Development and Application of Polygenic Risk Scores

Eric Boerwinkle
Silver Springs
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Why Do We Study Human Genomics?

1. Teaches us a little bit about who we are and where we came from…

2. The biology of disease and novel therapeutic strategies…

3. Prediction…

“It’s Difficult to Make Predictions, Especially About the Future.”
Niels Bohr (maybe)
Some editorial comments about GRS/PRS:
1. They are not new.


(MS. received June 15, 1918. Read July 8, 1918. Issued separately October 1, 1918.)

Analysis of several hundred genetic polymorphisms may improve assessment of the individual genetic burden for coronary artery disease.

Prediction of Coronary Heart Disease Risk using a Genetic Risk Score: The Atherosclerosis Risk in Communities Study.
Steps of Genetic Risk Scores

1. Selection of SNPs from discovery studies (usually large GWAS).
   a. Independent sentinel SNPs
   b. p-value threshold
2. Building/Calculating the GRS/PRS
   a. Weighted vs Unweighted
   b. Parameter estimation
3. Estimation of an individuals risk of disease
   a. Relative
   b. Absolute
Strong Methodologic Underpinnings

1. Parameter estimation
   Shrinkage (take into account other info)

2. Relative risk to absolute risk

\[ R_{a,a+s} = \int_a^{a+s} l(u|Z) \exp\left(-\int_a^u \{l(v|Z) + m(v|Z)\} dv\right) du \]

3. Evaluation

![Comparing ROC Curves](image)
GWAS of CHD


Now Surpassed the 1 million person mark

Genome-Wide Association Study of Coronary Heart Disease and Its Risk Factors in 8,090 African Americans: The NHLBI CArRe Project Lettre et al. 2011. Plos Genetics
9p21 SNP rs10757274 and CHD Risk

Relative Risk

<table>
<thead>
<tr>
<th></th>
<th>AA</th>
<th>AG</th>
<th>GG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
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<tr>
<td>1</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>1.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

Absolute Risk

<table>
<thead>
<tr>
<th></th>
<th>AA</th>
<th>AG</th>
<th>GG</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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</tr>
<tr>
<td>10</td>
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<tr>
<td>12</td>
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</tr>
<tr>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

ARIC
• GRS ranges from minus 10 to plus 10
• High-GRS group comprises 18% of the ARIC population
• The HRR for CHD was 2.1 for the high GRS group compared to the low GRS group
## Predictive Ability of Risk Scores

### Blacks

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>ΔAUC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD Risk Score only</td>
<td>0.7588</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Add GRS</td>
<td>0.7719</td>
<td>0.013</td>
<td>Significant</td>
</tr>
<tr>
<td>Remove Hypertension</td>
<td>0.6988</td>
<td>0.06</td>
<td>Significant</td>
</tr>
<tr>
<td>Remove LDL</td>
<td>0.7578</td>
<td>0.001</td>
<td>Not significant</td>
</tr>
<tr>
<td>Add CRP</td>
<td>0.7608</td>
<td>0.002</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

*Individual risk factors do not cause large changes in the area under the CHD Risk Score ROC curve*
Some editorial comments about GRS/PRS:

2. So, why now?

A. We have genes (maybe?)......

B. ...now do something with them.
Putting the Pieces Together

Possible clinical decisions

- General advice on having a healthy lifestyle
- Mammography screening frequency tailored to risk
- Lifestyle changes
  - Frequent mammography screening
  - Discuss preventive therapies
- Individual counselling in primary care and referral to secondary or tertiary care
- Enhanced screening and surveillance
- Chemoprevention and/or endocrine therapy
- Risk-reducing surgery (mastectomy, salpingo-oophorectomy)

Absolute risk

Near or lower than average risk (≤15%)
Moderately increased risk (15–25%)
High risk (≥25%)

Possible risk factor profile

- No family history of breast cancer, low to moderate polygenic risk, and none or few environmental risk factors
- No family history of breast cancer, moderate polygenic risk and several environmental risk factors
- Moderate to high polygenic risk with family history of breast cancer and many environmental risk factors, or known BRCA1 and BRCA2 or TP53 mutation carriers for very high risk

Chatterjee et al. Nat Rev Genet 17: 392
Example Patient #1

- Female, age 57, taking hypertension medications
- LDL-C of 150 mg/dL
- 10-year CHD risk of 15%
- According to ATP III, “intermediate high” category
- The addition of 9p21 genotype (GG) for this woman puts her 10–year risk at 21%
- Recommend initiating drug therapy at >130 mg/dL, with a goal of <100 mg/dL
# ATP III Guidelines

<table>
<thead>
<tr>
<th>CHD and CHD risk equivalents</th>
<th>ATP III classification using ACRS alone</th>
<th>ATP III classification using ACRS + 9p21 allele</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-year risk &gt;20%</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>LDL-C goal &lt;100 mg/dL</td>
<td>1,870 (372)</td>
<td>1760 (360)</td>
</tr>
<tr>
<td></td>
<td>18.69%</td>
<td>3.95%*</td>
</tr>
<tr>
<td>Multiple (2+) risk factors</td>
<td>Mid-high</td>
<td>2,049 (219)</td>
</tr>
<tr>
<td>10-year risk 10–20%</td>
<td></td>
<td>20.48%</td>
</tr>
<tr>
<td>LDL-C goal &lt;130 mg/dL</td>
<td>Mid</td>
<td>1,737 (80)</td>
</tr>
<tr>
<td></td>
<td>17.36%</td>
<td>10.31%*</td>
</tr>
<tr>
<td>Multiple (2+) risk factors</td>
<td>Low</td>
<td>4,349 (107)</td>
</tr>
<tr>
<td>10-year risk &lt;10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C goal &lt;130 mg/dL</td>
<td>Total</td>
<td>10,004 (778)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(100%)</td>
</tr>
</tbody>
</table>

* Percentage of people re-classified. (Number of events on 10 years of follow-up.)
Genes, Environments and Time
Genes & Life Style & Risk

A 50 Locus GRS

Smoking, BMI, Exercise, Diet

Atherosclerosis Risk in Communities
Genetic Risk

- Genetic Risk: Low (Reference)
- Intermediate, HR 1.27 (1.09 – 1.49)
- High, HR 1.75 (1.46 – 2.10)

Atherosclerosis Risk in Communities
Lifestyle Risk

- Lifestyle Risk: Favorable (Reference)
- Intermediate, HR 1.18 (1.02 – 1.36)
- Unfavorable, HR 1.71 (1.47 – 1.98)
Genes & Life Style & Risk

Atherosclerosis Risk in Communities

Data from Khera et al, (NEJM)
AD Rates by ApoE and GRS
Early Genotype-Directed Primary Prevention Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants</th>
<th>Treatment</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>API: Alzheimer’s Prevention Initiative</td>
<td>300 members of Colombian families, including 100 carriers of a mutated <em>PSEN1</em> gene</td>
<td>Crenzumab (Genentech)</td>
<td>Primary: Cognitive. Secondary: Biomarkers, including brain scans to measure amyloid accumulation and brain atrophy</td>
</tr>
<tr>
<td>DIAN: Dominantly Inherited Alzheimer Network</td>
<td>240 members of families with early-onset Alzheimer’s; 60 have a mutation in one of three genes</td>
<td>Three anti-amyloid therapies to be determined</td>
<td>An initial phase will use biomarkers to identify the most promising drug candidate for a follow-up phase to examine cognitive effects</td>
</tr>
<tr>
<td>A4: Anti-Amyloid Treatment of Asymptomatic Alzheimer’s</td>
<td>1500 healthy seniors, including 500 with amyloid-positive brain scans</td>
<td>One anti-amyloid therapy to be determined</td>
<td>Primary: Cognitive Secondary: Biomarkers</td>
</tr>
</tbody>
</table>
Performance of GRS/PRS across ancestry groups

1. Selection of SNPs from large GWAS.
   Different SNPs
2. Building/Calculating the GRS/PRS
   Different parameter estimates
3. Estimation of an individuals risk of disease
   Different absolute risk equations and inputs

From Martin et al, Nature Genetics, 51: 584.
“PRS are of burgeoning interest to the clinical community”

1. Risk score use was dependent on several factors, including IT support, clinical relevance for daily practice, rotation of staff and workload.
2. The scores were seen as valuable support systems in improving uniformity in treatment practices, educating interns, conducting research and quantifying a practitioner’s own risk assessment.

1. No evidence of harm.
2. No evidence of improved endpoint outcomes
3. Evidence of improved risk factor control.

1. 34% report regular use of risk scores.
2. Use correlates with increased use of prescribed meds.
Some editorial comments about GRS/PRS:
3. But what is their future?
Time to take a Deep Dive into Healthcare!

1. Hierarchical Conditional Categories (HCC).

2. Determines per member per month for CMS and many ACO plans.

3. How’s it calculated? You guessed it…….
But Don’t Despair: Dive into the Deep End!

1. Hierarchical Conditional Categories.

2. Determines per member per month for CMS and many ACO plans.

3. It is based on risk scores, which are then used to calculate a risk adjustment factor.

4. The RAF is used to estimate prospective health care costs which turn into monthly payments.
HCC: Critical Element of Risk Management

Implement an HCC Best Practice – PYA’s HCC Checkup

Since 2004, Hierarchical Condition Categories (HCC) have been a foundational element of the Centers for Medicare & Medicaid’s (CMS) capitated payments, value-based reimbursement methodology.

HCC risk-adjusted framework is used through private and public plan contracts to better manage and modulate payments.

Precise HCC Coding

The core of reimbursement

HCCs use RAFs to:
- Capture complex health conditions
- Determine capitated payments with reimbursement rates based on 12-month retrospective patient diagnostic record
- Renew HCC scores every year

Risk Adjustment Factors (RAFs)

Our second goal is for virtually all Medicare fee-for-service payments to be tied to quality and value; at least 85% in 2016 and 90% in 2018.

- Sylvia Burwell, the Secretary of HHS

Seismic financial implications are associated with inaccurate HCC coding.

Coding needs to accurately reflect
Inputs into the Risk Score Modeling

Characteristics of CMS-HCC Model

- HCCs/Multiple Chronic Diseases
  Base payment for each member based on HCCs and influenced by Medicare Costs for Chronic Diseases

- Disease Interactions
  Additional factors applied when hierarchy of more severe and less severe conditions co-exist

- Characteristics of CMS-HCC Model
- Prospective in Nature
  Diagnosis from base year used to predict payment for next year
  New Enrollee vs Existing Enrollee

- Demographics
  Final adjustment due to: age, sex, original Medicare entitlement, disability & Medicaid status

Uses ICD-10 codes

Diagnostic Sources
CMS will only consider diagnoses from IP & OP Hospital & Physician Data
Inputs into the Risk Score Modeling

Characteristics of CMS-HCC Model

- **HCCs/Multiple Chronic Diseases**: Base payment for each member based on HCCs and influenced by Medicare Costs for Chronic Diseases.
- **Disease Interactions**: Additional factors applied when hierarchy of more severe and less severe conditions co-exist.
- **Prospective in Nature**: Diagnosis from base year used to predict payment for next year. New Enrollee vs Existing Enrollee.
- **Demographics**: Final adjustment due to: age, sex, original Medicare entitlement, disability & Medicaid status.

Diagnostic Sources: CMS will only consider diagnoses from IP & OP Hospital & Physician Data.

Add genes here
The HeartCare Gene Panel tests 158 genes associated with Cardiovascular Disease. See page 2 for more details.

**Patient:** PFirstNameTEST6 PMidNameTEST6 PLastNameTEST6

**Date of Birth:** 01/31/1990

**MRN:** CT006

**Reason for Testing:** Other, Arrhythmia, Cardiomyopathy

**Ordered By:** Dr CHI A

### 158 Cardiac Gene Panel: NEGATIVE

No pathogenic or likely pathogenic variants were found.

### Coronary Artery Disease Polygenic Risk Score: HIGH

The patient is in the high genetic risk group (top 5%) for developing coronary artery disease. This result is independent of the high impact variants identified in the 158 Cardiac Gene Panel described above that may provide a more accurate estimation of overall cardiovascular disease risk.

**Recommendations:** Studies show that a healthy lifestyle like the AHA’s Life’s Simple 7 is associated with a nearly 50% lower risk of coronary artery disease. Learn more at https://www.heart.org/MyLifeCheck. Other factors may influence risk of developing cardiovascular disease, including environment and ancestry. This score was developed in a group of Caucasian subjects and its applicability to other ethnicities is unclear.

### Pharmacogenetics Findings

Individual carries two normal function alleles in SLC01B1.

**Recommendations:** Prescribe desired starting dose and adjust doses of simvastatin based on disease-specific guidelines. Avoid drugs that are known to interact with simvastatin.

This individual is predicted to be a normal responder to Warfarin.

**Recommendations:** This individual may respond to normal maintenance Warfarin doses. A Warfarin dosing algorithm based on common genetic variants, race, and clinical information is available at WarfarinDosing.org.
Summary

1. Mendelian and common disease gene discovery are supporting the foundation of GRS/PRS.

2. They are likely a useful research tool, including clinical trials, but their application to healthcare is questionable.

3. Human genomics needs to engage in implementation science focused on real-world healthcare settings.