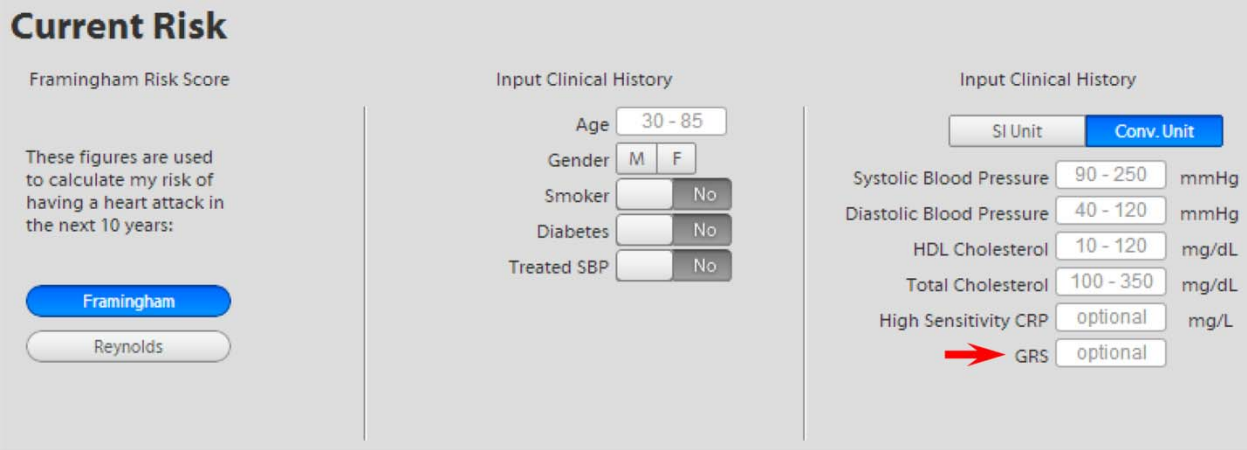

Figure 2. Data entry screen for the decision aid
The risk factor entry screen of the decision aid was modified to implement the genetic risk score (GRS) as highlighted in the figure. Implementation of GRS into the conventional risk score was embedded into the coding of the decision aid application.

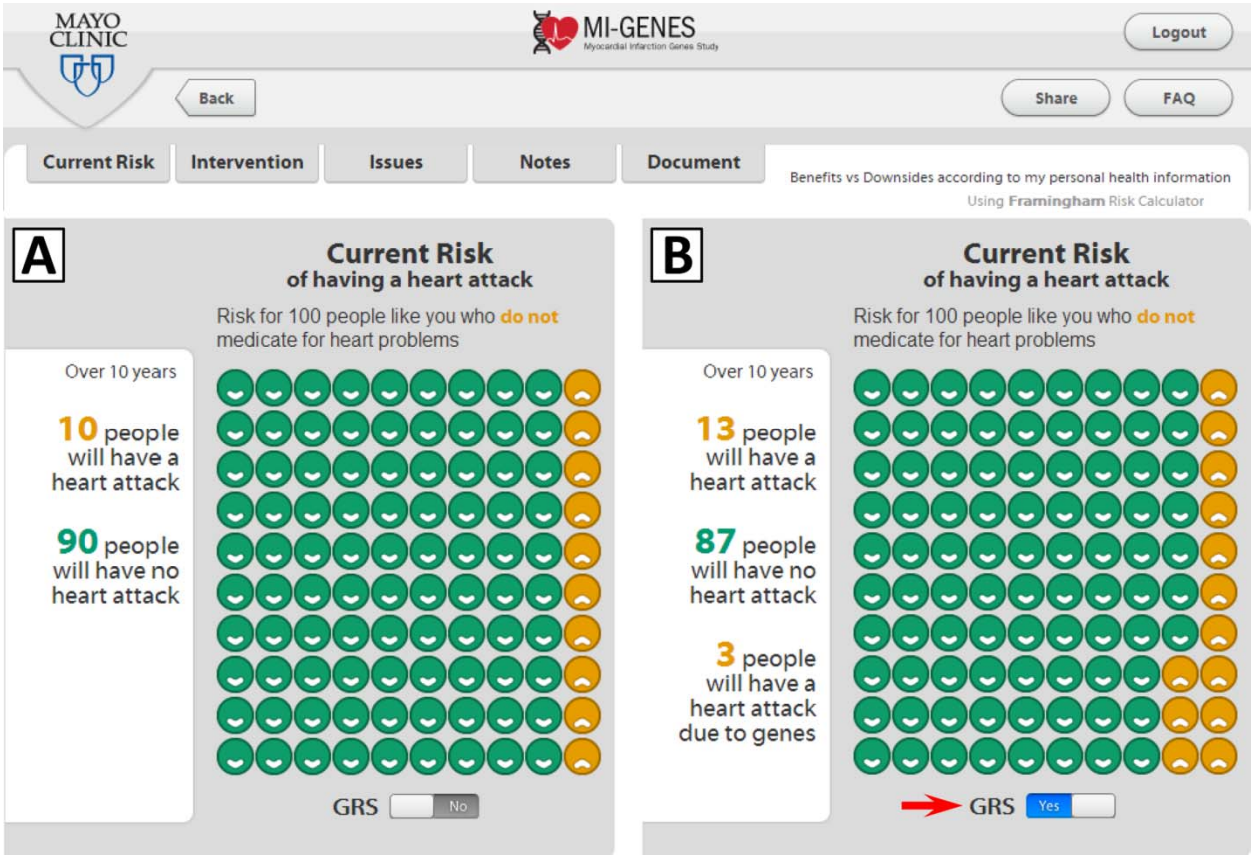

Figure 3. Disclosure of CHD risk
Disclosure of CHD risk estimates based on the conventional risk score (CRS, panel A) and after implementing the genetic risk score ($^{+}$GRS, panel B) by clicking the GRS button (arrow). In this example, the patient's 10-year CHD risk based on CRS is displayed as 10%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

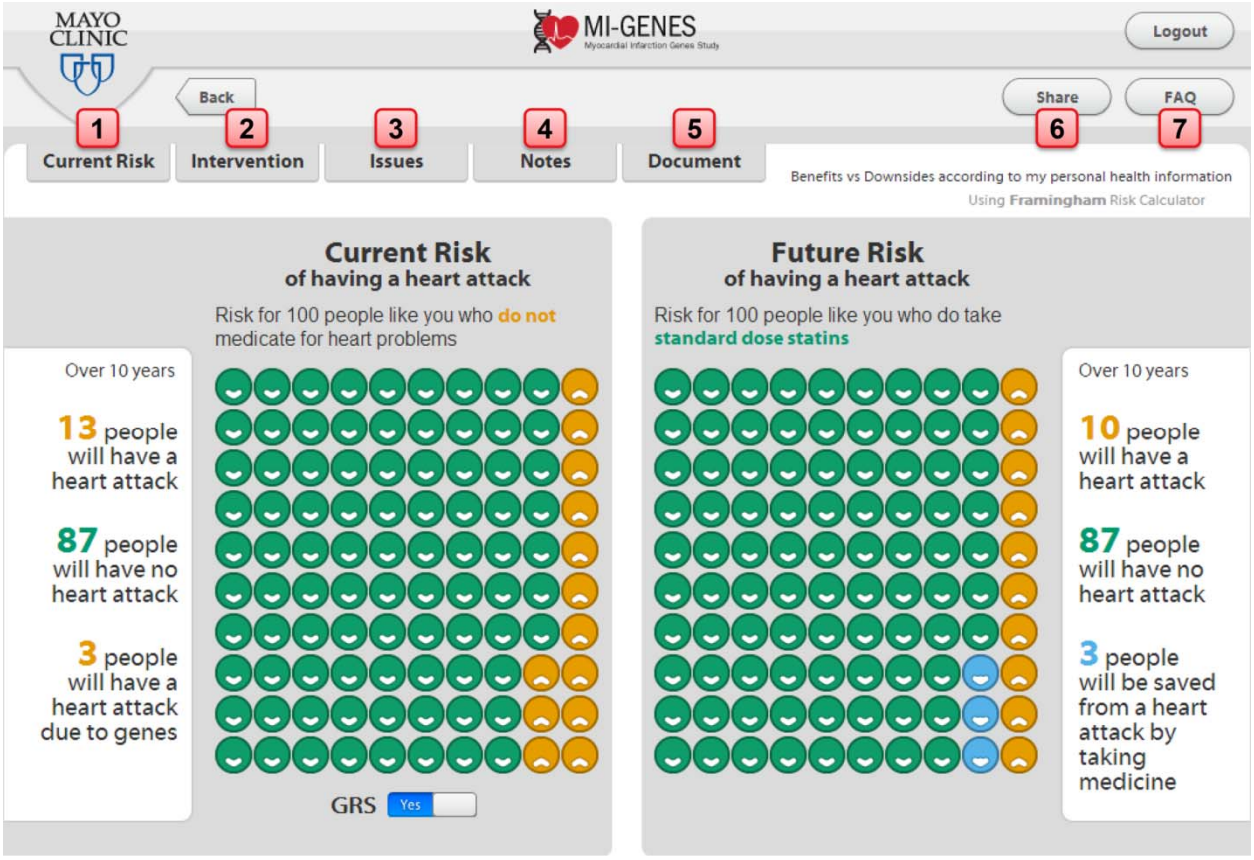

Figure 4. Summary of features included in the decision aid
Features included in this tool are: (1) CHD risk estimates which can be modified to show patients how risk can change according to their risk factors. (2) The healthcare provider can select an intervention such as standard dose versus high dose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

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