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# When customers know more about own genetic profile: a threat or opportunity?

**David Lu, Chief Medical Officer, Asia, Swiss Re**

# What is genetic testing?


- Genetic testing is a type of medical test that identifies changes in chromosomes, genes, or proteins.
- The results of a genetic test can **confirm or rule out** a suspected genetic condition or help determine a person's **chance of developing** or passing on a genetic disorder.

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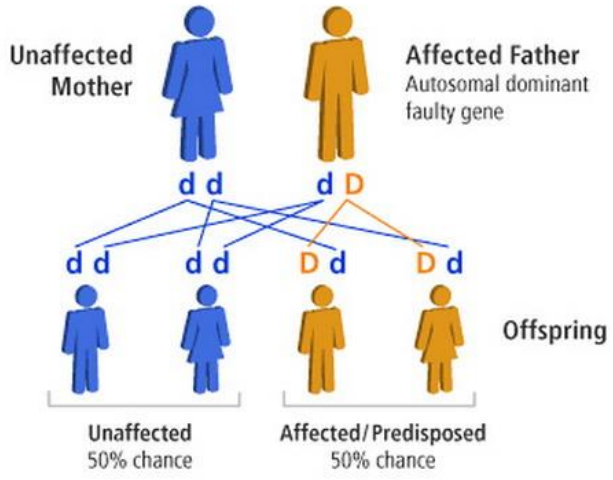
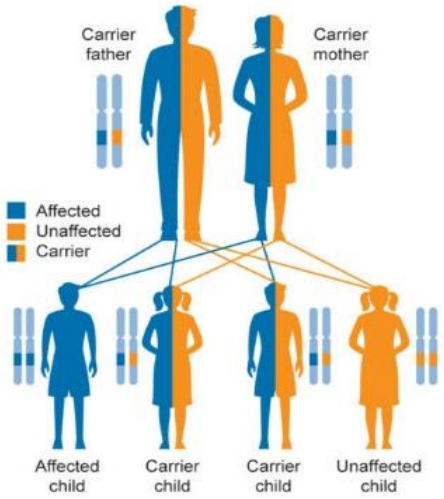
# Mono-genetic disorders

- Mono-genetic disorders are caused by DNA changes in one particular gene, and often have predictable inheritance patterns.

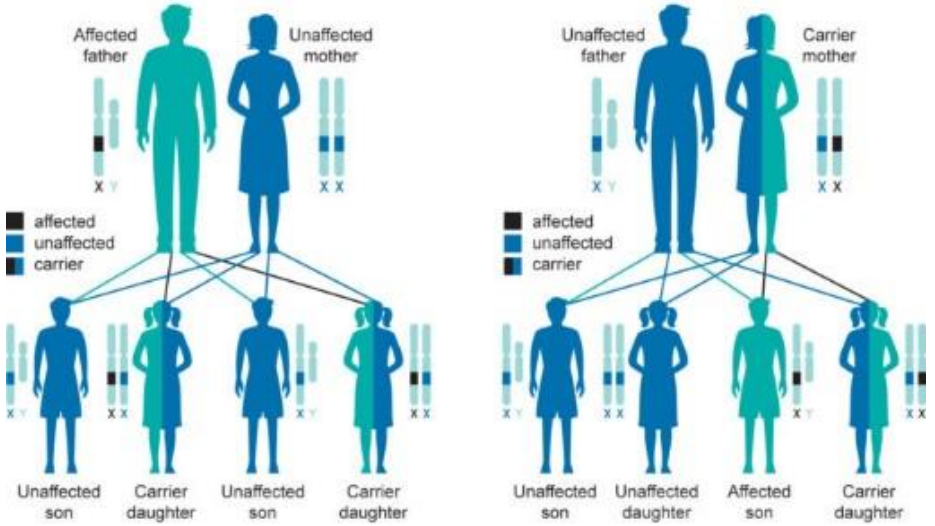
Autosomal dominant inheritance




Autosomal Recessive Inheritance




X-Linked Recessive Inheritance

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# Multifactorial / Polygenic (complex) genetic disorders

- Polygenic and environmental factors contribute significantly to chronic, non-communicable diseases such as coronary heart disease, cancer, diabetes mellitus, asthma, gout, schizophrenia and osteoporosis.
- A genetic component to the disease contributes a certain percent (for schizophrenia it is estimated to be approximately 70%), but no single gene is responsible.

| Selected examples of available multi-gene NGS panels | | # Genes |
|---|---|---|
| Cancer | Hereditary cancers (breast, colon, ovarian) | 10-50 |
| Cardiac diseases | Cardiomyopathies | 50-70 |
| | Arrhythmias (ex Long QT syndrome) | 10-30 |
| | Aortopathies (Marfan's syndrome) | 10 |
| Neurologic disorders | Parkinsons disease | 30 |
| | Alzheimers disease | 30 |
| | Epilepsy | 53-120 |
| | Muscular dystrophy | 12-45 |

Rehm H, Nature Genetics 2013 14:295-300

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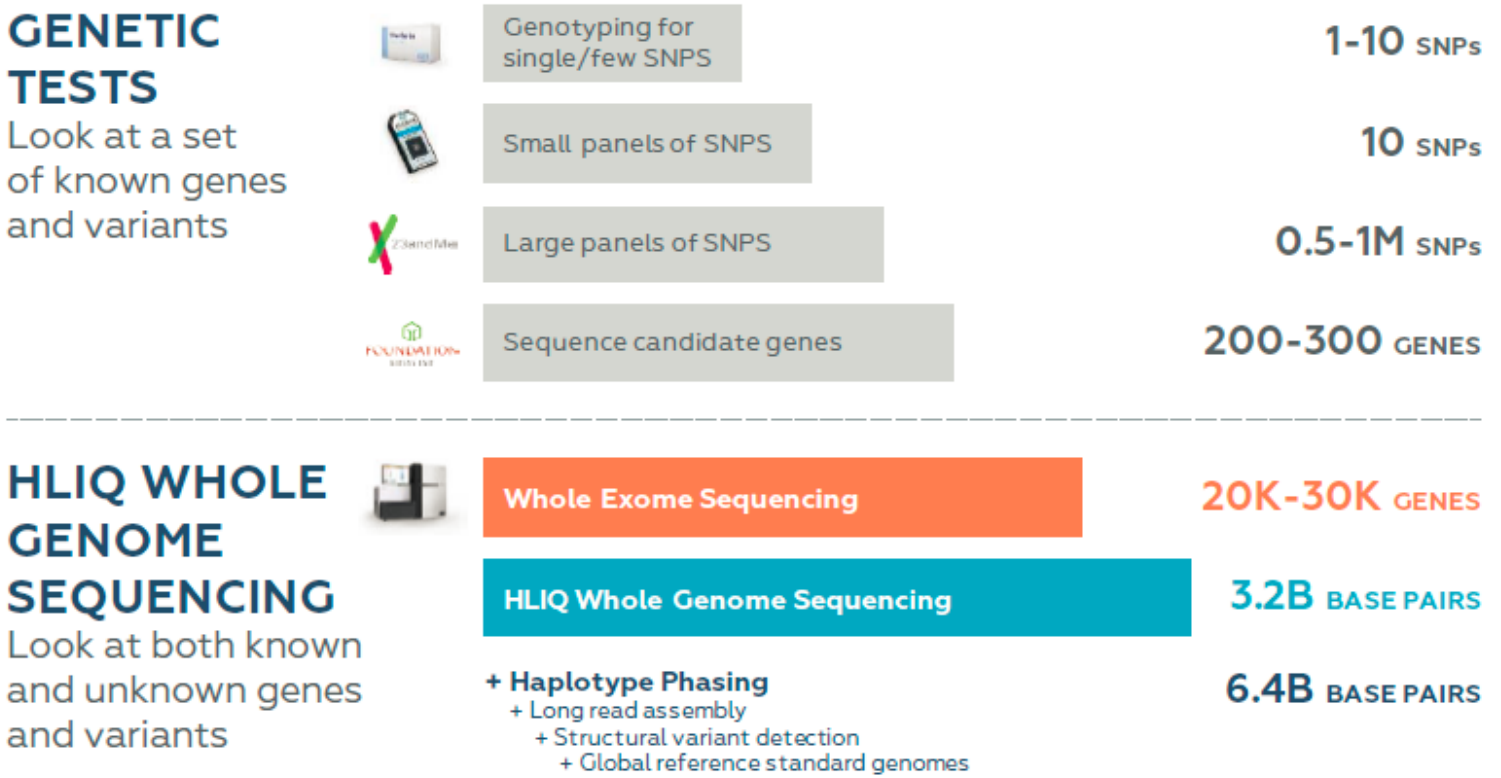
# Moving from genetic testing to whole genome sequencing




Source: http://www.humanlongevity.com/

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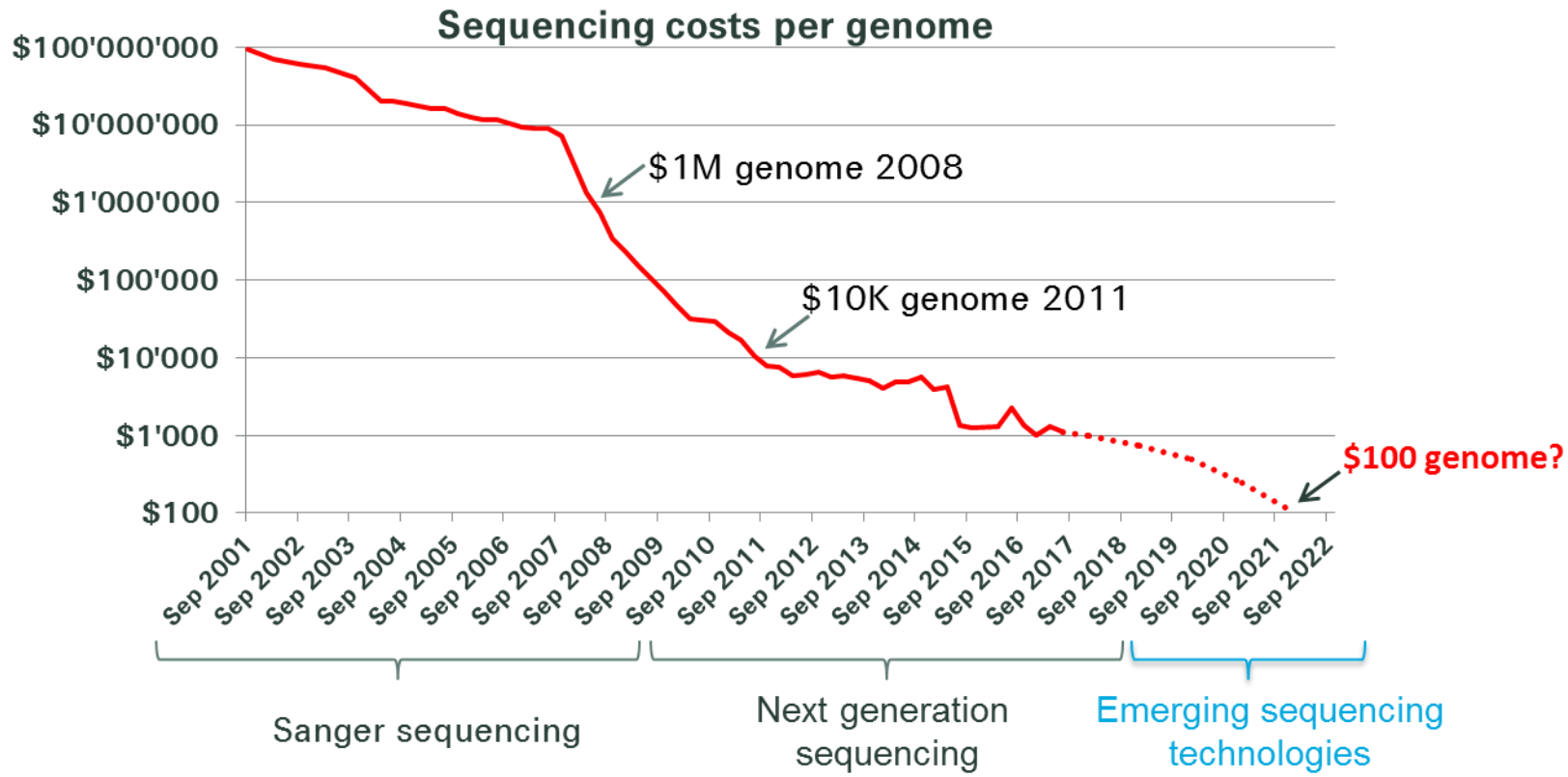
# Full genome sequencing becomes affordable




Source: NIH National Human Genome Research Institute http://www.genome.gov/sequencingcosts/

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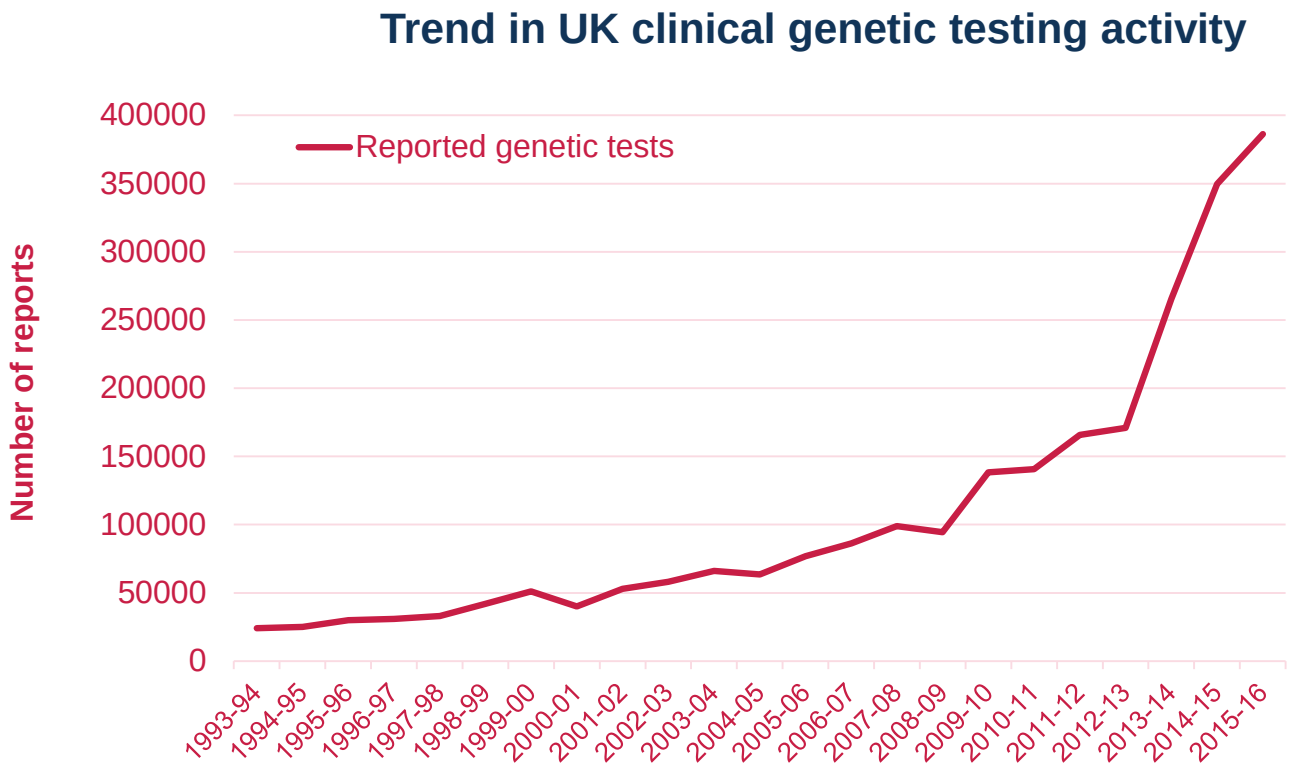
# Genetic testing in clinical practice has increased more than 20% annually in recent years




Source: ACGS audits

**There are positive correlations between better understanding of human genetics and availability and uptake of genetic testing in clinical practice**

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# 23and Me & Co: A booming Direct-To-Consumer market

### Carrier Status**

If you are starting a family, find out if you are a carrier for certain inherited conditions.

**40+ reports including:**
- Polycystic Kidney Disease
- Cystic Fibrosis
- Hereditary Hearing Loss

### Genetic Health Risks**

Learn how your genetics can influence your risk for certain diseases.

**5 reports including:**
- BRCA1/2 (selected variants) **NEW!**
- Late-Onset Alzheimer's
- Disease  Parkinson's Disease

### Ancestry

Discover where your DNA is from out of 31 populations worldwide - and more.

**5 reports including:**
- Ancestry Composition
- Your DNA Family
- DNA Relative Finder tool

### Traits

Learn how your DNA influences your facial features, taste, smell and other traits.

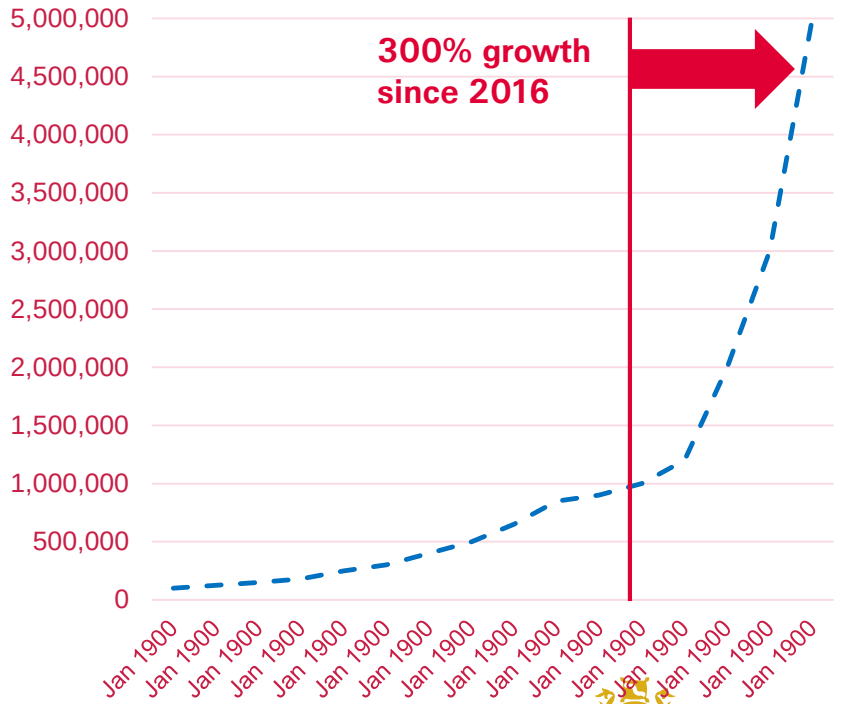
**5 reports including:**
- Hair loss
- Sweet vs. salty
- Unibrow, freckles…

### Wellness

Learn how your genes play a role in your well-being and lifestyle choices.

**21 reports including:**
- Deep sleep
- Lactose intolerance
- Genetic weight

## 23andMe customer development

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# There are many types of genetic testing

**Diagnostic / confirmatory**

Identifies or confirms a specific genetic condition in a symptomatic individual

**Pharmacogenomic**

Guides individual drug dosage, selection and response

**Nutrigenomic**

Studies the effect of genetic variations in relation to the interaction between diet/nutrition and health

**New-born screening**

Identifies genetic disorders that can be treated early in life

**Predictive and pre-symptomatic medical tests**

Medically prescribed. Estimates the risk of developing adult-onset disease or predicting future disease onset

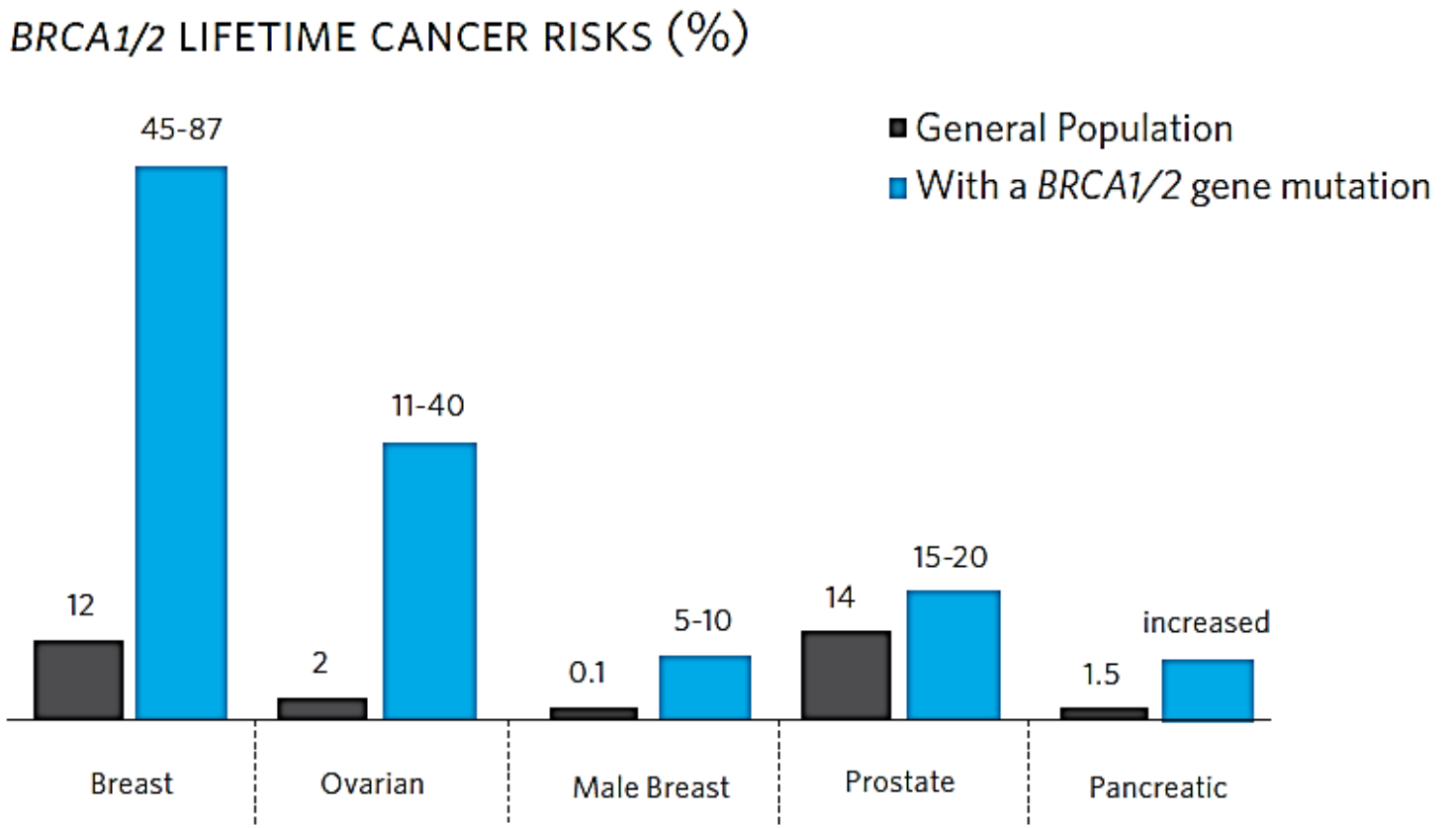
**Direct-to-consumer (DTC) tests**

Genetic tests marketed directly to consumers without involving healthcare professionals

**Liquid biopsy (entering the clinics)**

Detects molecular biomarkers in blood & other body fluids for diagnosis, prognosis and treatment. Still under development.

# BRCA mutations increase the risk of multiple cancers




Source: http://www.ambrygen.com/

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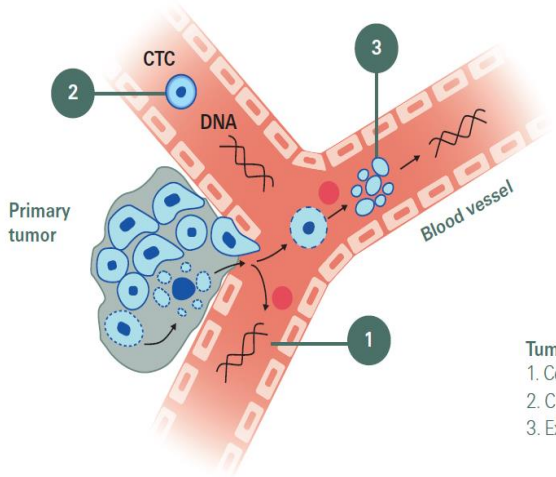
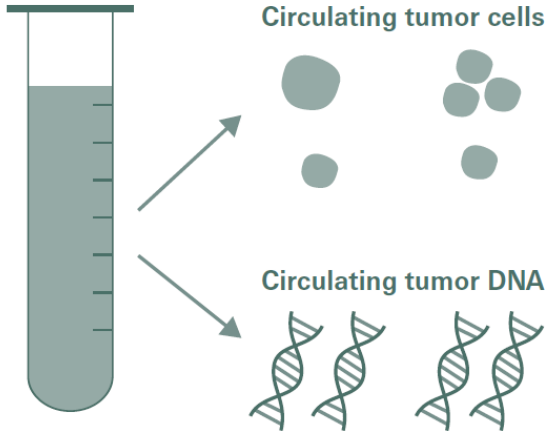
# Liquid biopsy




**Tumor biomarkers in blood**
1. Cell-free DNA (cfDNA)
2. Circulating tumor cells (CTCs)
3. Exosomes and micro vesicles

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**A blood test that can detect cancer?**
Liquid biopsy: A potential diagnostic to watch closely

"Liquid biopsy" is a new molecular technology being explored for its use in helping to treat – and detect – cancer. While the new test could ultimately benefit cancer patients and improve survival outcomes, it also creates new risks and exposures for life and health insurers, particularly for critical illness and cancer products.

A liquid biopsy is not really a "biopsy" but rather a molecular cancer test that uses body fluids.

Traditional tumour biopsies remain the standard for diagnosis and should be used for underwriting and claims assessment.

Key facts

- Liquid biopsy is a minimally invasive technique that can identify genetic material from tumour cells shed into the blood from a primary tumour or metastatic site.
- Liquid biopsy is being tested for its use to monitor a patient's response to treatment, to identify actionable genetic markers for targeted therapy, to support disease prognosis and to detect disease recurrence.
- Only one liquid biopsy test has obtained US FDA approval for use as a companion diagnostic in clinical practice to identify lung cancer patients eligible for a targeted therapy.
- For the foreseeable future, histopathology will remain the standard for cancer diagnosis and staging.
- Far more research and clinical trials are needed to establish liquid biopsy as an acceptable screening tool and as a substitute or adjunct for conventional cancer diagnosis.
- A "negative" liquid biopsy test does not rule out the presence of cancer.
- A "positive" liquid biopsy test does not meet today's clinical standard for cancer diagnosis, and therefore any critical illness claims should continue to require histopathological proof.

Risk considerations for insurers

Liquid biopsy is less invasive than extracting tissue, easier to obtain and holds the potential to transform clinical practice, if it should become an accepted and routine alternative to help diagnose, define and treat cancer. However, it raises the stakes for insurers and requires careful consideration to manage issues like anti-selection, over-diagnosis and to ensure our products remain sustainable and able to cover the people who need them the most.

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# Circulating tumor-derived DNA testing for nasopharyngeal carcinoma (NPC) screening

ORIGINAL ARTICLE

## Analysis of Plasma Epstein–Barr Virus DNA to Screen for Nasopharyngeal Cancer

K.C. Allen Chan, F.R.C.P.A., John K.S. Woo, F.R.C.S., Ann King, F.R.C.R., Benny C.Y. Zee, Ph.D., W.K. Jacky Lam, F.R.C.S., Stephen L. Chan, F.R.C.P., Sam W.I. Chu, B.Sc., Constance Mak, B.S.N., Irene O.L. Tse, B.N., Samantha Y.M. Leung, B.N., Gloria Chan, R.N., Edwin P. Hui, F.R.C.P., et al.

**Table 2. Sensitivity and Specificity of the Two-Stage Screening Protocol for the Detection of Nasopharyngeal Carcinoma.***

| Finding | Screen-Positive (N=308)† | Screen-Negative (N=19,865) |
|---|---|---|
| Confirmed nasopharyngeal carcinoma by the screening protocol or nasopharyngeal carcinoma reported to have developed within 1 yr — no. | 34 | 1 |
| No nasopharyngeal carcinoma within 1 yr after screening — no. | 274 | 19,864 |
| Sensitivity — % (95% CI) | 97.1 (95.5–98.7) | |
| Specificity — % (95% CI) | 98.6 (98.6–98.7) | |
| Positive predictive value — % (95% CI) | 11.0 (10.7–11.3) | |
| Negative predictive value — % (95% CI) | 99.995 (99.99–100.00) | |
| Proportion of stage I/II disease in the 34 cases of nasopharyngeal carcinoma identified by screening — % (95% CI) | 70.6 (69.6–72.5) | |

* Screen-positive is defined as persistently positive for plasma EBV DNA at baseline and at follow-up. Screen-negative is defined as negative for plasma EBV DNA either at baseline or at follow-up.
† The participant who had declined further investigation but in whom advanced nasopharyngeal carcinoma developed 32 months after screening is not included in this number.

https://www.nejm.org/doi/full/10.1056/nejmoa1701717

## Sequencing-based counting and size profiling of plasma Epstein–Barr virus DNA enhance population screening of nasopharyngeal carcinoma

W. K. Jacky Lam[a,b,c,d,1], Peiyong Jiang[a,b,c,1], K. C. Allen Chan[a,b,c,1], Suk H. Cheng[a,b], Haiqiang Zhang[a,b], Wenlei Peng[a,b], O. Y. Olivia Tse[a,b], Yu K. Tong[a,b], Wanxia Gai[a,b], Benny C. Y. Zee[e], Brigette B. Y. Ma[c,f], Edwin P. Hui[c,f], Anthony T. C. Chan[c,f], John K. S. Woo[d], Rossa W. K. Chiu[a,b,c], and Y. M. Dennis Lo[a,b,c,2]

**Extrapolated performance of the new protocol**

Sensitivity : 97.1% (CI: 85.1 – 99.9%)
Specificity : 99.3% (CI: 99.2 – 99.4%)
False positive rate : 140 / (20174-34-1)
= 0.70% (CI: 0.59 – 0.82%)
Positive predictive value : 19.5% (CI: 13.9 – 26.2%)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5984543/pdf/pnas.201804184.pdf

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# Liquid biopsy can detect lung cancer 1 - 4 years earlier than CT

**Table 2.** Clinical and pathological characteristics of CTC-positive COPD patients.

| Patients | Sex | Age (years) | Smoking status (PY) | Year of COPD diagnosis | GOLD score | Year of CTC Detection (Study entry) | CTCs/CTM | | Year of Lung cancer diagnosis | Lung Cancer size (cm) | Histology | Stage | Mutation tumor status | One-year follow-up after surgery |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | CTCs | CTM | | | | | | |
| P1 | M | 54 | 60 | 1998 | 3 | 2009 | 43 | 1 | 2012 | 1.9 | Invasive papillary adenocarcinoma | IA | *KRAS* p.Gly12Cys | No recurrence |
| P2 | F | 48 | 45 | 1995 | 2 | 2009 | 67 | 3 | 2010 | 1.5 | Invasive papillary adenocarcinoma | IA | *KRAS* p.Gly12Val | No recurrence |
| P3 | M | 47 | 35 | 1999 | 2 | 2008 | 32 | 1 | 2012 | 1.4 | Invasive acinar adenocarcinoma | IA | *KRAS* p.Gly12Cys | No recurrence |
| P4 | M | 52 | 45 | 1994 | 3 | 2009 | 19 | 1 | 2013 | 2 | Squamous cell carcinoma | IA | *STK11* (missense mutation) | No recurrence |
| P5 | M | 63 | 55 | 2001 | 3 | 2009 | 28 | 1 | 2013 | 1.5 | Invasive acinar adenocarcinoma | IA | No mutation | No recurrence |

Ilie M, Hofman V, Long-Mira E, Selva E, Vignaud J-M, et al. (2014) ‘‘Sentinel’’ Circulating Tumor Cells Allow Early Diagnosis of Lung Cancer in Patients with Chronic Obstructive Pulmonary Disease. PLoS ONE 9(10): e111597. doi:10.1371/journal.pone.0111597

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# And the headlines…

Forbes / Pharma & Healthcare / #Medicine

JAN 18, 2018 @ 02:00 PM

## A New $500 Blood Test Could Detect Cancer Before Symptoms Develop

ABC NEWS

Just In | Politics | World | Business | Sport | Science | Health | Arts | Analysis

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**Blood test that can detect eight of the most common cancers could be available in next few years**

AM By Jane Lee

Updated 19 Jan 2018, 2:52pm

BBC NEWS Health

Sign in

## Cancer blood test 'enormously exciting'

By James Gallagher
Health and science correspondent, BBC News

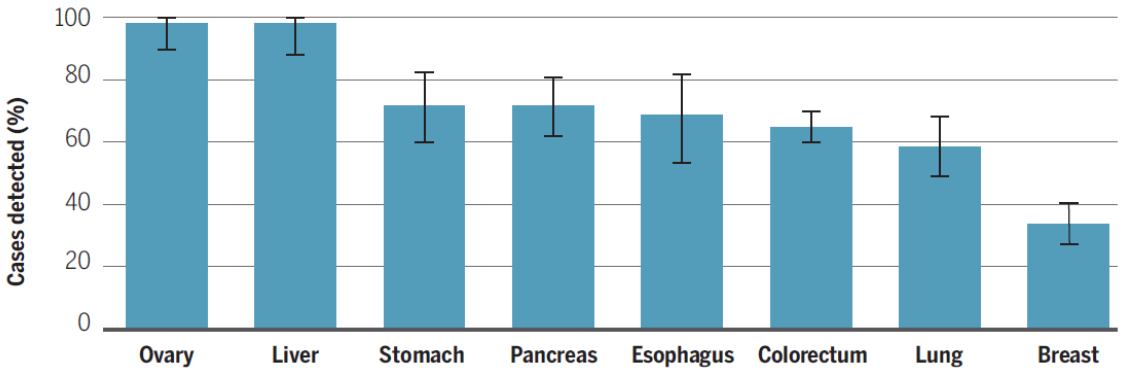
19 January 2018

Share

Science, 19 Jan 2018

## A screening scorecard

A new cancer blood test worked better for some types than others, and caught only 43% of stage 1 cancers. (Error bars represent 95% confidence intervals.)




CancerSEEK is a liquid biopsy test for 8 cancer sites (based on ctDNA from 16 genes, combined with 8 protein biomarkers), developed by a team led by scientists at Johns Hopkins.

1,005 people known to have cancer were tested with 70% detected (but only 46% in Stage 1). 812 healthy people with no cancer history were also tested with 7 (false) positives. Next step will be years of larger prospective clinical trials to demonstrate that the test improves overall cancer survival.

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# Studies on genetic testing and its impact on insurance purchasing behaviour

| Genetic disease (Gene) | Insurance product | Odds ratio of over- insuring after positive test | Study |
|---|---|---|---|
| Breast cancer (BRCA1/2) | Life insurance | 5.1x more likely to increase coverage | Armstrong et al.; 2003 (USA) |
| Alzheimer's disease (APOE4) | Long-term care insurance | 5.7x more likely to change coverage | Taylor et al.; 2005 (USA) |
| Alzheimer's disease (APOE4) | Long-term care insurance | 2.3x more likely to increase coverage | Zick et al.; 2010 (USA) |
| Huntington's disease (HD) | Long-term care insurance | 5x more likely to purchase insurance | Oster et al.; 2010 (USA & Canada) |
| Colorectal cancer (HNPCC) | Life insurance | 1.3x more likely to purchase insurance | Aktan-Collan et al.; 2001 (Finland) |

Understanding of consumers acceptance of and concerns about genetic testing is key to investigate the potential impact on insurance purchasing behaviour and level of adverse selection against insurers.

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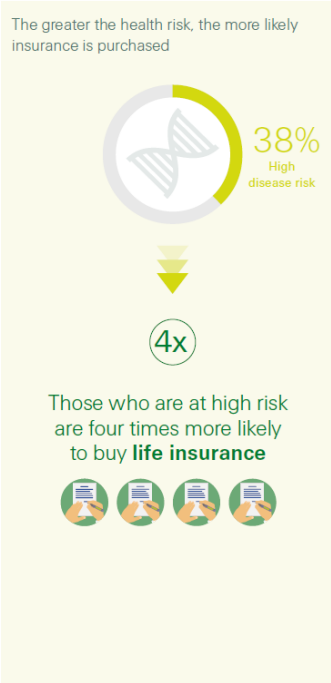
# Swiss Re's genetic testing consumer survey 2018

## US




## Australia


## UK


Restrictions on access to risk-relevant genetic data will increase insurer's exposure to anti-selection

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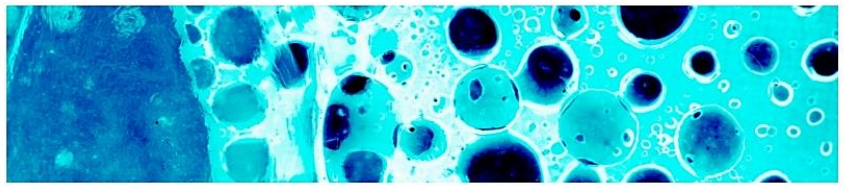
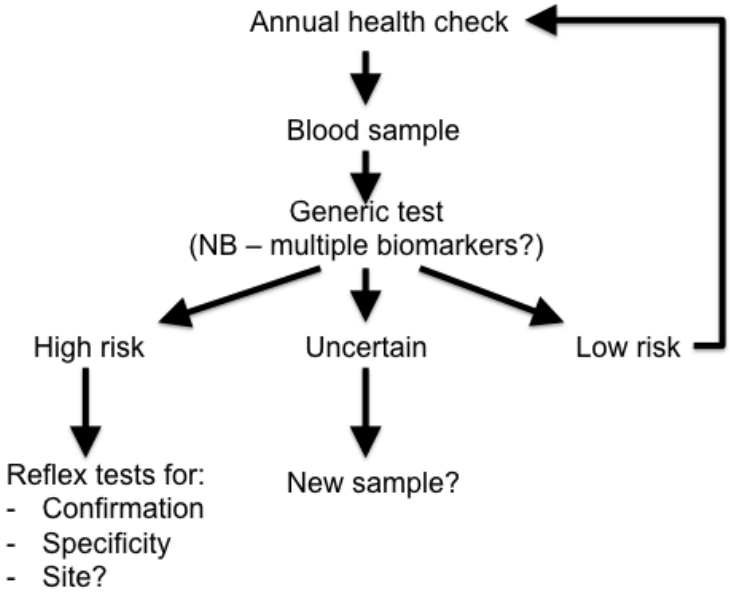
# Early Cancer Detection Consortium

Early Cancer Detection Consortium






Funded by CANCER RESEARCH UK

Consortium Members

The consortium has members from the following University partners:

- University of Cambridge
- Coventry University
- Dublin
- University of Edinburgh
- Lancaster University
- University of Leeds
- University of Leicester
- University of Manchester
- Middlesex University
- University of Nottingham
- University of Oxford
- University of Portsmouth
- Queen Mary University London
- University of Sheffield
- University of St Andrews
- University College London
- University of Warwick

https://warwick.ac.uk/fac/sci/med/about/centres/uk-ecdc

- The biology of cancer is reflected in the blood, suggesting a blood-based screening test for multiple cancer types could be developed. This could revolutionise cancer screening and significantly improve early detection.
- The Early Cancer Detection Consortium brings together expertise from many disciplines to conduct the studies necessary to develop blood-based testing for multiple cancer types.
- The ultimate goal is to produce a strategy for generic cancer screening that can go into clinical practice. This is likely to take the form of a single blood sample on which multiple tests can be done, depending on the results of initial screens.

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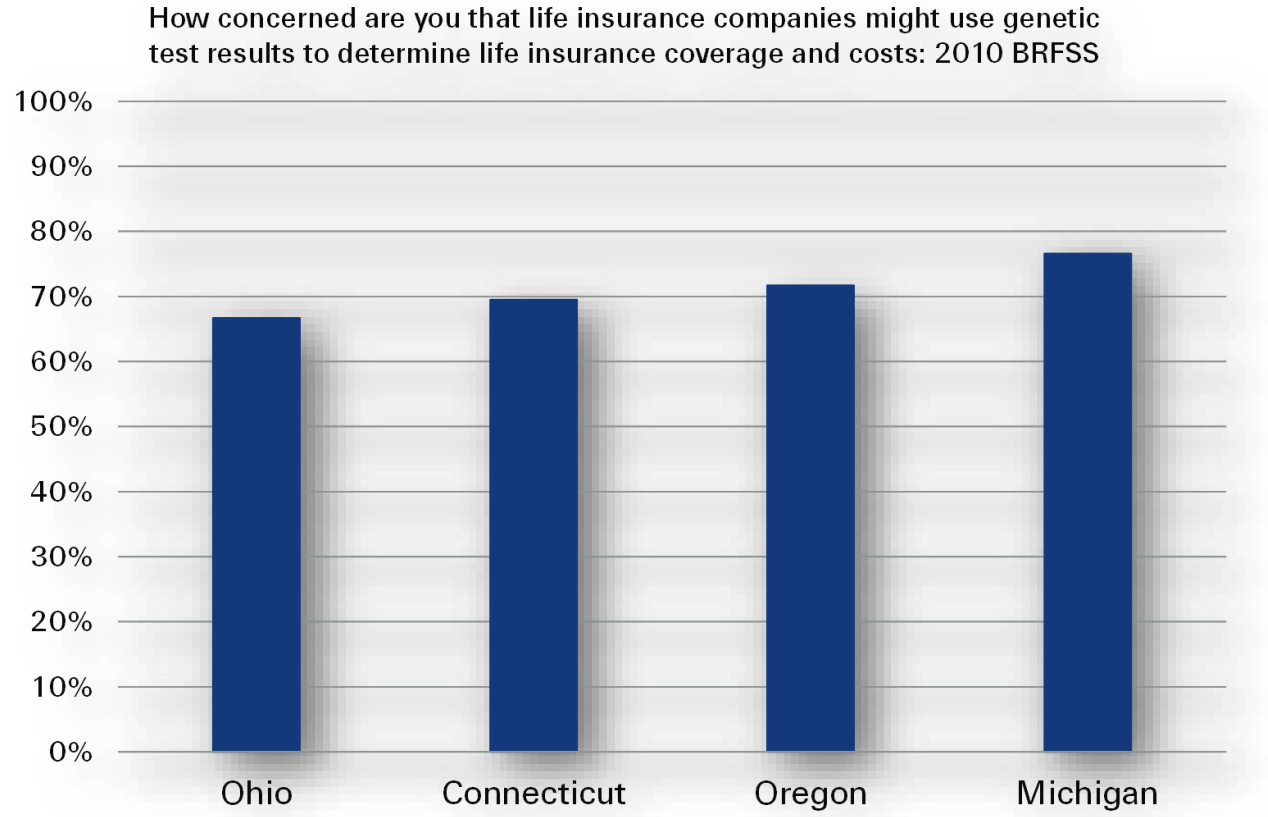
# Concerns on insurers using genetic test results for underwriting

- Four states added questions on genetic testing to the Behavioral Risk Factor Surveillance System health survey.
- The results indicate the majority are concerned about the use of genetic test results by life insurance companies.

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# Can insurers make use of genetic test results if presented at application stage?


Swiss Re regulatory update 2016

(23 EU countries and 7 other European countries included, alongside 10 Asia and a single African country)

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# Regulatory pressure has increased in major life insurance markets

Each market takes a different approach in how it requests/uses genetic testing information to underwrite and assess risk

**Insurers generally allowed to:**

- Use diagnostic genetic information to *confirm* disease for underwriting
- Use family history as risk selection tool

**Insurers generally *not* allowed to:**

- Ask applicants to undergo genetic testing
- Use existing predictive genetic information for underwriting

**Unless:** Regulation specifically allows the use of predictive genetic data for **high sums insured** and/or **actuarially justified**

Regulation around how insurers can use genetic data falls into three major categories


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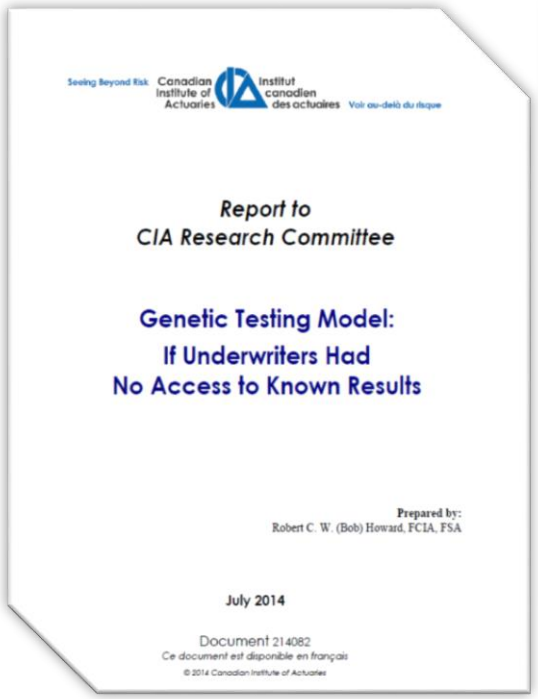
# Modelling around the world - Attempt in quantifying the anti-selection impact


Seeing Beyond Risk Canadian Institute of Actuaries Institut canadien des actuaires Voir au-delà du risque

*Report to*
*CIA Research Committee*

**Genetic Testing Model:**
**If Underwriters Had**
**No Access to Known Results**

Prepared by:
Robert C. W. (Bob) Howard, FCIA, FSA

July 2014

Document 214082
*Ce document est disponible en français*
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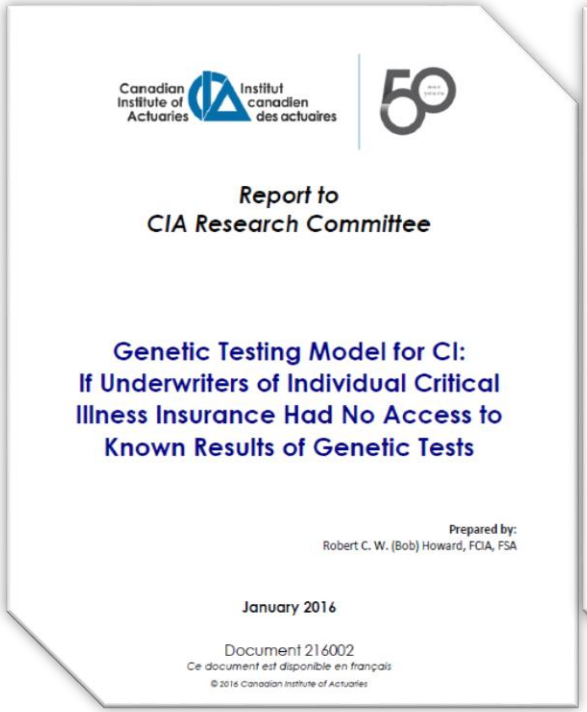
Canadian Institute of Actuaries Institut canadien des actuaires

*Report to*
*CIA Research Committee*

**Genetic Testing Model for CI:**
**If Underwriters of Individual Critical Illness Insurance Had No Access to Known Results of Genetic Tests**

Prepared by:
Robert C. W. (Bob) Howard, FCIA, FSA

January 2016

Document 216002
*Ce document est disponible en français*
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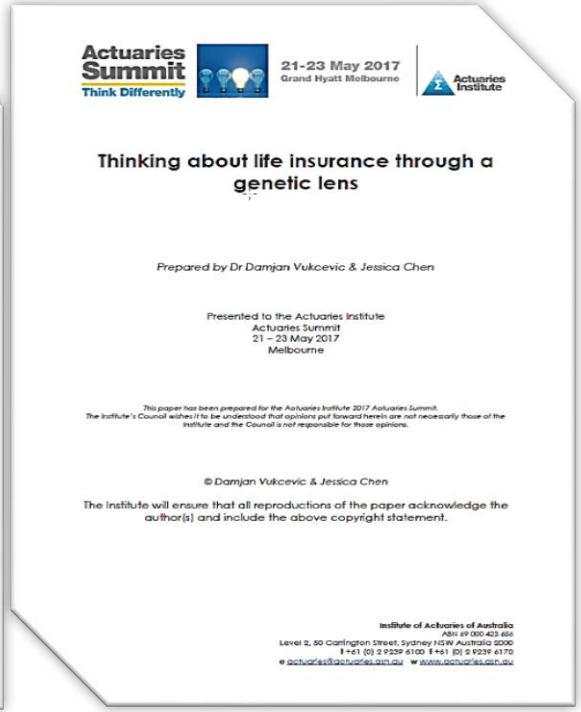
SOA commissioned report

The SOA has commissioned a report to illustrate the potential impact on the U.S. life insurance industry if legislation existed prohibiting the use of and/or disclosure of genetic information during the underwriting process.


Actuaries Summit
Think Differently
21-23 May 2017
Grand Hyatt Melbourne
Actuaries Institute

**Thinking about life insurance through a genetic lens**

*Prepared by Dr Damjan Vukcevic & Jessica Chen*

Presented to the Actuaries Institute
Actuaries Summit
21 – 23 May 2017
Melbourne

*This paper has been prepared for the Actuaries Institute 2017 Actuaries Summit.*
*The Institute's Council wishes it to be understood that opinions put forward herein are not necessarily those of the Institute and the Council is not responsible for those opinions.*

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Institute of Actuaries of Australia
ABN 69 000 423 656
Level 2, 50 Carrington Street, Sydney NSW Australia 2000
T +61 (0) 2 9239 6100 F +61 (0) 2 9239 6170
E actuaries@actuaries.asn.au W www.actuaries.asn.au

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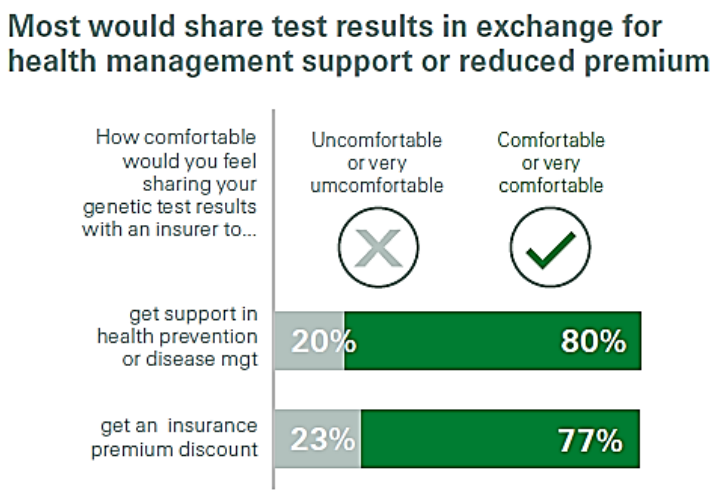
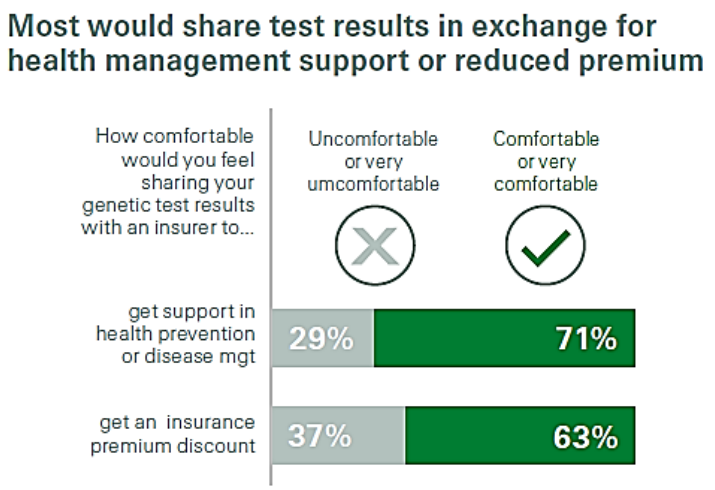
# Consumer would share test results in exchange for health management support or reduced premium

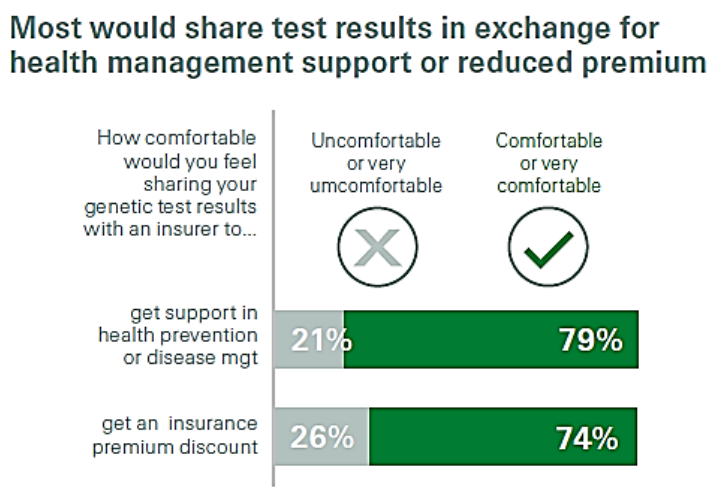
## US




## Australia




## UK




Swiss Re's genetic testing consumer survey 2018

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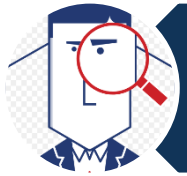
# Summary



Regulatory restrictions on access and use of genetic information for insurers will increase

Concerns on insurance company using genetic test results for underwriting

Genome sequencing costs will continue to decline


Quick improvement in predictive and pre-symptomatic genetic testing

Anti-selection risk through additional insurance purchase or purchase delay

Acceptance of genetic testing results for underwriting for health promotion or premium discounts

Genetic testing rates in the general population will continue to increase

The future unknown

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# Thanks