



# The Effect of Disclosing Genomic Risk of Coronary Heart Disease on LDL Cholesterol Levels: The Myocardial Infarction Genes (MI-GENES) Study

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Late-breaking Clinical Trials  
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# Background

- GWAS have identified 46 susceptibility loci for CHD *Deloukas P, Nat Genet 2012; 45: 25–33*
- Whether knowledge of genetic risk influences relevant clinical outcomes is unknown
- We investigated whether disclosing a genetic risk score (GRS) derived from 28 SNPs not related to BP/lipids would lower LDL-C levels

# Hypotheses

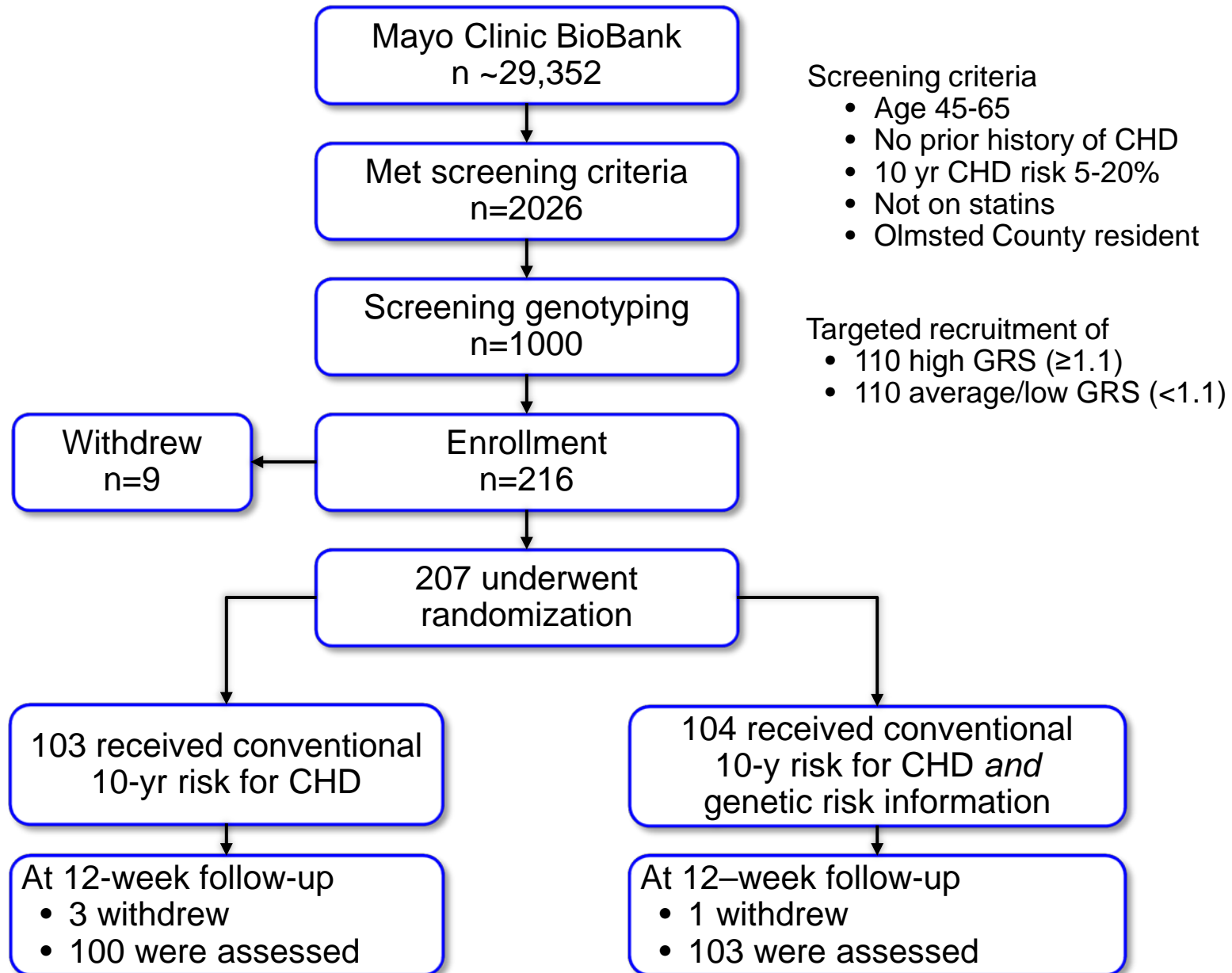
- In patients randomized to +GRS, LDL-C levels at 6 months would be lower than in participants randomized to receive a conventional risk score (CRS)
- Participants with a high +GRS would have lower LDL-C than participants with average/low +GRS and those randomized to receive CRS alone

$$+GRS = GRS \times CRS$$

# Outcome measures

- Primary outcome: LDL-C at 6 months after disclosure of CHD risk
- Secondary outcomes:
  - Dietary fat intake, physical activity levels and new statin initiation
  - Changes in anxiety levels

# Study flow chart



# Study design



Blood  
draw

**Genotyping  
of 28 CHD  
susceptibility  
SNPs**



**GRS**

**Visit 1**

**Completed  
n=216**

**Randomization  
Risk Disclosure**



Meet with  
genetic  
counselor



Meet with  
clinician

**Visit 2**

**Completed  
n=207**



Blood  
draw

LDL-C at 3 months

- Diet & activity
- Anxiety levels
- Statin initiation

**Visit 3**

**Completed  
n=203**



Blood  
draw

**1° outcome**

- LDL-C at  
6 months

**2° outcomes**

- Diet & activity
- Anxiety levels
- Statin initiation

**Visit 4**

**Completed  
n=202**

# Incorporating GRS into risk estimates

10-year risk of heart attack (CRS)



Genetic Risk Score (GRS, from 28 SNPs)



Updated 10-year risk of heart attack (+GRS)

# Integration into EHR

Current Risk
Intervention
Issues
Notes
Document

Benefits vs Downsides according to my personal health information  
Using **Framingham** Risk Calculator

**3. View Issues**

### Current Risk of having a heart attack

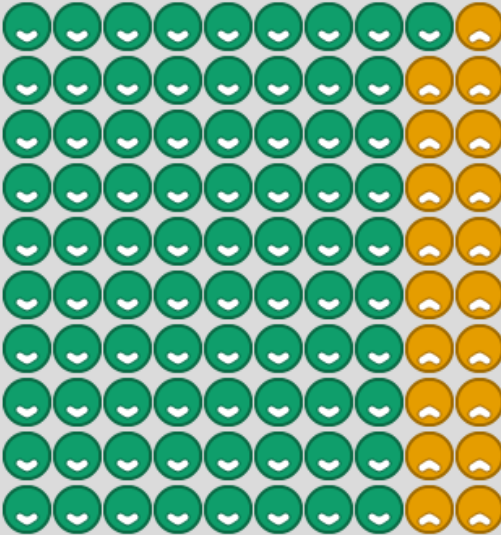
Risk for 100 people like you who **do not** medicate for heart problems

Over 10 years

**19** people will have a heart attack

**81** people will have no heart attack

**6** people will have a heart attack due to genes



GRS  Yes

### Future Risk of having a heart attack

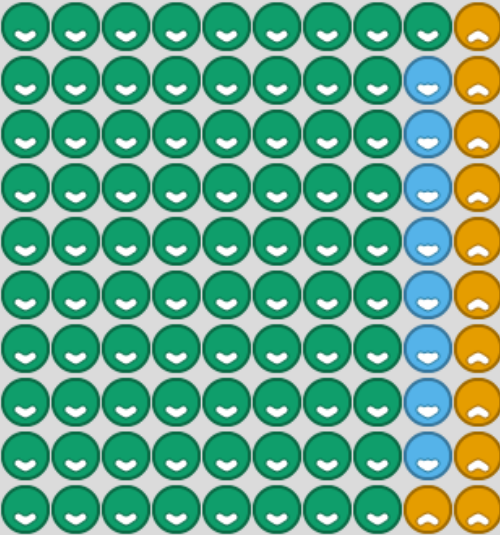
Risk for 100 people like you who do take **standard dose statins** with **aspirin**

Over 10 years

**11** people will have a heart attack

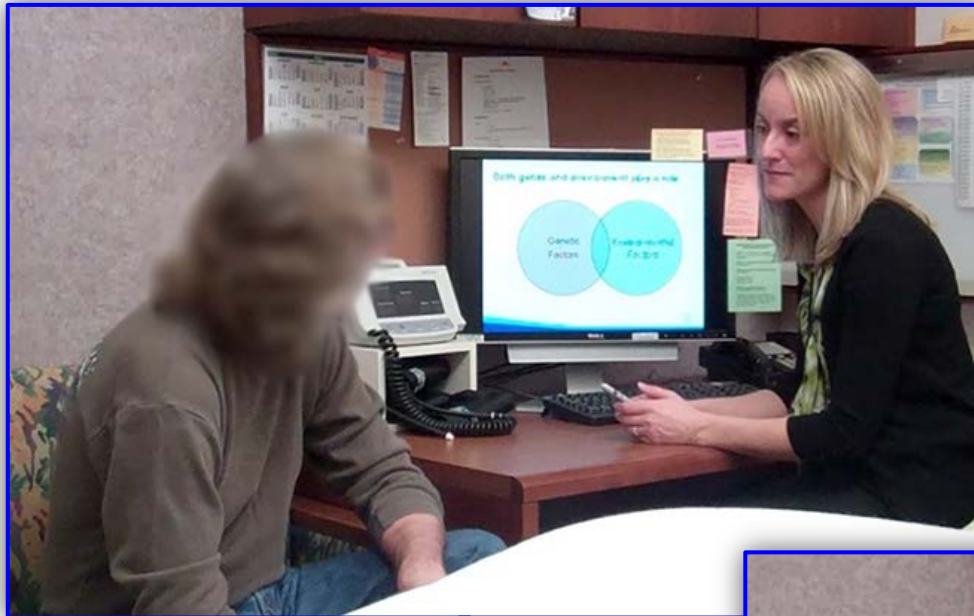
**81** people will have no heart attack

**8** people will be saved from a heart attack by taking medicine

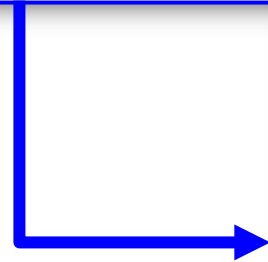


Credits & Contacts

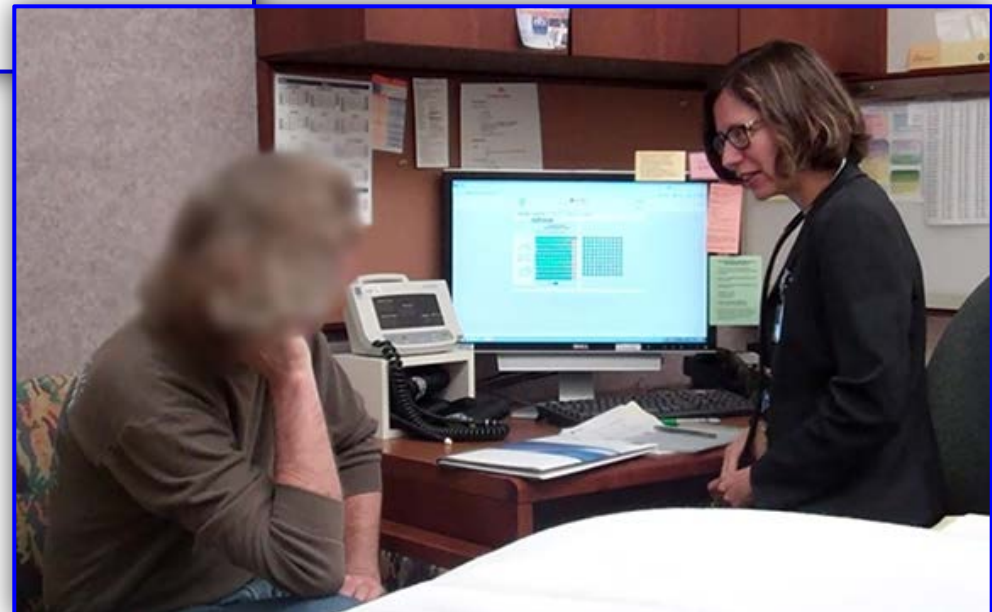




**Disclosure of risk**  
(Genetic Counselor)



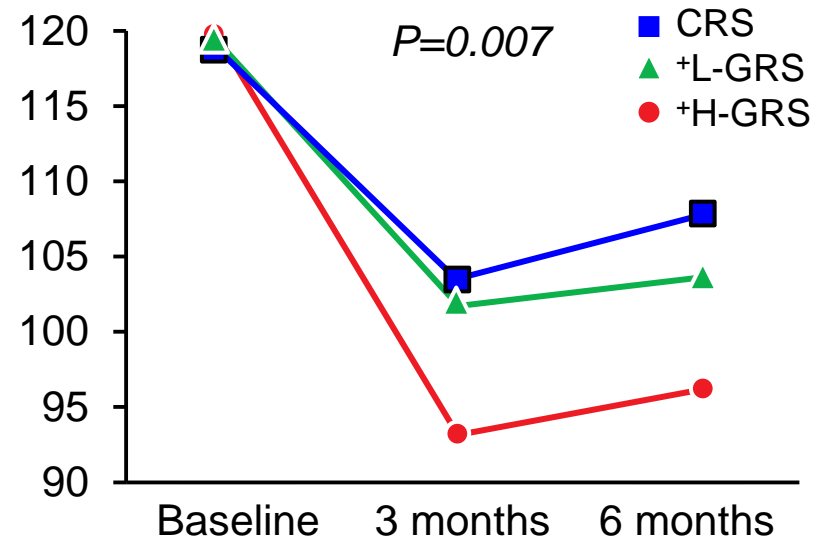
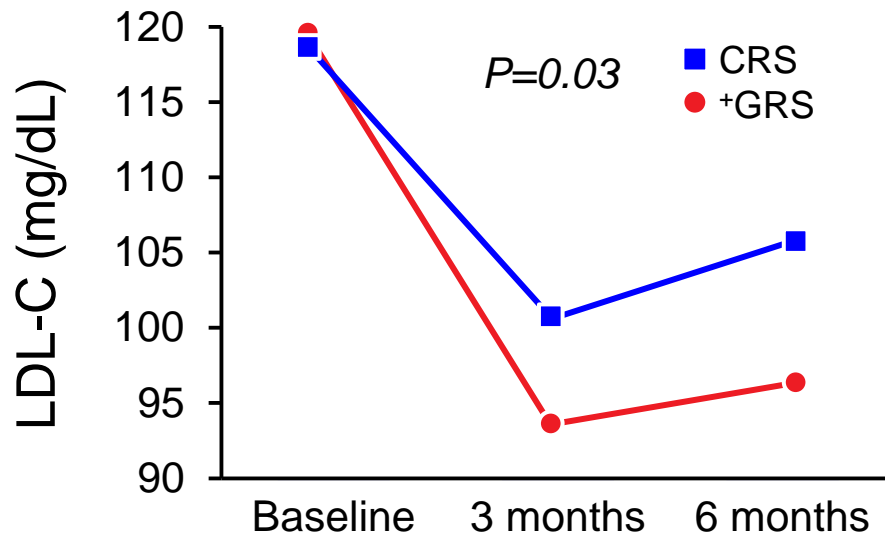
**Shared decision making**  
(Physician)



# Participant characteristics

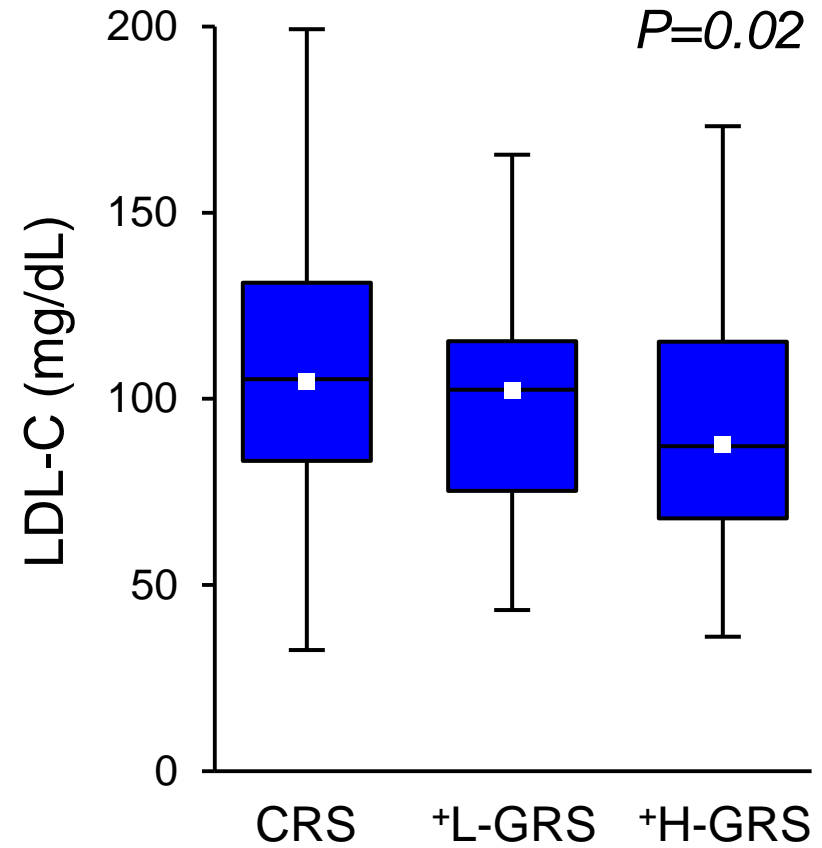
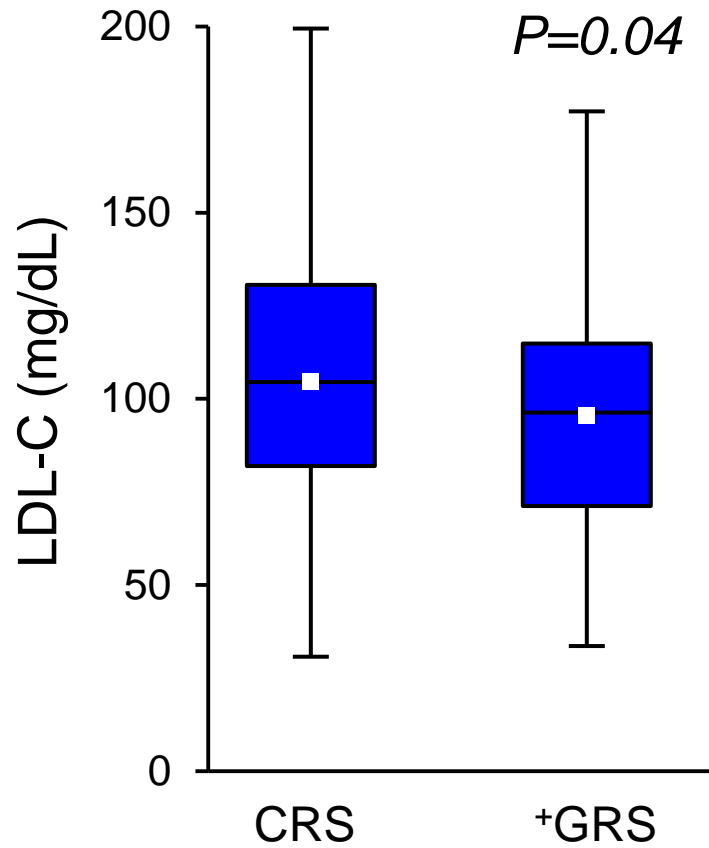
	<b>CRS n=100</b>	<b>+GRS n=103</b>
Age, years	59.4±5.3	59.4±4.9
Male sex, no. (%)	49 (49.0%)	48 (46.6%)
Ever smoker, no. (%)	41 (41.0%)	32 (31.1%)
Family history of CHD, no. (%)	30 (30.0%)	25 (24.3%)
Body mass index (kg/m <sup>2</sup> )	30.5±7.0	30.2±6.1
Total cholesterol (mg/dL)	200.8±30.2	203.3±27.6
LDL-C (mg/dL)	118.8±23.9	119.8±26.4
College education or higher, no. (%)	67 (67.0%)	58 (56.3%)
GRS	1.11±0.30	1.14±0.29
CRS	8.48±3.76	8.56±4.47

# LDL-C levels over the study period

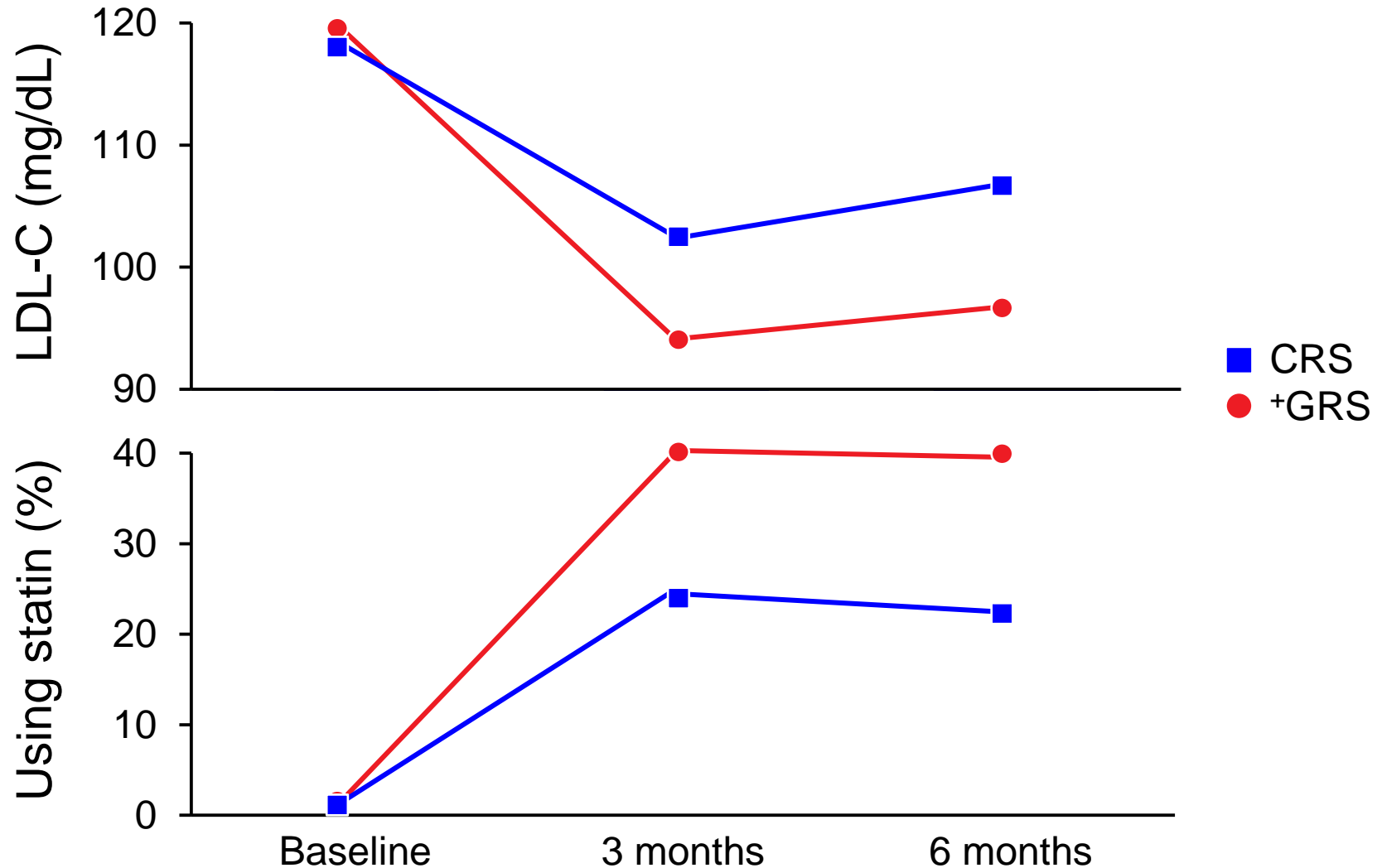


*The between group difference in the slope of LDL-C after randomization was assessed in a mixed effects model*

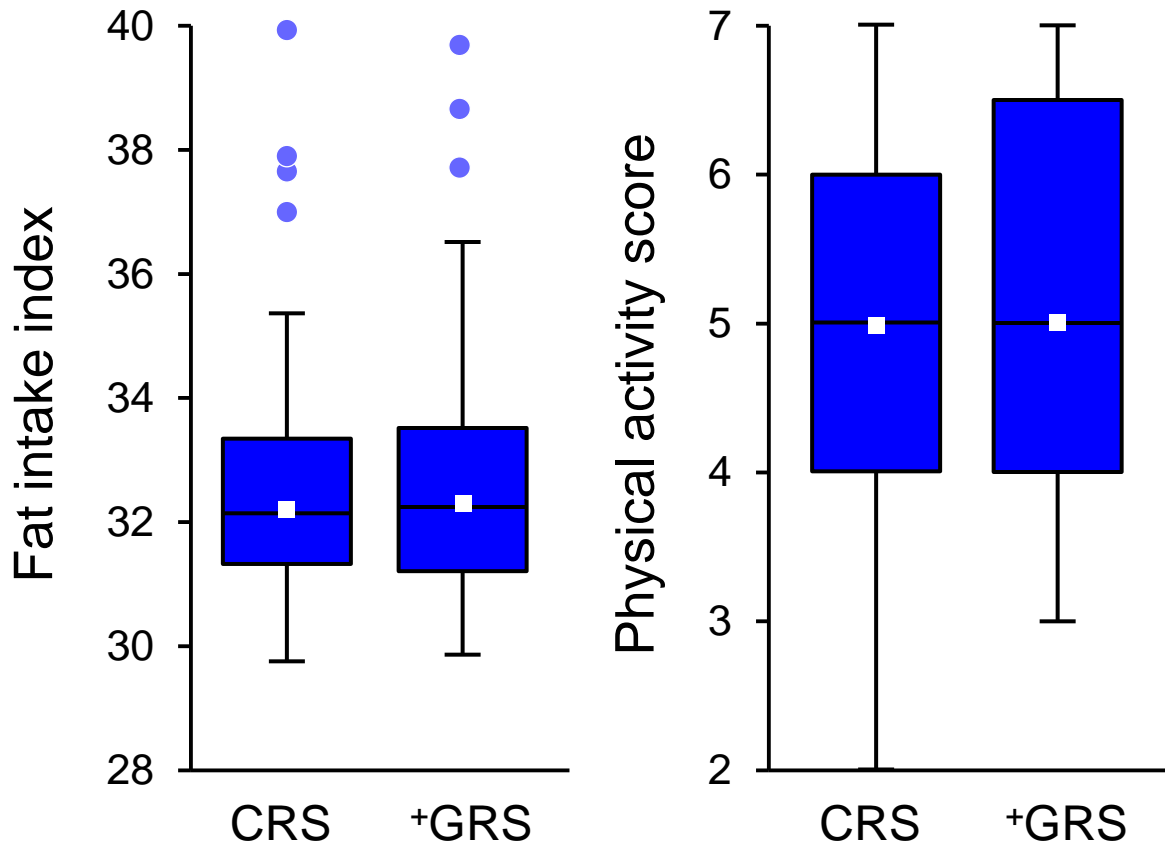
# 6-month LDL-C levels



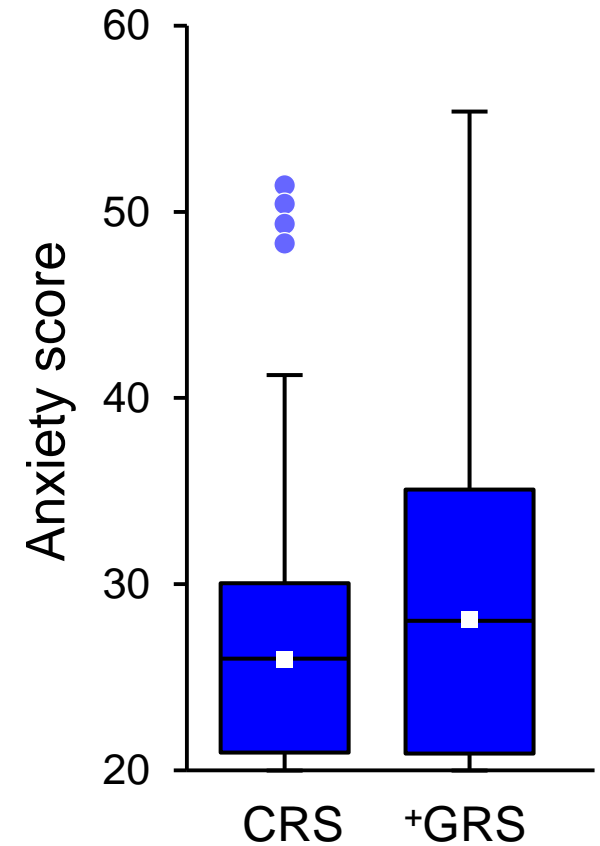
# LDL-C decrease and statin initiation



# Fat intake and physical activity



# Anxiety levels



Thompson FE, J Am Diet Assoc 2007;107:760-767.  
Mayer CJ, Prev Chronic Dis 2008;5:A24.

Spielberger C. Consulting Psychologists Press 1983.

# Conclusions

- Individuals who received a GRS in addition to a conventional risk estimate for CHD had lower LDL-C levels 6 months after disclosure than participants who received a CRS alone
- The lowering of LDL-C was greatest in individuals with a high GRS for CHD compared to participants who did not receive GRS
- Disclosure of a GRS was associated with higher frequency of statin initiation but there were no significant changes in dietary fat intake, physical activity levels, or anxiety

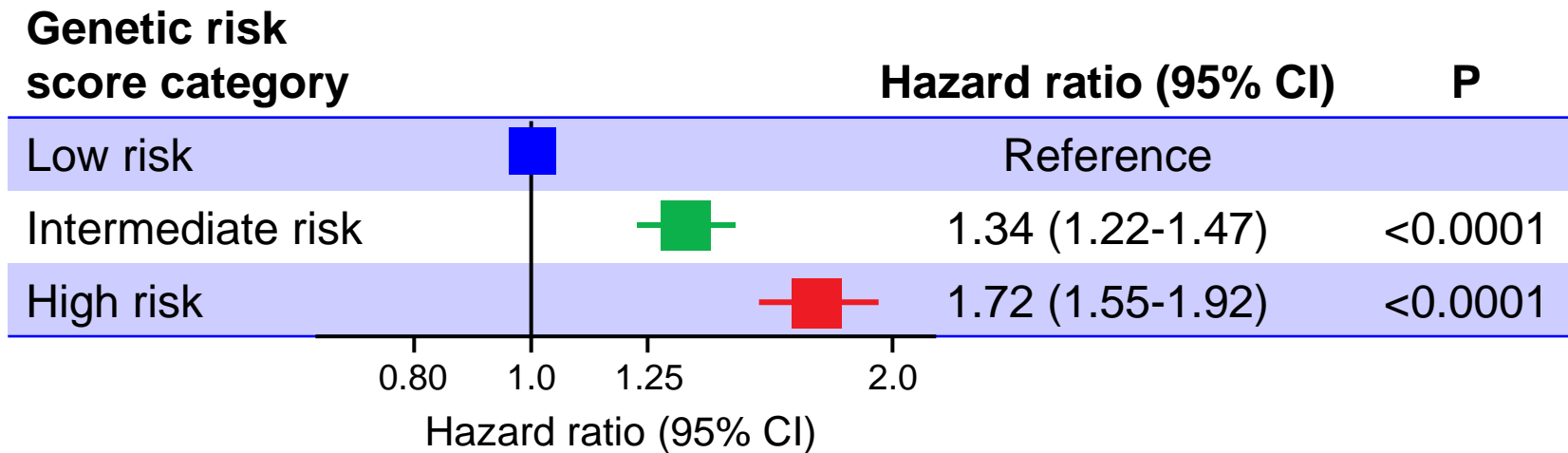
# Strengths

- Investigation of a health outcome (LDL-C) after incorporating a GRS into disease risk estimates
- Integration of genetic risk information for CHD in the EHR with linkage to a genomic decision aid
- Shared decision making in the context of GRS disclosure
- Significant implications for public health since CHD is leading cause of death



# Limitations

- Did not prospectively validate GRS



- GRS derived from odds ratios not hazard ratios
- Additional studies needed for individuals of non-European ethnicity

# Clinical implications & future directions

- We demonstrated feasibility of incorporating a GRS for a common disease in the EHR to enable shared decision making regarding drug therapy
- Disclosure of a GRS led to lower LDL-C levels, particularly in those with high GRS
- These results motivate further investigation of the utility of genetic risk assessment for CHD

# MIGENES Team

- Iftikhar J. Kullo, MD
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- Erin E. Austin, PhD
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**e**merge network  
ELECTRONIC MEDICAL RECORDS AND GENOMICS

**NHGRI HG-06379**



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