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# The Importance Of Genetics On Mortality and Morbidity Risk

## A Study Based On Half A Million Lives In The UK Biobank Cohort

**Peter Banthorpe**
SVP, Global Head of Research and Data Analytics

**Richard Russell**
Lead Health Data Scientist

**Institute and Faculty of Actuaries 2018 Life Convention**
Liverpool, November 2018

Institute and Faculty of Actuaries

## Agenda

Institute and Faculty of Actuaries

- Use of Genetics in Insurance and Growing Opportunities for Anti-selection
- Genetics 101
- Genetic Risk to Disease and Polygenic Risk Scores
- RGA / King's College London Research Collaboration
- Genetics and Risks of Anti-selection
- Key Messages

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## Increasing levels of interest in Genetics and Genomics* 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

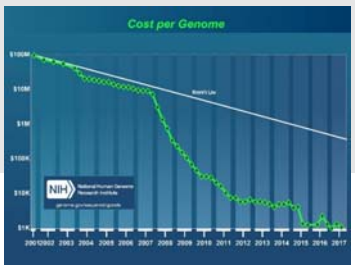


**Image source**: Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP).

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

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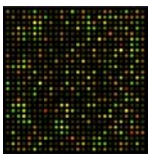
## Growing opportunities for genetic anti-selection

**7 million**

**Consumer genetic tests sold last year**

**600,000**



**DNA variants measured by 23andMe**

**800+**


**Diseases tested for genetic susceptibility**

**No. 14**

**Genetic counsellors are the 14th fastest growing occupation according to US Bureau of Labour Statistics (2016 to 2026)**

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# Genomic medicine in the next 5 to 10 years…

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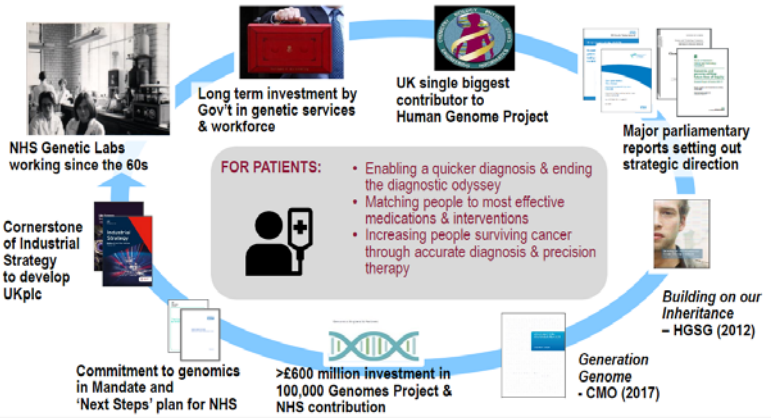
## Why genomic medicine? Why now?

NHS England

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# Genomic medicine in the next 5 to 10 years…

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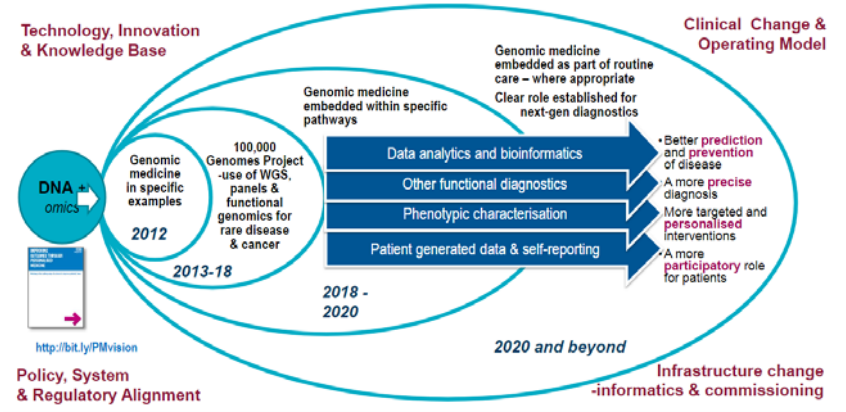
## The personalisation journey

NHS England

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# Genomic medicine in the next 5 to 10 years…

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## The genomic medicine journey to 2025

NHS England

**Today:**

- Variable patient access to cutting-edge genetic technologies
- Proof of concept project demonstrating benefits
- 'One size fits all' treatment based on symptoms
- Limited use of genomic markers
- Diagnostic & clinical data not linked

**By 2020:**

- National Genomic Medicine Service driving personalised treatments and interventions with consistent & equitable access across the country – underpinned by a National Genomic Test Directory
- Improved diagnosis of rare conditions and better understanding of cancer
- Integrated informatics platform to support comprehensive linking of genomic and clinical data to give a full picture to patients
- Routine care and treatment closely linked through to clinical research, academia and industry with many more patients eligible for clinical trials

**By 2025:**

- New taxonomy of medicine based on underlying case & personal response
- Integrated clinical services taking a 'whole pathway' approach
- Routine use of Whole Genome Sequencing and newer genomic technologies embedded across multiple clinical pathways
- Genomics included as a fundamental part of clinical training across all professions and levels
- Tailored, optimised & more effective therapies for better outcomes

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# Front Page News – August 2018

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THE TIMES

**Genes put millions at triple risk of heart attack**

£40 test would spot danger even with no symptoms

Five million Brit… attack despite la…

nature genetics

The Telegraph

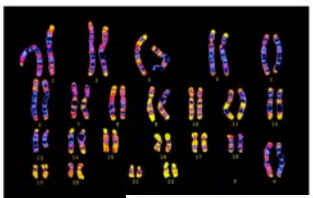
News

**Scientists hail DNA breakthrough that can detect if people are likely to have heart attacks**

The New York Times

***Clues to Your Health Are Hidden at 6.6 Million Spots in Your DNA***

With a sophisticated new algorithm, scientists have found a way to forecast an individual's risks for five deadly diseases.



…k Chaffin[4,5], Kr…
…eep Natarajan[2]
…d Sekar Kathires

FINANCIAL TIMES

**Genetic screening set to identify common serious conditions**

Aim is to give people a risk score from birth for illnesses such as heart disease and breast cancer

Clare Elwell and Clive Cookson AUGUST 14, 2018

A genetic test is set to identif… artery disease, breast cancer … any symptoms are evident.

Scientists hope to eventually …

The "polygenic risk test" uses … genome to look for small vari…

Forbes

**A Harvard Scientist Thinks He Has a Gene Test for Heart Attack Risk. He Wants to Give It Away Free.**

MailOnline

**$50 blood test could spot killer diseases from heart attacks to breast cancer BEFORE symptoms show: Millions who are at risk due to their genes could be saved**

- Harvard Medical School developed the test called 'polygenic risk scoring'
- It measures a person's risk of developing five life-threatening diseases based on their DNA
- The diseases they currently measure are: coronary artery disease, atrial fibrillation, type 2 diabetes, inflammatory bowel disease, and breast cancer
- It could be administered at birth to spot at-risk people from the earliest age

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# Genetics 101

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## DNA, chromosomes and single nucleotide polymorphisms (SNPs)

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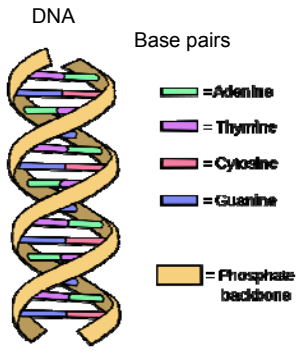
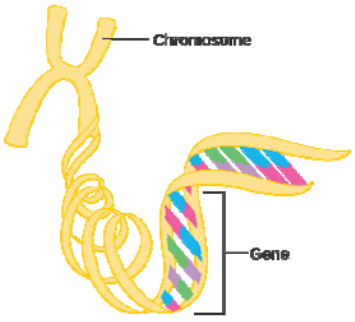
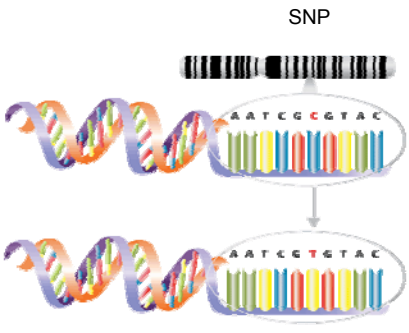



DNA is composed of four 'building blocks' (nucleotides) : **adenine** (A), **cytosine** (C), **guanine** (G) and **thymine** (T)




Human DNA is packaged into 23 pairs of chromosomes




A single nucleotide polymorphism (SNP) describes variation in a single nucleotide position. E.g., here, a **Thymine** nucleotide exists instead of **Cytosine**, which is most commonly observed.

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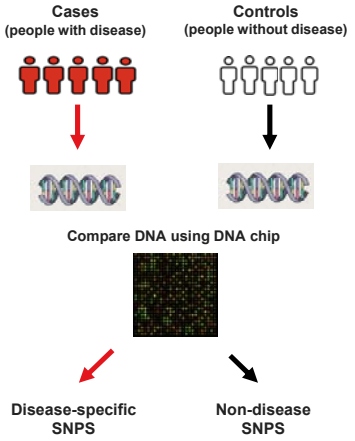
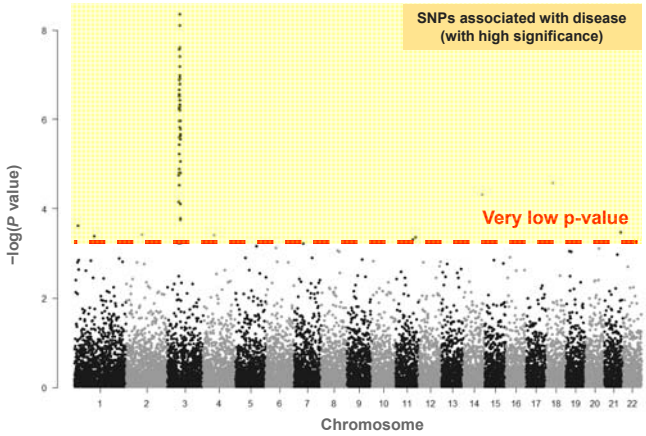
# Genome wide association studies ('GWASes')

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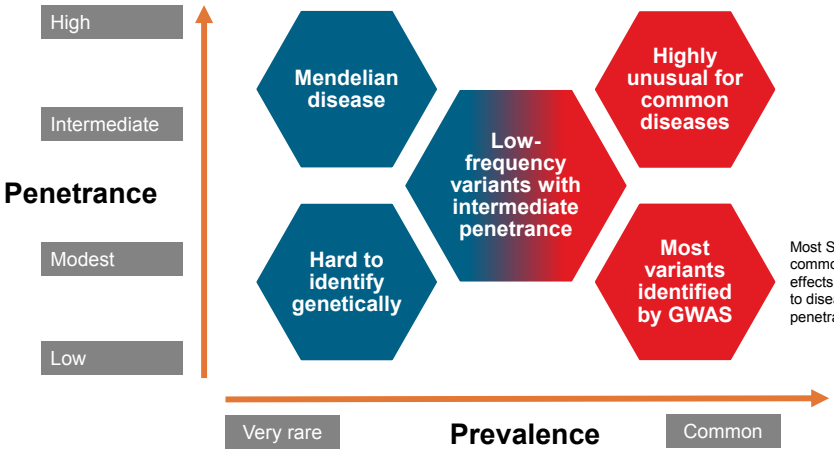
# Prevalence vs. penetrance of genetic variants




Most SNPs identified by GWAS are common but have small genetic effects. I.e., a marginal contribution to disease susceptibility ('low penetrance')

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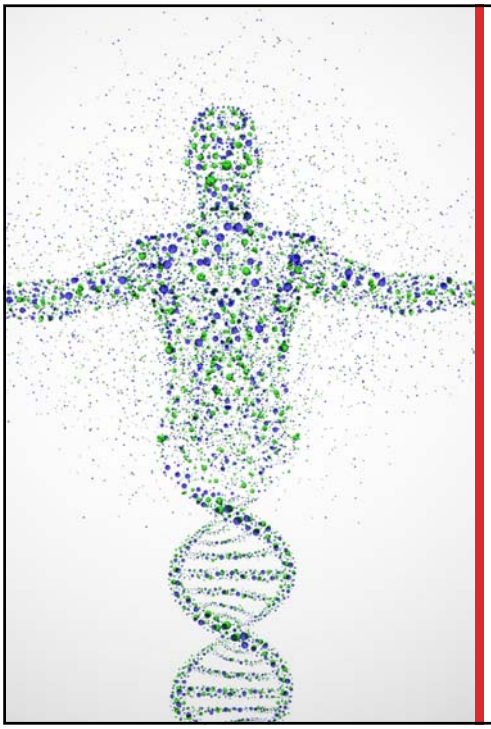
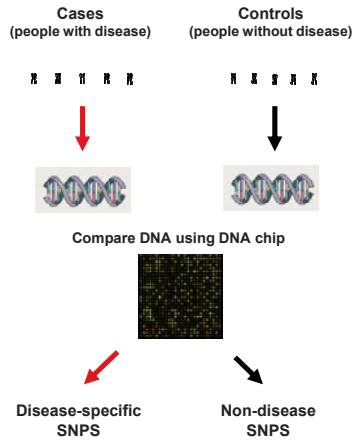
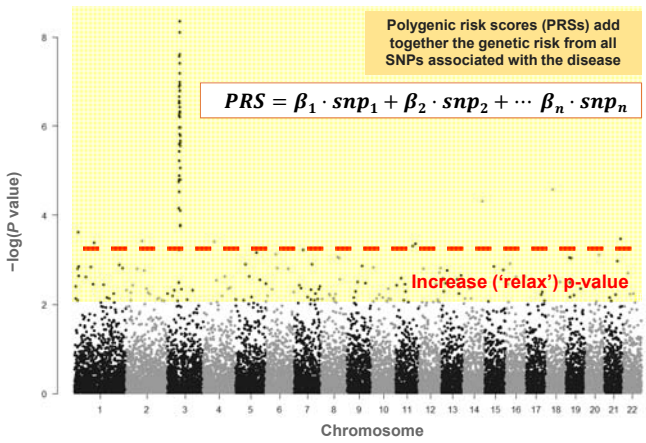


# Genetic Risk to Disease and Polygenic Risk Scores (PRS)



## GWAS → Polygenic risk scores



# 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 |

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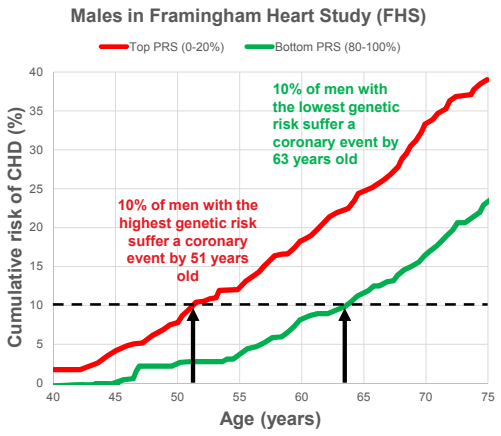
# PRS for coronary heart disease increases predictive power, even after adjustment for clinical risk factors

- A study by Abraham and colleagues* 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 (FINRISK and Framingham Heart Study [FHS]; combined *n* = 16,802 with 1,344 incident CHD events)
- **The PRS was tested alongside the best clinical risk factors as well as family history. After controlling for these risk factors, the PRS still proved to be a very powerful differentiator of CHD risk.**




*Paper: Abraham et al., Genomic prediction of coronary heart disease. Eur Heart J 2016, 37(43):3267-3278

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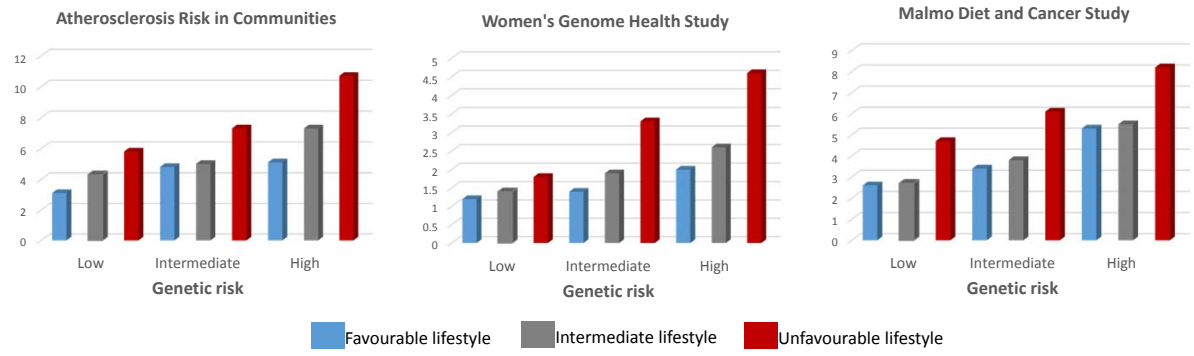
# How do PRS interact with lifestyle?

- A genetic predisposition to coronary artery disease is not deterministic but attenuated by a favorable lifestyle; standardized 10-year coronary event rates in 3 studies:




Paper: Khera et al., Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease. N Engl J Med 2016, 375:2349-2358

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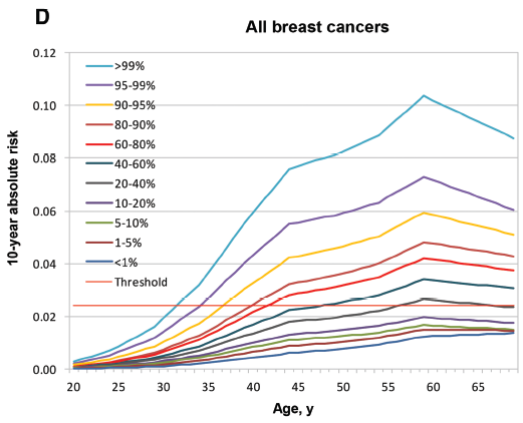
# How PRS could be adopted into clinical medicine – cancer screening

- 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




Paper: 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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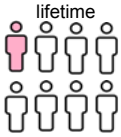
# Potential for anti-selection in breast cancer

In Canada and 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 to 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'?**

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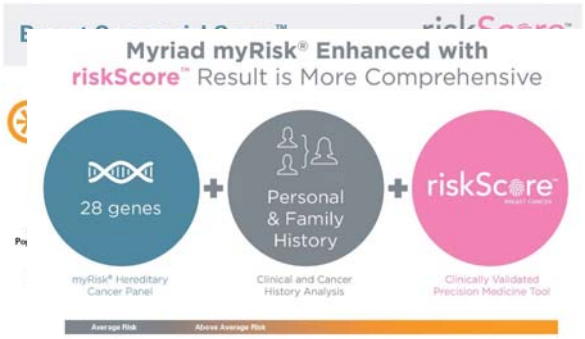
# Myriad's *myRisk* and *riskScore*…

- 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, clinical and family history information

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Approved project: 23203

# RGA Research Collaboration with King's College London

Prof. Cathryn Lewis
(Senior Lecturer)
**Co-Principal Investigator**

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**

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## 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**

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# Why UK Biobank?

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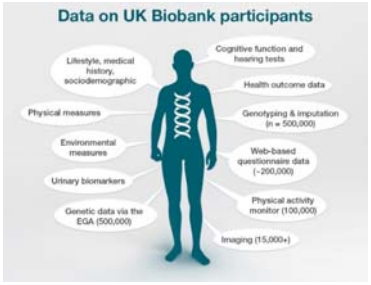
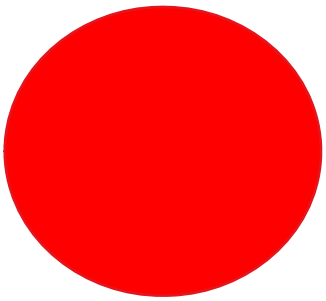
**Breadth and Depth**

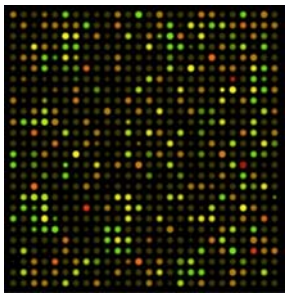



https://www.ebi.ac.uk/about/news/feature-story/biobanks-genetic-data-demand. Accessed 12 May 2018

**Long-term follow up of multiple outcomes**



**Genotyping on all 500k participants**



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# 'Underwriting' UKB participants and predicting disease incidence

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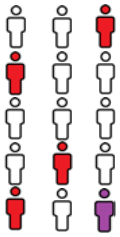
UKB:
c. ½ million individuals



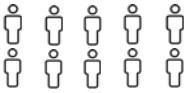
**'Underwriting' Process**

- Prevalent disease in hospital records

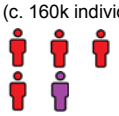
+

- Self-reported illness at baseline verbal interview (with nurse)

'Standard' Risk (disease-free at baseline)
c. 340k individuals



Non-Standard Risk
(c. 160k individuals)



**Prediction Model**

- Phenotypic risk factors (age, gender, smoking, family history, BMI, BP, etc.)

+

- Genetics (PRS for disease)

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

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Total Participants: 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 (reference group) |
| 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 Participants: 143,958
Number of breast cancers: 2,684 (1.86%)

| Percentile | Standard 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 (reference group) |
| 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) |

Decreased risk ↑ / ↓ Increased risk

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

Institute and Faculty of Actuaries

Total Participants: 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 (reference group) |
| 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 Participants: 261,204
Number of CAD events: 2,334 (0.89%)

| Percentile | Standard 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 (reference group) |
| 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) |

Decreased risk ↑ / ↓ Increased risk

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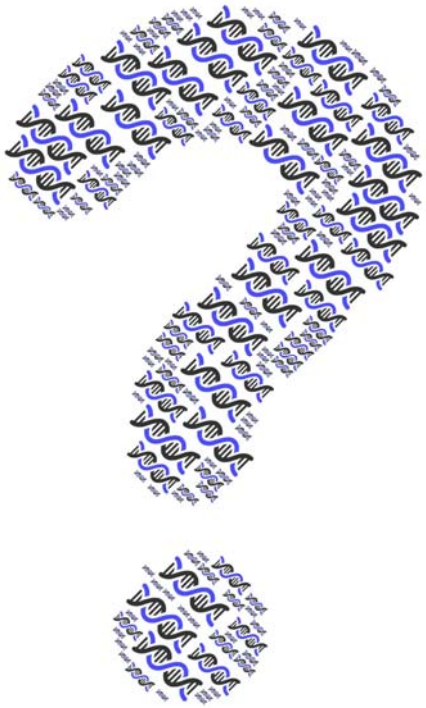


## Genetics and Risks of Anti-selection



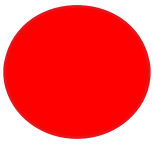
## Research into anti-selection risk from genetics

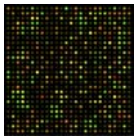
- There have been several research papers…..
  - Huntington's disease anti-selection (Oster et al, 2009)
  - Work of GIRC / Angus MacDonald
  - **CIA Genetic Testing (Mortality and Morbidity)**
  - SOA reproduction of CIA work for US Markets
  - Australian paper, May 2017
- ….suggesting a wide range of possible impacts
- Many modelling assumptions being made
  - Insurance buying behavior pre/post tests
  - Probability of disease and impact thereof

## Research into anti-selection risk from genetics: Assumptions

| Genetic Risk Assumptions | | Insurance Assumptions |
|---|---|---|
| • **Prevalence** of disease variants<br>• **Penetrance** of disease variants | + | • Testing Rate<br>• Seeking insurance etc. |

**Strengthen assumptions using UK Biobank results**





**Still great uncertainty and more research is needed**

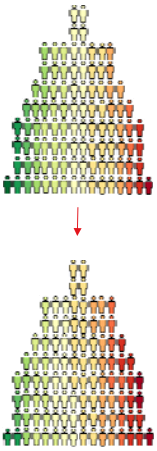


## Predicting impact of PRSs is still early

- 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. Scenario 1:

| Percentile | % in general population | Hazard ratio for breast cancer | Probability of purchasing insurance * | % in new risk pool |
|---|---|---|---|---|
| 0-1 | 1% | 0.41 | 0.41x | 0.4% |
| 1-5 | 4% | 0.56 | 0.56x | 2.1% |
| 5-10 | 5% | 0.6 | 0.6x | 2.8% |
| 10-20 | 10% | 0.71 | 0.71x | 6.5% |
| 20-40 | 20% | 0.84 | 0.84x | 15.4% |
| **40-60** | **20%** | **1** | **1x** | **18.4%** |
| 60-80 | 20% | 1.22 | 1.22x | 22.4% |
| 80-90 | 10% | 1.41 | 1.41x | 13.0% |
| 90-95 | 5% | 1.87 | 1.87x | 8.6% |
| 95-99 | 4% | 1.96 | 1.96x | 7.2% |
| 99-100 | 1% | 2.61 | 2.61x | 2.4% |



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

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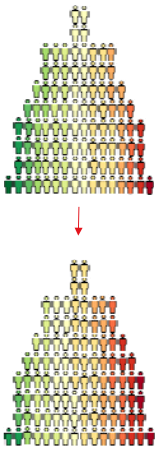
# Potential for anti-selection – example in breast cancer. Scenario 2:

| 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)**

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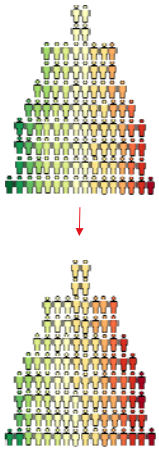
# Potential for anti-selection – example in breast cancer. Scenario 3:

| 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)**

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# Key Messages

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## Conclusions

- 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

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# Thank you for your attention

Any Questions?