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

Iftikhar J. Kullo, M.D.

Late-breaking Clinical Trials
AHA Scientific Sessions, Orlando FL
November 9, 2015
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 x 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
Mayo Clinic BioBank  
n ~29,352

Met screening criteria  
n=2026

Screening genotyping  
n=1000

Enrollment  
n=216

Withdraw  
n=9

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-y risk for CHD and genetic risk information

At 12–week follow-up  
• 1 withdrew  
• 103 were assessed

Screening criteria
• Age 45-65
• No prior history of CHD
• 10 yr CHD risk 5-20%
• Not on statins
• Olmsted County resident

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

3. View Issues
Disclosure of risk
(Genetic Counselor)

Shared decision making
(Physician)
## Participant characteristics

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

- **CRS vs. +GRS**
  - P = 0.04

- **CRS vs. +L-GRS vs. +H-GRS**
  - P = 0.02

LDL-C (mg/dL) range from 50 to 200.
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

- Using statin (%)

- Baseline 3 months 6 months

- LDL-C (mg/dL)
Fat intake and physical activity

Fat intake index

Physical activity score

Anxiety score

CRS  +GRS

CRS  +GRS

CRS  +GRS

CRS  +GRS


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

<table>
<thead>
<tr>
<th>Genetic risk score category</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>1.34 (1.22-1.47)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High risk</td>
<td>1.72 (1.55-1.92)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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