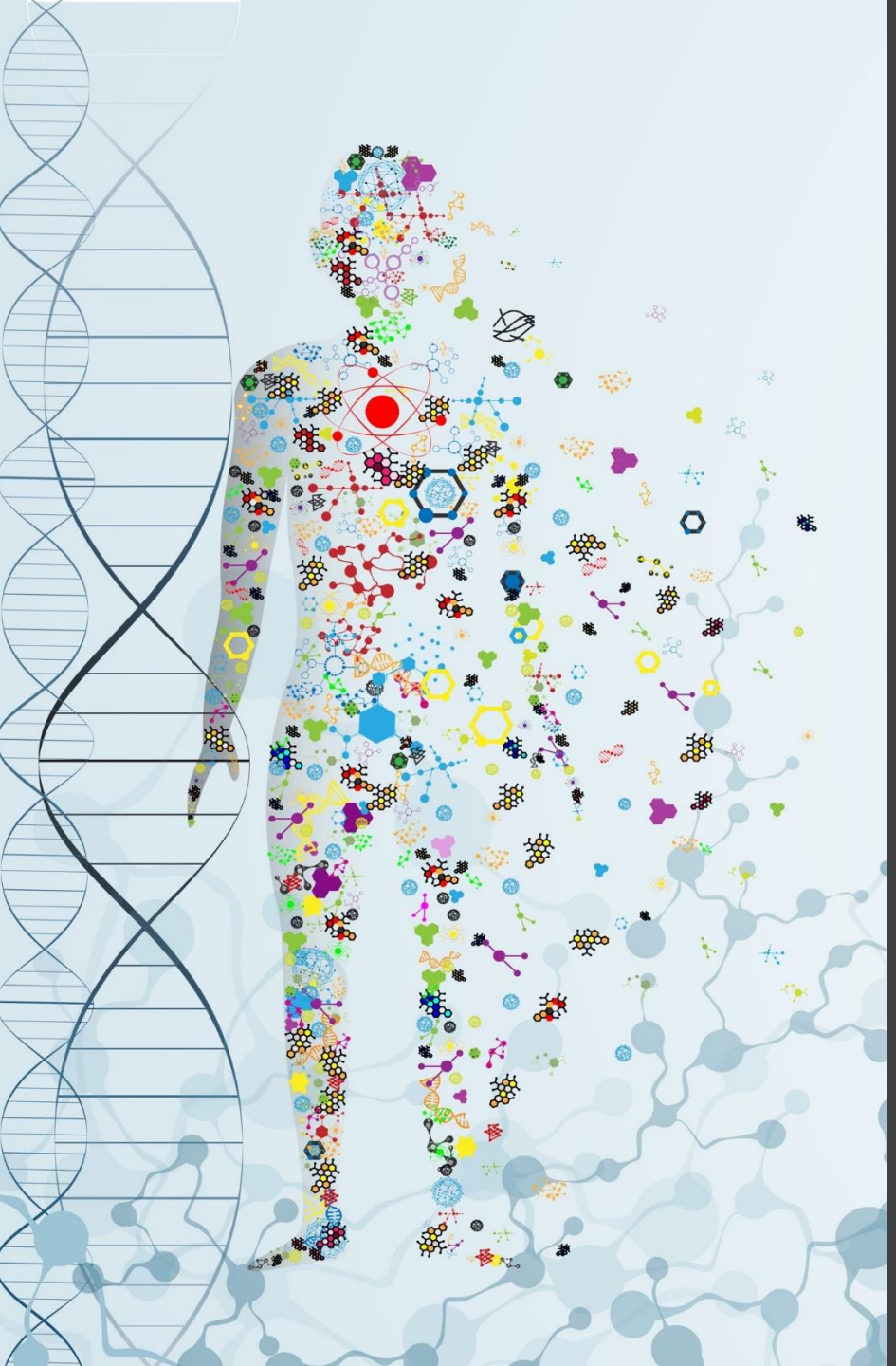


RGA

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

Stephen Courquin
VP, UK Head of Actuarial Research

Institute and Faculty of Actuaries
Highlights of the Life Conference 2018
March 2019

Institute and Faculty of Actuaries

Agenda

- Genetic Data and Insurance
- Genomic Medicine Today and in the Next 5 to 10 Years
- Genetic Risk to Disease and Polygenic Risk Scores
- RGA / King's College London Research Collaboration
- Genetics and Risks of Anti-selection
- Key Messages

Institute and Faculty of Actuaries

Genetic Data and Insurance

RGA

Genetics is a great case study for a potential future vision of risk selection

If the **Future of Medicine** = **Precision Medicine**,

Does **Future of Risk Selection** = **Precision Underwriting**?

Precision Underwriting brings a range of **ethical**, **legal, competitive** and **social** concerns.

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

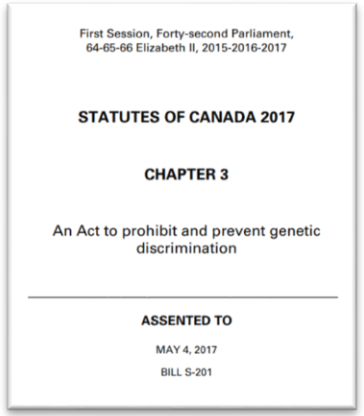
JOY LARSEN HAIDLE, NATIONAL SOCIETY OF GENETIC COUNSELORS

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 from governments and regulators

[Council of Europe Recommendation](#)
October 2016


First Session, Forty-second Parliament,
64-65-66 Elizabeth II, 2015-2016-2017

STATUTES OF CANADA 2017

CHAPTER 3

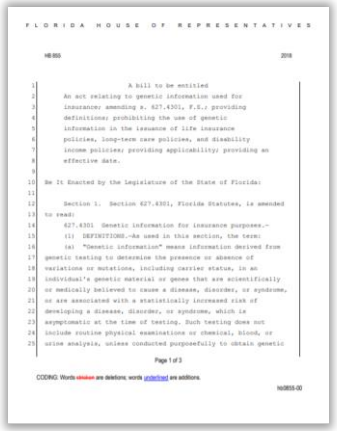
An Act to prohibit and prevent genetic discrimination

ASSENTED TO

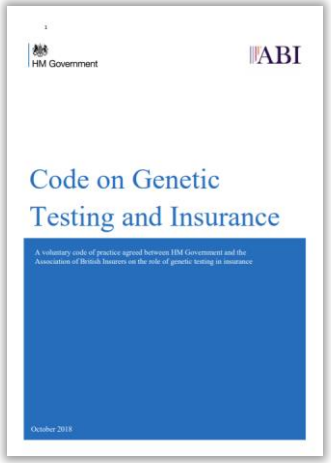
MAY 4, 2017

BILL S-201

[Canadian Genetic Non-discrimination Act](#)
May 2017


FLORIDA HOUSE OF REPRESENTATIVES

[United States – Various Bills](#)
2017-2019


HM Government

ABI

Code on Genetic Testing and Insurance

A voluntary code of practice agreed between HM Government and the Association of British Insurers on the role of genetic testing in insurance

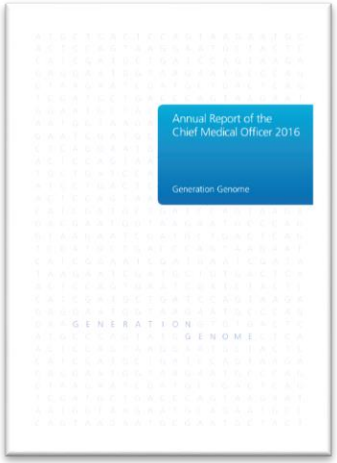
October 2018

[Code Genetic Testing and Insurance](#)
October 2018


FSC

FSC ANNOUNCES MORATORIUM ON GENETIC TESTS FOR LIFE INSURANCE TO START IN JULY 2019

[Australian Moratorium](#)
July 2019


Annual Report of the Chief Medical Officer 2016

Generation Genome

[England CMO Annual Report: Generation Genome](#)
July 2017

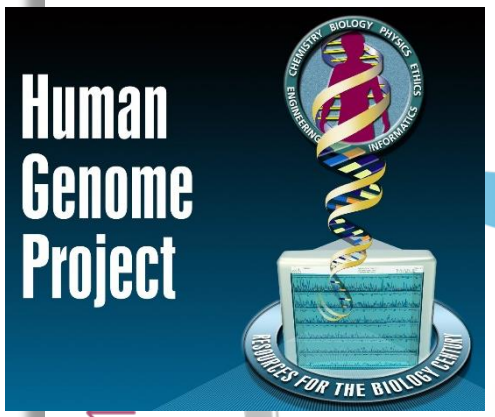
Whole genome sequencing costs today

Institute and Faculty of Actuaries

€259 Full DNA Analysis (**Offer Valid Until Feb. 28th**). **Get the test**

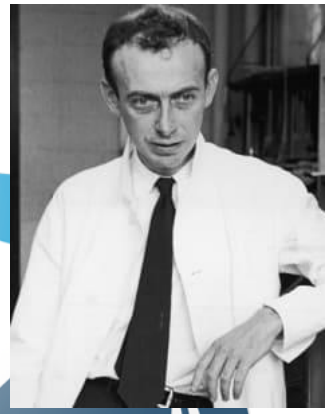
Home / Home Page Europe / My Full DNA: Whole Genome Sequencing with mtDNA

2003



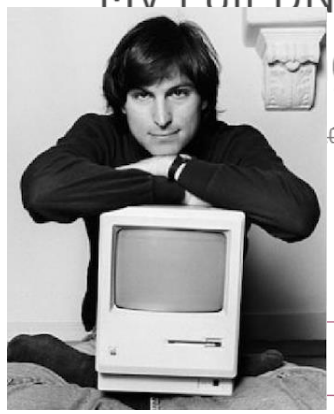
$2.7 billion

2007



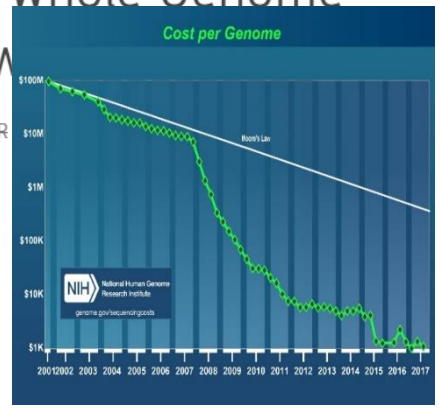
$2 million

2011



$100,000

2015



$1,000

2018

$199

DESCRIPTION

Dante Labs Rare Disease Month: Dante Labs celebrates the Rare Disease Day offering "My Full DNA (Whole Genome Sequencing Test)" at a special price. **To get more information about the "Rare Disease Month", take a look at our FAQ**

RGA

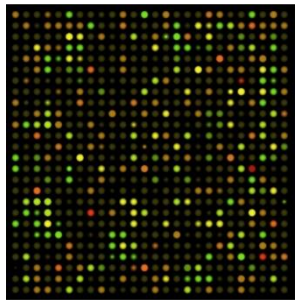
Growing opportunities for genetic anti-selection

Institute and Faculty of Actuaries

26 million

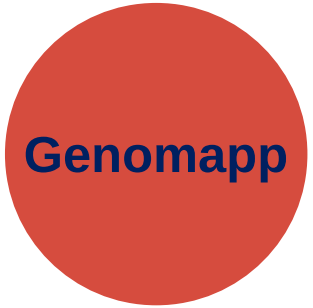
Consumer genetic tests sold since 2012

600,000



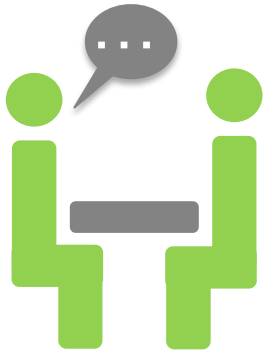
DNA variants measured by 23andMe

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)

40 billion

Gigabytes of new genomic data generated a year by 2030

RGA

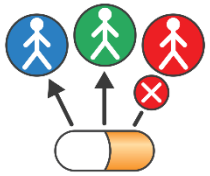
Genetic anti-selection risk: are these beliefs still valid?

1. Genetic risk information will not be widely available in the near future
2. Monogenic mutations that confer significantly higher risk of disease are rare therefore the cost imposed on insurers by any associated adverse selection is deemed small
3. Most common diseases are multifactorial, and the genetic contribution to these diseases is modest
4. Genetic test results will not deliver significant risk information that is not already available from traditional clinical/biometric measures used in underwriting
5. The genetic contribution to disease is adequately captured by family history

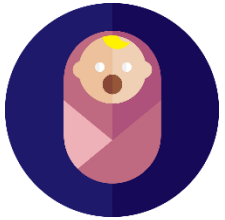
Genomic Medicine Today and in the Next 5 to 10 Years

Genomics medicine today

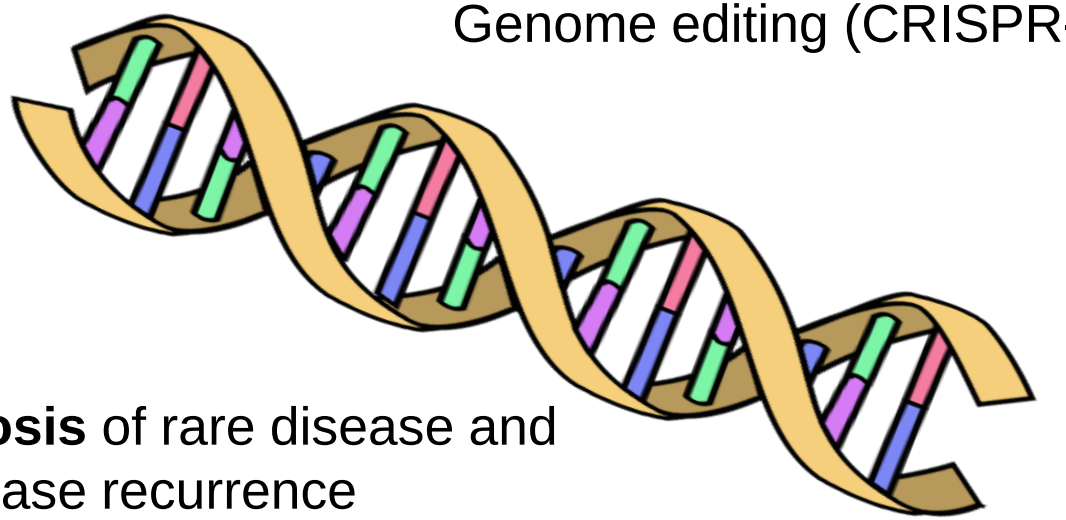
Precision medicine: pharmacogenetics, cancer treatments

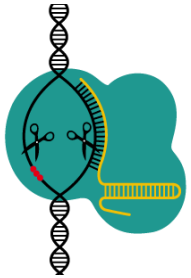


Prenatal and newborns **screening**



Genome editing (CRISPR-Cas9)



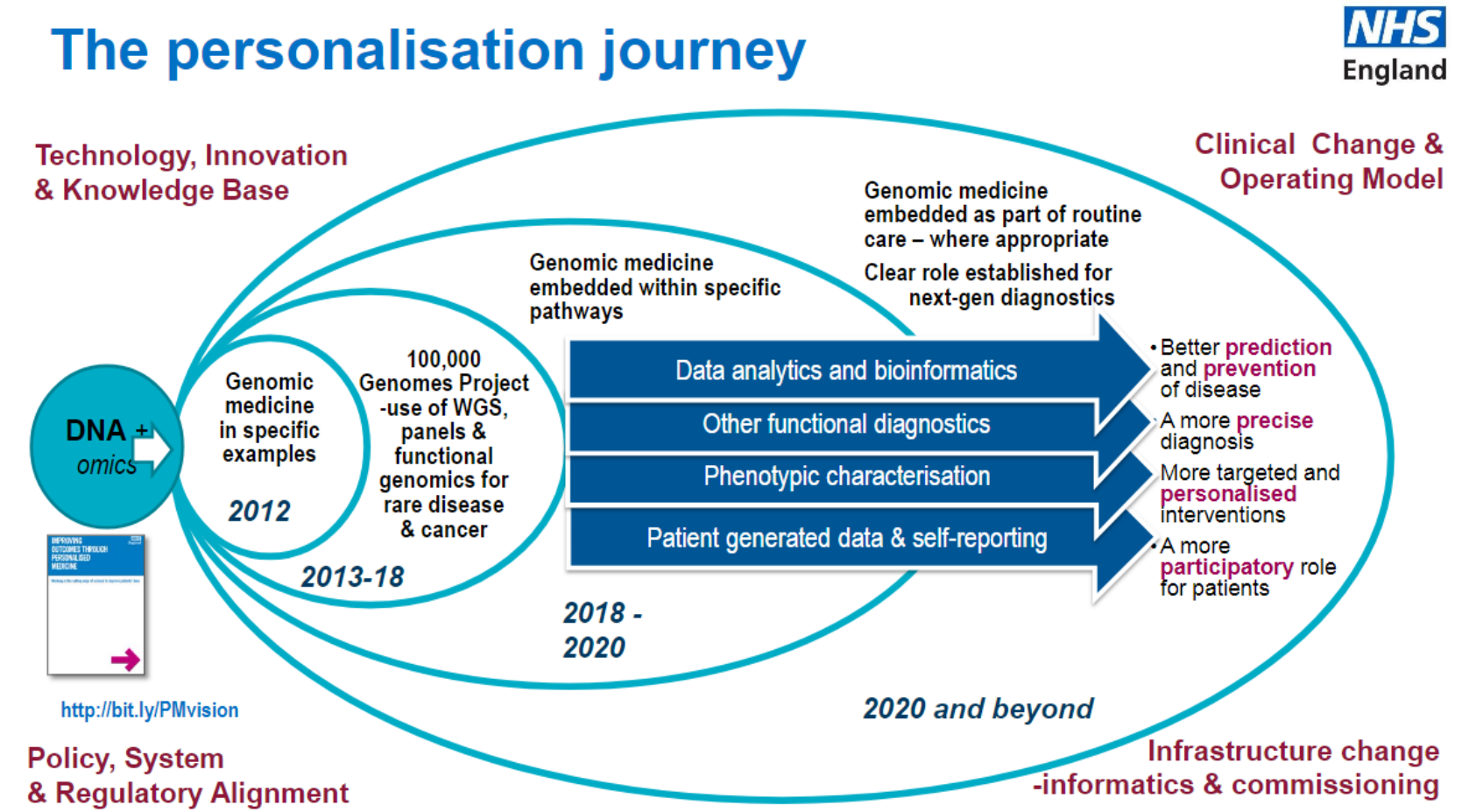


Accurate **diagnosis** of rare disease and detection of disease recurrence

More accurate disease **prognosis**

Motivating lifestyle modification

Genomic medicine in the next 5 to 10 years…



5 million genomes in 5 years – January 2019

Institute and Faculty of Actuaries

theguardian

NHS to sell DNA tests to healthy people in push to find new treatments

Service will be free for patients with serious genetic conditions as health service in England aims to recruit 5 million volunteers

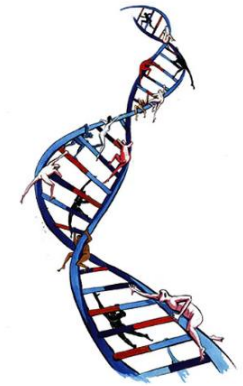
THE SPECTATOR

FEATURES

The future of your health could soon be in the NHS's hands

Home testing kits are all the rage – but do you really want to know the secrets of your genome?

Robert Plomin



INDEPENDENT

NHS to sell patients genetic tests showing risk of killer diseases such as cancer and dementia

Sequencing will cost a few hundred pounds and patients will have to agree to DNA data being retained for research

Colin Drury | @colin_drury | Saturday 26 January 2019 14:00 | 196 shares |

Like Click to follow The Independent

NEWS

Health

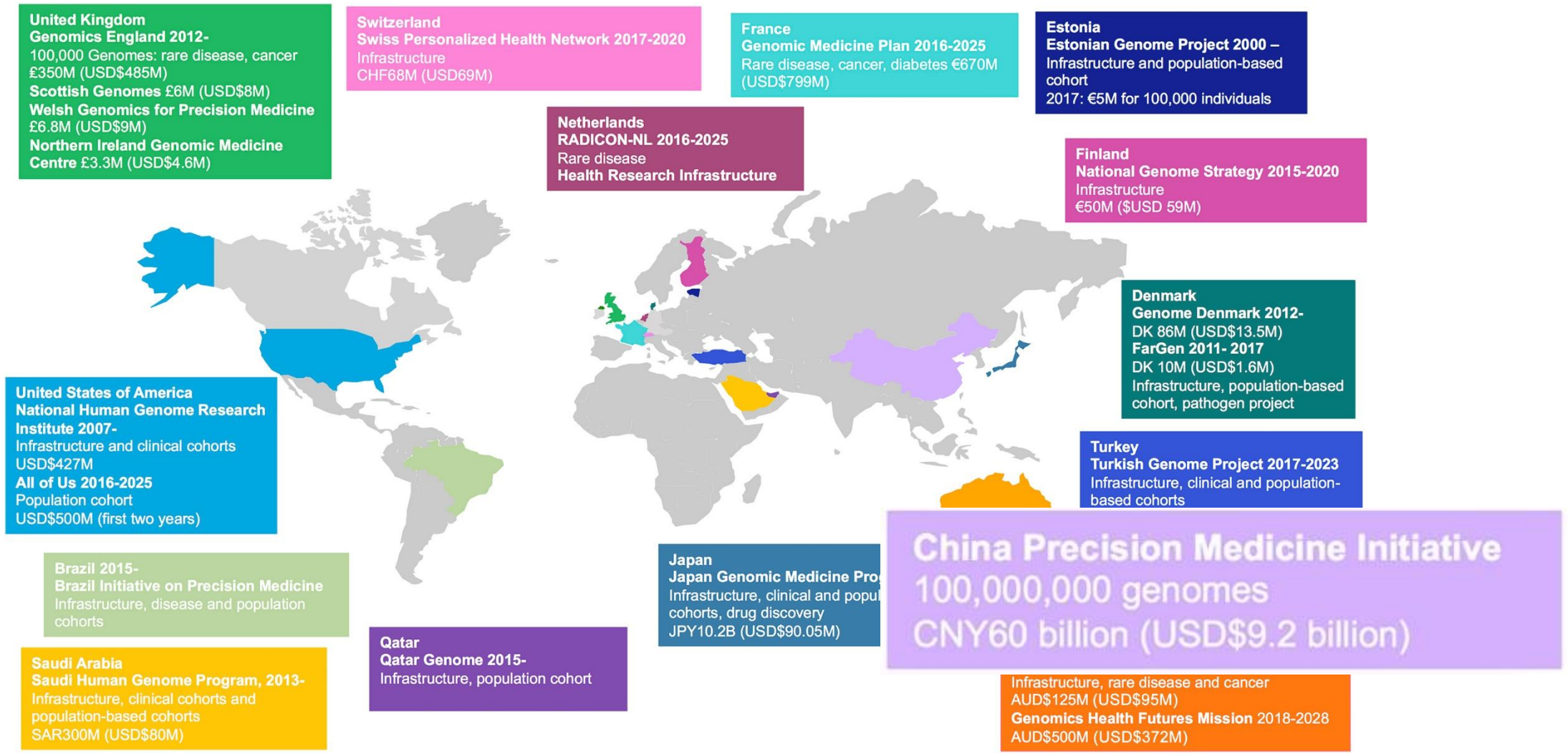
NHS to offer paid-for DNA tests if patients share data

26 January 2019 Share

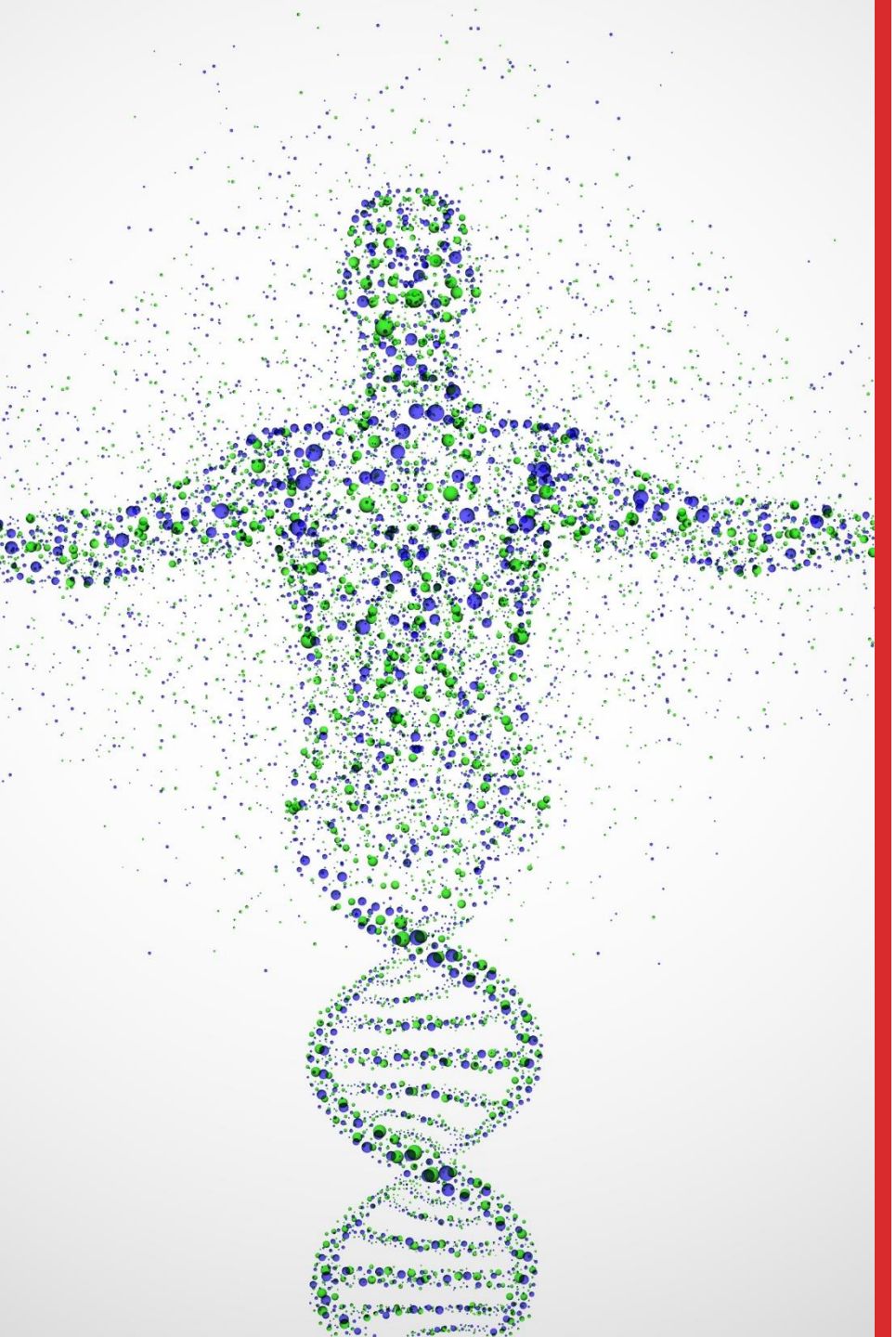
Health Secretary Matt Hancock said he wants healthy people to become "genomic volunteers" to help scientists better understand diseases and human genetics

RGA

‘Generation genome’: national programmes and spending



Source: *The American Journal of Human Genetics* 2019 104, 13-20DOI: (10.1016/j.ajhg.2018.11.014)



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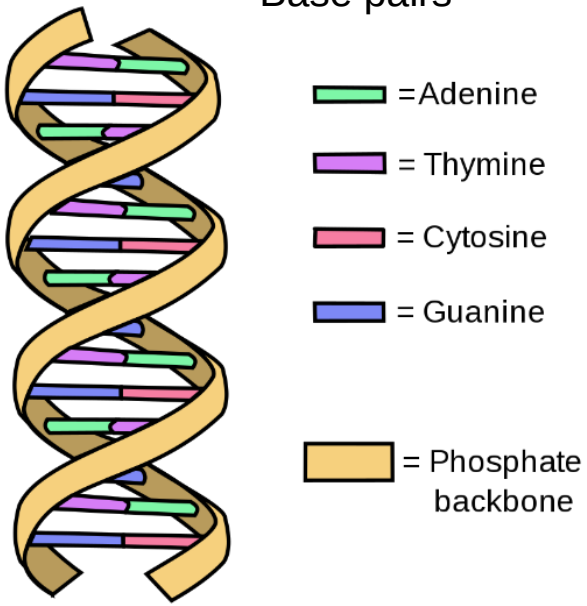
Genetic Risk to Disease and Polygenic Risk Scores (PRS)

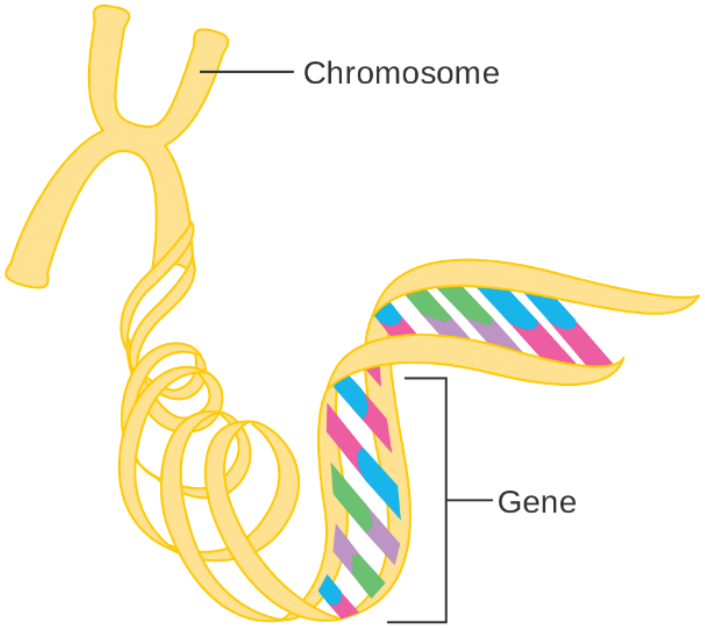
RGA

Genetics 101: DNA, chromosomes and single nucleotide polymorphisms (SNPs)

DNA

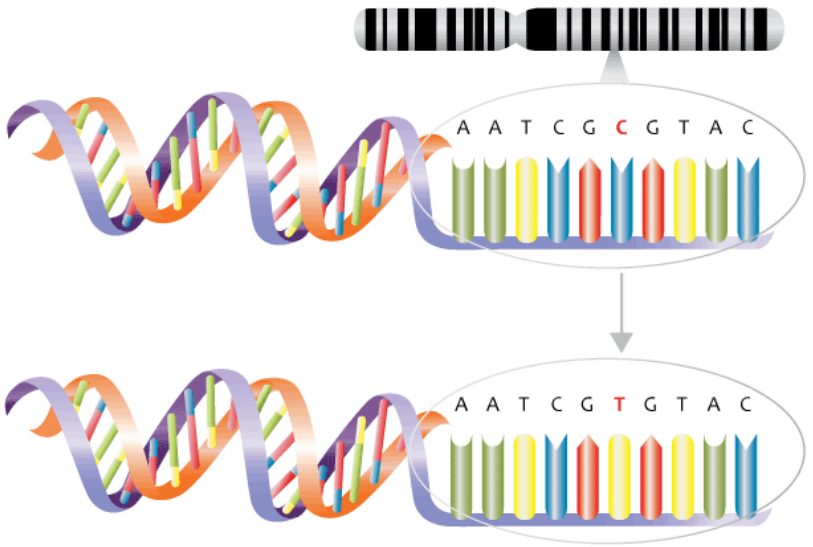


DNA is composed of four 'building blocks' (nucleotides) : **adenine** (A), **cytosine** (C), **guanine** (G) and **thymine** (T)



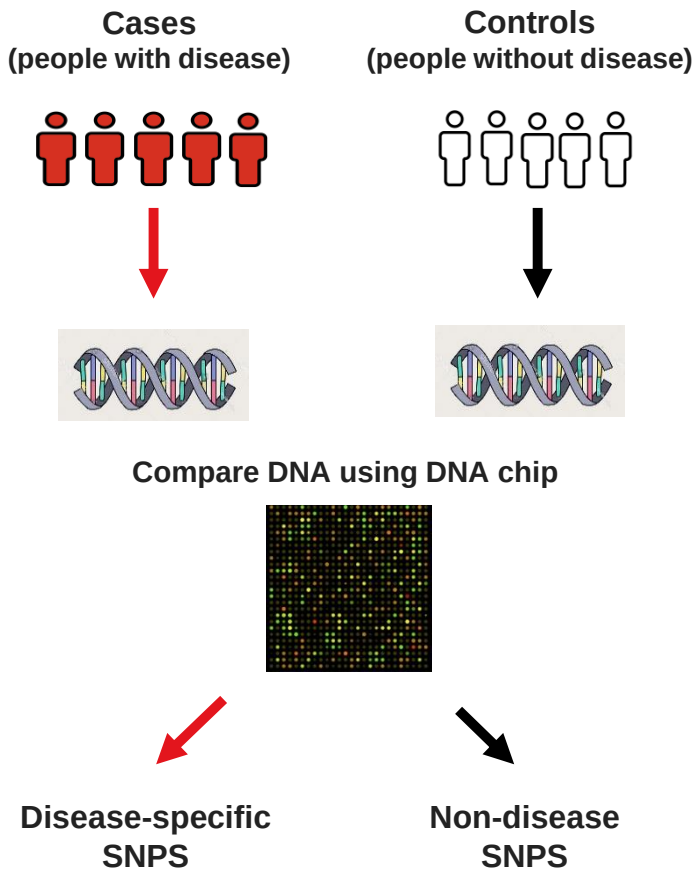
Human DNA is packaged into 23 pairs of chromosomes

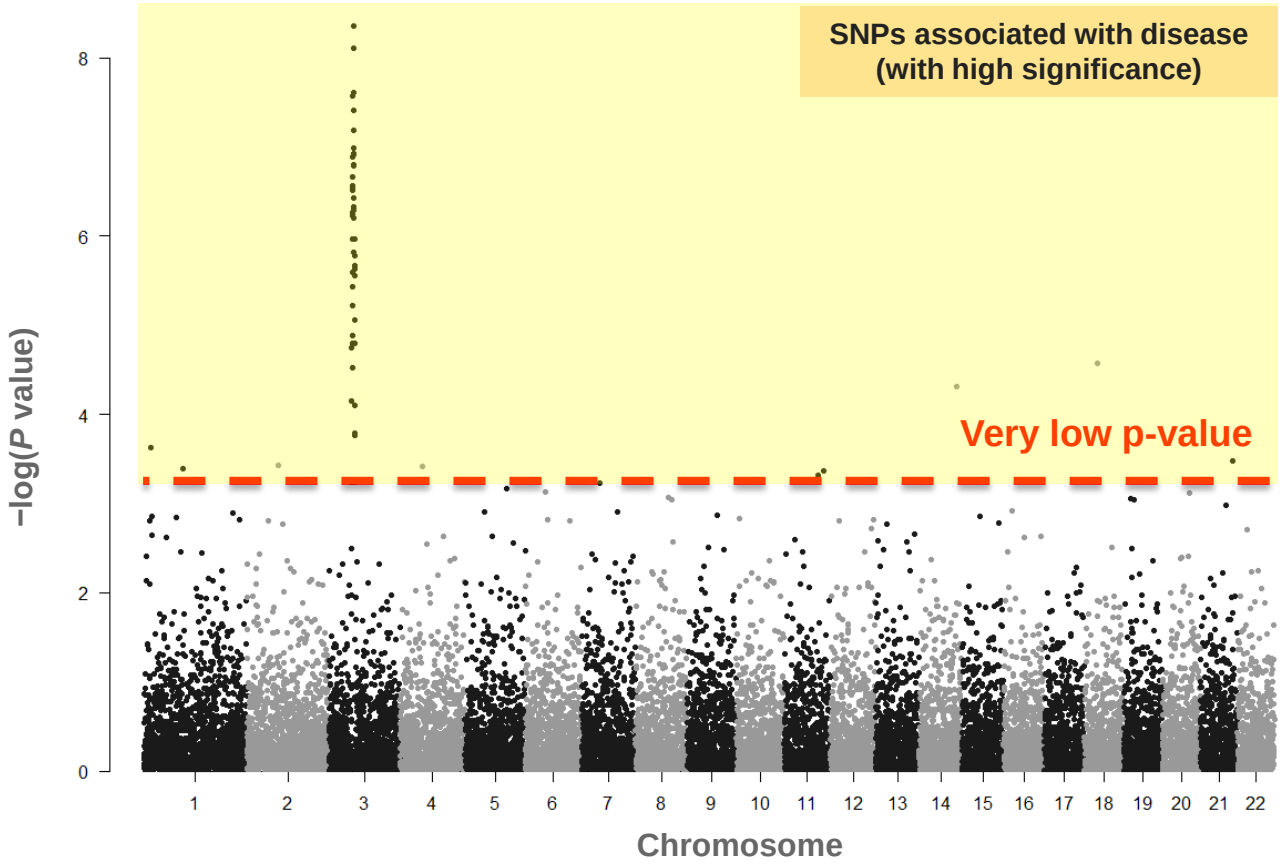
SNP



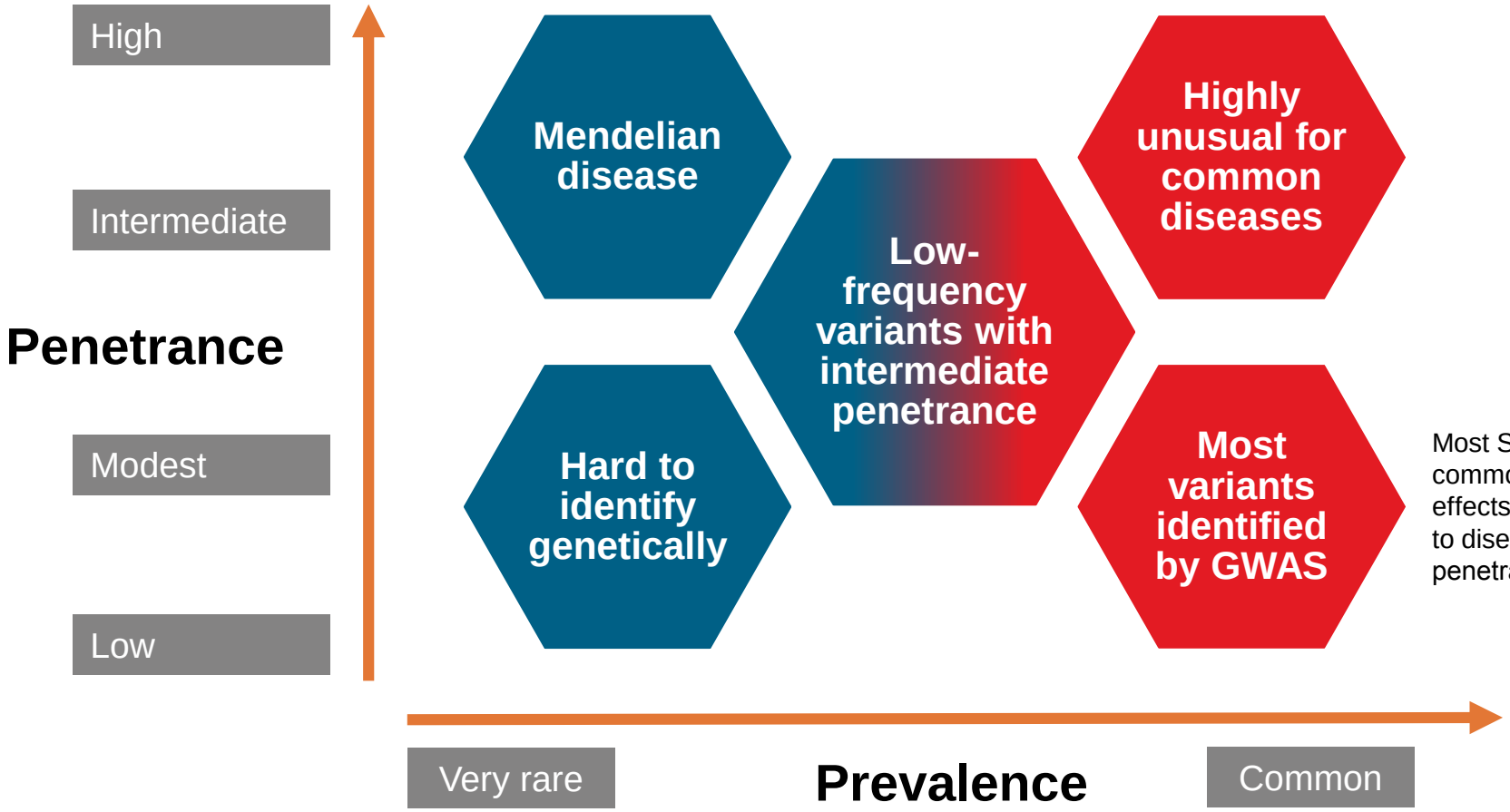
A single nucleotide polymorphism (SNP) describes variation in a single nucleotide position. E.g., here, a **Thymine** nucleotide exists instead of **Cytosine**, which is most commonly observed.

Genome wide association studies ('GWASes')



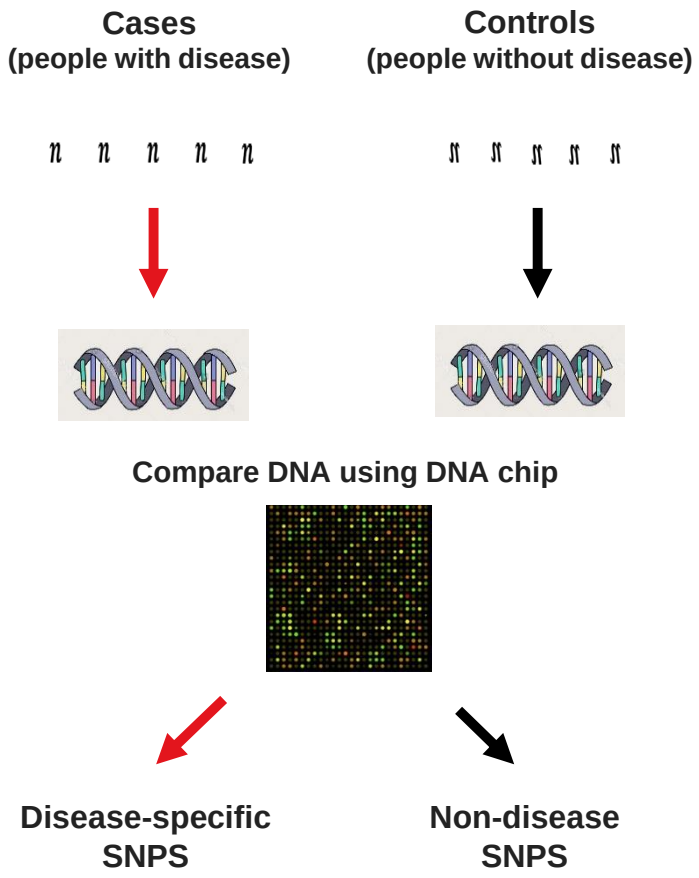


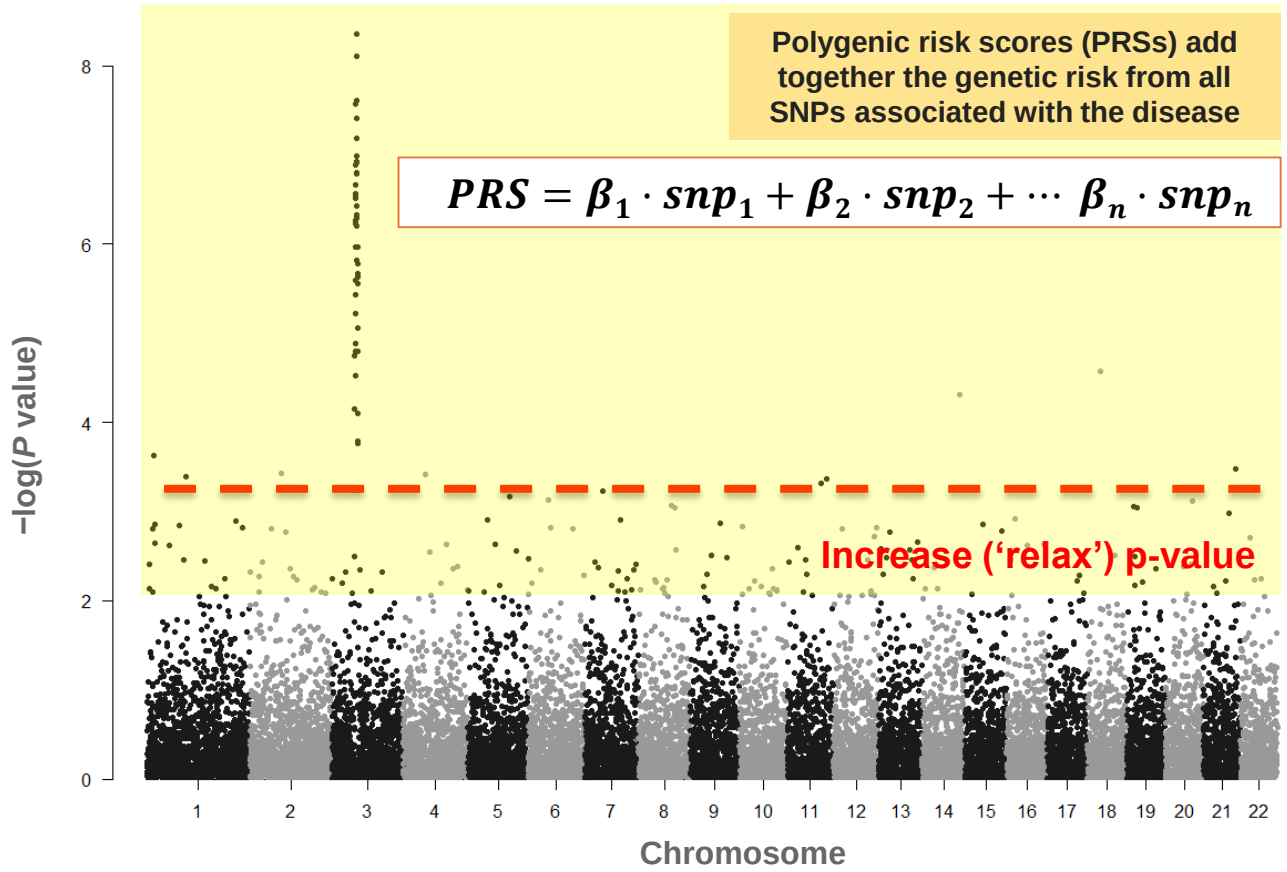
Prevalence vs. penetrance of genetic variants



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

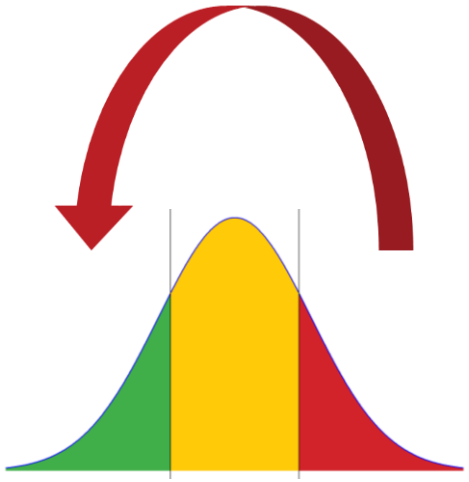
GWAS → Polygenic risk scores





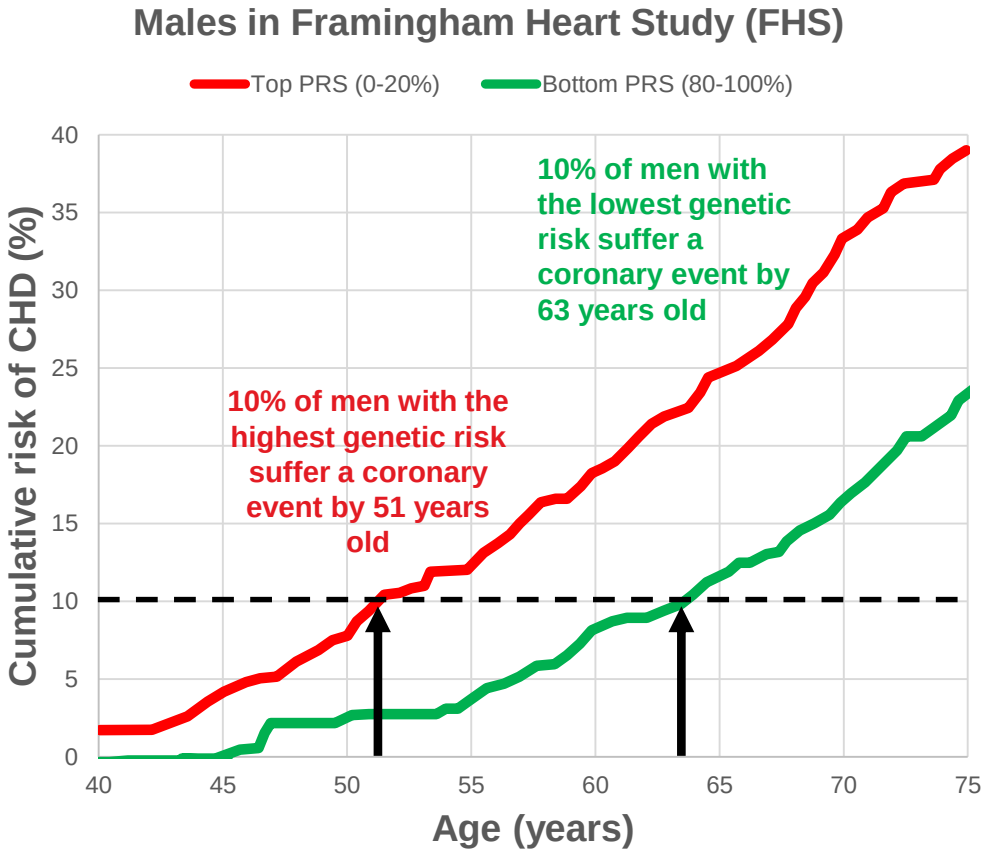
Sample of PRS in literature

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



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

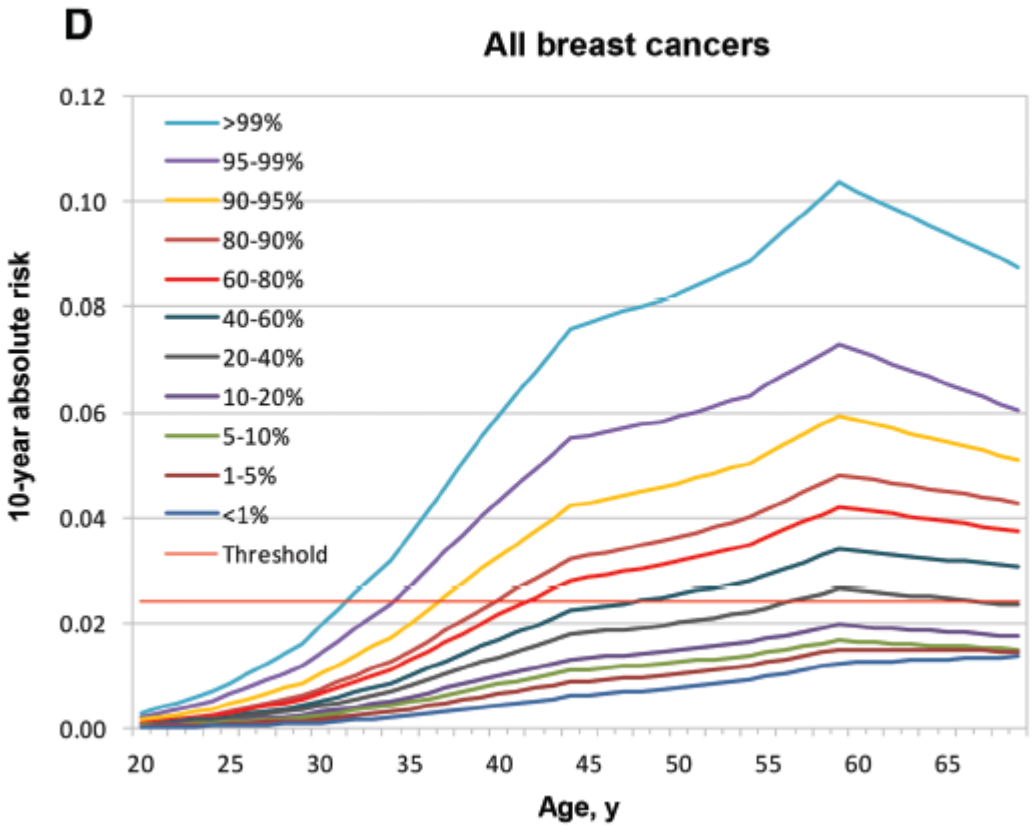
- A study by Abraham and colleagues* tested the clinical utility of a PRS for coronary heart disease (CHD), in terms of lifetime CHD risk and relative to traditional clinical risk
- PRS tested in independent cohorts (FINRISK and Framingham Heart Study [FHS]; combined *n* = 16,802 with 1,344 incident 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

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)

PRS make front page news – August 2018

Institute and Faculty of Actuaries

THE TIMES

Genes put millions at triple risk of heart attack

£40 test would spot danger even with no symptoms

Coronary heart disease is
ALAMY

Five million Britc
attack despite lac

nature genetics

The Telegraph

News

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

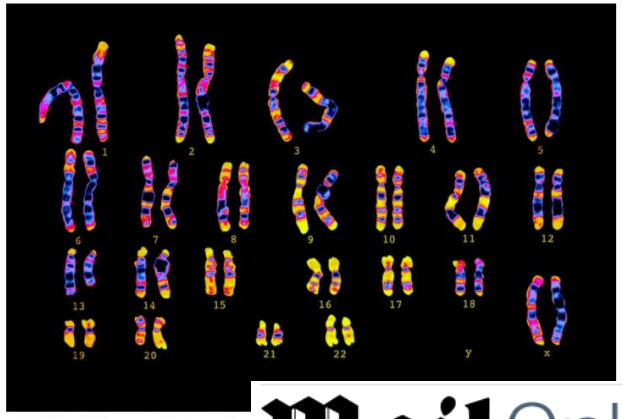
share Save

American scientists identified genetic variants in the DNA of patients that increase the risk of five common disorders CREDIT: ISTOCKPHOTO

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.



A set of human chromosomes. Researcher
and millions of points in the genome. Philij

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

Mail Online

$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

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

1

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

Scientists hope to eventually

The "polygenic risk test" uses
genome to look for small varia

Forbes

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

Matthew Herper Forbes Staff
Healthcare
I cover science and medicine, and believe this is biology's century.

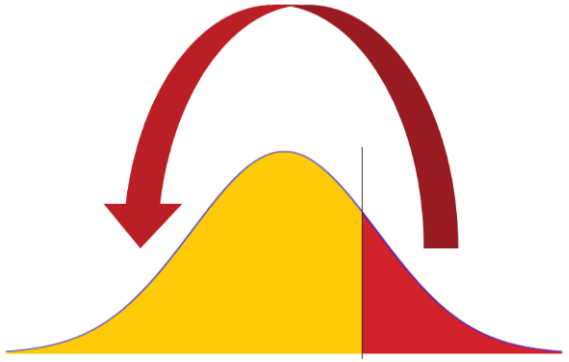
Sekar Kathiresan SEKAR KATHIRESAN

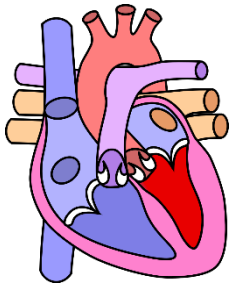
RGA

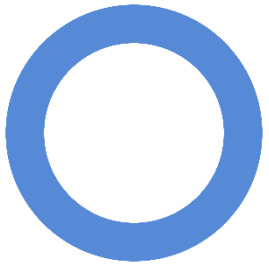
PRS make front page news – August 2018

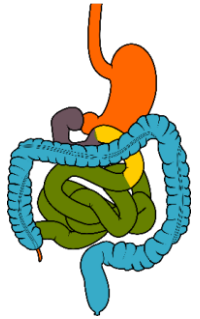
- Authors showed that common diseases can be predicted using PRSs for: coronary artery disease, type 2 diabetes, atrial fibrillation, breast cancer and inflammatory bowel disease

Risk in top 20% vs. bottom 80%:	**2.55x**	**2.33x**	**2.43x**	**2.07x**	**2.19x**









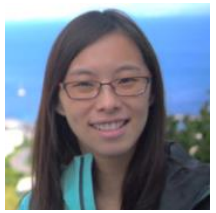
Approved project: 23203

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

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**

Why UK Biobank?

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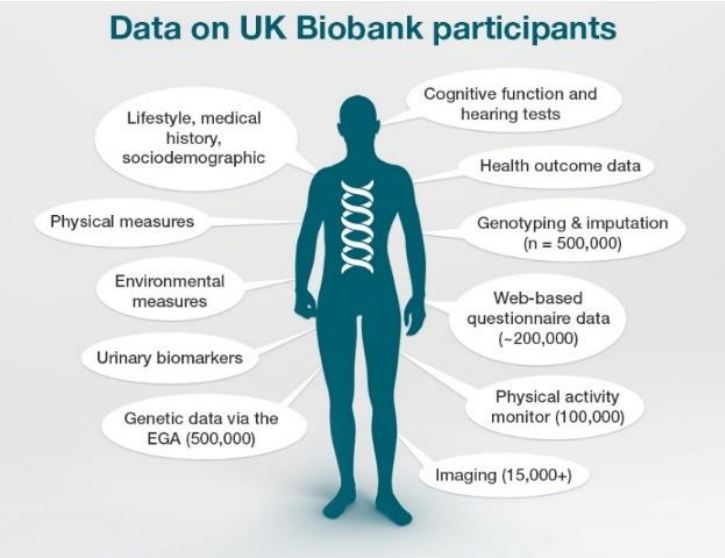
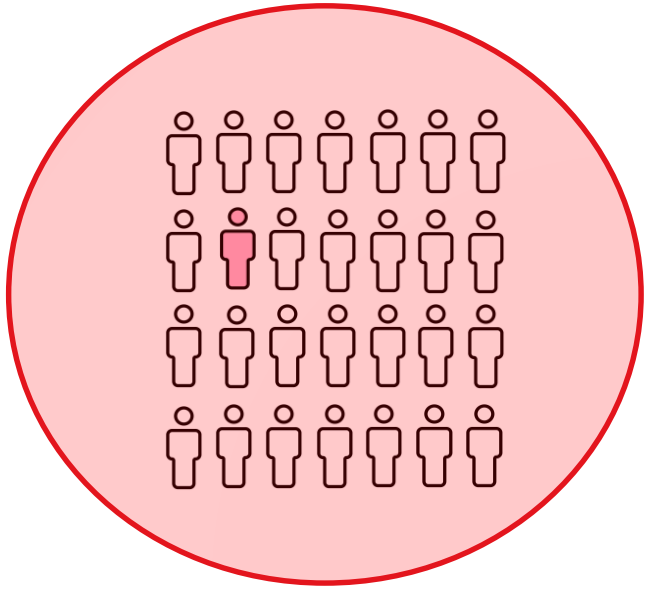
Breadth and Depth

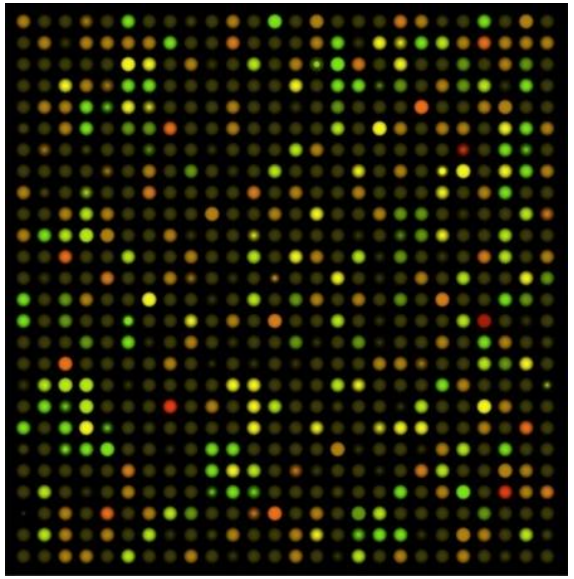


https://www.ebi.ac.uk/about/news/feature-story/biobanks-genetic-data-demand. Accessed 12 May 2018

Long-term follow up of multiple outcomes

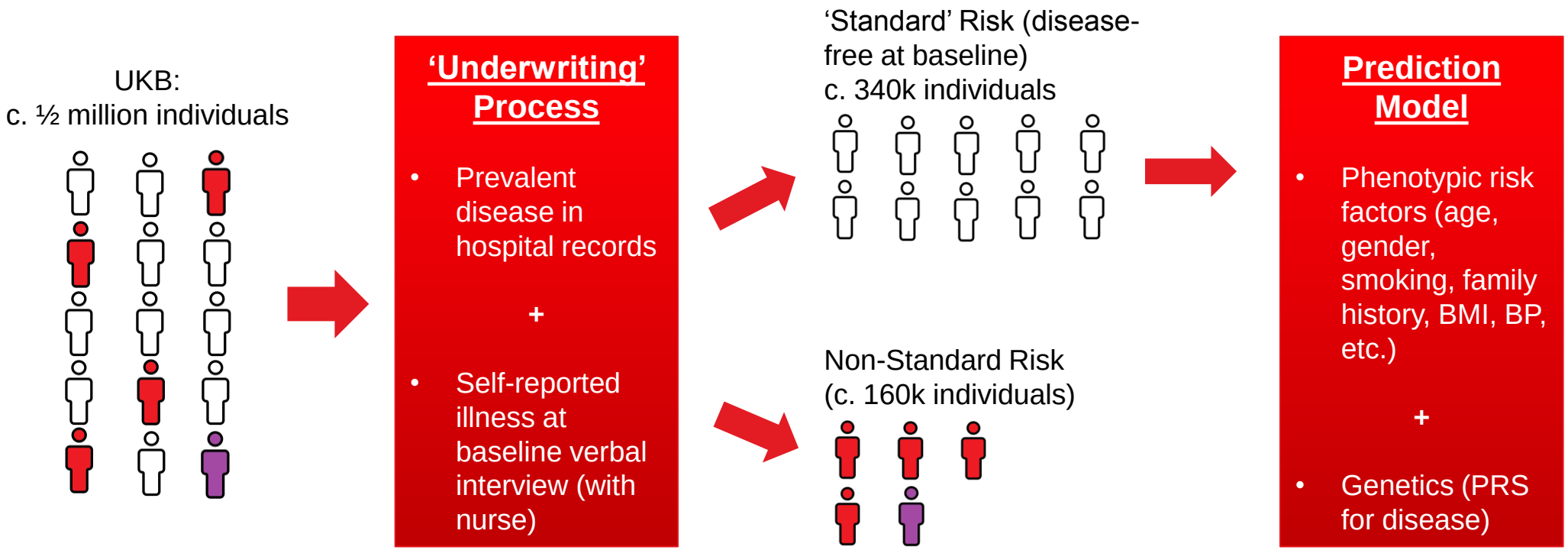


Genotyping on all 500k participants



RGA

‘Underwriting’ UKB participants and predicting disease incidence



Maxwell J, Russell R, Wu B, Sharapova N, Banthorpe P, O’Reilly PF, Lewis CM. *Multifactorial disorders and polygenic risk scores: predicting common diseases and the possibility of adverse selection in life and protection insurance.* Manuscript under review. *2019*.

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

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Total Participants: 199,322
Number of breast cancers: 3,947 (1.98%)

Percentile	Full cohort: Hazard ratio (95% CI)
0-1	0.39 (0.23 - 0.65)
1-5	0.6 (0.49 - 0.75)
5-10	0.63 (0.51 - 0.76)
10-20	0.67 (0.58 - 0.78)
20-40	0.88 (0.79 - 0.98)
40-60	1 (reference group)
60-80	1.22 (1.1 - 1.34)
80-90	1.5 (1.35 - 1.68)
90-95	1.73 (1.51 - 1.97)
95-99	2.02 (1.76 - 2.32)
99-100	2.47 (1.97 - 3.11)

Total Participants: 143,898
Number of breast cancers: 2,835 (1.97%)

Percentile	Standard cohort: Hazard ratio (95% CI)
0-1	0.44 (0.25 - 0.79)
1-5	0.68 (0.53 - 0.87)
5-10	0.66 (0.52 - 0.83)
10-20	0.69 (0.58 - 0.82)
20-40	0.9 (0.8 - 1.02)
40-60	1 (reference group)
60-80	1.25 (1.12 - 1.41)
80-90	1.58 (1.38 - 1.8)
90-95	1.74 (1.49 - 2.05)
95-99	2.04 (1.73- 2.4)
99-100	2.71 (2.08 - 3.53)

Decreased risk

Increased risk

Decreased risk

Increased risk

Maxwell J, Russell R, Wu B, Sharapova N, Banthorpe P, O'Reilly PF, Lewis CM. *Multifactorial disorders and polygenic risk scores: predicting common diseases and the possibility of adverse selection in life and protection insurance.* Manuscript under review. *2019*.

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

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Total Participants: 373,022
Number of CAD events: 6,430 (1.72%)

Percentile	Full cohort: Hazard ratio (95% CI)
0-1	0.56 (0.4 - 0.79)
1-5	0.49 (0.41 - 0.59)
5-10	0.71 (0.62 - 0.82)
10-20	0.73 (0.65 - 0.81)
20-40	0.82 (0.75 - 0.89)
40-60	1 (reference group)
60-80	1.17 (1.09 - 1.27)
80-90	1.45 (1.33 - 1.58)
90-95	1.49 (1.34 - 1.66)
95-99	1.88 (1.68 - 2.09)
99-100	2.78 (2.35 - 3.29)

Total Participants: 260,791
Number of CAD events: 3,489 (1.34%)

Percentile	Standard cohort: Hazard ratio (95% CI)
0-1	0.51 (0.31 - 0.82)
1-5	0.43 (0.33 - 0.56)
5-10	0.7 (0.58 - 0.86)
10-20	0.75 (0.65 - 0.87)
20-40	0.86 (0.77 - 0.96)
40-60	1 (reference group)
60-80	1.27 (1.14 - 1.41)
80-90	1.57 (1.4 - 1.77)
90-95	1.56 (1.35 - 1.82)
95-99	2.2 (1.9 - 2.54)
99-100	3.46 (2.79 - 4.29)

Decreased risk

Increased risk

Decreased risk

Increased risk

Maxwell J, Russell R, Wu B, Sharapova N, Banthorpe P, O'Reilly PF, Lewis CM. *Multifactorial disorders and polygenic risk scores: predicting common diseases and the possibility of adverse selection in life and protection insurance.* Manuscript under review. *2019*.

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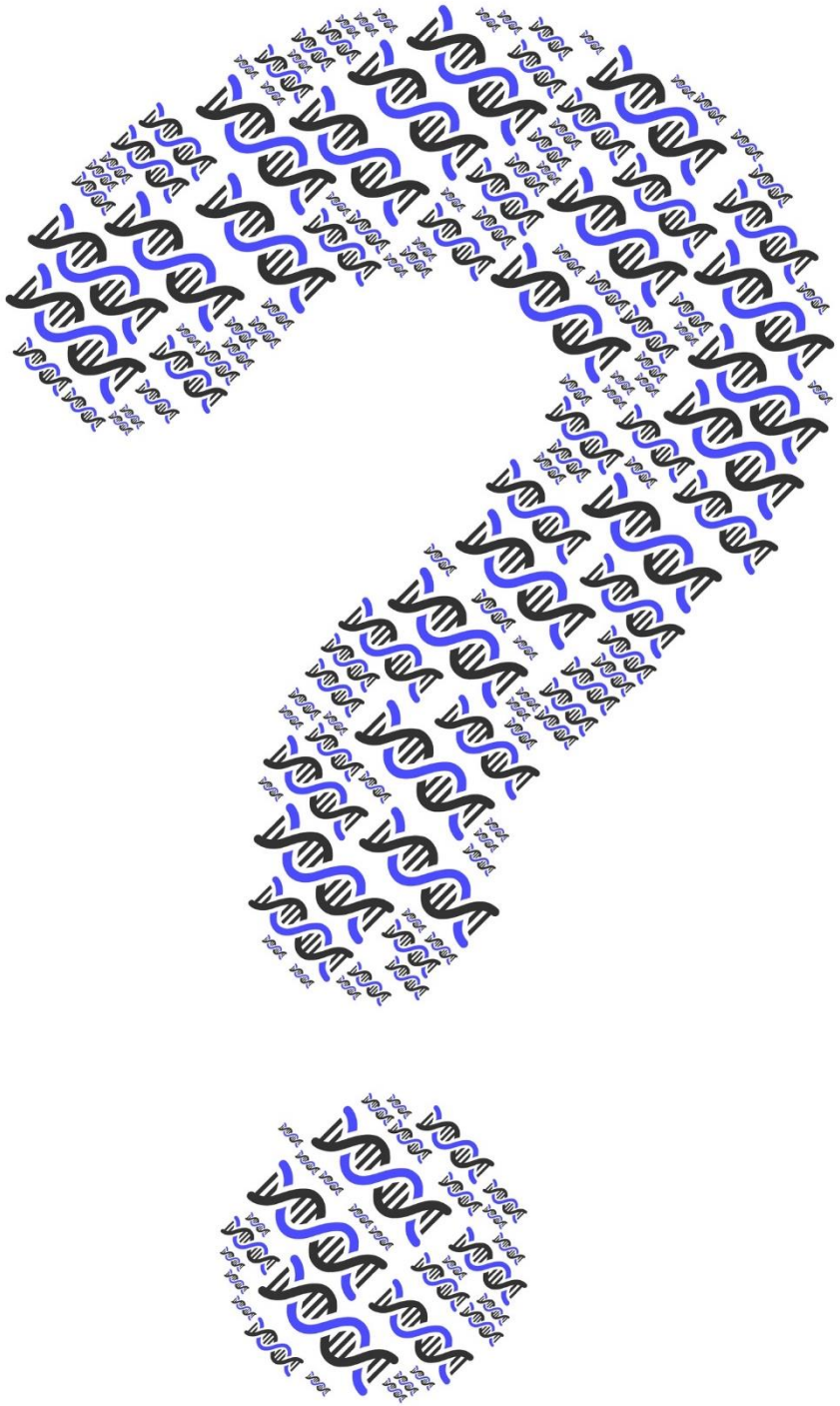

Genetics and Risks of Anti-selection

Research into anti-selection risk from genetics

- There have been several research papers…..
  - Alzheimer's disease anti-selection (Zick *et al.*, 2005)
  - 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

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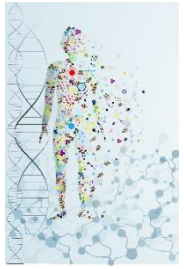
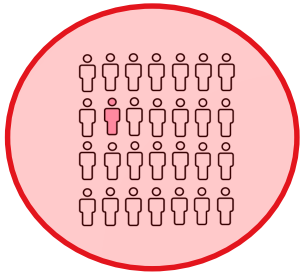
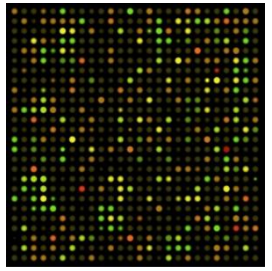
Genetic Risk Assumptions

- **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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Predicting impact of PRSs is still early

- Many scientific, clinical, and social obstacles must still be overcome to bring PRSs into clinical practice
- 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

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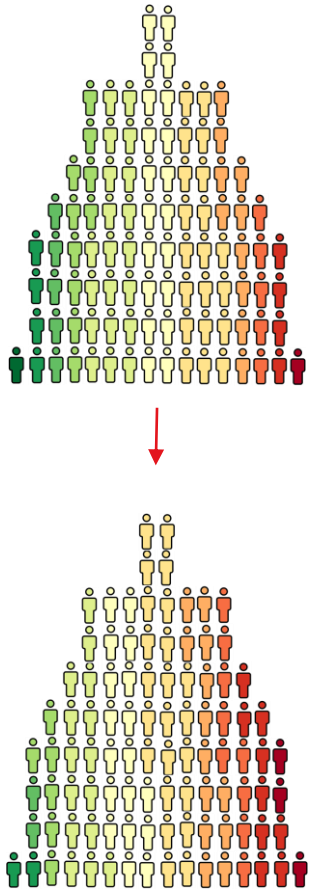
Potential for anti-selection – example in breast cancer. Scenario 1:

Percentile	% in general population	Hazard ratio for breast cancer	Probability of purchasing insurance *	% in new risk pool
0-1	1%	0.44	0.44x	0.4%
1-5	4%	0.68	0.68x	2.4%
5-10	5%	0.66	0.66x	3.0%
10-20	10%	0.69	0.69x	6.2%
20-40	20%	0.9	0.9x	16.1%
40-60	**20%**	**1**	**1x**	**17.9%**
60-80	20%	1.25	1.25x	22.4%
80-90	10%	1.58	1.58x	14.1%
90-95	5%	1.74	1.74x	7.8%
95-99	4%	2.04	2.04x	7.3%
99-100	1%	2.71	2.71x	2.4%

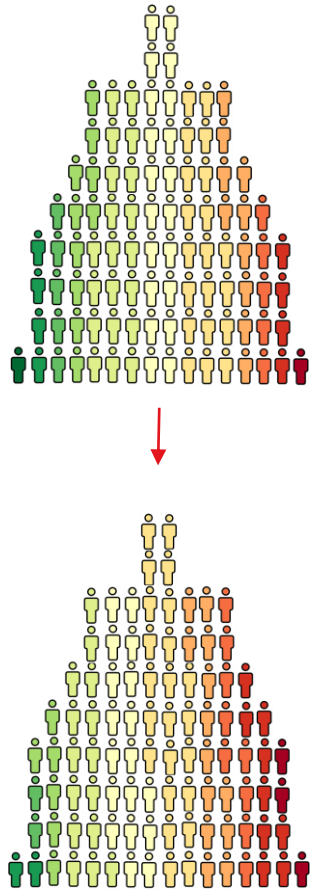


- **+12.6% increase in incidence**
- **Further +2.2% if include BRCA1/2 mutations** (assuming 0.2% prevalence and 5x odds ratio)

Maxwell J, Russell R, Wu B, Sharapova N, Banthorpe P, O'Reilly PF, Lewis CM. *Multifactorial disorders and polygenic risk scores: predicting common diseases and the possibility of adverse selection in life and protection insurance.* Manuscript under review. *2019*.

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%	0.44	0.73x	0.7%
1-5	4%	0.68	0.84x	3.2%
5-10	5%	0.66	0.83x	3.9%
10-20	10%	0.69	0.85x	8.0%
20-40	20%	0.9	0.96x	17.9%
40-60	**20%**	**1**	**1x**	**18.9%**
60-80	20%	1.25	1.13x	21.3%
80-90	10%	1.58	1.29x	12.2%
90-95	5%	1.74	1.37x	6.5%
95-99	4%	2.04	1.53x	5.7%
99-100	1%	2.71	1.87x	1.8%



- **+6.6% increase in incidence**
- **Further +1.2% if include BRCA1/2 mutations** (assuming 0.2% prevalence and 5x odds ratio)

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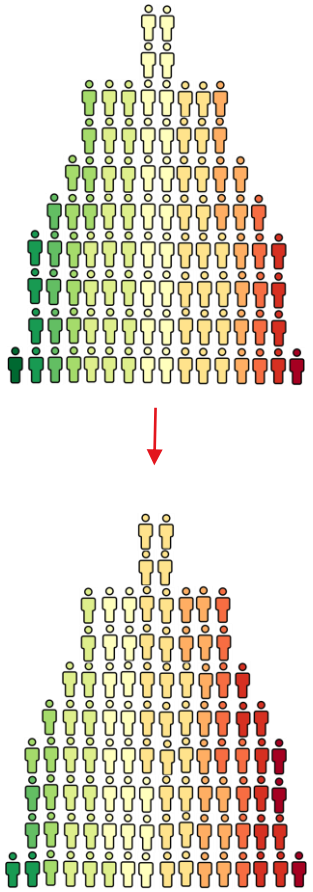
Potential for anti-selection – example in breast cancer. Scenario 3:

Percentile	% in general population	Hazard ratio for breast cancer	Probability of purchasing insurance *	% in new risk pool
0-1	1%	0.44	1x	0.9%
1-5	4%	0.68	1x	3.6%
5-10	5%	0.66	1x	4.5%
10-20	10%	0.69	1x	9.1%
20-40	20%	0.9	1x	18.2%
40-60	**20%**	**1**	**1x**	**18.2%**
60-80	20%	1.25	1.13x	20.4%
80-90	10%	1.58	1.29x	11.7%
90-95	5%	1.74	1.37x	6.2%
95-99	4%	2.04	1.53x	5.5%
99-100	1%	2.71	1.86x	1.7%



- **+5.0% increase in incidence**
- **Further +1.1% if include BRCA1/2 mutations** (assuming 0.2% prevalence and 5x odds ratio)

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Key Messages

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Genetic anti-selection risk: are these beliefs still valid?

1. Genetic risk information will ~~not~~ be widely available in the near future
2. Monogenic mutations that confer significantly higher risk of disease are rare therefore the cost imposed on insurers by any associated adverse selection is deemed small, while genetic risk information remains not widely available
3. Most common diseases are multifactorial, and the genetic contribution to these diseases is ~~modest~~ much greater than previously thought
4. Genetic test results will ~~not~~ deliver significant risk information that is not already available from traditional clinical measures used in underwriting
5. The genetic contribution to disease is ~~adequately~~ inadequately captured by family history

Closing Remarks

- Polygenic risk scores increase our concerns about anti-selection risk from genetic information asymmetry. It is a classic emerging risk for our industry
- Advances in genomic medicine will undoubtedly improve disease diagnosis and ultimately disease prognosis which will drive improvements in life expectancy and healthy life expectancy
- Genetic data is one example of data that has the potential to enable “Precision Underwriting”. There are a range of social, ethical, regulatory and competitive issues that need to be addressed before that happens

Thank you for your attention

Any Questions?

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