The Importance Of Genetics On Mortality and Morbidity Risk
A Study Based On Half A Million Lives In The UK Biobank Cohort

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

Agenda

- 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
**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

*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)

*Image source: Wetterstrand KA. DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP).*
Genomic medicine in the next 5 to 10 years…

Why genomic medicine? Why now?

- Long term investment by Gov in genetics services & workforce
- UK single biggest contributor to Human Genome Project
- NHS Genomic Labs working since the 90s
- Conversion of Industrial Strategy to develop UKgenomics
- Commitment to genomics in Manchester and ‘Next Steps’ plan for NHS
- £500m investment in 100,000 Genomes Project & NHS contribution
- Major parliamentary reports setting out strategic direction
- Building on our inheritance - M366 (2012)
- Generation Genome - CMO (2017)

FOR PATIENTS:
- Enabling a quicker diagnosis & ending the diagnostic odyssey
- Matching people to the most effective medications & interventions
- Increasing people surviving cancer through accurate diagnosis & precision therapy

The personalisation journey

Technology, Innovation & Knowledge Base

Genomic medicine in specific examples

2012

DNA

2013-18

2018 - 2020

2020 and beyond

Clinical Change & Operating Model

Policy, System & Regulatory Alignment

- Better prediction and prevention of disease
- A more precise diagnosis
- More targeted & personalised interventions
- A more responsive care system for patients

- Data analytics & bioinformatics
- Other functional diagnostics
- Phenotypic characterisation
- Patient generated data & self-reporting

- Infrastructure change & commissioning
Genomic medicine in the next 5 to 10 years...

The genomic medicine journey to 2025

**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 diagnostic of rare conditions
- Better understanding of cancer
- Integrated informatics platforms to support comprehensive linking of genomic and clinical data
- Full picture to patients
- Routine care and treatment closely linked through clinical research, academic and industry
- Many more patients eligible for clinical trials

**By 2025:**
- New taxonomy of medicine based on underlying cause & 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 and more effective therapies for better outcomes

Front Page News – August 2018

**The New York Times**

*Genes put millions at triple risk of heart attack*

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

**Forbes**

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

**The Telegraph**

*$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 ‘cardiogenic 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, diabetes, heart failure, and breast cancer
- It could be administered at birth and stop at-risk people from the earliest age
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.
Genome wide association studies (‘GWASes’)  

Cases  
(pople with disease)  

Controls  
(pople without disease)  

Compare DNA using DNA chip  

Disease-specific SNPs  

Non-disease SNPs  

SNPs associated with disease  
(with high significance)  

Very low p-value  

Chromosome  

Prevalence vs. penetrance of genetic variants  

High  
Intermediate  
Modest  
Low  

Mendelian disease  
Low-frequency variants with intermediate penetrance  
Hard to identify genetically  
Most variants identified by GWAS  
Highly unusual for common diseases  

Most SNPs identified by GWAS are common but have small genetic effects, i.e., a marginal contribution to disease susceptibility (‘low penetrance’).
Genetic Risk to Disease and Polygenic Risk Scores (PRS)

GWAS → Polygenic risk scores

Polygenic risk scores (PRSs) add together the genetic risk from all SNPs associated with the disease.

\[ PRS = \beta_1 \cdot snp_1 + \beta_2 \cdot snp_2 + \cdots + \beta_n \cdot snp_n \]
Sample of PRS in literature

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

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.

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:

  - Atherosclerosis Risk in Communities
  - Women’s Genome Health Study
  - Malmo Diet and Cancer Study

![Graphs showing risk levels across genetic risk and lifestyle categories.](image)


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

![Graph showing 10-year breast cancer risk across ages and PRS categories.](image)

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%

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, clinical and family history information.
RGA Research Collaboration with King’s College London

- 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
Why UK Biobank?

Breadth and Depth
- Long-term follow up of multiple outcomes
- Genotyping on all 500k participants

'Data on UK Biobank participants
- Lifestyle: medical history, exercise, smoking
- Physical measurements: height, weight, BMI
- Risk factors: cardiovascular disease, diabetes
- Smoking, alcohol consumption
- Diet, exercise, sleep, mental health
- Medical history: hospital admissions, medications
- Genetic information

Non-Standard Risk (c. 160k individuals)
- 'Underwriting' process
  - Prevalent disease in medical records
  - Self-reported illness at baseline verbal interview (with nurse)
- 'Standard' Risk (disease-free at baseline) c. 340k individuals

Prediction Model
- Phenotypic risk factors (age, gender, smoking, family history, BMI, BP, etc.)
- Genetics (PRS for disease)
### PRS to predict incidence of breast cancer (RGA-KCL study results)

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

**Total Participants:** 199,517  
**Number of breast cancers:** 3,882 (1.95%)

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

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

**Total Participants:** 376,675  
**Number of CAD events:** 4,598 (1.22%)

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

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Standard cohort: Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>0.41 (0.22 - 0.76)</td>
</tr>
<tr>
<td>1-5</td>
<td>0.56 (0.42 - 0.74)</td>
</tr>
<tr>
<td>5-10</td>
<td>0.6 (0.47 - 0.77)</td>
</tr>
<tr>
<td>10-20</td>
<td>0.71 (0.59 - 0.84)</td>
</tr>
<tr>
<td>20-40</td>
<td>0.84 (0.74 - 0.95)</td>
</tr>
<tr>
<td>40-60</td>
<td>1 (reference group)</td>
</tr>
<tr>
<td>60-80</td>
<td>1.22 (1.09 - 1.38)</td>
</tr>
<tr>
<td>80-90</td>
<td>1.41 (1.23 - 1.61)</td>
</tr>
<tr>
<td>90-95</td>
<td>1.87 (1.6 - 2.18)</td>
</tr>
<tr>
<td>95-99</td>
<td>1.96 (1.66 - 2.31)</td>
</tr>
<tr>
<td>99-100</td>
<td>2.61 (2.02 - 3.38)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Standard cohort: Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>0.66 (0.4 - 1.11)</td>
</tr>
<tr>
<td>1-5</td>
<td>0.41 (0.29 - 0.57)</td>
</tr>
<tr>
<td>5-10</td>
<td>0.77 (0.61 - 0.97)</td>
</tr>
<tr>
<td>10-20</td>
<td>0.78 (0.65 - 0.93)</td>
</tr>
<tr>
<td>20-40</td>
<td>0.81 (0.7 - 0.93)</td>
</tr>
<tr>
<td>40-60</td>
<td>1 (reference group)</td>
</tr>
<tr>
<td>60-80</td>
<td>1.15 (1.01 - 1.3)</td>
</tr>
<tr>
<td>80-90</td>
<td>1.54 (1.33 - 1.77)</td>
</tr>
<tr>
<td>90-95</td>
<td>1.43 (1.19 - 1.72)</td>
</tr>
<tr>
<td>95-99</td>
<td>1.92 (1.61 - 2.29)</td>
</tr>
<tr>
<td>99-100</td>
<td>2.78 (2.11 - 3.67)</td>
</tr>
</tbody>
</table>

**Total Participants:** 261,204  
**Number of CAD events:** 2,334 (0.89%)
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
- Prevalence of disease variants
- Penetration of disease variants

Insurance Assumptions
- Testing Rate
- 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 penetration 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:**

<table>
<thead>
<tr>
<th>Percentile</th>
<th>% in general population</th>
<th>Hazard ratio for breast cancer</th>
<th>Probability of purchasing insurance *</th>
<th>% in new risk pool</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>1%</td>
<td>0.41</td>
<td>0.41x</td>
<td>0.4%</td>
</tr>
<tr>
<td>1-5</td>
<td>4%</td>
<td>0.56</td>
<td>0.56x</td>
<td>2.1%</td>
</tr>
<tr>
<td>5-10</td>
<td>5%</td>
<td>0.6</td>
<td>0.6x</td>
<td>2.8%</td>
</tr>
<tr>
<td>10-20</td>
<td>10%</td>
<td>0.71</td>
<td>0.71x</td>
<td>6.6%</td>
</tr>
<tr>
<td>20-40</td>
<td>20%</td>
<td>0.84</td>
<td>0.84x</td>
<td>15.4%</td>
</tr>
<tr>
<td>40-60</td>
<td>20%</td>
<td>1</td>
<td>1x</td>
<td>18.4%</td>
</tr>
<tr>
<td>60-80</td>
<td>20%</td>
<td>1.22</td>
<td>1.22x</td>
<td>22.4%</td>
</tr>
<tr>
<td>80-90</td>
<td>10%</td>
<td>1.41</td>
<td>1.41x</td>
<td>13.0%</td>
</tr>
<tr>
<td>90-95</td>
<td>5%</td>
<td>1.87</td>
<td>1.87x</td>
<td>8.6%</td>
</tr>
<tr>
<td>95-99</td>
<td>4%</td>
<td>1.96</td>
<td>1.96x</td>
<td>7.2%</td>
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<td>99-100</td>
<td>1%</td>
<td>2.61</td>
<td>2.61x</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

* note, we make no assumptions for preventative measures

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

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

<table>
<thead>
<tr>
<th>Percentile</th>
<th>% in general population</th>
<th>Hazard ratio for breast cancer</th>
<th>Probability of purchasing insurance *</th>
<th>% in new risk pool</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>1%</td>
<td>0.41</td>
<td>0.71x</td>
<td>0.7%</td>
</tr>
<tr>
<td>1-5</td>
<td>4%</td>
<td>0.56</td>
<td>0.78x</td>
<td>3.0%</td>
</tr>
<tr>
<td>5-10</td>
<td>5%</td>
<td>0.6</td>
<td>0.80x</td>
<td>3.9%</td>
</tr>
<tr>
<td>10-20</td>
<td>10%</td>
<td>0.71</td>
<td>0.86x</td>
<td>8.2%</td>
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<tr>
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<td>20%</td>
<td>0.84</td>
<td>0.92x</td>
<td>17.7%</td>
</tr>
<tr>
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<td>20%</td>
<td>1</td>
<td>1x</td>
<td>19.2%</td>
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<td>20%</td>
<td>1.22</td>
<td>1.11x</td>
<td>21.4%</td>
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<td>10%</td>
<td>1.41</td>
<td>1.21x</td>
<td>11.6%</td>
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<tr>
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<td>1.44x</td>
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<td>1%</td>
<td>2.61</td>
<td>1.81x</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

- +7% increase in incidence
- +8% increase if include BRCA1/2 mutations (assuming 0.2% prevalence and 5x odds ratio)
Potential for anti-selection – example in breast cancer. Scenario 3:

<table>
<thead>
<tr>
<th>Percentile</th>
<th>% in general population</th>
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</tr>
<tr>
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<td>5%</td>
<td>0.6</td>
<td>1x</td>
<td>4.6%</td>
</tr>
<tr>
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<td>9.2%</td>
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<td>18.3%</td>
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<td>1</td>
<td>1x</td>
<td>18.3%</td>
</tr>
<tr>
<td>60-80</td>
<td>20%</td>
<td>1.22</td>
<td>1.11x</td>
<td>20.3%</td>
</tr>
<tr>
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<td>10%</td>
<td>1.41</td>
<td>1.21x</td>
<td>11.0%</td>
</tr>
<tr>
<td>90-95</td>
<td>5%</td>
<td>1.87</td>
<td>1.44x</td>
<td>6.6%</td>
</tr>
<tr>
<td>95-99</td>
<td>4%</td>
<td>1.96</td>
<td>1.48x</td>
<td>5.4%</td>
</tr>
<tr>
<td>99-100</td>
<td>1%</td>
<td>2.61</td>
<td>1.81x</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

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

Key Messages
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.

Thank you for your attention
Any Questions?