Session 2b – Cancer diagnostics 2.0 – What Does It Mean for Insurers?

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Cancer diagnostics 2.0 – What Does It Mean for Insurers?

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29 August 2016

A revolutionary blood test that can detect cancer
Liquid biopsies: A $20 billion market ready to explode(4)

New cheap highly-accurate saliva test will tell you at home in just 10 minutes if you have cancer ... could be available in UK within decade(3)

Liquid Biopsy Procedure May Be Next Big Thing In Fight Against Cancer(2)

New blood test could diagnose FIVE different cancers without the need for invasive biopsies, saving millions of lives(5)

Liquid Biopsy
Fast DNA-sequencing machines are leading to simple blood tests for cancer.
Availability: now.(1)

(1) MIT Technology Review, Feb 2015
(2) Tech Times, 12 May 2015
(3) Daily Mail online, 14 February 2016
(5) Daily Mail online, 5 February 2016
Long-term guaranteed cancer products in Korea sold around the year 2000

<table>
<thead>
<tr>
<th>General cancer</th>
<th>Cancer, excluding skin cancer and CIS</th>
<th>Entry age</th>
<th>Policy term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor cancer</td>
<td>Skin cancer, CIS</td>
<td>15 - 65 ages</td>
<td>Until age 80</td>
</tr>
</tbody>
</table>

1. Cancer benefit is paid for the 1st cancer diagnosis; minor cancer benefit is paid one time for each minor cancer
2. Waiting period for 1st cancer diagnosis is 90 days from policy issue; no waiting period for minor cancer diagnosis
3. Diagnosis is based on ICD code
Korean cancer incidence rates

Age-standardised cancer incidence rate (Korean population)

Korean cancer incidence rates (females only)

Age-standardised cancer incidence rate (Korean population)

Other cancers Thyroid cancer

Deterioration driven by the experience of thyroid cancer: 22% deterioration per annum during 1999 - 2012
Thyroid cancer experience in Korea

• South Korea has the highest incidence of thyroid cancer worldwide
• A 2009 study found that 13.2% of adults had undergone screening by thyroid ultrasonography at some stage (8.4% amongst men, 16.4% amongst females)
• Only 21.6% of women who underwent screening did so because they had experienced abnormal symptoms
• “In South Korea, thyroid cancer makes up a significant proportion of Critical Illness claims. Mortality from papillary thyroid cancer is very low, but prevalence is approximately 10% (based on post-mortem studies). People are having ultrasounds after buying a critical illness policy and then claiming.”


Long-term guaranteed cancer products in Korea sold around the year 2000

Loss ratios of cancer diagnosis products

<table>
<thead>
<tr>
<th>Year</th>
<th>0%</th>
<th>20%</th>
<th>40%</th>
<th>60%</th>
<th>80%</th>
<th>100%</th>
<th>120%</th>
<th>140%</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY 2003</td>
<td></td>
<td></td>
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<tr>
<td>FY 2004</td>
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<td></td>
</tr>
<tr>
<td>FY 2005</td>
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</tr>
</tbody>
</table>

Pricing
Based on historic company experience
Limited consideration for future trends
Cap on safety loading

Advancement in diagnostic techniques

Causes of losses

Informal screening campaigns

Guarantees

FSS Korea, 2006
Is the Korean thyroid cancer experience unique?

European Age-Standardised Thyroid Cancer (C73) Incidence Rates
Great Britain

Rate per 100,000


Males
Females

Source: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/thyroid/incidence/

Is the Korean thyroid cancer experience unique?

Thyroid Cancer (C73) Incidence Rates
China

Rate per 100,000


Males
Females

Gen Re, 6th DD Survey 2008 - 2012
Prostate cancer incidence rates
- United States -

64.6% of the eligible male population in the US reported getting a PSA test in the previous 12 months in 1999. Average annual decline of -3.6% from 1999 until 2010.

Prostate cancer incidence rates
- United States, Japan and Korea -

Annual report of cancer statistics in Korea in 2013, http://ganjoho.jp, SEER, Gen Re research
Extent of undetected prostate cancer

- Lifetime risk of clinical prostate cancer diagnosis: 9 out of 100 men
- Lifetime risk of latent prostate cancer detected by PSA screening: 4 out of 100 men
- Lifetime risk of latent prostate cancer not detected by PSA screening: 23 out of 100 men

Cancer diagnostics today...

• Tissue biopsy for solid cancers

• Staging systems:
  • T – tumour size
  • N – lymph node involvement
  • M – metastases

• TNM status determines group staging I-IV

... and tomorrow?

“Lucy, a mix between Labrador Retriever and Irish Water Spaniel, ... has learned the art of sniffing including bladder, kidney and prostate cancer. CNN reports that she has been doing way better compared with some lab tests when detecting cancer with an astonishing 95% accuracy rate.”

The Science Times (www.sciencetimes.com), Dogs Sniff Out Cancer With 95% Accuracy, According To Study, 23 Nov 2015
... and tomorrow?

Liquid Biopsy

- Circulating tumour DNA
- Circulating tumour cells
- Circulating RNA
- Autoantibodies
- Improved imaging (MRI) with tracers

Cell-free circulating tumour DNA (ctDNA)

DNA fragment

- Virtually all cancers carry somatic DNA mutations which make human tumours grow and progress.
- The somatic DNA mutations develop during a person's lifetime.
- The somatic mutations are only present in tumor cell DNA.

Dying tumours cells release DNA fragments that circulate in the bloodstream

- Analyse DNA fragments circulating in the bloodstream
- Testing for ctDNA involves finding known mutations

Bettegowda et al., Detection of Circulating Tumor DNA in Early- and Late-Stage Human Malignancies, Sci Transl Med. 2014 February 19; 6(224)
Circulating tumour DNA (ctDNA)

**Results**

- In a study, scientists found ctDNA mutations...
  - ... for 82% of patients with metastatic solid tumour outside the brain
  - ... for 55% of patients with early stage cancer
- Result varied with tumour type
- Concentration of ctDNA mutations increases as the cancer stage increases
- Survival rate decreases as ctDNA concentration increased

**Main applications**

- Shown to be more useful in cancer caused by viruses
  - Nasopharyngeal cancer – Ebstein Barr
  - Hepatocellular cancer – Hepatitis B
- Used to determine how advanced the cancer is
- Monitor tumour progression
- Test whether a patient’s tumour responds to treatment

**Circulating tumour cells (CTC)**

- It is estimated that CTCs are shed from solid tumours at a daily rate of 3.2 to $4.1 \times 10^6$ per gram of tissue
- Half of the CTCs perish within 2.4 hours
- Cancer patients have only between 5 and 50 CTCs per teaspoon of blood

Since their first description in 1869, a multitude of studies have provided evidence for CTCs in the blood of cancer patients
Circulating tumour cells (CTC)

**Results**

In studies, scientists found that

- CTCs are found in 36% of specimens taken from metastatic carcinoma patients, but almost never in healthy women and women with non-malignant disease.
- CTC# predicts prognosis in breast, prostate and colorectal cancer.
- Change in CTC# following initiation of therapy demonstrates predictive value for survival outcome.

**Main applications**

- Track the severity of a cancer
- Test whether a patient’s tumour responds to treatment

CTC# is expressed per standard 7.5 ml blood.


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**Circulating tumour cells (CTC)**

ASCO: American Society of Clinical Oncology
NACB: National Academy of Clinical Biochemistry
AACC: Academy of the American Association for Clinical Chemistry
AJCC: American Joint Committee on Cancer
FDA: Food and Drug Administration

2004

CellSearch was introduced, which is the only medical device currently cleared by the FDA for CTC based cancer diagnosis.

2007

ASCO decided not to recommend the CellSearch CTC test for the diagnosis of metastatic breast cancer or patient management.

2009

NACB & AACC declined to recommend various CTC assays for screening, detecting, and monitoring prostate cancer metastasis.

2010

The Breast Cancer Task Force did not incorporate CTCs into the TNM staging system based on input from AJCC.

CTC testing is still investigational and should be utilised with caution and only in specific clinical settings.

There is emerging evidence that tumour cells release substantial amounts of RNA into the bloodstream that strongly resist RNases in the blood and are present at sufficient levels for quantitative analyses.

What is in plasma?
- Cell-free DNA
- microRNA
- Exosome vesicles
- Proteins
- Metabolites

Extracellular circulating mRNAs are subjected to degradation, instability, low abundance, and intracellular mRNA contamination from specimen processing.

Widespread inconsistencies have been observed among studies.

Further steps of validation and standardisation of all procedures is required before translation into clinical practice.
Autoantibodies

- Autoantibodies can be detected up to 5 years before the tumours are detectable using diagnostic-imaging procedures such as CT\(^1\),\(^2\)

- A significant body of literature reports the presence of autoantibodies against cancer antigens in the bloodstream of cancer patients for lung, breast, cervical, and colorectal cancers\(^3\).

- These autoantibodies are produced in response to the presence of certain by-products from cancer cells.

\(^{1}\) Zhong et al, Profiling Tumor-Associated Antibodies for Early Detection of Non-small Cell Lung Cancer, Journal of Thoracic Oncology • Volume 1, Number 6, July 2006
\(^{2}\) Oncimmune Limited, www.oncimmune.com
\(^{3}\) Peek, Immunology for detection of early-stage, www.mlo-online.com, October 2010

Autoantibodies

- Recently one company has promoted using immunochemistry for early lung cancer detection even in stage I and stage II.
  - This is being piloted in Scotland as a first stage screening test in the higher risk population.
  - There are plans to use similar techniques in colorectal and ovarian cancers.
  - However the cost of this test has been unfavourably compared to that of screening with spiral CT scanning.
Improved imaging (MRI) with tracers

- Metabolism of cancers is different to ‘normal’ tissue
- When certain cells become cancerous, they shed sugar molecules from their outer membranes
- Johns Hopkins researchers create a cancer detection method using MRI
- Only tested on lab-grown cells in animal experiments

Source: Song et al, Label-free in vivo molecular imaging of underglycosylated mucin-1 expression in tumour cells, NATURE COMMUNICATIONS | DOI: 10.1038/ncomms7719

... and tomorrow?

Liquid Biopsy

- Circulating tumour DNA
- Circulating tumour cells
- Circulating RNA
- Autoantibodies
- Improved imaging (MRI) with tracers

Most successful
Most successful
Research
Research
Possibly higher potential for breakthrough
The pricing actuary’s challenge in Critical Illness insurance

- Estimate expected claims in line with the severity criteria (exclusions) used in the definition set out in the policy wording
- Take into account expected trends in Critical Illness claims
- Consider the whole policy duration
- Reflect any guarantees built into the product
Proportion of policies with guaranteed rates for the whole policy duration

- China
- Hong Kong
- Malaysia
- South Korea
- Indonesia
- Australia
- Singapore

Gen Re, 6th DD Survey 2008 - 2012

Medical progress
- Better diagnostic techniques
- Medical community working hard on earlier diagnosis
- The understanding of diseases and their causes evolves

Impact on Critical Illness insurance
- Impact on definitions
- Impact on claims experience
Impact on Critical Illness definitions

- Insurers are dependent on medical terminology, tests and diagnostic systems
- Current requirements can become obsolete
- Clinical description is a constantly “moving target”
- Pace of scientific change
  - More sensitive tests / machines will continue to diagnose earlier
  - Screening will detect unexpected levels of disease
  - Incidental investigations find things that would never have become clinically apparent
- New definitions reflecting updated medical status quo
  - Can be at the same level of the original intention
  - Is often under pressure to offer more generous cover

Changes in Definitions

- Stroke
  - Definition of Transient Ischaemic Attack (TIA) has changed in medicine => now based on a tissue-based definition, i.e. the presence or absence of tissue injury
  - TIA explicitly excluded under Stroke definition of Critical Illness policies
- Heart Attack
  - The preferred markers of myocardial injury changed from cardiac enzymes (CK-MB) to troponin
Impact on claims experience

- New types of evidence will be collected in claims department:
  - Are these valid claims?
  - What if new diagnostic results are provided but not the ones required per definition?

- Potentially
  - more claims?
  - earlier claims?

- How to quantify the impact?

Implications for incidence rates – Heart attack

- Current diagnostic threshold for Myocardial Infarction
  - 99th centile where assay precision can be shown with a coefficient of variation of ≤10% at this concentration

- Newly recommended diagnostic threshold for Myocardial Infarction
  - 99th centile for current sensitive troponin assays irrespective of whether the coefficient of variation is less than 10% at this concentration

- Increases the diagnosis of myocardial infarction by 47%

Mills et al, Implications of lowering threshold of plasma troponin concentration in diagnosis of myocardial infarction, BMJ 2012;344:e1533
Implications for incidence rates - Stroke

• The revised definition implies that some events that would have been previously called TIAs become strokes under a ‘Tissue based’ definition

• In the United States, tissue-based definition of TIA influences the annual incidence rate as follows:
  • Number of TIAs reduces by 33%
  • Number of Strokes increases by 7%

• But diagnosis requires scanning to prove tissue damage

Quantification of the impact in the context of Critical Illness Insurance

• Medical papers with advanced analyses of a new technology give some idea about the impact, but not all events may be valid claims for a Critical Illness policy

• The clinical definition is often different from the definition in the Critical Illness policy

• Concurrent effects, e.g. decreasing trend for cardiovascular diseases due to changes in smoking behaviour, may obscure impact of new diagnostic tools

Even with detailed medical research on its impact in a clinical setting, it is difficult if not impossible to quantify the impact on Critical Illness Insurance claims
The Oracle of Delphi

Interviews were held with leading experts in cancer research from:

- Germany
- Hong Kong
- Taiwan
- United Kingdom
- United States

and a panel of Dread Disease claims experts from Gen Re
The Oracle of Delphi - Observations

- New tests are in the vast majority performed after a positive cancer diagnosis based on conventional methods
  - Improving the outcome for cancer patients is the main motivation
- “Liquid biopsy” tests are not useful for screening at this stage and experts believe that this remains a long way off
- Current research is in the majority tailored to specific cancer sites – and there is no promising “catch-all” technique in the pipeline
- Research on patients with early-stage cancer has started, but
  - results could not be reproduced yet and
  - the value of currently available tests still needs to be confirmed

The Oracle of Delphi - Outlook

- Histopathology is unlikely to be replaced as the gold-standard in cancer diagnosis within the next 20 years
- A new test may replace the existing gold-standard only if the new test provides added value, i.e. more detailed information on staging and/or adequate treatment
- Application in population screening requires evidence for
  - Accuracy
  - Cost effectiveness
  - Available treatment for additionally detected cancers
- It can be expected that liquid biopsy tests will be offered in the private sector in view of...
  - Quickly dropping cost of DNA sequencing and
  - The amount of venture capital flowing into private biotech companies
The Oracle of Delphi - Concerns

• Additional diagnoses of minute asymptomatic, possibly dormant, cancers that are not diagnosed today, but which could be diagnosed with new technology
• There might be implications for severity based cancer products in the future if new technology influences the staging and alters the current TNM staging system
• Tests offered by biotech companies in the private sector, which could be of interest for high-net worth individuals who actively manage their health and cancer insurance status

The Oracle of Delphi – Impact on claims under Critical Illness policies

• The first few single claims based on positive Liquid Biopsy tests only would most likely not be considered valid claims
• The more additional evidence is provided – such as imaging, chemotherapy or radiotherapy being initiated, a stage being assigned – the more difficult it will be to decline such claims successfully
• The pressure to pay claims based on positive Liquid Biopsy tests only would increase significantly if Liquid Biopsy is accepted as the gold standard
  • Most likely irrespective of the wording of the definition
Summary & Conclusion
Challenges in predicting medical progress long-term

1965
First commercial ultrasound “Vidoson” manufactured by Siemens Medical Systems of Germany with real-time pictures

2065
Tools that would today be considered science fiction?

- 50 years 2015 + 50 years

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More sustainable approaches to cover cancer?

• Changes to the cancer definition
  • Require tumour of minimum size or stage, life-threatening, treated with specified therapy
  • Explicitly exclude cancers detected by molecular or biochemical probes only
    • Evidence of cancer cells or cancer genetic material detected by molecular or biochemical probes only (including but not limited to proteomic or DNA/RNA-based techniques) with no lesion amenable to tissue diagnosis.
  • Require permanent impairment / disablement in addition

It is challenging to define what “Cancer” shall not cover in a Critical Illness policy

Inspired by a sketch in The Little Prince by Antoine de Saint-Exupéry

More sustainable approaches to cover cancer?

• Changes to the product design
  • Design products with a decreasing sum at risk
  • Pay an annuity whilst policyholder is disabled / treated
  • Reimburse cancer treatment cost
• Switch to reviewable premiums / benefits / definitions
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