Polygenic Risk Research
Lessons Learned From the Pre-GWAS days

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Clinical validity of multiple genetic testing in complex diseases

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Many current issues in prediction look like what was discussed in pre-GWAS days.
First mentions of genetic information, susceptibility for common diseases, not yet polygenic models
2002

Polygenic susceptibility to breast cancer and implications for prevention

Paul D.P. Pharoah\textsuperscript{1,2}, Antonis Antoniou\textsuperscript{3}, Martin Bobrow\textsuperscript{4}, Ron L. Zimmern\textsuperscript{2}, Douglas F. Easton\textsuperscript{3} & Bruce A.J. Ponder\textsuperscript{1}

Published online: 4 March 2002, DOI: 10.1038/ng853

- First mention of risk distributions
- Fitted on cancer data from relatives of BC patients
- Concluded that polygenic model fitted well
- No mention of individual variants or how to build polygenic risk models

\textbf{Fig. 1} Distribution of breast cancer risk in the population and in individual cases. Risks are shown on a log scale; the arithmetic average risk for the entire population has been set at 1.0 (see Methods). The risk distribution in individuals who will develop breast cancer (cases) is shifted to the right. The standard deviation describes the spread of risk between high and low values within the population, and thus the potential to discriminate different levels in different individuals.
• **First** study to show how multiple genes can be combined to predict risk, using regression analysis
• Focused on posterior risk for carriers of one or more multiple risk alleles
• (very strong per-allele effects by today’s standards (RR 1.5-3.5))
Evaluation of test performance should include all people, also noncarriers of risk alleles

Proposed using Area under the Receiver Operating Curve (AUC)
Pre-GWAS ➔ no SNP data to work with

Two major advantages:

- Had to use simulated data: all parameters (# SNPs, ORs, allele freqs, population risk) can be varied to investigate and help understand impact on predictive performance of polygenic risk ➔ If simulation is valid, then its observations apply to real data too
- Were not in a hurry: there was time to think about how to evaluate polygenic risk
When can a risk factor be used as a worthwhile screening test?

N J Wald, A K Hackshaw, C D Frost

Summary points

To be a worthwhile screening test, a risk factor must be strongly associated with a disorder

Fig 4 Distribution of maternal serum α fetoprotein in pregnancies affected and unaffected by open spina bifida (derived from Wald et al²) and distribution of serum cholesterol in men who did and did not die of ischaemic heart disease (derived from Wald et al¹)
Type 2 diabetes

AUC = 0.60

AUC = degree of separation between risk distributions of affected and unaffected individuals—nothing more, nothing less

0.50: complete overlap ~ random prediction
1.0: complete separation ~ perfect prediction

AMD

AUC = 0.76

Lango et al Diabetes 2008

Seddon et al. IOVS 2009
How to get high AUC: common variants with strong effects

### Type 2 diabetes

AUC = 0.60

<table>
<thead>
<tr>
<th>Gene</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCF7L2</td>
<td>1.36</td>
</tr>
<tr>
<td>KCNJ11</td>
<td>1.25</td>
</tr>
<tr>
<td>CDKN2A/2B</td>
<td>1.21</td>
</tr>
<tr>
<td>PPARG</td>
<td>1.21</td>
</tr>
<tr>
<td>ADAM30</td>
<td>1.15</td>
</tr>
<tr>
<td>CDNK2A/2B</td>
<td>1.13</td>
</tr>
<tr>
<td>IGF2BP2</td>
<td>1.12</td>
</tr>
<tr>
<td>FTO</td>
<td>1.11</td>
</tr>
<tr>
<td>CDKAL1</td>
<td>1.11</td>
</tr>
</tbody>
</table>

### Hypertriglyceridemia

AUC = 0.80

<table>
<thead>
<tr>
<th>Gene</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOA5 19WW</td>
<td>7.36</td>
</tr>
<tr>
<td>APOA5 -1131CC</td>
<td>5.57</td>
</tr>
<tr>
<td>APOE non-e3</td>
<td>2.14</td>
</tr>
<tr>
<td>GCKR TT</td>
<td>2.11</td>
</tr>
<tr>
<td>TRIB1 AA</td>
<td>2.02</td>
</tr>
<tr>
<td>TBL2 CC</td>
<td>2.81</td>
</tr>
<tr>
<td>GALNT2 GG</td>
<td>2.10</td>
</tr>
</tbody>
</table>

No exception: only strong variants lead to higher AUC
(higher AUC = more separation risk distributions)

Simulation study: impact of number of genes and OR on AUC

All variants same OR

First 20 variants: ORs from <max> to 1.15
Allele freq from 0.05 to 0.30
Next 380 variants: OR from 1.15 to 1.05
Allele freq from 0.30 to 0.50

Predictive performance polygenic risk scores

- Mostly modest: AUC up to ~0.65
- AUC generally (much) lower than clinical prediction models
- Modest improvement beyond clinical models
- Exceptions when some SNPs have stronger effects, e.g., age-related macular degeneration, Crohn disease

- Can we do better?
Quality of Prediction = quality of data & quality of prediction model

<table>
<thead>
<tr>
<th>Data</th>
<th>Model</th>
<th>Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>Excellent</td>
<td>Excellent</td>
</tr>
<tr>
<td>Excellent</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Poor</td>
<td>Excellent</td>
<td>Poor</td>
</tr>
<tr>
<td>Poor</td>
<td>Poor</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Much focus on data these days: how are we doing on modeling risk?
Polygenic risk score poor reflection of pathways

\[ \text{score} = \beta_1 \cdot \text{snp}_1 + \beta_2 \cdot \text{snp}_2 + \ldots + \beta_n \cdot \text{snp}_n \]
How about modeling clinical + genetic models?
From pre-GWAS: genes ‘only’ improve prediction if not mediated

Adapted from: Janssens & van Duijn, Hum Mol Genet 2008
From pre-GWAS: genes ‘only’ improve prediction if not mediated

Adapted from: Janssens & van Duijn, Hum Mol Genet 2008
When predisposing genes are *combined* in polygenic risk score, the resulting score is no longer related to each clinical risk factor.
Because polygenic risk score is no longer associated to clinical risk factors, score seems independent risk factor.

- Polygenic Risk Score
- Blood pressure
- Cholesterol
- CHD

Janssens et al. Submitted
Modeling polygenic risk scores should be improved so that clinical risk factors get opportunity to mediate
e.g.:

\[ \text{PRS}_{\text{BP}} \rightarrow \text{Blood pressure} \]

\[ \text{PRS}_{\text{Chol}} \rightarrow \text{Cholesterol} \]

\[ \text{PRS}_{\text{Other}} \rightarrow \text{?} \]

\[ \text{CHD} \]
Can causal mechanisms of complex outcomes be modeled or are their causes too complex?
Herald of Free Enterprise
Capsized on March 6 1987, killing 193 people

Capsized because multiple factors happened simultaneously, among which:
- Bow doors open: responsible employee had fallen asleep and there was no double checking of doors
- Full ballast tanks → ship lower on water
- Delayed departure → higher speed → higher waves
- Open car compartment, cars not secured → adding imbalance

Janssens & van Duijn *Hum Mol Genet* 2008
Why-Because Graph
Herald of Free Enterprise,
March 6th, 1987

0
Herald of Free Enterprise (HFE) capsizes

0.1
HFE becomes unstable

0.1.1
Water accumulates along entire length of one side of the G deck (lower car deck)

2
No subdividing bulkheads present

1
Water flows onto main car deck

1.1
Bow wave rises above bow spade

1.1.1
HFE is trimmed by the head (0.8 m)

1.1.1.1
Not all the water is pumped out of tanks before leaving port

1.1.1.2
Water is pumped into bow tanks for car loading

1.1.1.3
Cost of high-capacity pump considered prohibitive

1.1.2
Master increases speed setting combinator 6 after passing outer mole

1.1.2.1
Master assumes that bow doors were closed on the way to the outer mole (18:05-18:24)

1.1.2.1.1
Design of bow doors (closing horizontally)

1.1.2.1.2
Master's position (bridge)

1.1.2.1.3
Suggested improvement based on near misses dismissed by Management

1.1.2.1.3.1
Standing orders contain "negative reporting"

1.2
Bow doors are open

1.2.1
Bow doors are not closed on the way to the outer mole (18:05-18:24)

1.2.1.1
Assistant Bosun does not close bow doors

1.2.1.2
Officer loading G deck did not ensure that bow doors were secure when leaving port (violation of instruction issued in July 1984)

1.2.1.2.1
Assistant Bosun is asleep in cabin

1.2.1.2.2
Assistant Bosun does not wake up at harbour station call (18:00)

Figure 2 - Why-Because Graph
ACCE model: evaluating genetic tests

• Comprehensive framework
• Key: Disorder & Setting: What is predicted in whom, for what purpose?
• Assessment changes if setting changes (different population or purpose)
• Claims often based on statistical significance of PRS association
  ➔ Association determines clinical validity but itself is not part of evaluation
Purpose: Increasing efficiency of healthcare

Then: keeping healthcare costs the same, but redistribute efforts
Now: often proposing ‘new’ care to high-risk groups, but is more care affordable?
Purpose: Changing health behavior

- Little (no?) evidence of long-term impact on health behavior
- Limitation: mostly simple tests or simple risk scores; impact unknown when polygenic risk scores are really predictive
- Future: not one PRS, but for every disease

What is behavioral response when:

**PRS report**

- **High**: CVD
- **Average**: type 2 diabetes, dementia
- **Low**: obesity, asthma, depression

Vineis et al., *Lancet*, 2001
Moving forward

• Improve modeling to better reflect underlying mechanisms
  – May increase predictive performance of polygenic risk scores
  – May reduce their value added to clinical factors

• Improve assessment of potential utility of polygenic risk scores
  – Assess scores in target population
  – Apply appropriate performance metrics
  – Interpret in appropriate context: predictive enough? Actionable/informative? Affordable?
  – Compare with existing (nongenetic) risk models
WILL GENETICS REVOLUTIONIZE MEDICINE?

In our rush to fit medicine with the genetic mantle, we are losing sight of other possibilities for improving the public health. Differences in social structure, lifestyle, and environment account for much larger proportions of disease\textsuperscript{42,43} than genetic differences. Although we do not contend that the genetic mantle is as imperceptible as the emperor’s new clothes were, it is not made of the silks and ermines that some claim it to be. Those who make medical and science policies in the next decade would do well to see beyond the hype.

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Theresa M. Marteau, Ph.D.