Genetics and Personalised Medicine

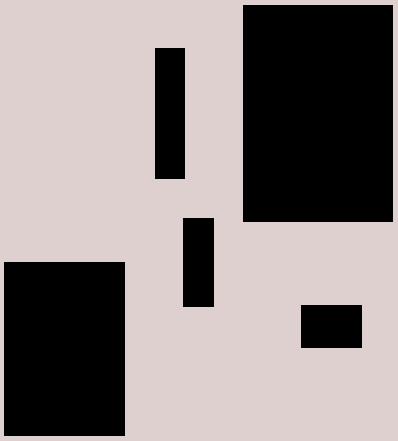
Matthew Edwards

19 November 2018

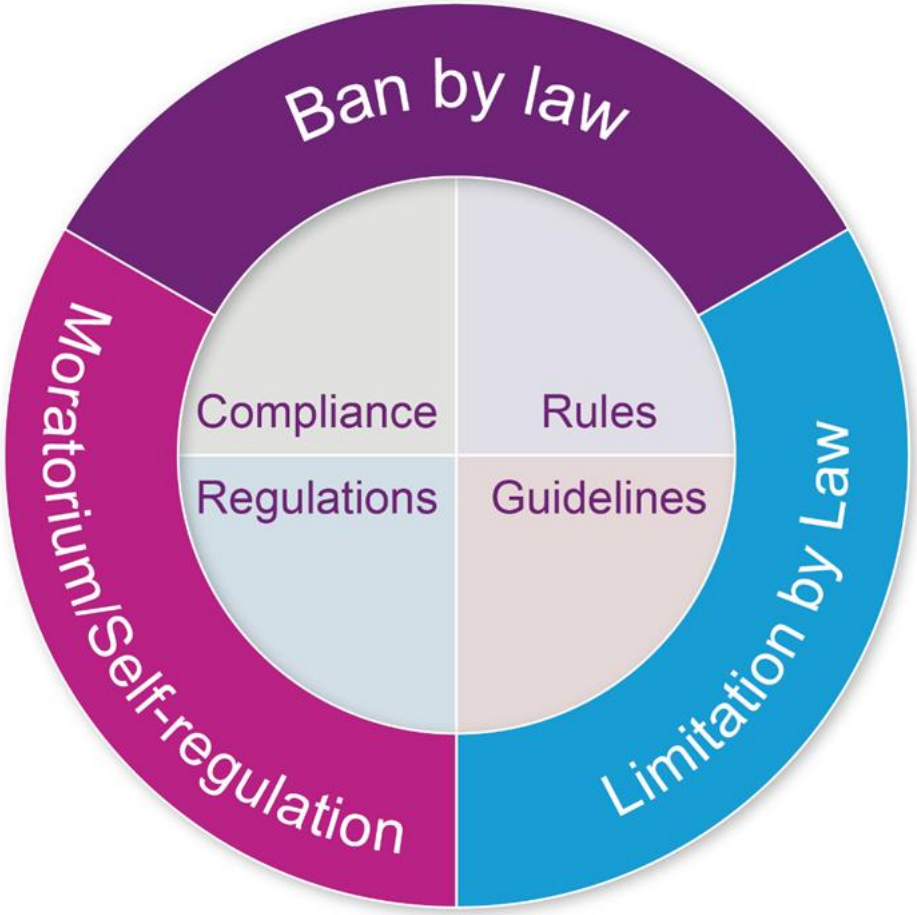
Willis Towers Watson

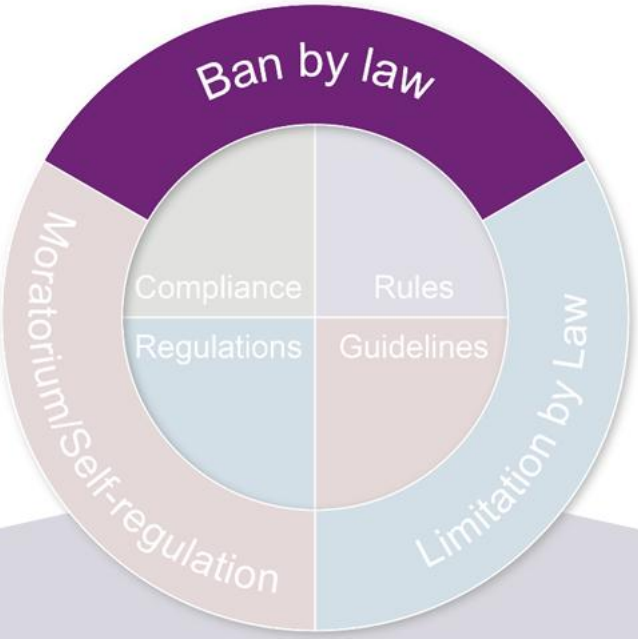
Contents

Background



Three approaches to genetic testing

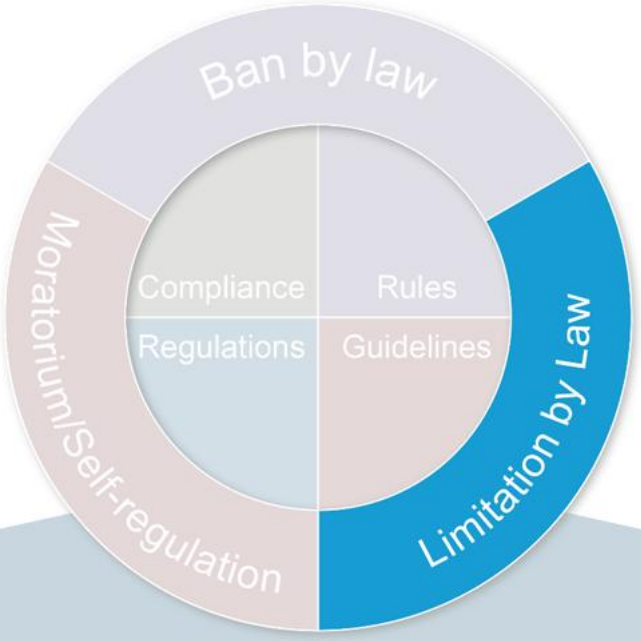




Portugal
Genetic Information Act (2005)

Poland
Insurance Act (2015)

Canada
Genetic Non-Discrimination Act (2016)

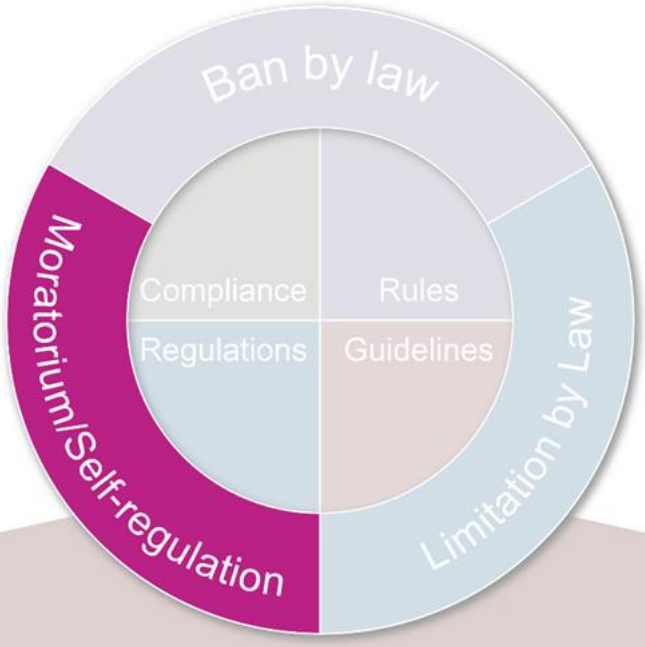


USA
Genetic Information Non-discrimination Act (2008)

Netherlands
The Act on Medical Examinations (1998)

Switzerland
Genetic Investigations in Humans (2004)

Germany
Human Genetic Examination Act (2009)



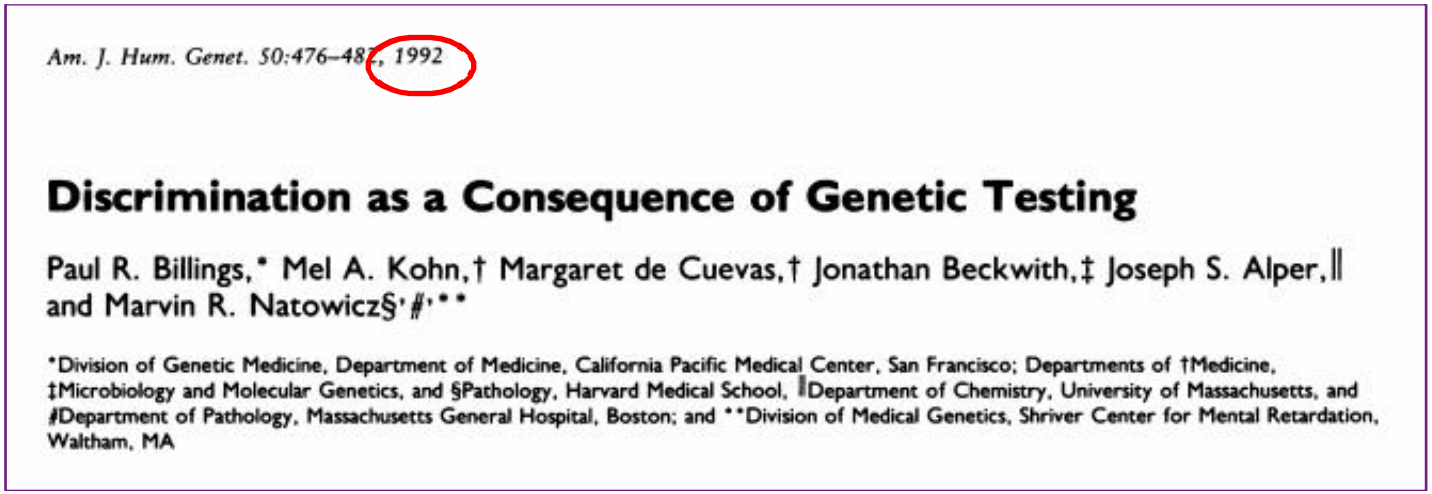
Japan
Life insurers impose self-restrictions

China
No restrictions for insurance companies asking for genetic tests or results

UK
Concordat & Moratorium (2001)

Australia
Insurers allowed to use genetic test results (but changes are afoot)

Discrimination?



Am. J. Hum. Genet. 50:476–487, 1992

Discrimination as a Consequence of Genetic Testing

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"Stigmatization, and denial of services or entitlements to individuals who have a genetic diagnosis but who are asymptomatic or who will never become significantly impaired, is noted."

Journal of Neurology, Neurosurgery & Psychiatry

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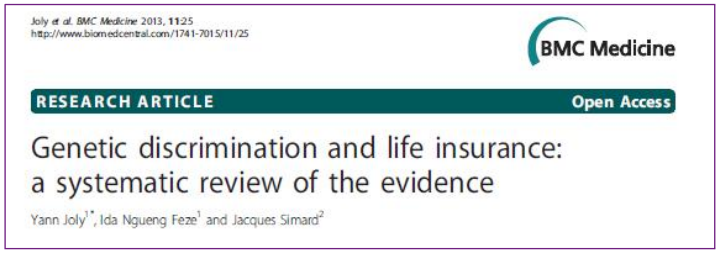
Genetic testing and counselling

K05 Genetic Discrimination and Predictive Testing for Huntington's Disease and Familial Cancer in Northern Scotland: The I-Respond-UK Study

S Wedderburn[1], D Rae[1], J Williams[2], R Carey-Heaton[1], Z Miedzybrodzka[1,3]

Author affiliations +

Avoidance of discrimination through refusing testing/



Joly et al. BMC Medicine 2013, 11:25
http://www.biomedcentral.com/1741-7015/11/25

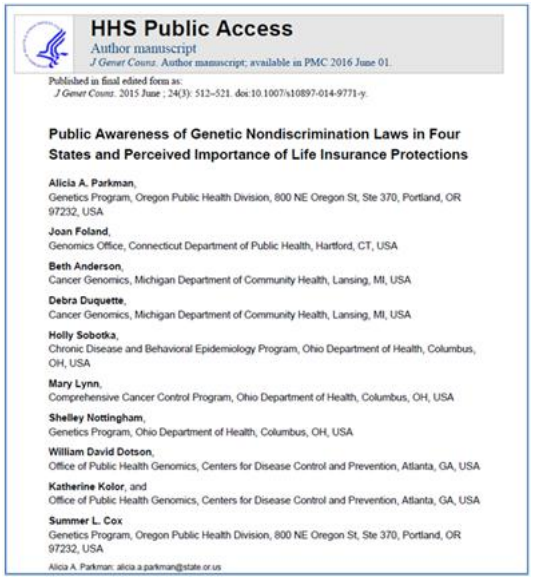
BMC Medicine

RESEARCH ARTICLE Open Access

Genetic discrimination and life insurance: a systematic review of the evidence

Yann Joly[1*], Ida Ngueng Feze[1] and Jacques Simard[2]

Lack of evidence that discrimination occurs but fear exists



HHS Public Access

Author manuscript

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J Genet Couns. 2015 June ; 24(3): 512–521. doi:10.1007/s10897-014-9771-y.

Public Awareness of Genetic Nondiscrimination Laws in Four States and Perceived Importance of Life Insurance Protections

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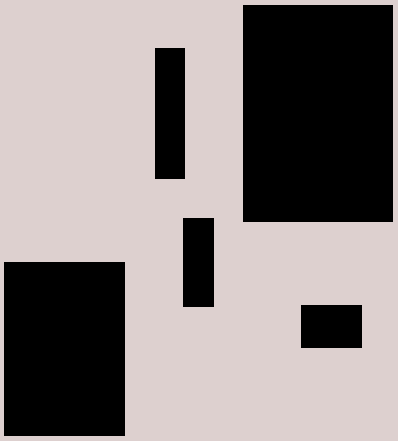
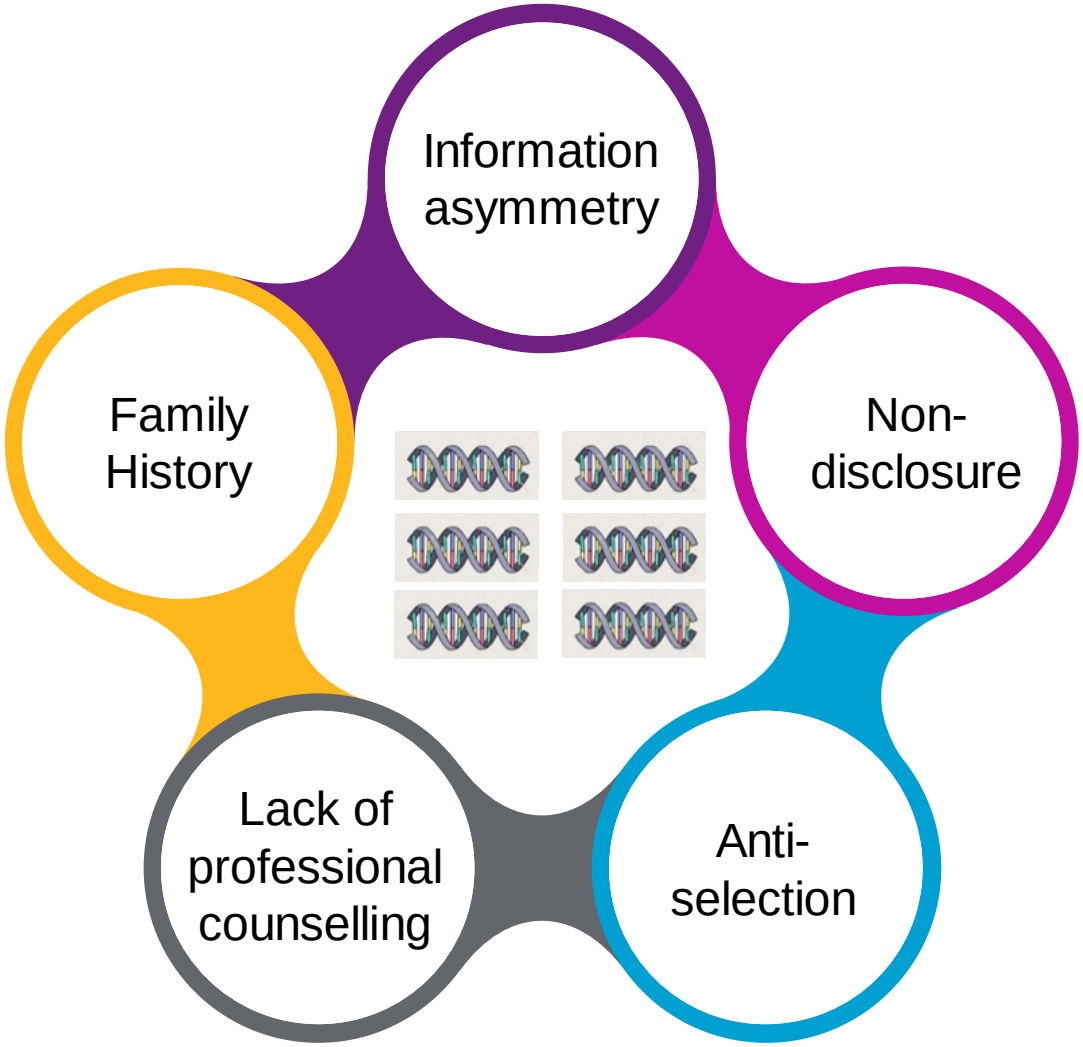
Low public awareness of legislation
High levels of concern
Limited physician awareness of legislation

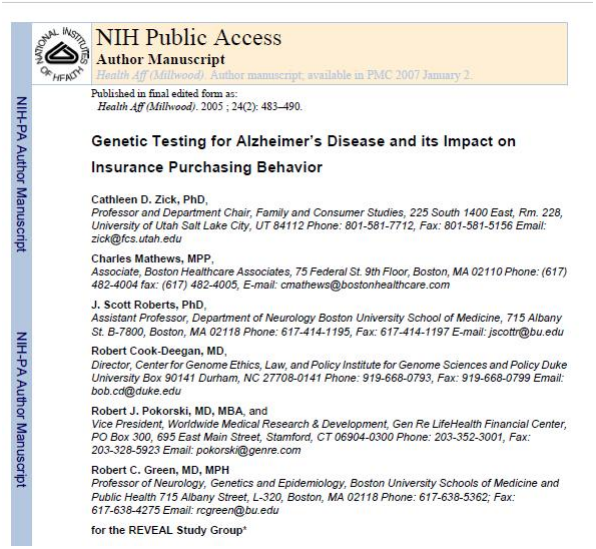
Self-selection by policyholders



Insurers versus policyholders?



Case study: testing for Alzheimer's



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Genetic Testing for Alzheimer's Disease and its Impact on Insurance Purchasing Behavior

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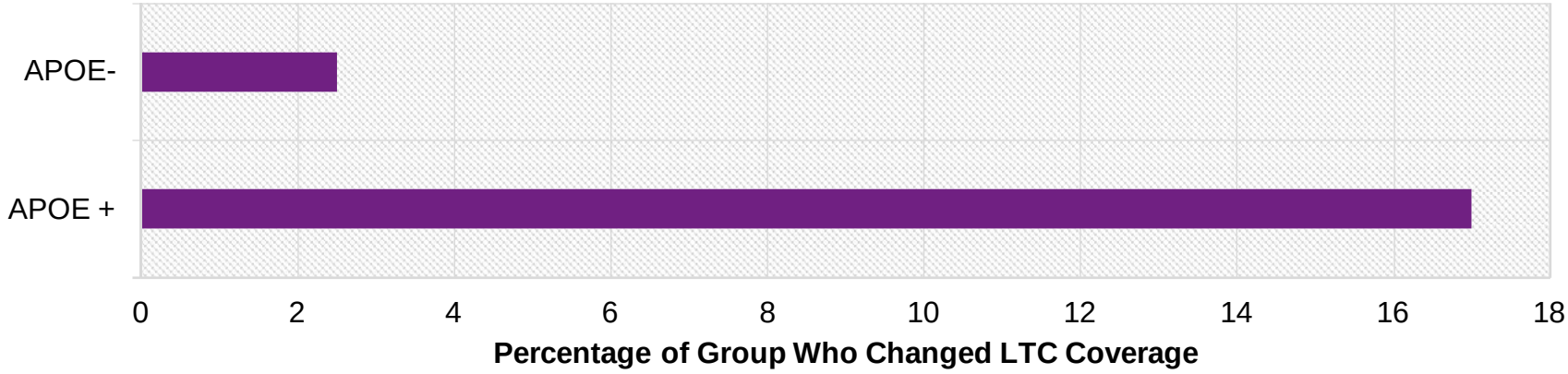
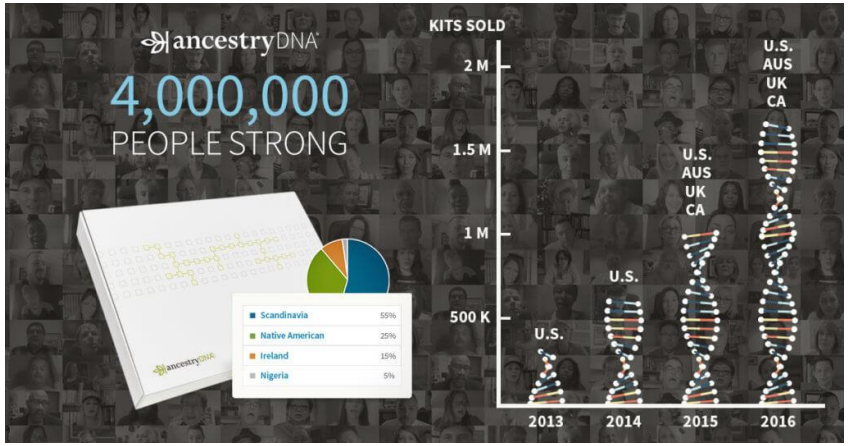
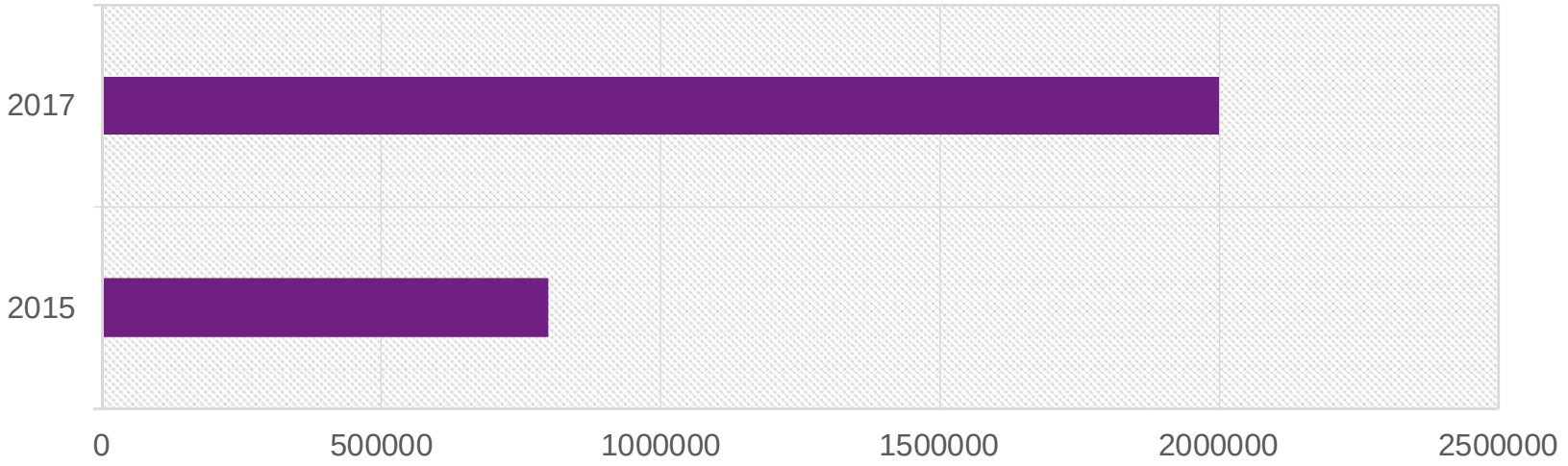
for the REVEAL Study Group*

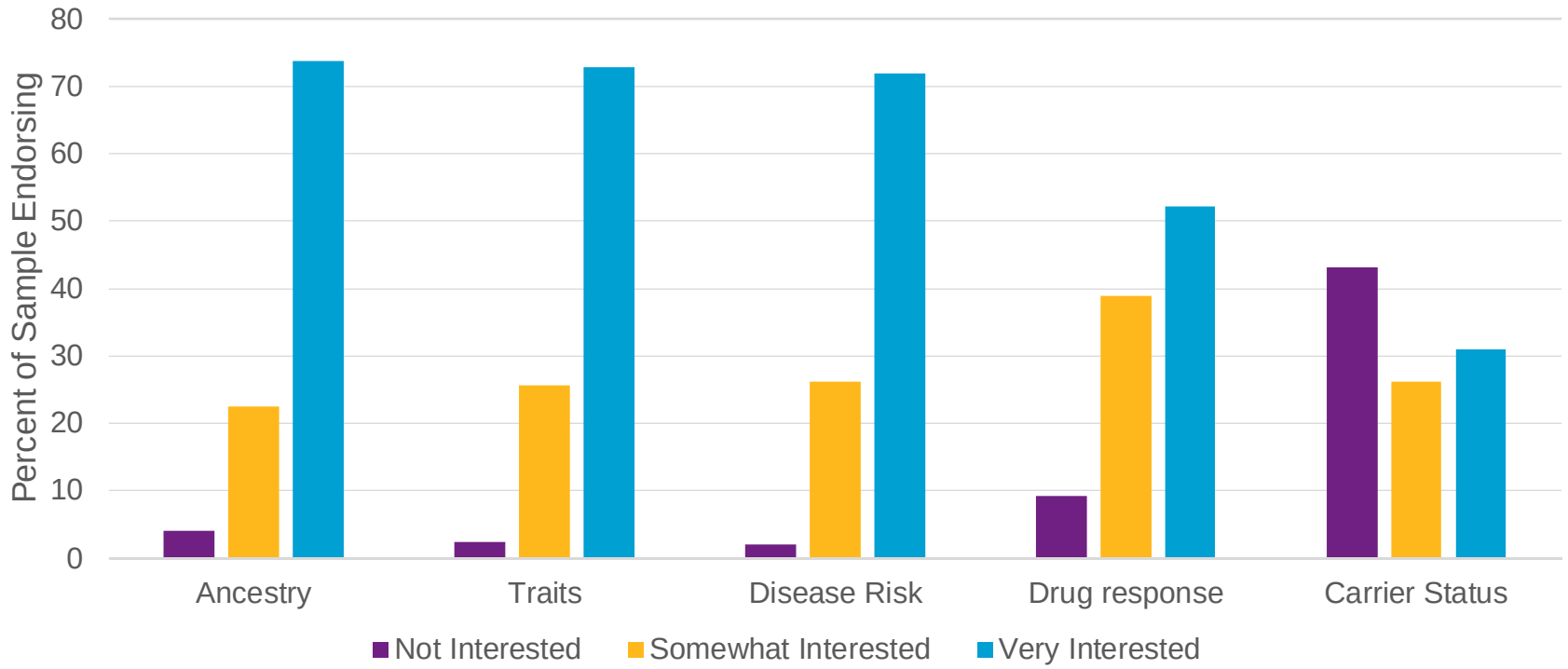


Knowledge of family history



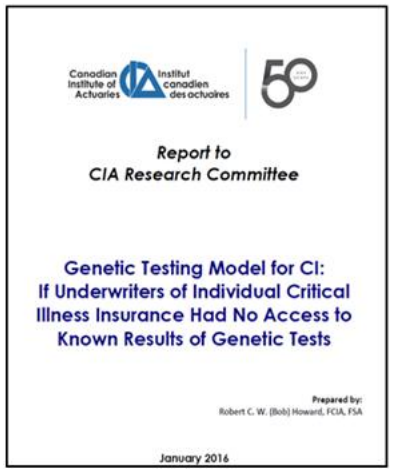


Level of interest across types of personal genetic information

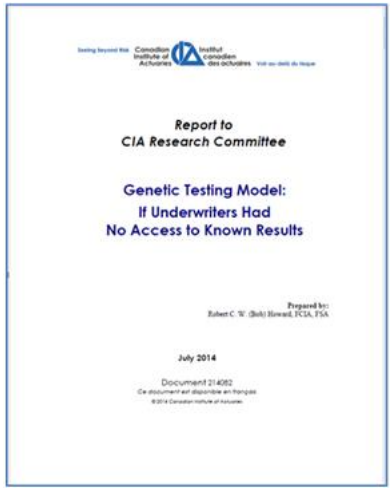


Roberts J et al (2017) Direct-to-Consumer Genetic Testing: User Motivations, Decision Making, and Perceived Utility of Results Public Health Genomics 2017;20:36–45

Further research

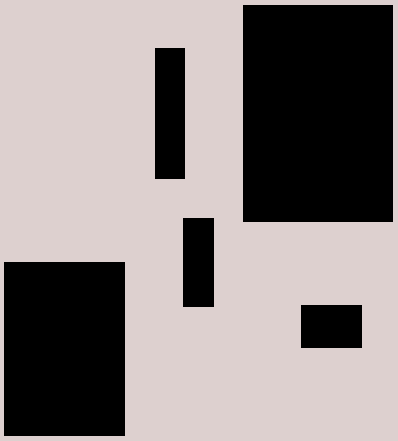


Material impact on insurer, average CI claim overall increase of 26% and concomitant increase in CI premium rates

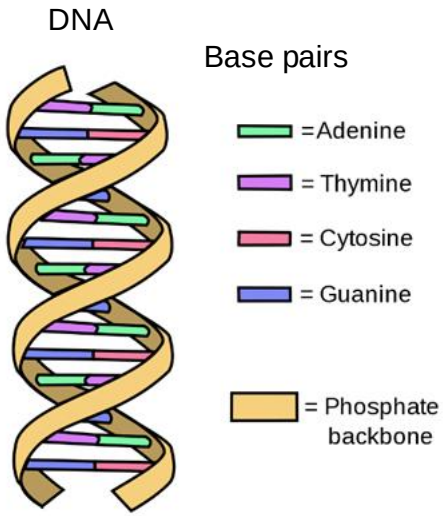


Valuation strain (pricing loss) for the industry from those who test positive in a single year (based on the assumptions) would be about 12% of the total death claims for the year. There may be a concomitant increase in term insurance premium rates

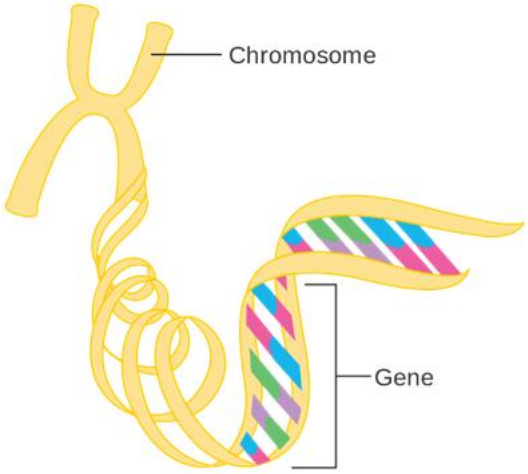
Case study – UK BioBank & KCL



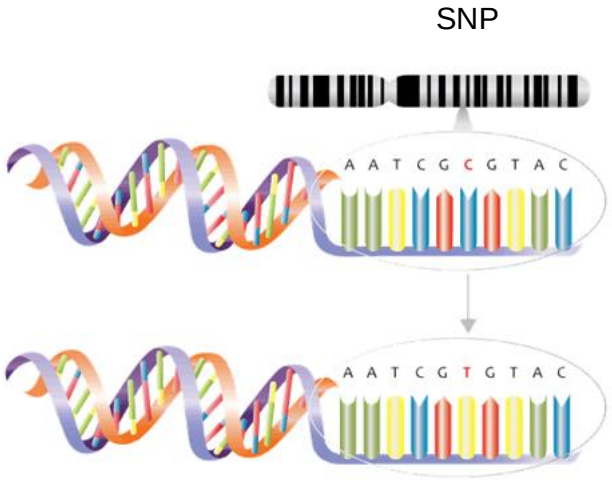
DNA, chromosomes and single nucleotide polymorphisms (SNPs)



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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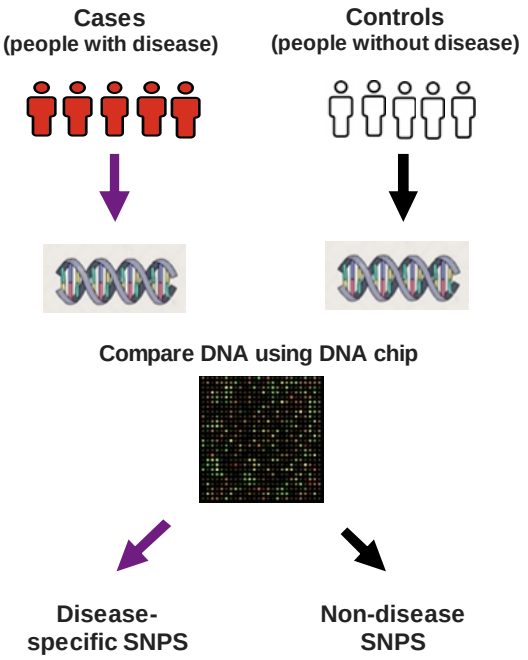
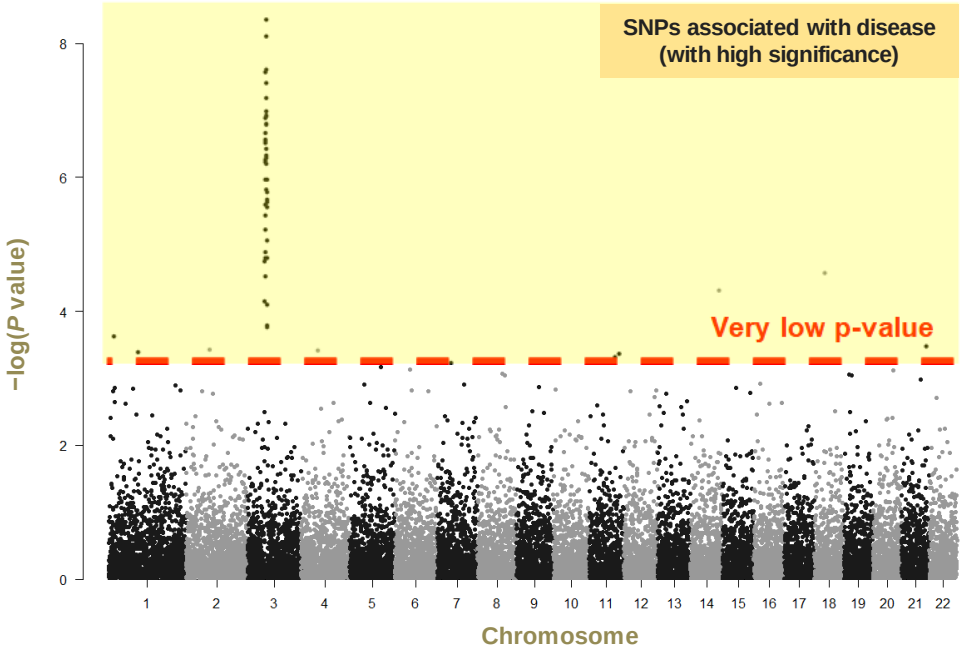
Genome wide association studies ('GWASes')





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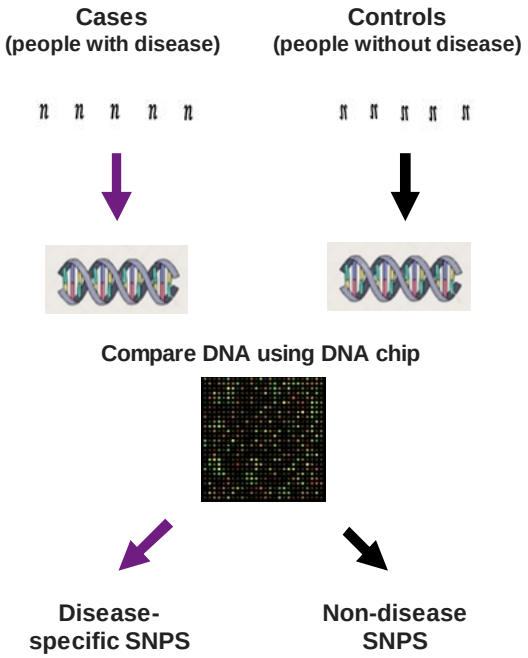
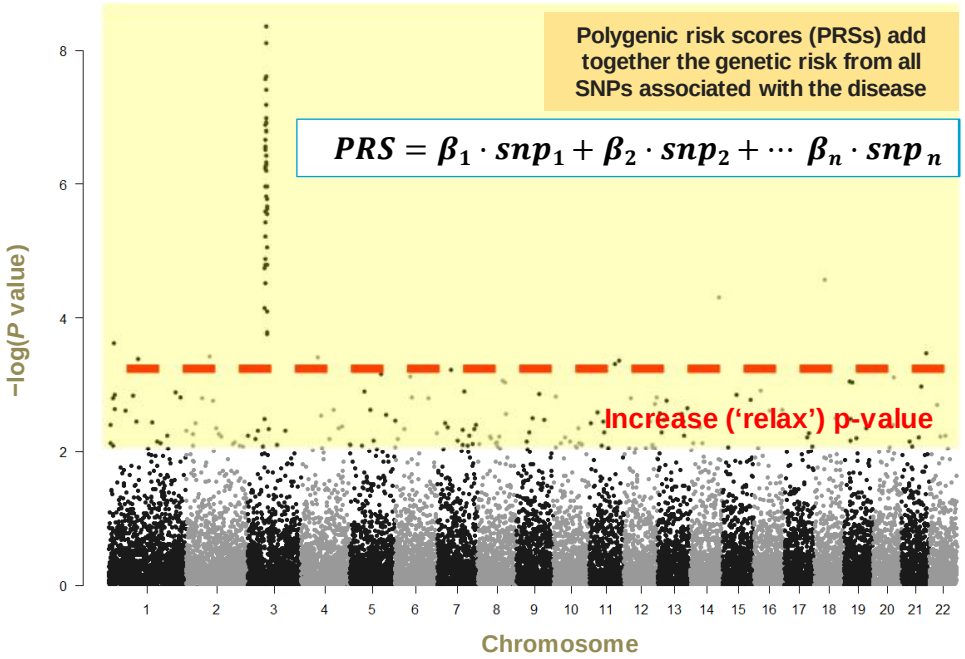
PRS: Polygenic Risk Scores





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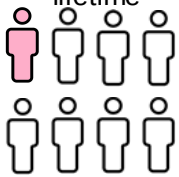
Potential for anti-selection in breast cancer

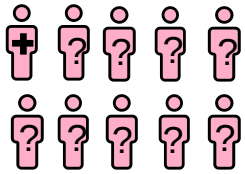
In Canada and the UK, about 1 in 8 women will be diagnosed with breast cancer in their lifetime



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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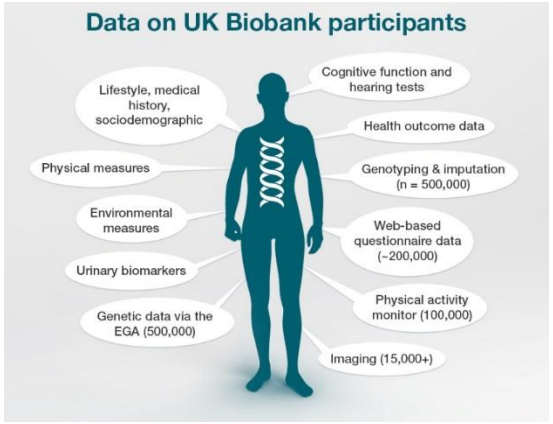
Origins of research

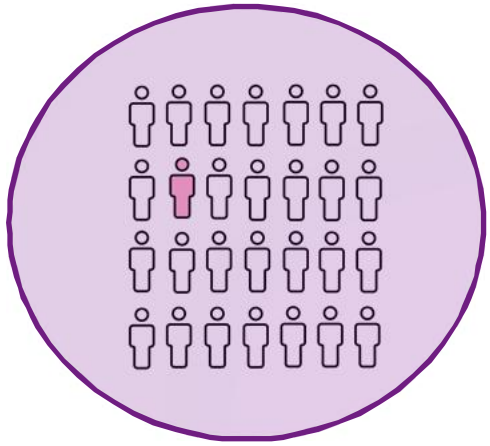
Why UK Biobank?

Breadth and Depth

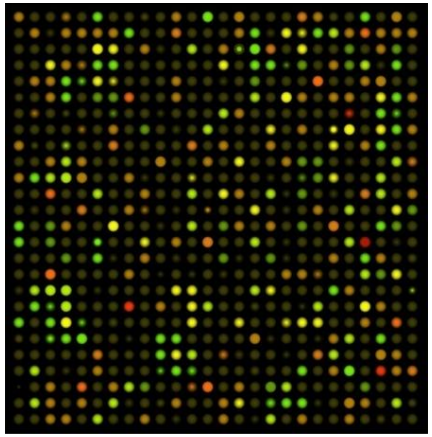


https://www.ebi.ac.uk/about/news/feature-story/biobanks-genetic-data-demand. Accessed 12 May 2018

Long-term follow up of multiple outcomes



Genotyping on all 500k participants



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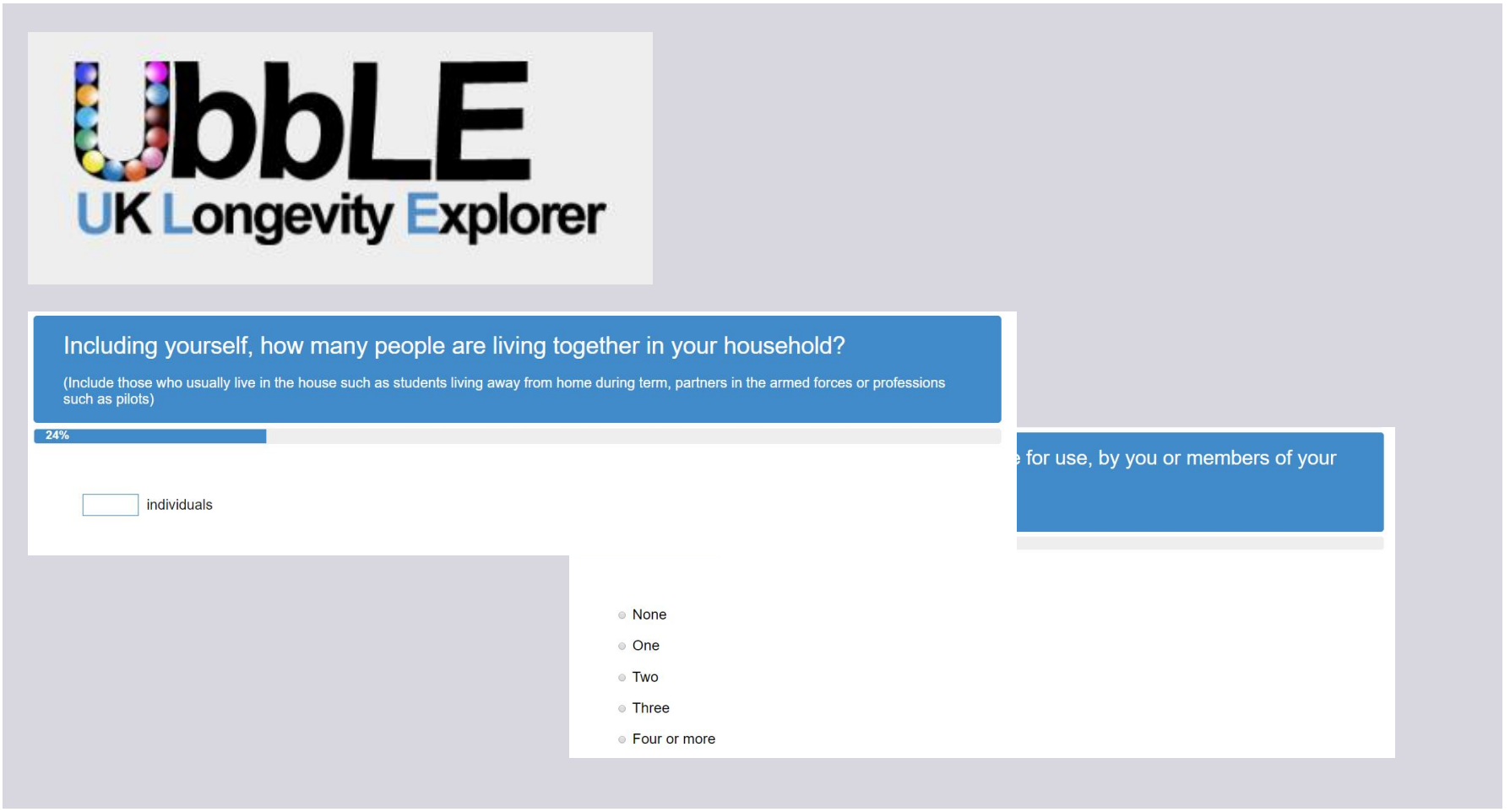
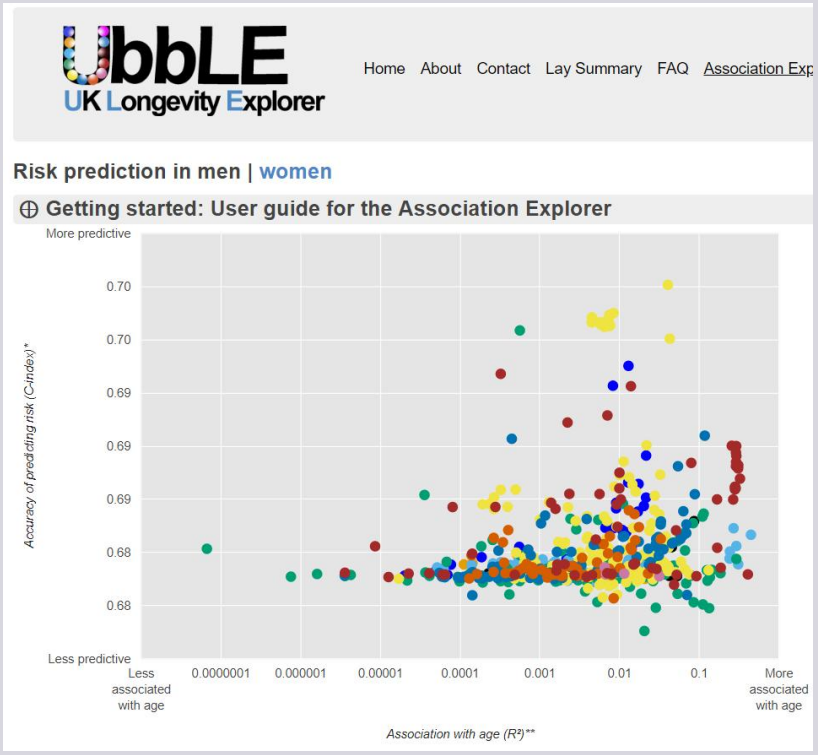
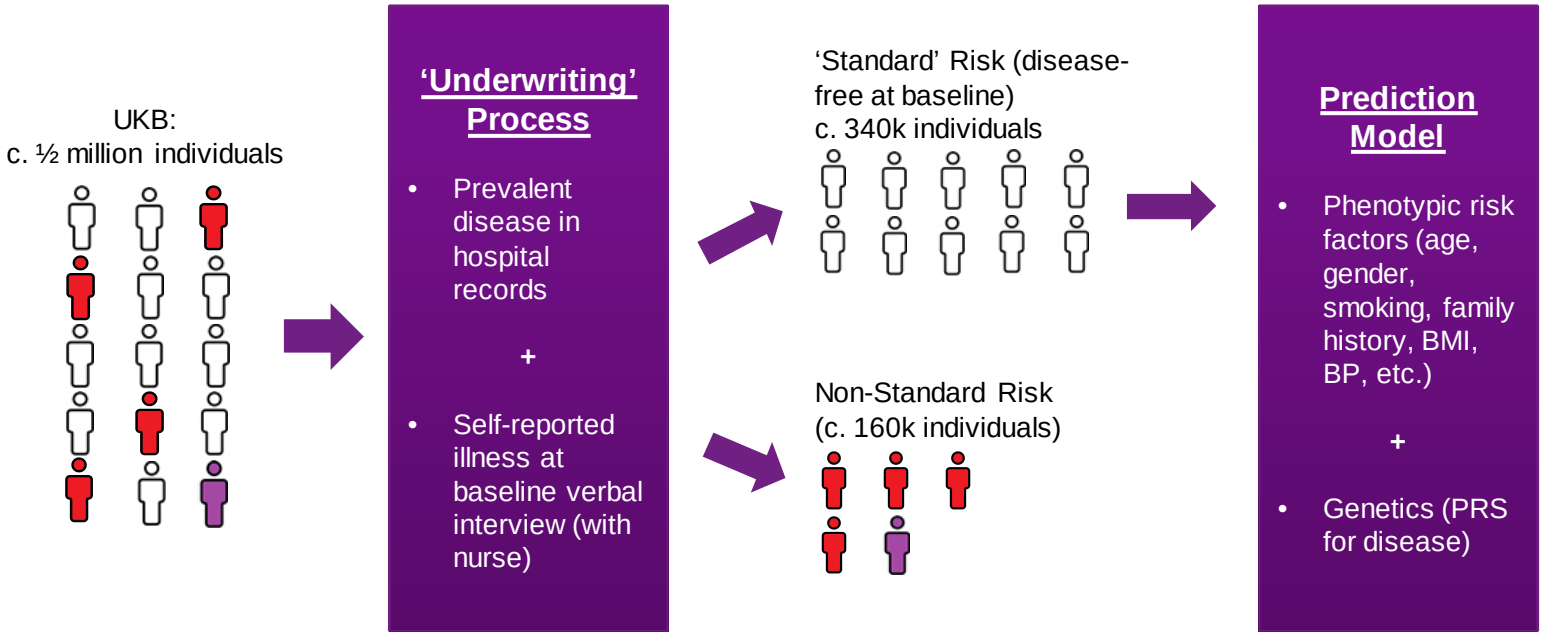
Other insights from UK BioBank



Other insights from UK BioBank (2)



‘Underwriting’ UKB participants and predicting disease incidence



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

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

Decreased risk

Increased risk

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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.

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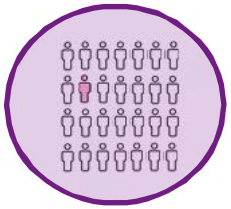
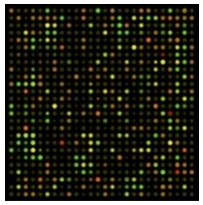
Research into anti-selection risk from genetics: Assumptions

Genetic Risk Assumptions

- **Prevalence** of disease variants
- **Penetrance** of disease variants

Strengthen assumptions using UK Biobank results





Insurance Assumptions

- Testing Rate
- Seeking insurance etc.

Still great uncertainty and more research is needed

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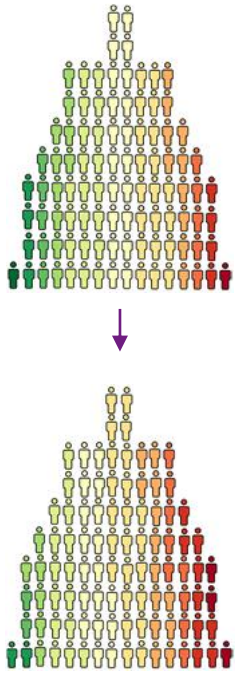
Potential for anti-selection – example in breast cancer
(Central of three scenarios)

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)**

Adapted with permission from RGA presentation materials (see slide 30)

Further information

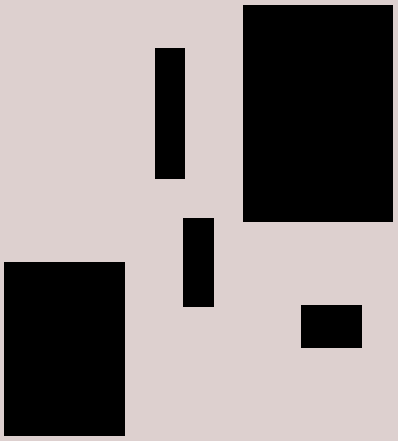
Peter Banthorpe, Senior Vice President and Head, Global Research and Data Analytics

https://www.rgare.com/knowledge-center/media/articles/the-risk-of-anti-selection-in-protection-business-from-advances-in-statistical-genetics

https://www.actuarial-center.org/the-importance-of-genetics-on-mortality-and-morbidity-risk-in-the-presence-of_6dcc60cd6.html

https://www.cass.city.ac.uk/__data/assets/powerpoint_doc/0009/437463/BANTHORPE-Peter.pptx

Pooling, trends, catastrophes

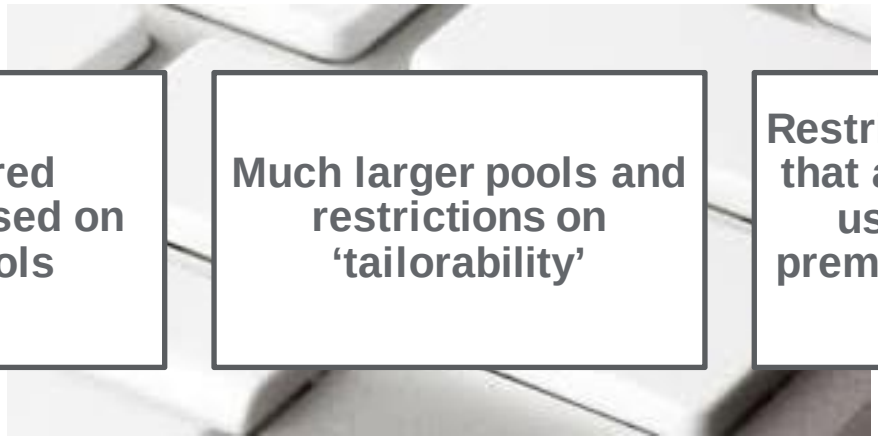


Pooling – to what extent do we want to pool varying risks?

Thinking about life insurance through a genetic lens, Dr Damjan Vukcevic & Jessica Chen

Potential lapse of in-force policies

Potential increase in claim cost



More-tailored premiums, based on smaller pools

Much larger pools and restrictions on 'tailorability'

Restrictions on factors that are allowed to be used for pricing premiums and setting exclusions

Actuaries Summit
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Trends

What are the likely impacts of personalised medicine on mortality trends?

- Negative contribution to trend from gradual impact of anti-selection
- Positive contribution from improving care following personalised treatment
  - Impact currently still relatively minor
  - Medium-term impact limited to a range of cancers?
  - Longer-term impact: ?
- Positive contribution from improving 'self care' following personal test results?
  - Likely to vary strongly by socio-economic class
- Overall impact will depend on culture, attitudes and health provision in different countries

What are the likely impacts of personalised medicine on CI trends?

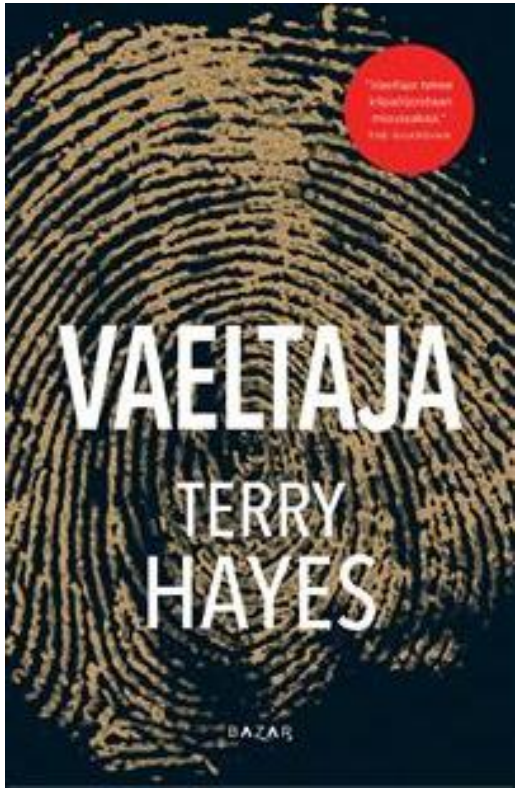
- Negative trend from gradual impact of antiselection
- Negative trend from earlier / more reliable claim diagnostics
  - … but earlier screening (from better diagnosis) could reduce emergence 'full' condition

'Negative' = negative improvements, ie a worsening of the claims impact

Catastrophes

Life insurers need to consider capital requirements in the event of a 1-in-200 mortality catastrophe

- Generally relate to heavy pandemic and/or terrorist (or similar) incident
- Availability of technology to 'make your own genes' could allow feasible scenario of easily bio-engineered super-pathogen?
  - Probability? – fits 1-in-200
  - Impact? – much worse than Spanish flu



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