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

• Whether knowledge of genetic risk influences relevant clinical outcomes is unclear

• We investigated whether disclosing a genetic risk score (GRS) for CHD derived from 28 genetic variants not related to BP/lipids would lower LDL-C
Hypotheses

• Incorporating a GRS into conventional risk estimates (\(^+\text{GRS}\)) would lead to lower LDL-C levels at 6 months than use of a conventional risk score (CRS)

• Participants with a high \(^+\text{GRS}\) would have lower LDL-C than participants with average/low \(^+\text{GRS}\) and those randomized to receive CRS alone

\(^+\text{GRS} = \text{GRS} \times \text{CRS}\)
Enrollment

Mayo Clinic BioBank
n ~29,352

Met screening criteria
n=2026

Screening genotyping
n=1000

Withdrew
n=9

Enrollment
n=216

207 underwent randomization

103 received conventional 10-yr risk for CHD
At 12-week follow-up
• 3 withdrew
• 100 were assessed

104 received conventional 10-yr risk for CHD and genetic risk information
At 12-week follow-up
• 1 withdrew
• 103 were assessed

Screening criteria
• Age 45-65
• 10-yr CHD risk 5-20%
• Not on statins
• Olmsted County resident

Targeted recruitment
• 110 high GRS (≥1.1)
• 110 average/low GRS (<1.1)
Outcome measures

- Primary outcome
  - LDL-C 6 mos after disclosure of CHD risk
- Secondary outcomes
  - Dietary fat intake
  - Physical activity levels
  - Anxiety levels
  - Statin initiation
Incorporating GRS into risk estimates

10-year risk of CHD (CRS)  

Genetic Risk Score (GRS, from 28 SNPs)  

Updated 10-year risk of CHD (+GRS)  

8% \times 1.3 = 10.4%  

Wilson et al  
Circulation 1998  

Ding et al  
BMC Genomics 2012
Genomic Decision Aid

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

Future Risk
of having a heart attack
Risk for 100 people like you who do take standard dose statins

- 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
Disclosure of risk
( Genetic Counselor)

Shared decision making
( Physician)
Study design

Visit 1
- Genotyping of 28 CHD susceptibility SNPs
- Meet with genetic counselor
- Completed n=216

Visit 2
- CHD Risk Disclosure
- Meet with genetic counselor
- Meet with clinician
- LDL-C at 3 months
  - Diet & activity
  - Anxiety levels
  - Statin initiation
- Completed n=207

Visit 3
- Blood draw
- LDL-C at 6 months
  - Diet & activity
  - Anxiety levels
  - Statin initiation
- Completed n=203

Visit 4
- Blood draw
- 1° outcome
  - LDL-C at 6 months
- 2° outcomes
  - Diet & activity
  - Anxiety levels
  - Statin initiation
- Completed n=202
## Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>CRS</th>
<th>+GRS</th>
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<tbody>
<tr>
<td></td>
<td>n=100</td>
<td>n=103</td>
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<tr>
<td>Age, years</td>
<td>59.4±5.3</td>
<td>59.4±4.9</td>
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<tr>
<td>Male sex, no. (%)</td>
<td>49 (49.0%)</td>
<td>48 (46.6%)</td>
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<td>Ever smoker, no. (%)</td>
<td>41 (41.0%)</td>
<td>32 (31.1%)</td>
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<tr>
<td>Family history of CHD, no. (%)</td>
<td>30 (30.0%)</td>
<td>25 (24.3%)</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>30.5±7.0</td>
<td>30.2±6.1</td>
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<tr>
<td>Total cholesterol (mg/dL)</td>
<td>200.8±30.2</td>
<td>203.3±27.6</td>
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<tr>
<td>LDL-C (mg/dL)</td>
<td>118.8±23.9</td>
<td>119.8±26.4</td>
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<tr>
<td>College education or higher, no. (%)</td>
<td>67 (67.0%)</td>
<td>58 (56.3%)</td>
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<tr>
<td>GRS</td>
<td>1.11±0.30</td>
<td>1.14±0.29</td>
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<tr>
<td>CRS</td>
<td>8.48±3.76</td>
<td>8.56±4.47</td>
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6-month LDL-C levels

Comparison:
- CRS
- +GRS

Statistical Significance:
- P=0.04
- P=0.02

Variables:
- LDL-C (mg/dL)
- CRS
- +GRS
- +L-GRS
- +H-GRS
LDL-C levels over the study period

Between group difference in the slope of LDL-C after randomization was assessed in a mixed effects model.

P=0.03

P=0.007
Fat intake and physical activity

Fat intake index

Physical activity score

Anxiety score


LDL-C decrease and statin initiation

- LDL-C (mg/dL)
- Using statin (%)

Baseline 3 months 6 months

LDL-C decrease and statin initiation

- CRS
- +GRS
Conclusions

• Disclosure of a CHD risk estimate that included genetic information led to lower LDL-C levels at 6 months than disclosure of a conventional risk estimate.

• The lowering of LDL-C was greatest in individuals with a high GRS for CHD.

• 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

• Integration of genetic risk information for a common disease in the EHR with linkage to a genomic decision aid

• Shared decision making in the context of GRS disclosure

• Incorporating a GRS into disease risk estimates to alter a relevant health outcome (LDL-C)
Limitations

• Prospective validation of GRS

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<tr>
<th>Genetic risk score category</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>Low risk</td>
<td>Reference</td>
<td></td>
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<tr>
<td>Intermediate risk</td>
<td>1.34 (1.22-1.47)</td>
<td>&lt;0.0001</td>
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<tr>
<td>High risk</td>
<td>1.72 (1.55-1.92)</td>
<td>&lt;0.0001</td>
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• Additional studies needed for individuals of non-European ancestry

Mega et al, Lancet 2015; 385: 2264-71
Clinical implications

• Genetic risk information for CHD can be effectively incorporated in the EHR and used at point of care to guide therapy

• Disclosure of a GRS led to lower LDL-C levels, more so in those at higher genetic risk

• Our study exemplifies Precision Medicine and motivates further investigation of the clinical utility of genetic risk assessment for prevention of CHD
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