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The Risk of Anti-selection in Protection Business from Advances in Statistical Genetics

Reinsurance Group of America

Peter Banthorpe
SVP, Global Head of Research and Data Analytics

Richard Russell, PhD
Health Data Scientist

23 November 2017

Agenda

- Use of Genetics in Insurance and DTC Genetic Testing
- Scientific Background
- Genetic Risk to Disease and Polygenic Risk Scores
- Genetics and Risks of Anti-selection
- Conclusions

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Use of Genetics in Insurance and Direct-To-Consumer (DTC) Genetic Testing

Genetics has always elicited a varied set of views across stakeholders

APRIL 14, 2014

DNA and Insurance, Fate and Risk

INTRODUCTION

Tubes of DNA to be tested for hereditary disorders.
Brendan Smialowski for the New York Times

As costs for DNA sequencing drop, hundreds of thousands of Americans are undergoing the procedure to see if they are at risk for inherited diseases. But while federal law bars employers and health insurers from seeking the results, insurers can still use them in all but three states when considering applications for life, disability and long-term care coverage.

Should insurance companies be barred from seeing genetic information when considering those policies so people can get the tests without fear that the results would be used against them?

DEBATERS

Risks Are Too Small for Insurers to Worry

ANGUS S. MACDONALD, PROFESSOR OF ACTUARIAL MATHEMATICS

Only the rarest hereditary disorders would create a major cost burden for insurers. They should agree to ignore genetic tests, and avoid a legal ban.

Guarantee Privacy to Ensure Proper Treatment

JEREMY GRUBER, COUNCIL FOR RESPONSIBLE GENETICS

If the promise of the genetic revolution is to be fulfilled, the public must know that genetic testing will not endanger their economic security.

Questions Remain; Some Rules Should Be Clear

FRANCIS S. COLLINS, NATIONAL INSTITUTES OF HEALTH

Even without barring insurers from seeing genetic tests, such tests should not be demanded of anyone. And research data must be kept private.

It's Yet to Be Shown That Discrimination Exists

BARTHA MARIA KNOPPERS, MCGILL UNIVERSITY

Only rare conditions can be predicted with certainty, and insurers can already access a variety of hereditary information about applicants.

Let Insurers Have Data and Trust to Get It Right

SHAWN HAUSMAN, AMERICAN COUNCIL OF LIFE INSURERS

Advances in medicine have made it possible for insurers to offer coverage to more people, not fewer.

Test Results Are Not Always What They Seem

JOY LARSEN HAIDLE, NATIONAL SOCIETY OF GENETIC COUNSELORS

Even if insurers are allowed to consider the tests, they need to ensure they fully understand what results do and do not reveal.

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Source: New York Times, April 14 2014. Accessed 4 October 2017

Increasing levels of interest in Genetics[1] and Genomics[2] for medical applications

High degree of promise

- Prevention of disease manifestation
- Motivate Lifestyle modification
- Precision medicine
  - Pharmacogenetics
  - Cancer treatment
- Prenatal and Newborns screening
- Accurate diagnosis of rare disease
- More accurate disease prognosis
- Disease recurrence detection
- Everything!

Falling costs and increased availability

- The first human genome took $2.7 billion and almost 15 years to complete
- Now it costs about $1,000 and the sequencing can be done in a few days
- In a few years it may only cost $100
- Multiple providers of DTC testing

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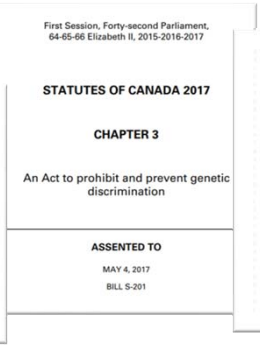
1: Genetics is the study of inherited traits and genes. (simplistic view)
2: Genomics is the study of how a set of genes behave. (complex view)

Increasing levels of interest in Genetics and Genomics from governments and regulators

Council of Europe Recommendation
October 2017

State of New York
Jan 2017



Canadian Genetic Non-discrimination Act
May 2017

England CMO Annual Report
July 2017

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DTC genetic tests (DTC-GT)… spreading the genetics dream or the Wild West?

- Companies selling genetic tests directly to the public are proliferating in both number and diversity. Minimal regulation in UK
- A 2017 paper in the *European Journal of Human Genetics* identified **65 DTC-GT companies** advertising their services online to consumers in the UK
- A 2017 market report from Credence Research, Inc. suggests that the annual revenue of the DTC-GT market is expected to grow to $340 million in 2022 (currently $70.2 million)

'We are going to have to explain to the public that there are *cowboys* out there giving you data that they don't understand and we won't be able to explain'

(Prof Dame Sally Davies, 2017)

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Example: 23andMe and disease risk

- 23andMe provide information about disease risk and susceptibility, carrier status, drug sensitivity, traits and ancestry
- New FDA approval from April this year allows 23andMe to tell US consumers about their risk for 10 conditions, including:
  - Late-onset Alzheimer's disease
  - Celiac disease
  - Parkinson's disease

Peter Banthorpe

Parkinson's Disease (LRRK2- and GBA-Related) • Genetic Risk Factor

Does not have any of the variants associated with Parkinson's disease reported by 23andMe. May still have other mutations associated with Parkinson's disease (not reported here). Other genetic and non-genetic factors can also influence risk.

Welcome to MyGeneRank

This app allows you to utilize your pre-existing genetic data to understand your estimated genetic risk for disease.

The app is for personal use and for participation in a research study designed to learn more about genetic risk.

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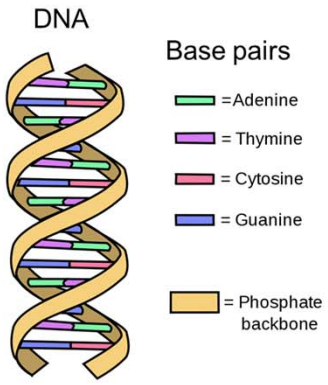
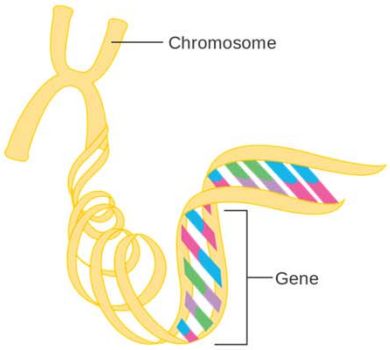
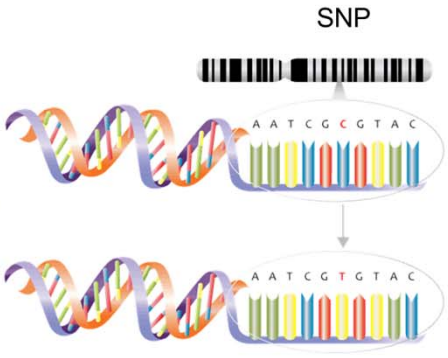
Scientific Background

Genetics 101







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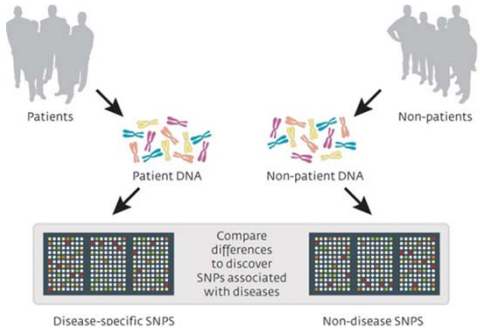
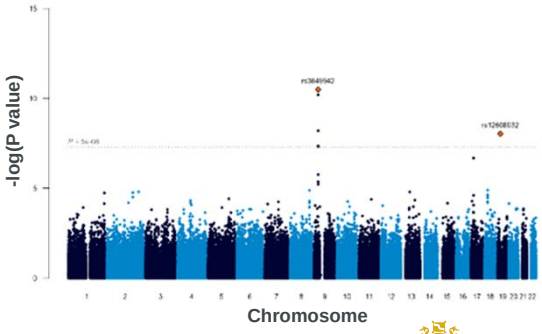
Genome wide association studies ('GWASes')

- A GWAS compares SNPs across thousands of people with and without a particular disease / phenotype





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Disease prediction using GWAS results

- GWASes have been highly successful at identifying genetic variants associated with disease
- The first GWAS, conducted in 2005, compared 96 patients with age-related macular degeneration with 50 healthy controls. It identified two SNPs with significantly altered allele frequency between the two groups
- Since the first landmark GWASes, sample sizes have increased (some in the range of 200,000 individuals!). This means SNPs with smaller odds ratios and lower frequency can be identified

The National Human Genome Research Institute (NHGRI) Catalog of Published GWAS provides a publicly available manually curated collection of published GWAS assaying over 38,000 SNP-trait associations from more than 2,800 publications as of May 2017.

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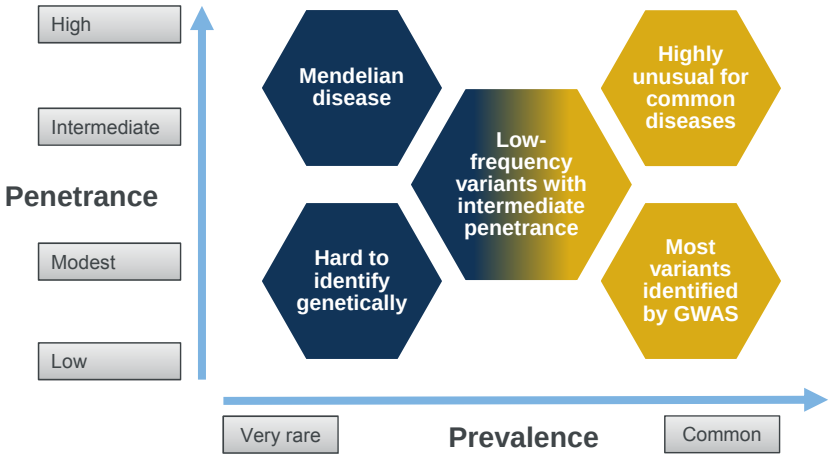
Prevalence vs. penetrance



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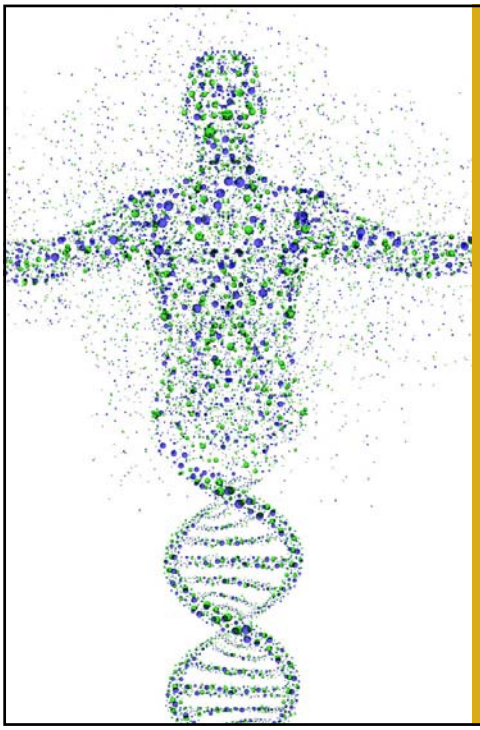

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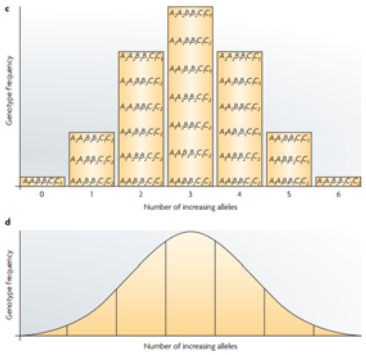
Genetic Risk to Disease and Polygenic Risk Scores (PRS)

Polygenic risk scores (PRS)

- A central point of debate on GWASes is that most SNPs are associated with only a small increased risk of the disease, and have only a small predictive value (especially when compared to classical risk factors such as family history or cholesterol)
- The finding that multiple DNA variants are associated with common disorders is leading to disorders being thought of in quantitative terms
- As multiple DNA variants are identified, they can be aggregated into composites that represent the polygenic liability that underlies common disorders
- Polygenic risk scores (PRS) capture much more information by looking at **a much larger number** of variants genome wide (not just the highly significant SNPs)



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Calculating PRS

- PRS are based on the selection of SNPs which, individually, do not have to achieve significance in large-scale GWAS
- The score is typically calculated by adding the number of risk alleles (0, 1, or 2) carried by each individual weighted by the effect size (β) of the SNP-trait association:

$$PRS = \beta_1 \cdot snp_1 + \beta_2 \cdot snp_2 + \cdots \beta_n \cdot snpn$$

- Since even large GWASes achieve only marginal evidence for association for many causal variants, PRS are usually calculated for a set of P-value thresholds (e.g., P = $1x10^{-5}$, $1x10^{-4}$, …, 0.05, 0.1, …, 0.5)

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Sample of PRS in literature (1)

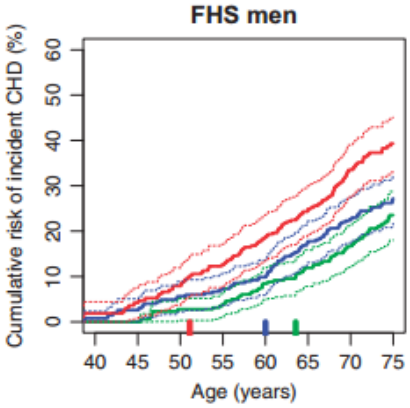
Condition	Genetic Variants	Difference in Risk
Coronary Artery Disease	60	2x (top to bottom 20%)
Coronary Heart Disease	49,310	1.8 to 4.5x (top to bottom 20%; depending on cohort tested in)
Type 2 Diabetes	1000	3.5x (top to bottom 20%; after adjustment for standard risk factors)
Ischemic Stroke	10	1.2x to 2x (top to bottom 20%)
Breast Cancer	77 (from 1 PRS)	3x (top to bottom 20%)
Breast Cancer (in women of East Asian ancestry)	44 (from 1 PRS)	2.9x (top to bottom 20%) – impressive given majority of SNPs associated with breast cancer risk have been conducted with European descendants
Prostate Cancer	77 (from 1 PRS)	4x (top to bottom 20%)
Lung cancer	38	4.6x (top to bottom 25%)

Sample of PRS in literature (2)

Condition	Genetic Variants	Difference in Risk
Sporadic early-onset Alzheimer's disease	21 (not including APOE alleles)	2.27 [6.44 when including APOE alleles] (top to bottom tertiles)
Alzheimer's disease	31 (not including APOE alleles)	3.34 (top to bottom deciles; in normal APOE [ε3/3] individuals)
Alzheimer's disease	356,033	AUC = 78.2% (logistic regression model with *APOE*, the polygenic score, sex and age as predictors)
IBD	2,986	5.69 for Crohn's disease and 3.35 for Ulcerative Colities [top to bottom deciles]
Colorectal cancer (in Japanese men)	6	Including PSR significantly improved c-stat for classification from 0.6 to 0.66
Alcohol problems	1,115,557	Higher polygenic scores predicted a greater number of alcohol problems (range of Pearson partial correlations 0.07–0.08, all p-values ≤ 0.01).
Migraine	21	Odds ratio equal to 1.6x (case vs. control; 2x for migraine without aura)
Psoriasis	16	12.3x (top to bottom 25%)
Cardiovascular mortality in patients with CAD	32	Hazard ratio of 1.5 (top to bottom 50%), after adjustment for classical risk factors)
Recurrent cardiovascular events in patients with CAD	45	Hazard ratio of 1.5 (top to bottom 50%)
Venous thromboembolism	16	1.5x (top to bottom tertile)
Melanoma risk	15	2.6x (top to bottom quintile)

PRS for coronary heart disease increases predictive power, even after adjustment for clinical risk factors

- This study tested the clinical utility of a PRS for coronary heart disease (CHD), in terms of lifetime CHD risk and relative to traditional clinical risk
- PRS tested in independent cohorts (combined n = 16,802 with 1,344 incident CHD events) and contrasted with the Framingham Risk Score (FRS)
- The HR for CHD from the PRS was 1.74 and 1.28 for the FRS. **Further, the PRS was largely unchanged by adjustment for known risk factors, including family history**
- Integration of the PRS with the FRS significantly improved 10 year risk prediction



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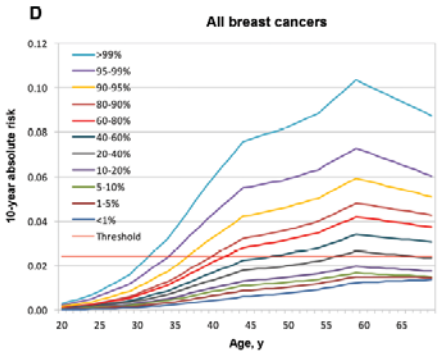
How could PRS be adopted into clinical medicine – cancer screening

- Individuals with the highest 1% or 5% of PRS values could be offered:
  - Regular screening
  - Encouraged to participate in lifestyle modifications
  - Prescribed therapeutic interventions
- For example, in the UK, mammogram screening is initiated at age 47, based on a 10-year risk of breast cancer in the average woman, but:
  - Women in the top 5% of PRS-risk reach the average level at age 37
  - Women in the lowest 20% of PRS-risk will never reach the average level

Source: Prospects for using risk scores in polygenic medicine. Forthcoming. Cathryn M. Lewis, Evangelos Vassos



Source: Mavaddat et al: Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst 2015, 107(5)

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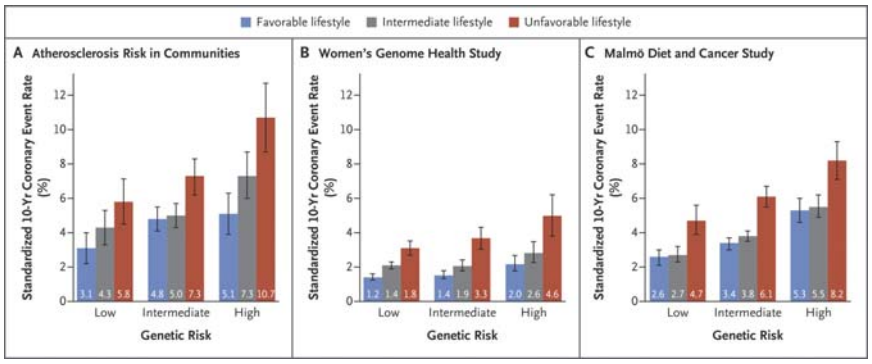
How do PRS interact with lifestyle?

- A genetic predisposition to coronary artery disease is not deterministic but attenuated by a favorable lifestyle. Khera et al. 2017 (NEJM):



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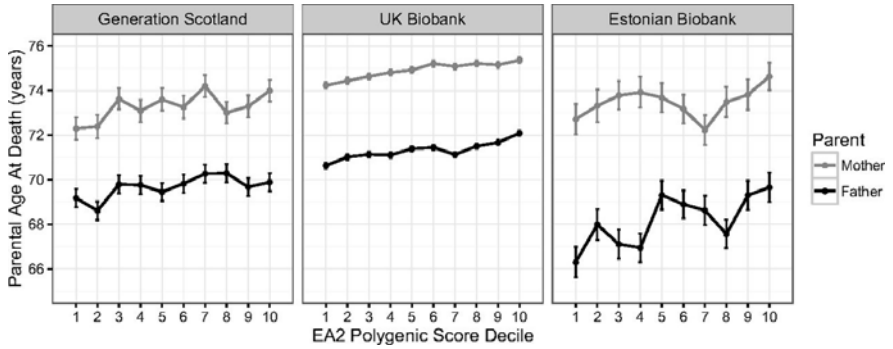
Offspring PRS for education and parental longevity

- Individuals with more education-linked genetic variants had longer-living parents. Marioni et al. 2016 (PNAS):



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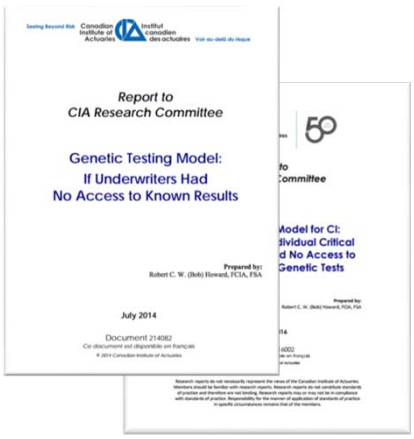
Genetics and Risks of Anti-selection

Canadian Institute of Actuaries Report, July 2014

- Considered 13 genetic conditions with known impact on mortality
- Concluded mortality experience in the long-run would increase by:
  - 35% for Males
  - 60% for Females
- January 16 paper considered 6 conditions impacting Critical Illness – showed lower impact



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Canadian Institute of Actuaries Report, July 2014: Assumptions

Genetic Risk Assumptions

Condition	Prevalence	Penetrance	Rating	Predicted	Tested	Male	Standard	Grading
BRCA1 or 2	500	25%	200%	50%	30	0%	0	15
HTCM	500	69%	0.01	50%	25	50%	0	0
DCM	2700	75%	0.04	25%	35	50%	0	10
ARVCM	1250	75%	0.023	25%	25	50%	0	0
Long QT	3000	50%	0.001	25%	20	50%	0	0
Brugada	2000	75%	0.015	25%	30	50%	0	0
Huntington	20000	90%	1000%	50%	25	50%	5	10
PKD	1000	100%	500%	75%	30	50%	20	15
DM1 or 2	8000	75%	500%	50%	25	50%	15	10
ADEO	2427	100%	1000%	50%	30	50%	15	10
HNPCC	500	50%	300%	50%	30	50%	0	15
Marfan	5000	50%	500%	50%	20	50%	0	0
CPVT	10000	75%	1000%	25%	20	50%	0	5

Source: Genetic Testing Model: If Underwriters Had No Access to Known Results. Robert Howard. Canadian Institute of Actuaries, July 2014

Insurance Assumptions

• Testing Rate	1/30 p.a.
• Seeking insurance	75%
• Declined (due to other conditions)	5%
• Face amount	$900,000
• Lapse	0.5% or 3% p.a.
• Conversion	50%-100%
• Policy modelled	Convertible Term to 65

Policies Purchased = Population * Prevalence * Tested % * Not declined * (1 – Predicted)

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Society of Actuaries analysis, October 2017

Slide to be completed once material from SOA Annual Meeting on October 17 is available

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Thinking about life insurance through a genetic lens, May 2017

- Discussed the concept of polygenic risk scores
- Considered Trauma (Serious Illness) Insurance
- Allowed for purchasing behavior ahead of genetic testing
- Model considered 3 conditions
- Only presented as “illustrative”
- Impact of 1.8% on claims costs (does not appear to consider larger insured pool to offset)
- Noted many the current research findings are based on studies of Europeans

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Thinking about Life Insurance through a genetic lens, May 2017: **Assumptions**

Genetic Risk Assumptions

Top 3 diseases	Prop. high risk	Increase in risk relative to the 'low risk' group*	Prop. trauma claims due to condition (ages 35 to 65)**
CAD	20%	45%	12%
Breast cancer	20%	71%	12%
Prostate cancer	1%	61%	10%
Total	**28%**	**31%**	**34%**

*For this analysis, 'low risk' means 'not high risk'.
**Based on the survey by FSC & KPMG (2017). However, the survey provided cancer claims as a whole; the further breakdown into breast and prostate cancer provided here was obtained from AIHW (2017).

- Proportion tested 0.5%
- Increase in risk 11%

Insurance assumptions

Insured already	8%
Low Risk Policy Lapses	20% (+5% to base)
Purchasing insurance prior to test	Everyone
Keep insurance post test	Only high risk
Face amount (implicit)	Average

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Predicting impact of PRS is still early

- Genetic loci associated with disease will continue to be found and could confer additional predictive power
- Correlations with other health and lifestyle factors could be more significant than high penetrance genes
- Correlations between PRS for different conditions
- Risk of developing a disease may be correlated with severity of disease
- Preventative or mitigating actions, such as:
  - Screening programs based on PRS may limit mortality impact
  - Impact of preventative lifestyle actions unknown
  - Pharmacogenomics
- Application of PRS to non-Caucasian populations

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Potential for anti-selection – example based on PRS for CAD: Input data

Input data based on the Khera et al. paper:

- 50 SNP PRS for CAD
  - Inter-quintile range between 1.75 – 1.98
- 4 Lifestyle factors
  - Smoking
  - Healthy BMI
  - Physical Activity once a week
  - Healthy Diet
- End points
  - MI, Revascularization, Death from CHD


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ORIGINAL ARTICLE

Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

Amit V. Khera, M.D., Connor A. Emdin, D.Phil., Isabel Drake, Ph.D., Pradeep Natarajan, M.D., Alexander G. Bick, M.D., Ph.D., Nancy R. Cook, Ph.D., Daniel I. Chasman, Ph.D., Usman Baber, M.D., Roxana Mehran, M.D., Daniel J. Rader, M.D., Valentin Fuster, M.D., Ph.D., Eric Boerwinkle, Ph.D., Olle Melander, M.D., Ph.D., Marju Orho-Melander, Ph.D., Paul M Ridker, M.D., and Sekar Kathiresan, M.D.

N Engl J Med 2016; 375:2349-2358 | December 15, 2016 | DOI: 10.1056/NEJMoa1605086

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Potential for anti-selection – example based on PRS for CAD: Simple Model

Environmental risk	Low (bottom 20%)	Intermediate (mid 60%)	High (highest 20%)	Assumed Proportion in Standard Insured Population	Relative Risk across group
High (Score = 0-1)	1.82	2.54	3.50	0%	n/a
Intermediate (Score =2)	1.16	1.54	2.24	70%	1.6
Low (Score ≥ 3)	1	1.33	1.90	30%	1.38
				100%	1.54

Genetic risk

Twice as likely to buy → 1.64 (+6.5%)

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Conclusions

Summary

- Huge ongoing interest in genomics and genetics
- Insurance industry benefits society and in a non-compulsory market needs to limit information asymmetry to remain viable
- Widespread adoption of polygenic risk scores would increase anti-selection risk over consideration of high penetrance genes only, if insurers were not able to assess the same genetic information
- The commensurate increase in premiums might be in the range 3%-10% based on very simple modelling and accepting the large degree of uncertainty in how PRS will emerge into clinical usage
- Additional research is needed to understand both the science and the interaction with insurance buying behavior

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Questions

Comments

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