Genomic medicine on cancer management - challenges for insurance industry

Dr David Lu, Deputy Regional Chief Medical Officer, Swiss Re
What is Genomic Medicine?

• An emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g., for diagnostic or therapeutic decision-making) and the health outcomes and policy implications of that clinical use.

  *The National Human Genome Research Institute*

• Part of so-called precision, or personalised medicine.

• New techniques combined with the growing availability of genomic information and new predictive methodologies will challenge how we as insurers define and classify cancer; how we structure and price our policies; and how we sustainably provide our products and services to our customers.
Today’s agenda

- The basics
- Genetic testing
- Liquid biopsy
- Gene therapy
- Challenges for insurance industry
The basics
Chromosomes

Chromosomes are thread-like molecules that carry hereditary information for everything from height to eye color.

- Walter Sutton (left) and Theodor Boveri (right) independently developed the chromosome theory of inheritance in 1902.

Full set of human chromosomes – 23 pairs
DNA (deoxyribonucleic acid) is the genetic material of living organisms. It contains the instructions an organism needs to develop, live and reproduce.

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1953, Watson & Crick proposed the DNA model
Gene and Genome

- **Genes** are sections of DNA which act as instructions to make proteins.

- A **genome** is an organism’s complete set of DNA including all genes. Genome contains all the information to build and maintain that organism.

- The **Human Genome Project** (HGP) was an international scientific research project with the goal of determining the sequence of nucleotide base pairs that make up human DNA, and of identifying and mapping all of the genes of the human genome from both a physical and a functional standpoint.

- HGP was formally launched in 1990 and was declared complete on April 14, 2003.
Full genome sequencing becomes affordable

Plummeting genome sequencing costs and advances in human genetics increases the availability for different types of genetic testing.

Source: NIH National Human Genome Research Institute http://www.genome.gov/sequencingcosts/
Genetic testing in the clinical practice grows at about 13% annually

Advances in the understanding of human genetics increases the availability and uptake of genetic testing in the clinical practice.

Trend in UK clinical genetic testing activity

Source: CMGS audits
Genetic testing
What is genetic testing?

Genetic testing looks for alterations in a person's genes or chromosomes to identify heritable or acquired mutations related to disease and health.
Mono-genetic disorders

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

![Autosomal dominant inheritance diagram](image)

![Autosomal Recessive Inheritance diagram](image)

![X-Linked Recessive Inheritance diagram](image)
Multifactorial and polygenic (complex) genetic disorders

Common medical problems such as heart disease, diabetes, and obesity do not have a single genetic cause - they are likely associated with the effects of multiple genes in combination with lifestyle and environmental factors.

Use polygenic risk score (PRS or PGS) to predict future risk of polygenic genetic disorders has shown great potential.

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

NGS=next generation sequencing

Rehm H, Nature Genetics 2013 14:295-300
Genetic inheritance versus Epigenetic inheritance

**Genetic Inheritance**
- Gene X on
- DNA sequence change
- Gene X off
- Multiplication of somatic cells
- Production of germ cells
- Coding

**Epigenetic Inheritance**
- Gene Y on
- Chromatin change
- Gene Y off
- or
- Access

Adapted from https://www.studyblue.com
Liquid biopsy
What is liquid biopsy?

• To look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood.

• Liquid also include CSF, urine and other body fluids.

- Circulating tumour cells (CTCs)
- Circulating tumour DNA (ctDNA)
  - exosomes – extracellular vesicles
  - tumour-educated blood platelets (TEPs)
Liquid biopsy is looking for somatic mutation

- Somatic mutations develop after conception in any cell in the body, and are passed down only to descendants of that particular cell, not to future generations.
- Germline mutations are passed from generation to generation through the germ cells; they are present at conception and therefore are passed down into every cell in the body.

adapted from the National Cancer Institute and the American Society of Clinical Oncology
Liquid biopsy and cancer management

- Early detection
- Diagnosis
- Predict prognosis
- Treatment monitoring
- Detect cancer recurrence
Predicting prognosis and monitoring treatments

- The number of CTCs links to survival.
- Persistent CTCs after treatment correlated with unfavorable prognoses.

CellSearch system was approved by the FDA in 2004 to predict outcomes for metastatic breast cancer patients, and to aid in monitoring colorectal (2007) and prostate cancer (2008) patients.

Liquid biopsy and cancer management

- Early detection
- Diagnosis
- Predict prognosis
- Treatment monitoring
- Detect cancer recurrence
CTCs were detected 1-4 years earlier than CT for lung cancer


* CTM: circulating tumor microemboli, a cluster of cancer cells
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, e, Wanchun Gai, a,b, Benny C. Y. Zee, e, Brigitte B. Y. Ma, c, Edwin P. Hui, c, Anthony T. C. Cham, f, John K. S. Woo, f, Rossa W. K. Chiu, a,b, and Y. M. Dennis Lo a,b, c, 1

In the meantime, Grail will launch its first commercial blood test, for nasopharyngeal cancer, in Hong Kong, where the disease is prevalent. Grail obtained the blood test when it merged with the Hong Kong-based company Cirina in May 2017.

https://cen.acs.org/business/startUps/Grail.raises.funds.advance.blood/96/i22

Grail raises more funds to advance a blood-based cancer test

Flush with another $300 million, Grail plans to enroll 135,000 people in studies this year to detect circulating tumor-derived DNA

by Ryan Cross
MAY 22, 2018 | APPEARED IN VOLUME 96, ISSUE 22

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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%) |

This review resulted in a final list of 788 cancer biomarkers.

Early Cancer Detection Consortium is funded by Cancer Research UK.

The ultimate goal is to produce a strategy for generic cancer screening that can go into clinical practice.

UK nation wide project

Research Paper

Building the Evidence Base of Blood-Based Biomarkers for Early Detection of Cancer: A Rapid Systematic Mapping Review

http://www2.warwick.ac.uk/fac/med/about/centres/uk-ecdc/

Liquid biopsy and cancer management

- Early detection
- Diagnosis
- Predict prognosis
- Treatment monitoring
- Detect cancer recurrence
Cancer definitions for critical illness

• Tissue biopsies (histopathology) presently remain the gold standard.

• Cancer definitions vary by market. Although most definitions explicitly require histopathological proof, some products only require pathology, rely on ICD coding or accept clinical diagnosis and would be less protected against a new wave of liquid biopsy diagnosis.

• Using explicit liquid biopsy exclusions in definitions could act as a safeguard.
Liquid biopsy and cancer management

- Early detection
- Diagnosis
- Predict prognosis
- Treatment monitoring
- Detect cancer recurrence
Detecting recurrence earlier than imaging

• In patients with non-metastatic cancers, ctDNA-based liquid biopsies could be optimized to capture and monitor genomic markers of Minimal Residual Disease following curative resection, possibly preceding the development of clinical or radiologic recurrence.

• Early detection of small micrometastatic lesions that are currently undetectable by clinical imaging procedures (CT or MRI scans) would largely increase the chances to prevent full-blown, incurable metastatic disease.

• CTC- and ctDNA-based screening of patients with higher risk of relapse may create opportunities for therapeutic interventions before the development of clinical metastasis.

Cancer Cell 31, February 13, 2017
Gene therapy
What is gene therapy?

• The FDA defines gene therapy as a medicine that “introduces genetic material into a person’s DNA to replace faulty or missing genetic material” to treat a disease or medical condition.
The “first gene therapy” approved by FDA

FDA Approves Groundbreaking Gene Therapy for Cancer

The treatment will be sold by Novartis for $475,000.

by Emily Mullin  August 30, 2017

Novartis’ Kymriah, the first approved CAR-T therapy worldwide, has performed far below sales expectations in the last quarter. The news highlights the challenges CAR-T therapies still face before becoming a commercially viable treatment option.

In the first quarter of 2018, the treatment brought in $12M, roughly four times below the sales needed to meet analyst expectations.

The question reflects one of the biggest challenges for cell and gene therapies: pricing.

https://labiotech.eu/kymriah-car-t-therapy-novartis-sales/

- CAR-T therapy, marketed as Kymriah
- A patient’s T cells are extracted and cryogenically frozen so that they can be transported to Novartis’s manufacturing center.
- There, the cells are genetically altered to have a new gene that codes for a protein—called a chimeric antigen receptor, or CAR. This protein directs the T cells to target and kill leukemia cells with a specific antigen on their surface.
- The genetically modified cells are then infused back into the patient.
- It takes an average of 22 days to create the therapy, from the time a patient's cells are removed to when they are infused back into the patient.
Challenges for insurance industry
Interest in testing, disclosure and actions to be taken

<table>
<thead>
<tr>
<th>Testing that reveals future risk of AD</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Important to be tested</td>
<td>70.4%</td>
</tr>
<tr>
<td>If required for research would you be tested?</td>
<td>94.9%</td>
</tr>
<tr>
<td>Do you want results if collected for research?</td>
<td>88.7%</td>
</tr>
<tr>
<td>If insurance paid for test</td>
<td>80.8%</td>
</tr>
<tr>
<td>If it cost you &gt;$100</td>
<td>58.7%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Who you would disclose result to</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Spouse</td>
<td>92.3%</td>
</tr>
<tr>
<td>Siblings</td>
<td>84.6%</td>
</tr>
<tr>
<td>Children</td>
<td>81.7%</td>
</tr>
<tr>
<td>Physician</td>
<td>79.4%</td>
</tr>
<tr>
<td>Lawyer</td>
<td>60.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If you were at high risk for AD would you</th>
<th></th>
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<tbody>
<tr>
<td>Begin a healthier lifestyle</td>
<td>90.5%</td>
</tr>
<tr>
<td>Get LTC insurance</td>
<td>76.3%</td>
</tr>
<tr>
<td>Spend all of your money for pleasure</td>
<td>18.4%</td>
</tr>
<tr>
<td>Seriously consider suicide</td>
<td>11.6%</td>
</tr>
</tbody>
</table>

Studies in affinity groups who have an interest in a specific genetic condition (registrants at Alzheimer’s Prevention Registry) n=4036 mean age 58, 81% women 66.2% college grads 78% perceived themselves to be at higher risk for AD. This could bias the group to potentially be more open to testing.

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

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

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.
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.

Parkman A, et al., J Genet Counsel 2015, 24:512-521
Insurers are faced with various levels of restriction on use of genetic data in different countries.

Protection of genetic data: Belgium, France, Austria, Portugal, Ireland, Germany, Switzerland, Netherlands, UK, Sweden, USA, Canada, Australia, South Africa, Ireland, Sweden, Italy.

Genetic data considered medical data: Legislative regulations range from voluntary moratoria, legislation to strict outright bans and approaches continue to evolve.
Can insurers make use of genetic test results if presented at application stage?

Swiss Re global survey results 2013*

Numerous restrictions are in place in Europe while fewer restrictions exist in Asia; mainly self-regulated

* 23 EU countries and 7 other European countries included, alongside 10 Asia and a single African country
How real of a concern is adverse-selection from genetic testing?

Canadian Institute of Actuaries (CIA)

- as a result of the prohibition in access to predictive genetic testing information in Canada, the total death claim costs for life insurance would increase by 12% and critical illness claim costs are likely to increase by about 26% overall (+16% for males and +41% for females).
Impacts on insurance

<table>
<thead>
<tr>
<th>Impacts</th>
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<tbody>
<tr>
<td>Anti-selection</td>
<td></td>
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<tr>
<td>Over-diagnosis, detect clinical indolent cancer, increase cancer incidence rate (diagnose rate)</td>
<td></td>
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<tr>
<td>Over-investigations, increase in medical expenses</td>
<td></td>
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<tr>
<td>Cancer shift to early stage, even pre-clinical stage</td>
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<tr>
<td>Better survival</td>
<td></td>
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<tr>
<td>Expensive gene therapy</td>
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<tr>
<td>Direct-to-Consumer test: mis-interpretation, not considered as medical evidence</td>
<td></td>
</tr>
<tr>
<td>Recurrence / cancer existence definition may change</td>
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<tr>
<td>Legal risk / reputation risk</td>
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