
Presenters:
Stephan Kwan, FSA
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The Wave on the Shore - Genetic Testing & Impact on Insurance
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Stephen Kwan
Swiss Re, Health & Medical Innovation Manager, Asia
Agenda

1. Overview
2. Evolving Regulations
3. Application in Insurance
4. Implication for Insurance
5. Attempt in quantifying the impact
6. Reflection
Overview
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.

- **New-born screening**: Identifies highly penetrant genetic disorders that can be treated early in life.
- **Predictive and pre-symptomatic genetic testing**: Estimates the risk of developing adult-onset disease or predicting future disease onset.
- **Nutrigenomic testing**: Studies the effect of genetic variations in relation to the interaction between diet/nutrition and health.
- **Liquid biopsy testing**: Detects molecular biomarkers in blood & other body fluids for diagnosis, prognosis, and treatment.
- **Diagnostic / confirmatory genetic testing**: Identifies or confirms a specific genetic condition in a symptomatic individual.
- **Pharmacogenomics testing**: Guides individual drug dosage, selection, and response.
- **Direct-to-consumer (DTC) genetic testing**: Genetic tests marketed directly to consumers without involving healthcare professionals.
Higher than expected US genetic testing consumer adaption rates of 15% observed in 2016

Source: https://rockhealth.com/reports/the-genomics-infection-point-implications-for-healthcare/#consumer-sentiments, 2016, n=1060

Other studies

<table>
<thead>
<tr>
<th>% taken a genetic test</th>
<th>#Participants</th>
<th>Year</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>6%</td>
<td>1'489</td>
<td>2016</td>
<td>STAT-Harvard Poll on Genetic Editing, Testing, and Therapy</td>
</tr>
<tr>
<td>3%</td>
<td>694</td>
<td>2016</td>
<td>Attitudes to return of incidental findings</td>
</tr>
<tr>
<td>18%</td>
<td>1’588</td>
<td>2011</td>
<td>Nature readers flirt with personal genomics</td>
</tr>
<tr>
<td>14.8%</td>
<td>890</td>
<td>2010</td>
<td>Science after the sequence</td>
</tr>
</tbody>
</table>
Additional 45% of consumers considering to get tested as prices for testing drop

At least half of consumers open to taking a genetic test in the future; most to satisfy personal curiosity but half wants to know more about potential disease risk

Source: https://rockhealth.com/reports/the-genomics-inflection-point-implications-for-healthcare/#consumer-sentiments, 2016, n=1060
Growing Market for DTC Genetic Testing in Asia

China’s Example
- Market size five folded from RMB 1.2b in 2012 to RMB 6b in 2016.¹
- Genetic testing industry listed as important force in the new momentum of China’s economic development by National Development and Reform Commission¹.
- Over 400 genetic testing suppliers by 2017.
- Cancer and prenatal tests are the top 2 most popular sectors

¹. Genetic testing industry boost China’s economic development, datenna, Nov 8, 2017
². Market CAP, Bloomberg, 24 April 2018 (Estimation only)
Liquid Biopsy

• Blood contains two types of cancer-derived materials that are susceptible to detailed molecular analysis:
  – intact circulating tumour cells (CTCs)
  – cell-free circulating tumour DNA (cfDNA; also referred to as circulating tumour DNA, or ctDNA)

• The evolution of sensitive CTC and cfDNA detection technologies has enabled the development of liquid biopsies with many clinical applications, including:
  – screening for presence of disease (yet to mature);
  – patient stratification and therapy selection (companion diagnostics);
  – monitoring treatment response and drug resistance;
  – detection of minimal residual disease after surgery/recurrence.
Liquid Biopsy – Holy Grail

Liquid biopsy for NPC screening proves effective in large-scale study

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

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

* 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.

The test was evaluated on 1,005 patients with nonmetastatic, stages I to III cancers of the ovary, liver, stomach, pancreas, esophagus, colorectum, lung or breast. The median overall sensitivity, or the ability to find cancer, was 70 percent and ranged from a high of 98 percent for ovarian cancer to a low of 33 percent for breast cancer. For the five cancers that have no screening tests—ovarian, liver, stomach, pancreatic and esophageal cancers—sensitivity ranged from 69 percent to 98 percent.

2. Single Blood Test Screens for Eight Cancer Types, Press Release, James Hopkins Medicine, Jan 18, 2018

Single Blood Test Screens for Eight Cancer Types

The image contains a reference to the Johns Hopkins Medicine logo.
Evolving Regulations
Genetic testing regulation

- Regulation acts between the poles of avoiding anti-selection and the fear of denied insurance for people with adverse test results

<table>
<thead>
<tr>
<th>No genetic test disclosure</th>
<th>Full genetic test disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policyholders who have more information about their health than the insurer might anti-select</td>
<td>Potential policyholders might be discriminated against or cancel/postpone planned genetic tests out of fear of being denied insurance based on the results</td>
</tr>
</tbody>
</table>

- Regulatory restrictions typically apply to
  - **predictive testing**. The use of diagnostic genetic information to confirm the presence of a disease is generally allowed for underwriting purposes as long as actuarially justifiable;
  - **life insurance/disability income/long-term care** as most developed countries offer public healthcare or mandate the purchase of health insurance

- Regulation is still developing in many countries
# Restrictions on use of genetic data for insurers

Last updated: Jan 2018. For reference only.

<table>
<thead>
<tr>
<th>No regulation/code of conduct</th>
<th>Code of conduct from insurance industry</th>
<th>Prohibited to require genetic test, but can use existing test</th>
<th>Prohibited to use tests below given SA</th>
<th>Prohibition/moratoria to use genetic tests at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>Greece</td>
<td>Australia</td>
<td>Germany</td>
<td>Austria</td>
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<td>Finland</td>
<td>Hong Kong</td>
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<td>Netherlands</td>
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<td>India</td>
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<td>Switzerland</td>
<td>Canada</td>
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<tr>
<td>Spain</td>
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<td></td>
<td>United Kingdom¹</td>
<td>Denmark</td>
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<tr>
<td>US (Life, DI, LTC)¹</td>
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<td>France</td>
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<td>Ireland</td>
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<td>South Korea</td>
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<td>Poland</td>
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<td>Portugal</td>
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<td>US (Medical</td>
</tr>
</tbody>
</table>

"Legislator might still be working to pass regulation"

"Certain level of life insurance/DI deemed basic right"

"Wait-and-see approach"

¹Legislation varies at state level. Approx. 1/3 of states have regulation restricting the use of genetic information in life insurance

²Only for list of approved tests. Currently only Huntington’s disease
Regulation in Canada

• Bill S-201 "An Act to prohibit and prevent genetic discrimination" passed in March 2017 prohibits an insurer from:
  – requiring a person to take a genetic test
  – requiring a person to disclose the results of a genetic test
  – discriminating against a person because they did not take a genetic test

• An earlier version allowed insurers to ask for prior test results for life insurance with SA ≥ 1 Million CAD or DI with annual payments ≥ 75’000 CAD.

• However, Federal Government is on record to seek clarity from the Supreme Court of Canada on the constitutionality of the law.

see https://openparliament.ca/bills/42-1/S-201/
Regulation in Australia

• Self-imposed industry standard
  – Life insurers will not initiate a request for a new genetic test or in any way coerce an applicant for insurance to undertake a new genetic test.
  – Where an applicant has already undertaken a genetic test, the results are required to be provided if that is requested by an insurer.
  – The insurer will take account of the benefits of special medical monitoring, early medical treatment, compliance with treatment and the likelihood of successful medical treatment when assessing overall risk.
  – The insurer will provide reasons for any adjustment to premiums or policy conditions imposed after their assessment of the application.

• Recommendation by the Australian genetic non-discrimination working group (December 2016)
  – For the Australian government to enact legislation to regulate the use of genetic information.
  – Until such legislation is in place, the Australian government to enact a ban or moratorium on the use of genetic data by life insurers.
Regulation in South Korea

• Act on bioethics and bio-securities:
  – No discrimination in social activities such as education, promotion, employment or insurance is allowed because of genetic test information.
  – Nobody can force the other person to have the genetic tests nor to submit the genetic test results.

• There is no specific legislation on family history or questions on any specific diseases. However, FSS (financial supervisory services) allowed questions on family history of some diseases related to CI cover for CI application form.
Regulation in China

- Regulator is reviewing the regulation around the use of genetic testing information for insurers. The direction is geared towards disallowing any usage.

- Genetic testing information and family medical history are considered as sensitive personal data under the Chinese law. The data subjects' informed consent is required for any collection, use and further sharing of sensitive personal data for legitimate business purposes.

- The collection, research, sale and cross-border transfer of genetic information of Chinese population is subjected to administration of the PRC Ministry of Science and Technology ("MST").

- Clinical use of genetic testing is not allowed without prior approval of the China Food and Drug Administration ("CFDA") and the Commission of Health and Family Planning ("CHFP").
Application in Insurance
Application by Insurers in Asia

Value-added-services (Common)

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

Pharmacogenomics testing
Guides individual drug dosage, selection and response

Value-added-services (Some Attempt)

Predictive and pre-symptomatic genetic testing
Estimates the risk of developing adult-onset disease or predicting future disease onset

Most offered to customers with family history but some attempted to extend beyond (unconditional)

Integrated with Product (Withdrawn)

Bundled Insurance Product
Insurance providing DTC predictive genetic testing for certain diseases and coverage varies by the genetic testing result – ranging from lump sum coverage to provision for cancer screening.
Insurers to offer genetic testing to clients/applicants

Human Longevity, Inc. and MassMutual Sign Groundbreaking Agreement to Offer HLIQ™ Whole Genome Sequencing to MassMutual’s Customers, Financial Professionals and Employees

...HLIQ Whole Genome, to eligible MassMutual customers, employees and financial professionals at a reduced price. The initiative should help enable HLI’s goal of providing up to 200,000 HLIQ Whole Genome reports.

HLIQ Whole Genome, which is ordered by a client’s physician, includes comprehensive sequencing and analysis of the individual’s whole genome. The report may give insight into health status and risk for disease, details on which pharmaceuticals may work better for individuals, carrier status for family planning decisions, along with ancestry and personal traits.

Implication for Insurance
Cancer Predictive Testing

How “predictive” is cancer predictive testing?

- Inherited (germline) mutations are thought to play a role in about 5%-10% of all cancers.¹
- >100 germline mutations identified conferring high or moderate risk of cancer (>2 fold relative risk, at least 5% develop cancer)².
- Most cancers (~80%) are sporadic (not due to inherited gene mutation).³

Who should take it?

- Most publications advise for person having **personal or family history** to take it.

How should results be interpreted?

- **Genetic counselling** is required to properly explain the result as inappropriate interpretation may lead to **unneeded anxiety, false assurance or important decisions about medical treatment.**¹
- Interpretation of results is complex (not straight yes or no). Follow up actions advised require careful considerations. For example, regulator in US advised caution towards nutrition advice by DTC companies.⁴

Positive result interpretation¹:

- Confirm diagnosis of a hereditary cancer syndrome.
- Indicate an increased risk for developing certain cancer.
- Indicate as carrier of a gene mutation without increased risk, but that might affect offspring.

Negative result interpretation¹:

*For person with strong family history / known genetic causing gene alteration in the family:*

- **True negative:** absence of specific known gene mutation; no increased genetic risk of developing cancer.
- **Uninformative negative:** absence of a known mutation associated with hereditary cancer.

*More generally:*

- **False negative:** Absence of tested gene mutation associated with cancer but is inconclusive of whether the person has higher or lower risk.
- **Variant of unknown significance:** Unknown variant today but might have significance in the future.

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¹ National Cancer Institute, the Genetics of Cancer, [https://www.cancer.gov/about-cancer/causes-prevention/genetics](https://www.cancer.gov/about-cancer/causes-prevention/genetics)
Predictive Testing: Possible Responses & Insurance Risk

**Improvement in mortality and morbidity risk:**
Extent depending how modifiable is the risk

**Impact on risk:**
Uncertain about Critical Illnesses depending on definitions and structure. Improvement in Mortality.

**Anti-selection:**
Additional purchase depending on effectiveness of UW, selective lapse

**False Assurance:**
Lapse, relaxed guard for screening / lifestyle modifications

**Counselling, Reputational**

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Swiss Re
An illustration
Liquid Biopsy as Screening - Considerations

The test was evaluated on 1,005 patients with nonmetastatic, stages I to III cancers of the ovary, liver, stomach, pancreas, esophagus, colon/rectum, lung or breast. The median overall sensitivity, or the ability to find cancer, was 70 percent and ranged from a high of 98 percent for ovarian cancer to a low of 33 percent for breast cancer. For the five cancers that have no screening tests — ovarian, liver, stomach, pancreatic and esophageal cancers — sensitivity ranged from 69 percent to 98 percent.

Despite the limited sample size, our data show very low congruence for same patient-paired samples in 2 CLIA-certified commercially available tests with self-reported high accuracy, specificity, and sensitivity to specifically detect and quantify tumor-specific alterations. These data cannot determine which test is more accurate but suggest that reported gene alterations will not be the same across different platforms, raising the specter that patients could potentially receive different treatments depending on the cfDNA platform. Insufficient genetic profiling congruence could jeopardize the clinical benefit of personalized medicine.1,8

Sources:
(1) Single Blood Test Screens for Eight Cancer Types, Press Release, James Hopkins Medicine, Jan 18, 2018
(2) Patient-Paired Sample Congruence Between 2 Commercial Liquid Biopsy Tests: Analysis of Geneva Cancer Trials
(3) A blood test that can detect cancer?, Swiss Re
Risk Considerations for Insurers

- Regulations around use of genetic testing information in underwriting
- Anti-selection risk through additional insurance purchase / persistence.
- Over-diagnosis and overtreatment risk
- Reputational Risk, ethical concern
- Healthcare cost may increase due to more screening, counselling, etc.
- Genetic counselling available and use of genetic testing result
- Legal risk – regulation, potential law suite
- The future unknown

Sources:
(1) Genetic testing and implications for life insurers, Swiss Re
Attempt in quantifying the impact
## Modelling around the world

<table>
<thead>
<tr>
<th>Institute</th>
<th>Year of Publish</th>
<th>Risk</th>
<th>Estimated impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian Institute of Actuaries$^1$</td>
<td>2014</td>
<td>Mortality</td>
<td>Average 44% (35% male, 60% female)</td>
</tr>
<tr>
<td>Canadian Institute of Actuaries$^2$</td>
<td>2016</td>
<td>Critical Illnesses</td>
<td>Average 26% (16% male, 41% female)</td>
</tr>
<tr>
<td>Institute of Actuaries of Australia$^3$</td>
<td>2017</td>
<td>Critical Illnesses</td>
<td>1.8% (assuming 0.5% population)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17.5% (assuming 5% population)</td>
</tr>
</tbody>
</table>

Sources:
(1) Genetic Testing Model: If Underwriters Had No Access to Known Results, Canadian Institute of Actuaries, Robert C. W. (Bob) Howard, July 2014
(3) Thinking about life insurance through a genetic lens, Damjan Vukcevic & Jessica Chen, May 2017
Key & Sensitive Assumptions

1. Impact of genetic factor to the claim
2. Proportion of claim due to those diseases under the study
3. Proportion of population taking the genetic test
4. Proportion of policies that may lapse if known to have lower genetic risk
5. Proportion of new application if known to have higher genetic risk
6. Effect of Underwriting (e.g. family history)
7. Anti-selection: How much higher face amount is bought, relative to the average person?
Reflection
Reflection

“Equality” for insurance entitlement? Discrimination?
Genetics, family history and beyond?

Known unknown – complexity of interactions of genes, linkage of
diseases is just at the beginning.
Beyond genetics? (e.g. epi-genetics, microbiomes)

Medical advancement, innovation & customer protection
Embracing changes with prudence
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