POLYGENIC RISK SCORES FOR RISK ASSESSMENT

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INTRODUCTION

Het begint met een idee
60% of total deaths are due to common medical conditions\(^1\)

- Largest contributors are CVDs (30%) and cancers (13%)

Common variants often explain 30–60% of variation\(^2\)

\(1\) Bloom. (2011). *World Economic Forum and the Harvard School of Public Health*

GENOME-WIDE ASSOCIATION STUDIES (GWAS)

- Rapid scientific revolution
  - Hundreds of common conditions
- GWAS “scan” the genome for association by comparing diseased versus healthy
- Pathways and biological mechanisms are not always direct
  - Lung cancer and smoking

Manolio et al. (2013). *Nature Reviews Genetics.*

THE BIG PROBLEM OF SMALL EFFECTS

$R^2$ vs. $N$ (50% power for $p = 5 \times 10^{-8}$)*

First GWAS hits for Alzheimer’s
First hits for BMI / height
First hits for Bipolar / Schizophrenia
First hits for IQ

* Bonferroni-corrected “genome-wide” significance threshold
GWAS FINDINGS

- Atrial fibrillation, $N = 1$ million
  - Predicts CVD, stroke, and dementia

**IMPORTANT ADVANCES**

- Decreasing cost of genotyping and low-depth sequencing
  - Below €20
  - Affordability of direct-to-consumer

- New biobank initiatives ($n > 500k$)

- Phenome-wide analyses
  - Efficient parallel computing

- Rare and structural variation
Het begint met een idee

POLYGENIC SCORES
Accuracy of many variants can be substantial

- Upper bound defined by the SNP heritability, often 20–50%\(^1\)

Polygenic scores (PGS) sum genetic liability across many variants into an index:

\[
\hat{S}_i = \sum_{j=1}^{J} \hat{\beta}_j g_{ij}
\]  

GWAS summary statistics (\(\hat{\beta}_j\)) as input

- Not only GWAS hits predictive, \(P\) value cutoff
- Many statistical purposes

\(^{1}\) Speed et al. (2017). *Nature Genetics.*
PROOF OF CONCEPT

- PGS *can* stratify diseased versus healthy

But the effect is limited!

PGS 20% vs. 80% (1% vs. 99%) \(^1\)
- CAD: OR = 2.55 (4.83)
- Atrial fibrillation: OR = 2.43 (4.63)
- Type 2 diabetes: OR = 2.33 (3.30)
- IBD: OR = 2.19 (3.87)
- Breast cancer: OR = 2.07 (3.36)

Smoking (>30/day) and lung cancer: OR = 100 \(^2\)

Index of blood lipids and heart attack: OR = 30 \(^3\)

BMI and CAD: OR = 1.25 / 5 BMI \(^4\)

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1 Khera et al. (2018). *Nature Genetics.*
3 Goswami et al. (2012). *Clinical Biochemistry.*
4 Labounty et al. (2013). *European Heart Journal Cardiovascular Imaging.*
Genetic risks increased/offset by lifestyle\(^1\)

Test can lead to early diagnosis, prevention, and treatment

Conceivable lifestyle changes

- Cancer risk – smoking, occupational choice
- CVD & Diabetes – diet, physical activity, medication

PGS informative of lifestyle, such as smoking intensity

- Can complement to expensive phenotyping

\(^1\) Inouye et al. (2018). *Journal of the American College of Cardiology.*
DIRECT-TO-CONSUMER GENETIC TESTS

- Limited accuracy and few polygenic risks
  - Hard to interpret
- Penetrant variants BRCA1/APOE
- Some PGS offered by free services
  - Requires genetic test from other service
- Conceivable behavioral changes
  - Lifestyle
  - Life-cycle and insurance decisions
SINGLE CONDITIONS VS. AGGREGATE RISK

- Studies focus on single conditions
  - Evaluate clinical utility of PGS
- But what about the aggregate polygenic risk on mortality?
- I have initiated study of aggregate polygenic risk
  - Estimate survival rates and hazard ratios
  - Influence on life-cycle decisions, such as insurance
IMPLICATIONS FOR UNDERWRITING
Future, PGS will be accurate enough for underwriting

Two main limitations:

1. Data access
2. Legal limitations

1. Limited data access for commercial purposes
   > Requires GWAS in millions of individuals
     > Restricted to non-commercial use
     > Private biobanks measure few medical conditions
   > Reference sample for relative risk, phenotyping problem
   > Limited accuracy in non-Europeans
2. Legal situation varies across countries

- Some take a permissive stance, others do not
- Self-regulation in industry

Sweden, not allowed to *require* genetic test for life, health, and disability insurance\(^1\)

In 2011, an exception amended\(^2\)

- Above 18, and >€133k, may use genetic information *but not a genetic test*
- Similar to Germany, the Netherlands, and Switzerland

\(^1\) FörsäkrLag. 2005:104
\(^2\) Lag om genetisk integritet m.m. (2006:351)
CONCLUSIONS

- Polygenic scores already predict medical conditions
  > Yet, accuracy is low

- More GWAS of many medical conditions
  > Accuracy increases with \( N \)

- Limitations for underwriting
  > Access to data
  > Various legal limitations
THANK YOU!

QUESTIONS?

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