Approved project: 23203

The Importance of Genetics on Mortality and Morbidity Risk in the Presence of Detailed Health and Lifestyle Data

A study based on half a million lives in the UK Biobank cohort

Peter Banthorpe (RGA)
Senior Vice President,
Global Head of Research & Data Analytics

Prof. Cathryn Lewis (King's College London)
Statistical Genetics Unit,
Division of Genetics and Molecular Medicine

About the speakers

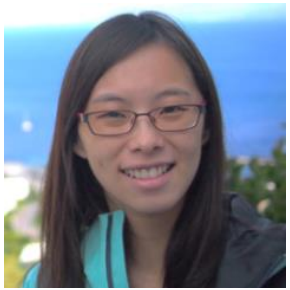
Peter Banthorpe is Senior Vice President and Head of Global Research and Development with RGA Reinsurance Company. In this role, he leads RGA's advanced analytics capabilities and international experience study unit, and oversees RGA's biometric research and related strategic research programme. Peter is also the Lead Risk Management Office for Mortality at RGA.

Cathryn Lewis is Professor of Genetic Epidemiology & Statistics at King's College London, where she leads the Statistical Genetics Unit. Her research applies statistical tools to identify and characterise the genetic contribution to human disease. Her research programme includes projects in risk prediction, and in gene identification for depression and stroke.

Research Team

Dr Paul O'Reilly
(Senior Lecturer)
Co-Principal Investigator

Miss Jessye Maxwell
(PhD Student)
Project Research Assistant



Dr Beatrice Wu
(Postdoctoral Researcher)
Project Research Associate

Dr Richard Russell
(Lead Health Data Scientist)
Project Advisor

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.

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

Increasing levels of interest in Genetics and Genomics*

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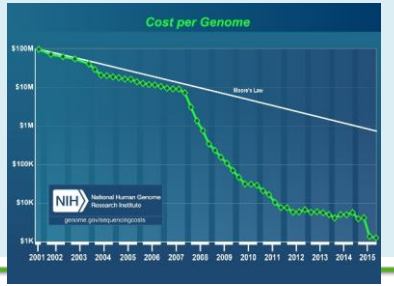
High degree of promise

- 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

- First human genome sequencing took $2.7 billion and almost 15 years
- 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



*Genetics is the study of inherited traits and genes. Genomics is the study of how a set of genes behave.

Growing opportunities for genetic anti-selection

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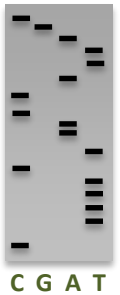
$22 billion



Estimated global market for DNA sequencing in 2025

7 million

Consumer genetic tests sold last year

No. 15

Genetic counsellors are the 15th fastest growing occupation according to US Bureau of Labour Statistics (2016 to 2026)

600,000

DNA variants measured by 23andMe

800+

Genomapp

Diseases tested for genetic susceptibility

Agenda

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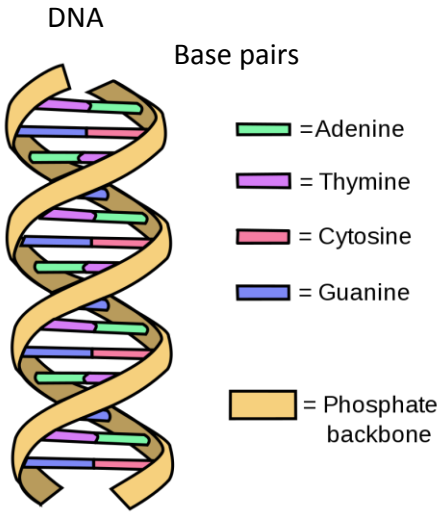
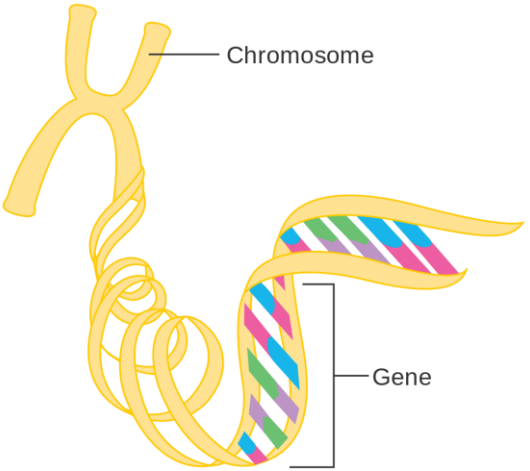
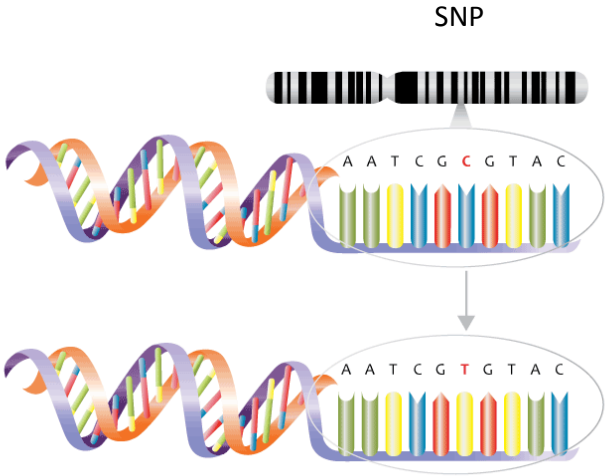
- Genetic Risk to Disease and Polygenic Risk Scores
- RGA and King's College London Research Collaboration
- Genetics and Risks of Anti-Selection
- Key Messages

Genetic Risk to Disease and Polygenic Risk Scores (PRS)

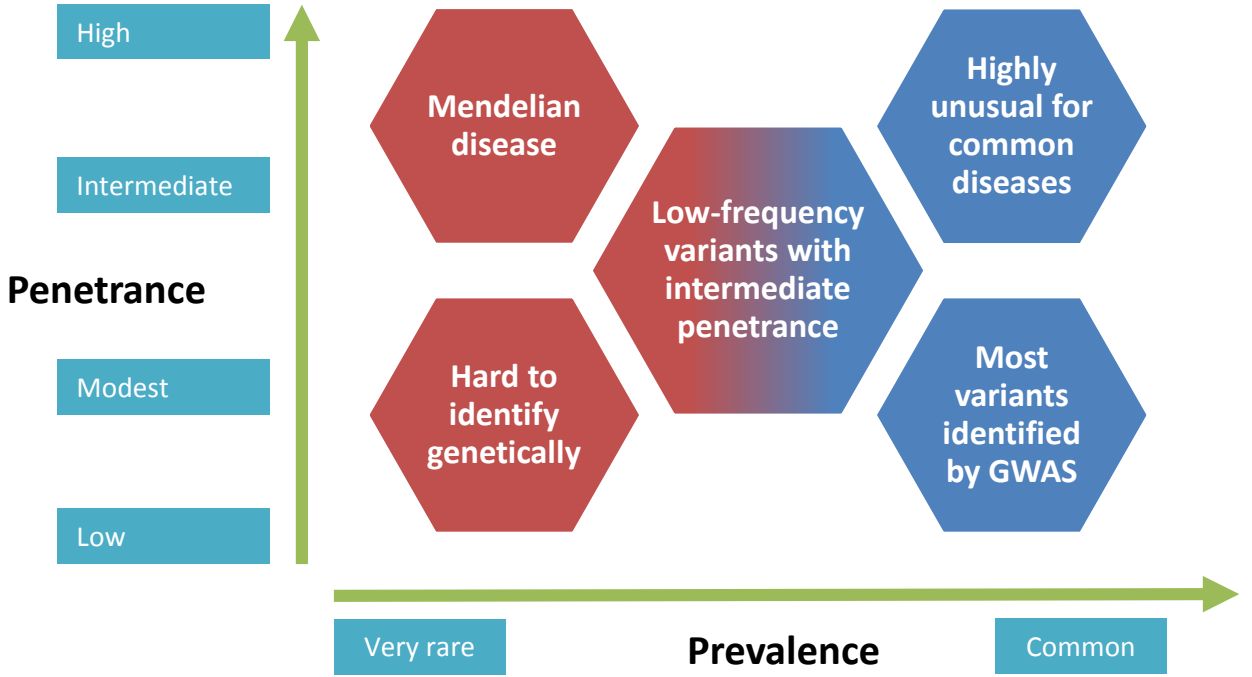
Genetics 101



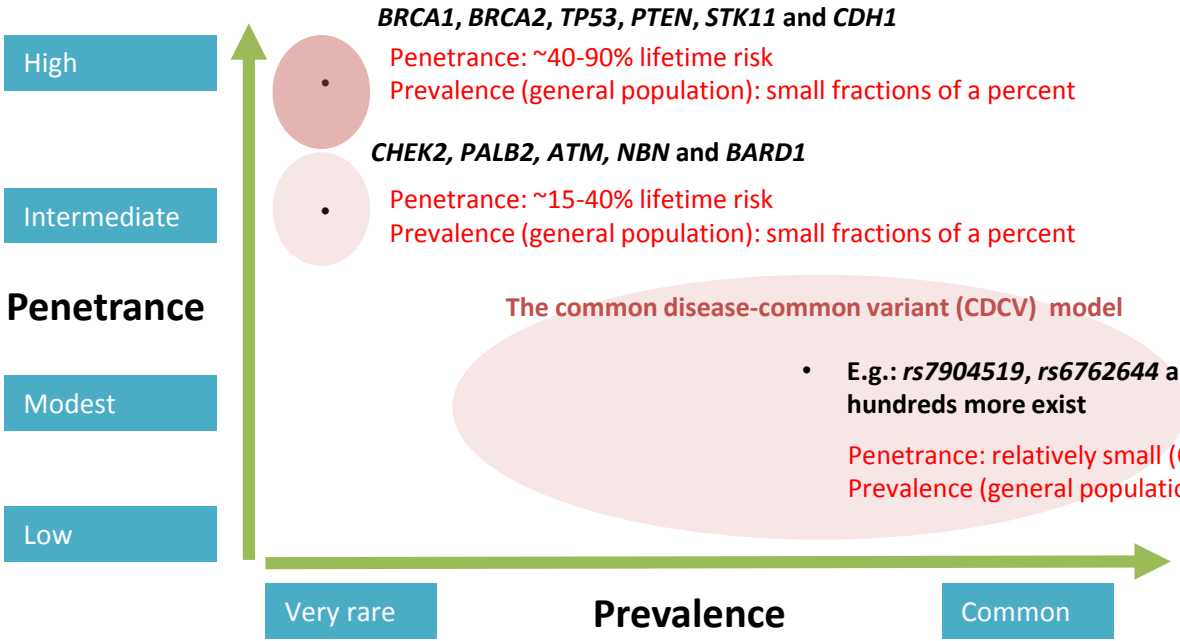




Prevalence vs. penetrance of genetic variants



Prevalence vs. penetrance of genetic variants in breast cancer (general population)



Battle of the acronyms: SNPs, GWASes and PRS!

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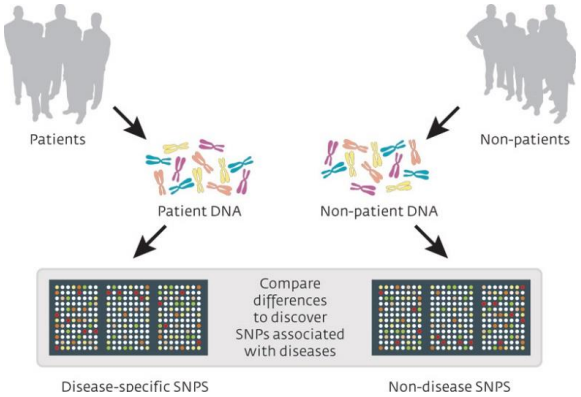

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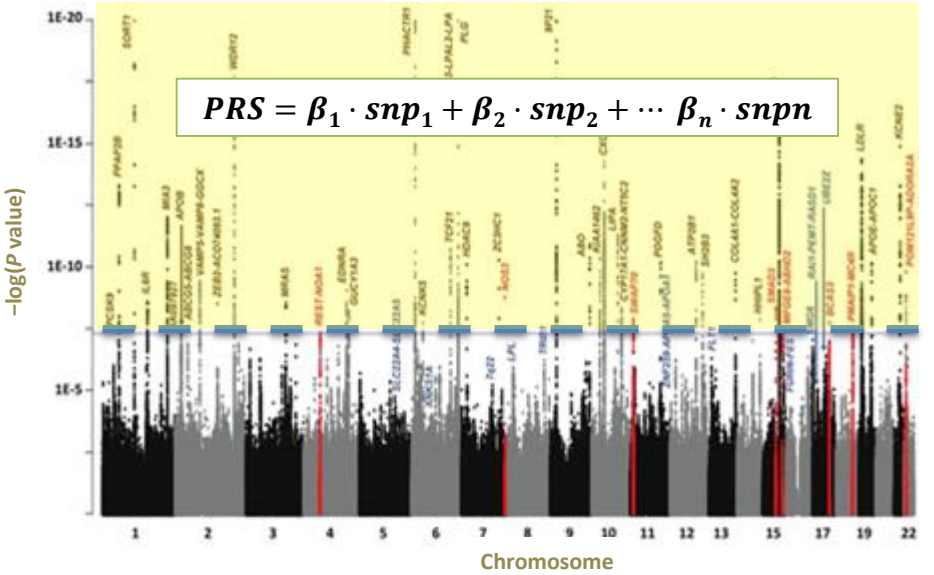

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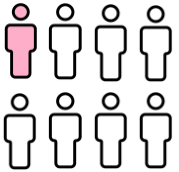
Potential for anti-selection – example in breast cancer

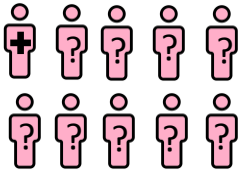
In the UK, about 1 in 8 women will be diagnosed with breast cancer in their lifetime



Prevalence of BRCA1/2 mutation in the general population: 0.2-0.3%

High penetrance

Only 5-10% of breast cancer cancers is attributed to mutations in high- or moderate-penetrant genes (including *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *STK11*, *CDH1*, *CHEK2*, *PALB2*, *ATM*, *NBN* and *BARD1*)

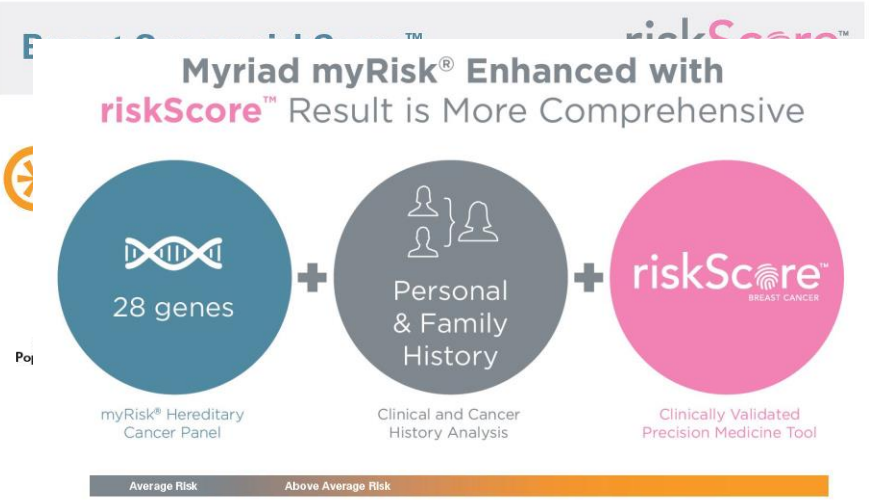


Prevalence of BRCA1/2 mutations in women with breast cancer: 3%

Roughly only 10% of women with a family history of breast cancer test positive for a hereditary cancer mutation… what explains the 'missing genetic component'?

Myriad's *myRisk* and *riskScore*…

- Myriad Genetics is an American molecular diagnostic company
- Myriad contributed to discovery of the breast cancer genes *BRCA1/2* and patented the tests on them
- *myRisk* is a hereditary cancer test to evaluate 28 clinically significant genes (including *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *STK11*, *CDH1*, *PALB2*, *CHEK2*, *ATM*, *NBN, BARD1*)
- *riskScore* is a follow-up test for women who have tested negative for hereditary cancer genes
- *riskScore* includes an 86-SNP PRS, plus clinical and family history information



Source: https://new.myriadpro.com/riskscore/. Accessed 12 May 2018

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

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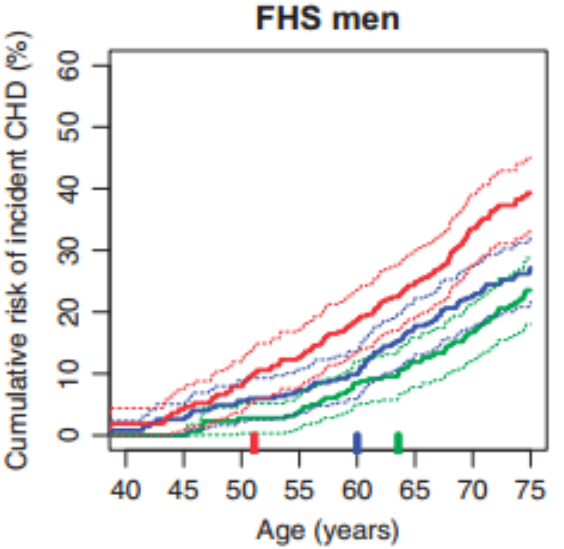
- This study tested the clinical utility of a PRS for coronary heart disease (CHD) in terms of lifetime CHD risk and relative to traditional clinical risk
- PRS tested in independent cohorts (combined *n* = 16,802 with 1,344 incident CHD events) and contrasted with the Framingham Risk Score (FRS)
- The hazard rates (HR) for CHD were
  - Polygenic risk score: HR = 1.74
  - Framingham risk score: HR = 1.28

- **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



Abraham, G. *et al*. (2016), Eur Heart J.

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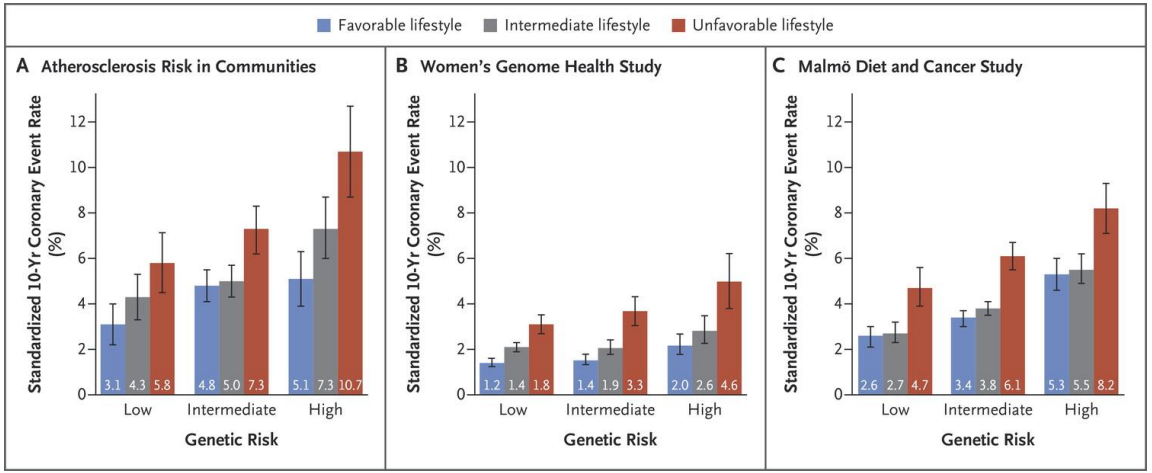
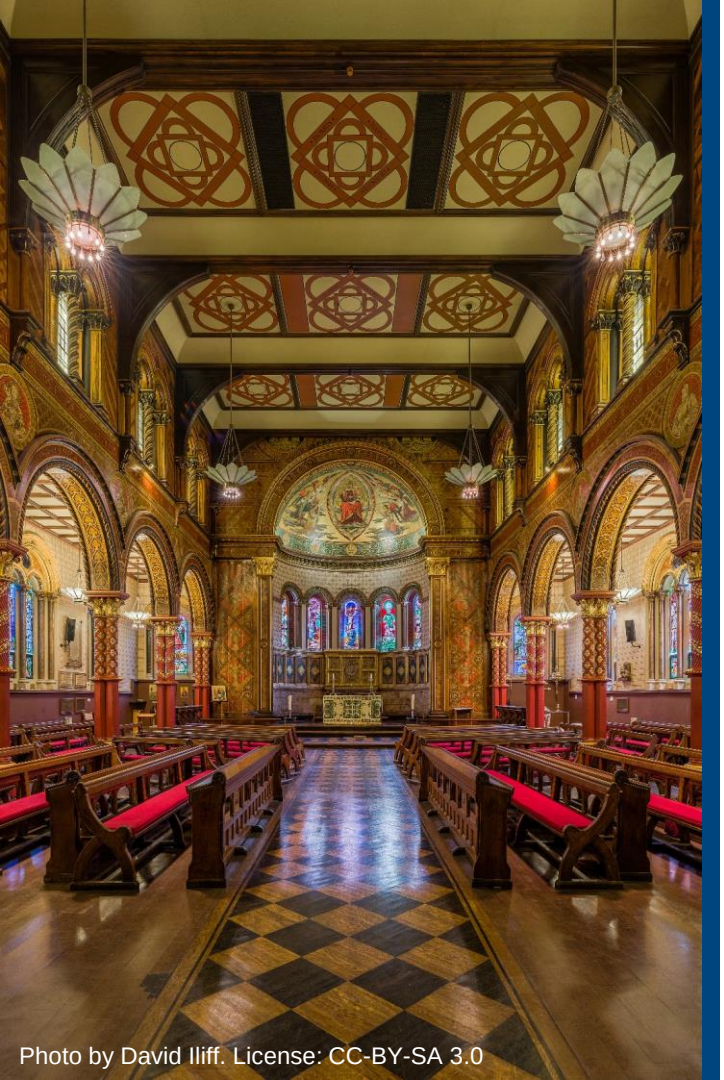
How do PRS interact with lifestyle?

- A genetic predisposition to coronary artery disease is not deterministic but attenuated by a favorable lifestyle



Sample of PRS in literature

Disorder	No. of Genetic Variants	Relative risk, comparing top 20% to bottom 20% PRS	Reference
Coronary artery disease	50	2.0	Khera AV. *et al*. (2016), N Engl J Med.
Coronary artery disease	49,310	1.8 to 4.5	Abraham G. *et al*. (2016), Eur Heart J.
Type 2 diabetes	1000	3.5	Läll K. *et al*. (2017), Genet Med.
Ischemic stroke	10	1.2 to 2.0	Hachiya T. *et al*. (2017), Stroke
Breast cancer	77	3.0	Mavaddat N. *et al*. (2015), J Natl Cancer Inst.
Breast cancer (East Asian ancestry)	44	2.9	Wen W. *et al*. (2016), Breast Cancer Res.
Prostate cancer	25	3.7 (25%)	Amin Al Olama A. *et al*. (2015), Cancer Epidemiol Biomarkers Prev.
Lung cancer	38	4.6 (25%)	Cheng Y. *et al*. (2016), Oncotarget



RGA and King’s College London (KCL) Research Collaboration

RGA Research Collaboration with KCL

- RGA funded one-year research project at KCL
- Desire to inform the debate around significance of (lack of) access to genetic information by insurers in non-compulsory insurance markets
- Collaborative agreement meets the principles set out in the UK Biobank Access Procedures, including commitment to publish all findings and results from the project so that they are available for other researchers to use for health-related research that is in the public interest
- **Only approved King's College London research staff have access to UK Biobank data**

The UK Biobank is a uniquely powerful resource to study the importance of genetics in insurance

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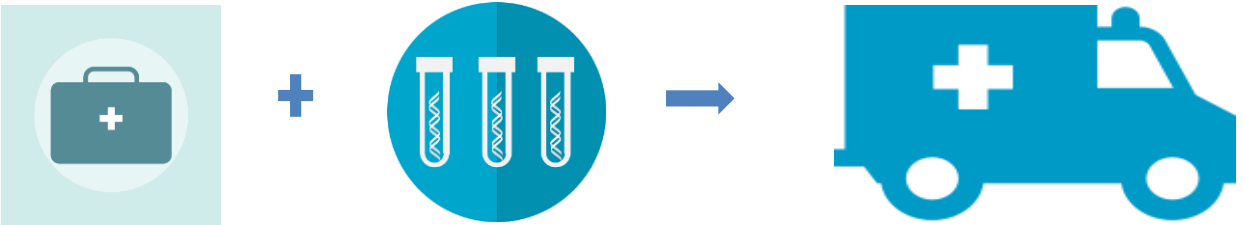
- Our research questions
  1. How accurately can the risk of mortality and major morbidity be estimated using multivariable prediction models based on detailed phenotypic information (medical history, physiology, behavioural and lifestyle risk factors)?
  2. Can such prediction models be significantly improved – both in statistical and clinical/absolute terms – by including genetic data?



About UK Biobank (UKB)

A robot stores and retrieves biological samples at UK Biobank

Summary

- The UK Biobank is a major national health resource with the aim of improving the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses
- UK Biobank recruited **500,000 people** aged 40-69 years in 2006-2010 from across the UK to take part in this project; all volunteers agreed to have their **health followed indefinitely**
- Participants underwent vigorous testing, shared blood, urine and saliva samples, and provided detailed personal and health information
- All data, including genetic, biochemistry and imaging data, are made available for research studies

Why UK Biobank?

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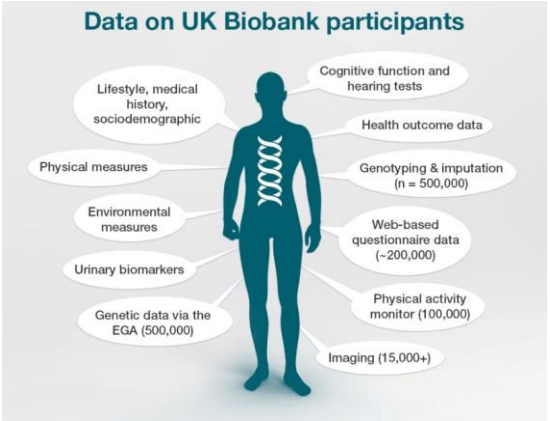
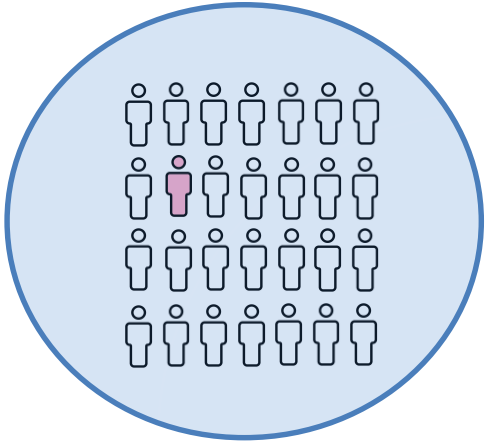
Breadth and Depth

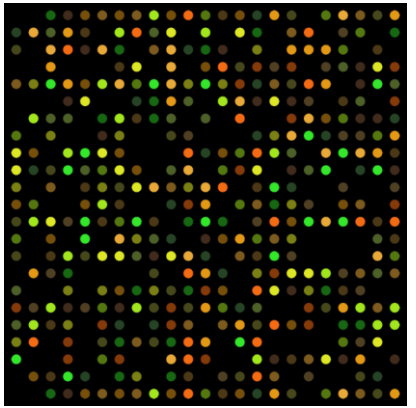


https://www.ebi.ac.uk/about/news/feature-story/biobanks-genetic-data-demand. Accessed 12 May 2018

Long-term follow-up of multiple outcomes



Genotyping on all 500k participants



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The UK Biobank data is a hugely powerful resource: a unique combination of breadth and depth

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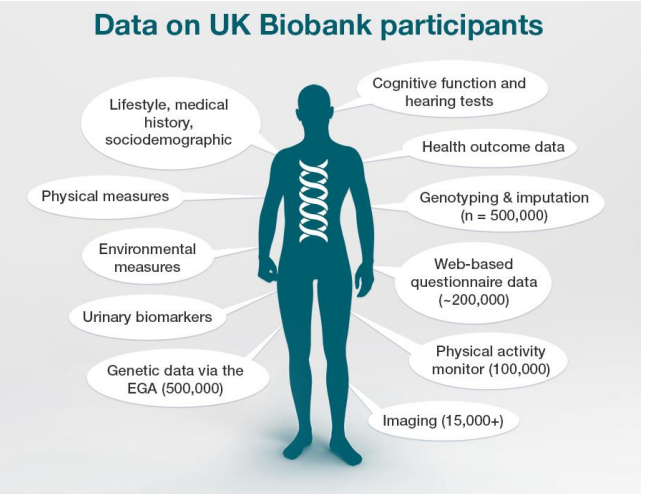
- **Prospective:** It can assess the full effects of a particular exposure (such as smoking) on all types of health outcomes (such as cancer, vascular disease, lung disease, dementia)
- **Detailed:** The wide range of questions, measures and samples at baseline allows an almost unparalleled assessment of exposures, and disease / mortality outcomes
- **Big:** Inclusion of large number of participants allows reliable assessment of the causes of a wide range of diseases, and of the combined impact of many different exposures

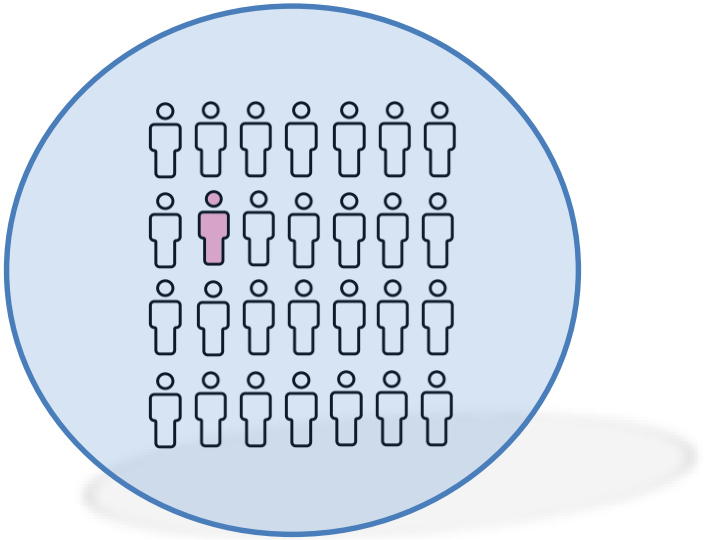


https://www.ebi.ac.uk/about/news/feature-story/biobanks-genetic-data-demand.

Accessed 12 May 2018

What makes UK Biobank special?
Centralised follow-up of health

- Death and cancer registry linkage
- In-patient and out-patient hospital episodes (including psychiatric) and related procedure registries
- Primary care records of health conditions, prescriptions, diagnostic tests and other investigations (linkage underway)
- Direct to participants: self-reported medical conditions; treatments actually being taken; degree of functional impairment; cognitive and psychological scores



What makes UK Biobank special?
Genotyping of all 500k participants

- A 820K Affymetrix Axiom® Array genotyping chip was used to study the genotypes of all participants:
  - 250,000 common markers, genome-wide
  - 200,000 markers for known disease risk factors
  - 150,000 exome markers for non-synonymous coding variants with allele frequency over 0.02%
  - Additional SNPs are imputed by combining measured genotypes with reference sequence data
- In European ancestry populations, array captures
  - >90% of common variation, frequency 5%-50%
  - >70% of rare variation, frequency 1%-5%
- Researchers can study associations of genotype data with biochemical risk factors and detailed phenotyping from baseline assessment, along with morbidity and mortality outcomes

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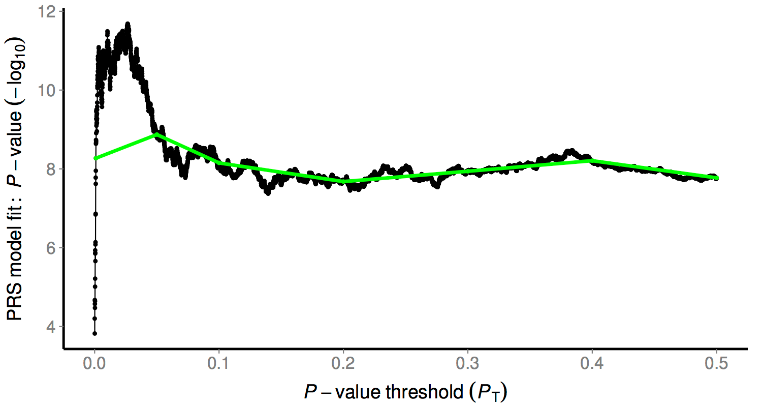
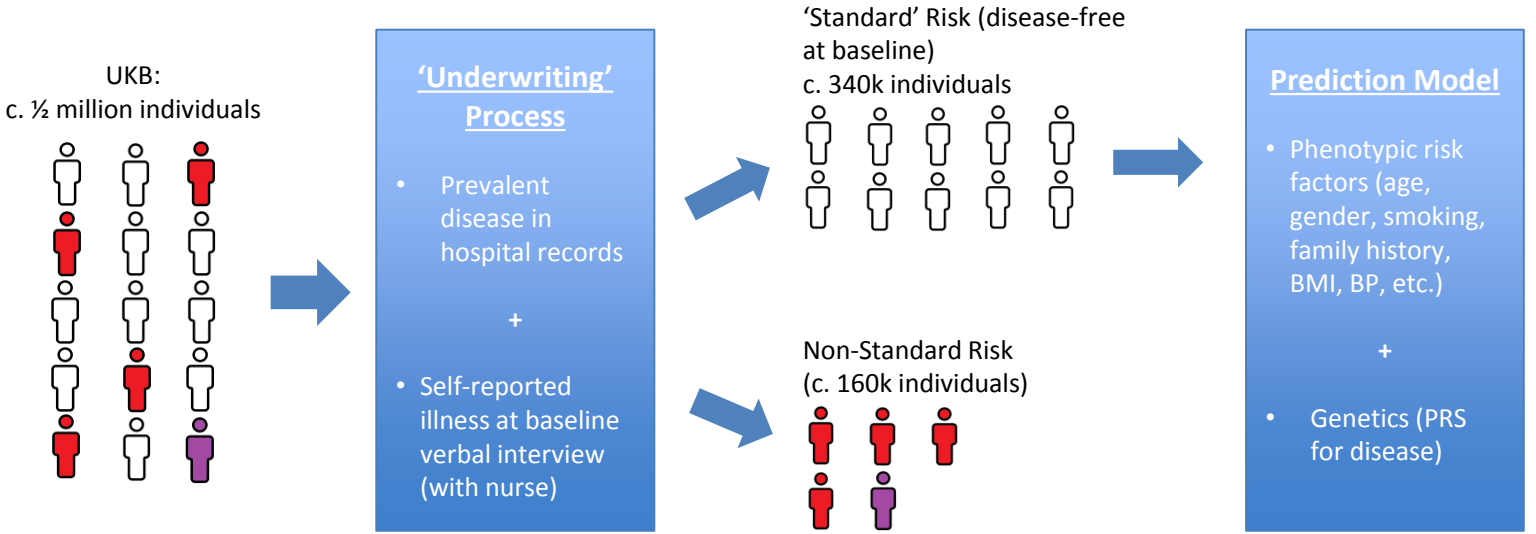
Modelling morbidity outcomes in UKB

- **Polygenic risk scores** for the morbidity of interest (number of SNPs included is calculated using our software *PRSice*)
- **Environmental risk factors**, as appropriate to disorder with measures available at baseline
- Modelling incident cases using Cox Proportional Hazard model



‘Underwriting’ UKB participants and predicting disease incidence



PRS to predict incidence of breast cancer (RGA-KCL study results):

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Total number of patients: 199,517
Number of breast cancers: 3,882 (1.95%)

Percentile	Full cohort: Hazard ratio (95% CI)
0-1	0.36 (0.21 - 0.63)
1-5	0.56 (0.44 - 0.7)
5-10	0.56 (0.46 - 0.69)
10-20	0.7 (0.6 - 0.8)
20-40	0.84 (0.76 - 0.94)
40-60	1
60-80	1.21 (1.09 - 1.33)
80-90	1.4 (1.25 - 1.57)
90-95	1.86 (1.63 - 2.12)
95-99	1.97 (1.72 - 2.26)
99-100	2.51 (2.02 - 3.13)

Total number of patients: 143,958
Number of breast cancers: 2,684 (1.86%)

Percentile	Full cohort: Hazard ratio (95% CI)
0-1	0.41 (0.22 - 0.76)
1-5	0.56 (0.42 - 0.74)
5-10	0.6 (0.47 - 0.77)
10-20	0.71 (0.59 - 0.84)
20-40	0.84 (0.74 - 0.95)
40-60	1
60-80	1.22 (1.09 - 1.38)
80-90	1.41 (1.23 - 1.61)
90-95	1.87 (1.6 - 2.18)
95-99	1.96 (1.66- 2.31)
99-100	2.61 (2.02 - 3.38)

PRS to predict incidence of cardiovascular disease: (RGA-KCL study results):

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Total number of patients: 376,675
Number of CAD events: 4,598 (1.22%)

Percentile	Full cohort: Hazard ratio (95% CI)
0-1	0.67 (0.47 - 0.97)
1-5	0.52 (0.42 - 0.65)
5-10	0.76 (0.65 - 0.9)
10-20	0.75 (0.66 - 0.85)
20-40	0.79 (0.72 - 0.88)
40-60	1
60-80	1.1 (1.01 - 1.2)
80-90	1.43 (1.29 - 1.58)
90-95	1.4 (1.24 - 1.6)
95-99	1.68 (1.47 - 1.91)
99-100	2.19 (1.78 - 2.69)

Total number of patients: 261,204
Number of CAD events: 2,334 (0.89%)

Percentile	Full cohort: Hazard ratio (95% CI)
0-1	0.66 (0.4 - 1.11)
1-5	0.41 (0.29 - 0.57)
5-10	0.77 (0.61 - 0.97)
10-20	0.78 (0.65 - 0.93)
20-40	0.81 (0.7 - 0.93)
40-60	1
60-80	1.15 (1.01 - 1.3)
80-90	1.54 (1.33 - 1.77)
90-95	1.43 (1.19 - 1.72)
95-99	1.92 (1.61 - 2.29)
99-100	2.78 (2.11 - 3.67)

Genetics and Risks of Anti-Selection

Research into Anti-Selection Risk from Genetics

- There have been several research papers…..
  - Huntington's disease anti-selection (Oster et al, 2009)
  - Work of GAIC/Angus MacDonald
  - CIA Genetic Testing (Mortality and Morbidity)
  - SOA reproduction of CIA work for US Markets
  - Australian paper, May 2017

  ….suggesting a wide range of possible impacts
- Many modelling assumptions being made
  - Insurance buying behavior pre/post tests
  - Probability of disease and impact thereof

Canadian Institute of Actuaries Report, July 2014: Assumptions

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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

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)

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

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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
- Application of PRS to non-Caucasian populations
- **Preventative or mitigating actions, such as:**
  - **Screening programs based on PRS may limit mortality impact**
  - **Impact of preventative lifestyle actions unknown**
  - **Pharmacogenomics, precision medicine etc.**

Potential for anti-selection – example in breast cancer (RGA-KCL study results):

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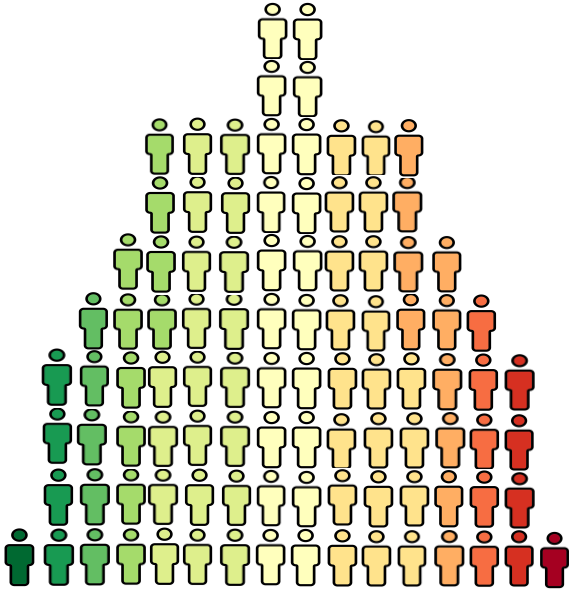
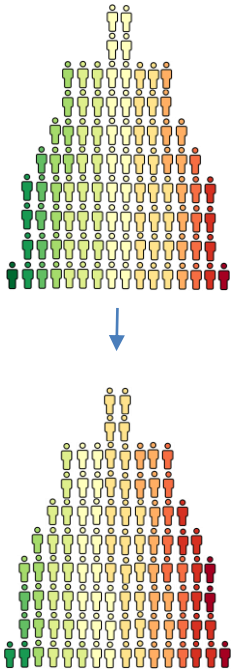
Percentile	Hazard ratio for breast cancer
0-1	0.41
1-5	0.56
5-10	0.6
10-20	0.71
20-40	0.84
40-60	**1**
60-80	1.22
80-90	1.41
90-95	1.87
95-99	1.96
99-100	2.61



Potential for anti-selection – example in breast cancer: Scenario 1

Percentile	% in general population	Hazard ratio for breast cancer
0-1	1%	0.41
1-5	4%	0.56
5-10	5%	0.6
10-20	10%	0.71
20-40	20%	0.84
40-60	**20%**	**1**
60-80	20%	1.22
80-90	10%	1.41
90-95	5%	1.87
95-99	4%	1.96
99-100	1%	2.61



- +13% increase in incidence
- +16% increase if include BRCA1/2 mutations (assuming 0.2% prevalence and 5x odds ratio)

* note, we make no assumptions for prophylactic measures

Potential for anti-selection – example in breast cancer: Scenario 2

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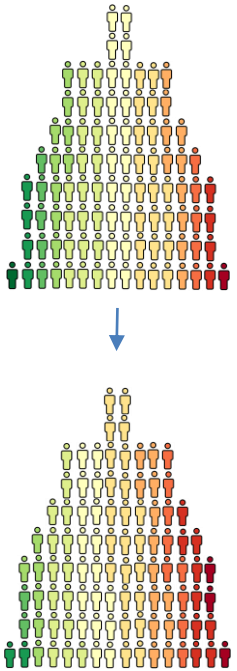
Percentile	% in general population	Hazard ratio for breast cancer	Probability of purchasing insurance *	% in new risk pool
0-1	1%	0.41	0.71x	0.7%
1-5	4%	0.56	0.78x	3.0%
5-10	5%	0.6	0.80x	3.8%
10-20	10%	0.71	0.86x	8.2%
20-40	20%	0.84	0.92x	17.7%
40-60	**20%**	**1**	**1x**	19.2%
60-80	20%	1.22	1.11x	21.4%
80-90	10%	1.41	1.21x	11.6%
90-95	5%	1.87	1.44x	6.9%
95-99	4%	1.96	1.48x	5.7%
99-100	1%	2.61	1.81x	1.7%

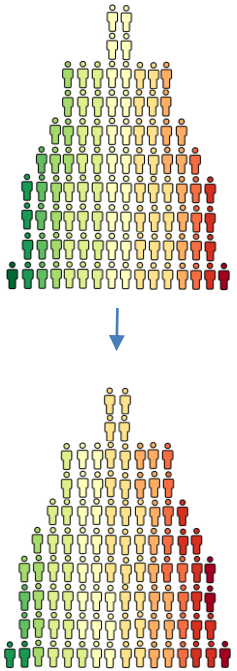


- +7% increase in incidence
- +8% increase if include BRCA1/2 mutations (assuming 0.2% prevalence and 5x odds ratio)

* note, we make no assumptions for prophylactic measures

Potential for anti-selection – example in breast cancer: Scenario 3

Percentile	% in general population	Hazard ratio for breast cancer	Probability of purchasing insurance *	% in new risk pool
0-1	1%	0.41	1x	0.9%
1-5	4%	0.56	1x	3.7%
5-10	5%	0.6	1x	4.6%
10-20	10%	0.71	1x	9.2%
20-40	20%	0.84	1x	18.3%
40-60	**20%**	**1**	**1x**	18.3%
60-80	20%	1.22	1.11x	20.3%
80-90	10%	1.41	1.21x	11.0%
90-95	5%	1.87	1.44x	6.6%
95-99	4%	1.96	1.48x	5.4%
99-100	1%	2.61	1.81x	1.7%



- **+4.8% increase in incidence**
- **+5.4% increase if include BRCA1/2 mutations (assuming 0.2% prevalence and 5x odds ratio)**

*** note, we make no assumptions for prophylactic measures**

Source:
https://www.ted.com/playlists/357/how_does_dna_work.
Accessed 12 May 2018.

Key Messages

Key Messages

- Our work concentrates on common genetic variants, not the rare high-penetrance gene mutations studied for insurance to date (e.g. *BRCA1*, Huntington's)
- These common variants, assessed using PRS, provide population risk information that is largely additive/independent to normal underwriting risk factors
- For incidence of and death from CAD and cancers, we see material differentiation from PRS
- We can expect further asymmetry of medical health information in the future
- Use of PRS remains an emerging risk issue for the insurance industry and we must continue to monitor and develop research on both the science and consumer behavior on the potential impact
- Equally, we should also consider the opportunities and the positive impact on the insurance industry

Thank you very much for your attention!

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