Seeing the Future?
How Genetic Testing Will Impact Life Insurance

Dr David Lu  M.D.  Ph.D.
Deputy Regional Chief Medical Officer, Asia
2017
Table of Contents / Agenda

• The basics
• Beyond single gene diseases
• Potential impacts on insurance
The basics
Basic Genetic Concept

- Organism
- Cell
- Chromosome
- DNA
Schleiden, Virchow and Bütschli were among the first scientists who recognized the structures now familiar as chromosomes.

• Walter Sutton (left) and Theodor Boveri (right) independently developed the chromosome theory of inheritance in 1902.
1953, Watson & Crick proposed the DNA model
DNA diagram – a double helical structure
**Genes & Genome**

- **Genes** are sections of DNA which act as instructions to make molecules called 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 has estimated that humans have between 20,000 and 25,000 genes.
From genes to protein

Source: http://www.voidspace.org.uk/technology/genome/1.shtml
Evolution of genetic testing technologies

- Single Gene Testing
- Gene Panels
- Whole Exome Sequencing
- Whole Genome sequencing

Chromosome 17
- Allele (gene)
- Locus (spot on gene)

Chromosome 13
- Allele (gene)
- Locus (spot on gene)

78 tumor samples

70 breast cancer prognosis genes

Evolution of genetic testing technologies
Plummeting genome sequencing costs and advances in human genetics increases the availability for different types of genetic testing.
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.
Beyond single gene diseases
Single gene disease

• Single gene disorders are caused by DNA changes in one particular gene, and often have predictable inheritance patterns.

• Individually, single gene disorders are each very rare, but as a whole, they affect about one per cent of the population.

• Since only a single gene is involved, these disorders can be easily tracked through families and the risk of them occurring in later generations can be predicted.

• Single gene disorders can be divided into different categories: dominant, recessive and X-linked. Example:
  – Huntington’s Disease (autosomal dominant)
  – Haemophilia (x-linked recessive)
Inheriting pattern of single gene disorders

**Autosomal dominant inheritance**

- Unaffected Mother
- Affected Father

**Offspring**
- Unaffected (50% chance)
- Affected/Predisposed (50% chance)

**Autosomal Recessive Inheritance**

**X-Linked Recessive Inheritance**
Germline mutation vs 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.
Liquid Biopsy

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.

• Conditions caused by many contributing factors are called complex or multifactorial disorders.

• Although complex disorders often cluster in families, they do not have a clear-cut pattern of inheritance. This makes it difficult to determine a person’s risk of inheriting or passing on these disorders.

• Complex disorders are also difficult to study and treat because the specific factors that cause most of these disorders have not yet been identified.

• Researchers continue to look for major contributing genes for many common complex disorders.
Disease linkage to multi genes

Many diseases of underwriting importance involve multiple genes substantially increasing the complexity of identifying meaningful variations on one or more genes.

Newer sequencing technologies will allow for further investigation of these more complex gene-disease interactions.

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

NGS=next generation sequencing

Rehm H, Nature Genetics 2013 14:295-300
Epigenetics- Control of Gene Expression

• Epigenetics is the study of potentially heritable changes in gene expression.

• This gene expression change does not involve changes to the underlying DNA sequence: a change in phenotype without a change in genotype.

• It affects how cells read the genes, and subsequently how they produce proteins.

• Lifestyles change can eventually cause chemical modifications around the genes that will turn those genes on or off over time.

• Researchers hope to make use of epigenetic mechanisms to correct cancer and other diseases that are caused by gene misregulation.
Genetic inheritance versus Epigenetic inheritance

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

**EPIGENETIC INHERITANCE**
- Gene Y on
- Chromatin change
- Gene Y off
- Gene Y off
- Access
- Gene Y on
- Gene Y off
- or
- Gene Y off

ACGATTACAGCTTACGGATTACA
TGCTAATGTCGAATGCCTAATGT

ACGATTACGGCTTACGGATTACA
TGCTAATGCGGAATGCCTAATGT

Adapted from https://www.studyblue.com
Moving towards personalized cancer therapy

Conventional approach to chemotherapy

Assess biomarkers

Patients with no clinical benefit

Side effects responders

Targeted drugs

Higher response rate in those identified as potentially benefiting
The Future – gene editing with CRISPR/Cas9
Genetic tests and impacts on insurance
Insurance underwriting and risk classification

Many factors that influence the risks of ill health or death may be used in underwriting, based on statistical evidence. Such risk factors may include:

• **Non-medical factors:**
  - Financials: occupation, income, sum assured, ...
  - Habits: sport, travelling, alcohol, drugs, ...

• **Medical factors:**
  - age, (gender), medical records, family history, smoking status, blood pressure, lipid levels, .....  
  - **Genotype** as a valid risk factor candidate in insurance pricing?
The spectrum of risk associated with rare and common genetic variants

- **Rare alleles causing Mendelian disease**
  - Huntington's disease
  - Myotonic Dystrophy
  - Cystic Fibrosis

- **Low-frequency variants with intermediate effect**

- **Common variants implicated in common disease by GWA**
  - Alzheimer's disease
  - Diabetes
  - CVD
  - many cancers

- **Few examples of high-effect common variants influencing common disease**
  - her.BC
  - Lynch syndrome
  - EOAD

- **Rare variants of small effect very hard to identify by genetic means**

Source: adapted from Green R.C. et al.; *Genomic and Personalized Medicine, 2nd edition, 2013, 102-122*
Genetic test definitions: Diagnostic vs. Predictive genetic test

**Diagnostic genetic test**
- To confirm or rule out a known or suspected genetic disorder in a **symptomatic** individual.
- Generally no restrictions on the use of diagnostic tests in insurance underwriting.

**Predictive genetic test**
- Offered to **asymptomatic** individuals with a family history of a genetic disorder to predict future risk of disease.
- Disclosure obligation and use of predictive genetic test results in insurance underwriting **vary by market practice and legislation**.
## Genetic testing types, predictive value and UW capture

<table>
<thead>
<tr>
<th>Type of test</th>
<th># of genes or variants tested</th>
<th>Analytical validity *</th>
<th>Clinical validity (Predictive value) #</th>
<th>UW capture $§$</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-gene testing</td>
<td>1</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>Good coverage for majority of inherited monogenic disorders by family history questionnaire.</td>
</tr>
<tr>
<td>Disease-specific gene-panels</td>
<td>2-100</td>
<td>average</td>
<td>average-high</td>
<td>average</td>
<td>Majority of gene-panel tests for diagnostic and confirmatory analysis. Predictive gene-panel conditions partially covered by family history questionnaire.</td>
</tr>
<tr>
<td>WGS/WES</td>
<td>~20,000</td>
<td>average</td>
<td>low (high)$°$</td>
<td>low</td>
<td>Currently interpretation of clinical WGS/WES is limited, with few reported results clinically relevant and actionable.$°$</td>
</tr>
<tr>
<td>SNP genotyping</td>
<td>10,000-1,000,000</td>
<td>average</td>
<td>low</td>
<td>low</td>
<td>At present SNP genotyping remains unreliable for risk assessment due to low predictive value and clinical significance of results.</td>
</tr>
</tbody>
</table>

* low, <80%; average, 80-98%; high, >98%; # low, <50%; average, 50-80%; high, >80%; $§$ low, <25%; average, 25-50%; high, >50%

**Advances and accuracy in sequencing technology and identification of causal gene variants for diseases will improve the predictive power of WGS/WES**
Five to ten percent of cancers diagnosed in the US are associated with hereditary cancer susceptibility syndromes.\textsuperscript{1} Most diseases represent a complex interplay between genes, environment and behaviors. A negative genetic test can lower but does not eliminate the possibility of one of these conditions appearing.

Roberts(2012) estimated the capacity of whole-genome sequencing to identify individuals at clinically significant risk for 24 different diseases.\textsuperscript{2}

Does a negative test eliminate disease risk?

Implications

- We are at the beginning of a process to identify multi-gene genetic variants for more common diseases with validated prognostic significance.

- Availability of economical testing that yields useful information that might be used to anti-select will continue to grow, especially thru direct to consumer genetic testing.
  - What’s happening with DTC genetic testing?
  - What’s the publics attitude about testing and disclosure?
Growing market for personal genetic testing
Interest in testing, disclosure and actions to be taken

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

1. Even in “at risk” individuals cost appears to be a determining factor for testing.
2. 20% would not tell a physician about result
3. Insurance purchasing

### Testing that reveals future risk of AD

- Important to be tested: 70.4%
- If required for research would you be tested: 94.9%
- Do you want results if collected for research: 88.7%
- If insurance paid for test: 80.8%
- If it cost you >$100: 58.7%

### Who you would disclose result to

- Spouse: 92.3%
- Siblings: 84.6%
- Children: 81.7%
- Physician: 79.4%
- Lawyer: 60.5%

### If you were at high risk for AD would you

- Begin a healthier lifestyle: 90.5%
- Get LTC insurance: 76.3%
- Spend all of your money for pleasure: 18.4%
- Seriously consider suicide: 11.6%

Changes in insurance purchasing behavior

Participants in the first REVEAL study (2000-2002) reporting an insurance change during the 1st year after genetic risk disclosure (n=162).

These individuals were adult children of people with Alzheimer’s disease.

### 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.

How concerned are you that life insurance companies might use genetic test results to determine life insurance coverage and costs: 2010 BRFSS

Ohio: 70%
Connecticut: 60%
Oregon: 50%
Michigan: 40%

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
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
Use of family history at application stage?

Limitation: Belgium, Finland, Netherlands*, Norway, Portugal, Sweden**, Japan and Taiwan

* limited by amount and cause
** limited by amount
Use of genetic tests result in insurance assessment - examples

<table>
<thead>
<tr>
<th>Country</th>
<th>Self-regulation</th>
<th>Limitation by law</th>
<th>Legal Ban</th>
<th>Comment relating to private insurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong Kong</td>
<td></td>
<td>X</td>
<td></td>
<td>In 2000, the HKFI issued a Code of Practice. Genetics Testing &amp; Insurance based primarily on the code issued by the ABI. The Equal Opportunities Commission suggests that insurers in Hong Kong who wish to rely on genetic information should exercise care. Discriminatory decisions based on such information may be unlawful, unless reasonably based on actuarial or other data or justifiable under the Disability Discrimination Ordinance. Family history questions are widely used.</td>
</tr>
<tr>
<td>Australia</td>
<td>X</td>
<td></td>
<td></td>
<td>No specific genetic test law has been enacted. Life insurers comply with FSC Genetic Testing Standard No. 11 (operational since 2002), which allows insurers to use existing genetic test results. With regard to family history, life insurers comply with FSC Family Medical History Standard No. 16 (effective 2005) which states that only first degree relatives will be used for underwriting purposes. Standard 11 &amp; 16 are being reviewed by an FSC Working Group during 2016 to ensure alignment with a Life Insurance Code of Conduct which is also currently being developed by the FSC.</td>
</tr>
<tr>
<td>Canada</td>
<td></td>
<td></td>
<td>X</td>
<td>The Canadian Insurance Code on Genetic Testing does not allow insurers to ask applicants to undergo genetic testing. Where genetic testing has been undertaken and a person is aware of the results, the insurer needs to be made aware of relevant information derived from the test in order to properly assess the risk. In April 2016, the Senate passed Bill S-201, also known as the Genetic Non-Discrimination Act, which would make it illegal for insurance companies or employers to request genetic testing or ask for results. Bill S-201 is currently in the House of Commons.</td>
</tr>
</tbody>
</table>
Seeing the future? How genetic testing will impact life insurance
Summary
Summary

• Clinical and over-the-counter genetic testing is rapidly growing.

• A steady increase of genetic tests results disclosed to the L&H insurance industry can be observed.

• The use of genetic information is highly regulated in mature markets and tendency towards legislation in new markets is further limiting the private insurers medical risk selection process.

• The growing availability of predictive health information from genetic testing leads to increased exposure to anti-selection.

• Substantial financial impact of non-disclosure and/or restrictions on use of genetic information for L&H insurers.

• Family history is a key life insurance risk factor and a good proxy for genetic risk.
©2017 Swiss Re. All rights reserved. You are not permitted to create any modifications or derivative works of this presentation or to use it for commercial or other public purposes without the prior written permission of Swiss Re.

The information and opinions contained in the presentation are provided as at the date of the presentation and are subject to change without notice. Although the information used was taken from reliable sources, Swiss Re does not accept any responsibility for the accuracy or comprehensiveness of the details given. All liability for the accuracy and completeness thereof or for any damage or loss resulting from the use of the information contained in this presentation is expressly excluded. Under no circumstances shall Swiss Re or its Group companies be liable for any financial or consequential loss relating to this presentation.