



Institute  
and Faculty  
of Actuaries

# Cancer Diagnostics 2.0

## Implications for Insurers

by Karin Neelsen, Gen Re, Cologne

24 May 2016

“New cheap highly-accurate saliva test will tell you at home in just 10 minutes if you have cancer”<sup>i</sup> – such promising headlines in respect of saliva and blood tests appear in the tabloids on a regular basis. With such eye-catchers, the general public has been informed about promising medical research in the field of cancer diagnostics. Gen Re has conducted its own research within the medical community to look behind the – at times – rather simplified information played out in the media. The ultimate goal has been to gauge what these emerging techniques imply for pricing and claims handling in insurance, especially Critical Illness (CI) products where protection against the risk of cancer plays an important part. According to Gen Re’s Dread Disease survey<sup>ii</sup> and claims statistics provided by UK insurers, cancer is the cause of more than 60% of all CI claims.

The continued success of Critical Illness depends on whether we are able to establish effective risk management in the area of pricing, risk acceptance and claims management. In pricing we need to be able to forecast future claims rates with reasonable accuracy in a changing medical environment with its implications for which events meet the claim definition. In risk acceptance we need to mitigate the risk of anti-selection caused by asymmetric information due to availability of genetic testing. At the same time, the management of claims must be dealt with in a practical, cost-effective, transparent way and in line with what the customer expects when they submit their claim.

This article will describe new technology currently in development – focussing on circulating tumour cells (CTCs) or circulating tumour (or cell-free) DNA (ctDNA) testing for solid cancers – that certainly has an impact on cancer diagnosis: the way a cancer diagnosis is made itself is subject to change. The new technology may also lead to additional cancer claims or bring diagnosis forward in general. We can already observe changes to the way cancer is managed and treated and can expect further developments with respective consequences for the mortality of cancer patients and the impact this might have on mortality improvements.

While this is certainly something we need to keep an eye on, the new technologies are currently quite far from application as diagnostic tools. So far, research is vastly focussed on specific cancer sites with their different characteristics and no biomarker is expected to find each and every type of cancer.

## **Current cancer detection**

Currently, cancer is diagnosed or confirmed by histopathological evidence from a tissue sample extracted in a biopsy and examined under a microscope. This methodology is essential for diagnosis of almost all cancers, unless the tumour site means taking a tissue sample is too risky (for example, in the brain).

Results of the histopathology, together with physical examination and imaging tests, form the basis of cancer staging. Staging is the method of describing the extent to which a cancer has grown and spread, either locally or to distant sites in the body.

Staging systems, as described by the American Joint Committee on Cancer (AJCC) or almost identically by the Union for International Cancer Control (UICC), in the majority rely on tumour size, lymph node involvement and existence of metastasis. Could the overall characterisation of invasive cancer be overhauled with the advent of biomarkers offering a different type of information on cancerous cells? With the new technology just being in its infancy it is too early to make a prediction on the probability let alone the timing of such massive change.

## **New cancer diagnostics**

The most prominent emerging techniques are based on blood samples – often combined with DNA sequencing methods – referred to as “liquid biopsies.” These are targeted at finding CTSS or ctDNA.

## Circulating Tumour Cells

CTCs in the peripheral blood were first described in the 19th century.<sup>iii</sup> More recently, methods have been developed for detecting, isolating and characterising CTCs in multiple different cancers arising in solid organs. The stage at which a tumour may shed tumour cells in the bloodstream is not fully understood by medical scientists and is assumed to vary by tumour type, size and/or aggressiveness.

“CELLSEARCH” is the only technology to date that has been approved by the U.S. Food and Drug Administration (FDA) for evaluating CTCs in order to assess patient prognosis.

For advanced cancers, CTCs are present only in very low concentrations, e.g. 10-100 cells per millilitre of blood compared to more than 1 million white blood cells per millilitre of blood. Looking at the tests’ specificity, CTCs are rarely found in healthy people or in people with non-malignant tumours.<sup>iv</sup>

A significant part of samples from patients with metastatic carcinomas in various cancer sites showed no detectable CTCs, without clear evidence as to which factors – such as vascularisation of the tumour, sites of metastasis or aggressiveness of the tumour – had contributed to the wide range of results in number of detected CTCs.

The vast majority of publications discuss the application of CTC testing in patients with advanced cancers for improvement of treatment and prognosis, and one of the rare studies applying CTC testing as a diagnostic tool touched upon screening a high-risk group of 168 patients with chronic obstructive pulmonary disease (COPD) for lung cancer. CTCs proved to be useful sentinels for early detection of lung cancer in 3% of this high-risk group of patients.<sup>v</sup>

## Circulating Tumour DNA

ctDNA originates from tumour cells and can be found in the blood of a cancer patient. Testing for ctDNA provides opportunities for minimally invasive cancer diagnosis, prognosis and tumour monitoring. In the context of cancer, testing for ctDNA involves finding known mutations identical to those in common tumours. Cancer has heterogeneous genetic mutations that may alter at different stages.

While some common mutations can be searched for, ctDNA testing may miss the cancer DNA if the test is not specifically aimed at the mutation that exists at that time. The need to test for separate cancers means ctDNA is unlikely to be useful for screening all cancers. Abnormal cells commonly develop but can be killed by host immune cells. ctDNA may simply be part of this process rather than from any tumour that could ever be identified.

Testing for ctDNA is thought simpler than testing for CTCs because fewer technological adaptations are needed and sampling windows are longer.<sup>vi</sup> It is also a more sensitive marker since it is present in over 80% of advanced cancers, including in many patients in whom CTCs are not detectable. Another aspect is that there is more ctDNA than CTCs detectable in the blood of cancer patients. Most studies include numbers based on detectable ctDNA in people with advanced malignancies or tumours that are already large enough to be diagnosed easily using current techniques, again aiming at improved outcomes in these patients.

This early in the process of validating this new technology, one small study of patients with various cancer types found ctDNA in more than 75% of those with advanced pancreatic, ovarian, colorectal, bladder, gastroesophageal, breast, melanoma, hepatocellular, and head and neck cancers, but the study found ctDNA in less than 50% of primary brain, renal, prostate or thyroid cancers.<sup>vii</sup>

Trials of ctDNA are underway to predict hepatocellular cancer in hepatitis B virus carriers and to detect nasopharyngeal cancer in Epstein-Barr virus carriers.<sup>viii</sup> Here, however, the test only identifies the persistent virus associated with the cancer and not the cancer itself; histology is still required to confirm cancer diagnosis. Furthermore, for 20 out of 1,318 patients identified with persistent raised levels of ctDNA, only three were

diagnosed with nasopharyngeal cancer, the other 17 being false positive samples identified at the same time. Further research and trials are necessary in order to improve specificity and thus lessen the potential for overdiagnosis and creating unfounded anxiety in patients not actually in need of treatment.

## Ready for use in diagnosis?

It is important to be clear that none of the new tests has been tailored to cancer diagnosis. The vast majority are being applied to patients whose cancer diagnosis has already been made with conventional methods. The goal in using the new technology is therefore to improve outcomes in cancer patients and this will remain the focus for the near future.

Despite this clear focus, media attention has been on the tests' potential as diagnostic tools. Clearly, the idea of a simple blood test to find cancer is appealing, in contrast to the often burdensome requirement for a tissue biopsy. A rush of companies is offering new blood-based cancer tests – unsurprising as the global market for CTC testing alone is estimated to be worth \$11.55 billion by 2022.<sup>ix</sup> An inevitable degree of hype surrounds manufacturers' claims, and while press releases fuel consumer enthusiasm, they also help generate investment for the companies involved.

With the tests being predominantly applied to patients with established cancer, research is just starting on patients who have early-stage cancer, but it is not clear if the currently available tests will prove to have any value. A liquid biopsy is not useful for screening at this time, because the test accuracy is unknown, with experts arguing that this remains a long way off.

In summary, the majority of current research and biomarkers up for testing are highly tailored to the cancer site; no promising "catch-all" technique is in the pipeline. While some correlation between positive results of blood tests and tumour size appears to exist, the influential factors for the outcome of any such test are not yet fully understood.

## Challenges and opportunities for the insurance industry

The current ABI definition of cancer (excluding less advanced cases) requires the finding of "any malignant tumour positively diagnosed with histological confirmation and characterised by the uncontrolled growth of malignant cells and invasion of tissue"<sup>x</sup>. Discussions with medical experts show a consensus amongst them that histopathology is most unlikely to be replaced as the gold standard in cancer diagnosis in the near future. This is expected to change only if and to the extent that new diagnostic means provide added value, i.e. more detailed information on staging and/or adequate treatment.

Even if the technology is available, its wide application is not necessarily a certainty. To be used in population screening in the context of national health systems, any of these tests will have to successfully pass high hurdles in terms of evidence-based accuracy, cost-effectiveness and treatability of additionally detected cancers, which experts expect to take probably around 15 years based on the need for large scale population studies.

There is evidence of a desire by the NHS to embrace new technology like this. For instance, the NHS England cancer strategy aims at "...rolling out a molecular diagnostic service [...] enabling more personalised prevention, screening and treatment;"<sup>xi</sup>. Clearly, this approach is based on the view early diagnosis reduces harm beneficially for patients, but may not fully reflect the risks to them of overdiagnosis and overtreatment.

While there is a clear statement that "the NHS should deliver molecular diagnostic testing to inform [...] screening [...] of cancer"<sup>xii</sup>, one also needs to take into account the severe budget constraints the service faces.

The technology is in its infancy so it is too soon to assess the potential for cancer diagnosis in the public sector where high hurdles for test effectiveness and cost-benefit ratios have to be met – in the private sector

however the outlook is different. The rapidly falling cost of DNA sequencing, combined with the amount of venture capital flowing into private biotech companies, will lead to tests being offered in the private sector with no such formal hurdles as in the public sector. Such tests could be of interest to high net-worth individuals who are effectively managing both their health and their insurance portfolios. These people might be more inclined to undergo such tests in exchange for a potential pay-out of the sum insured under their Critical Illness policy. Similarly, people might be more inclined to take out a policy after learning their risk or diagnosis from such a test. We need to monitor the uptake of such tests, which could prove popular in the broad population despite the doubtful tangible benefit and a high potential for anxiety.

## **What to expect for claims management?**

While these new technologies develop, it makes good sense to revisit the language of the CI benefit trigger, especially in a standard definition context, where changes to any definition can only be implemented after a comprehensive process of discussion and incorporation of feedback. In fact, already today we need to think about a potential future scenario where new tests may lead to vastly different evidence for cancer claims than what is common today. In the case of a cancer claim, how would a claims manager make a decision based on just a positive result of a liquid biopsy with confirmation by the attending physician that cancer is present?

As seen above, the standard cancer definition in the UK protection market requires uncontrolled growth, invasion of tissue and histopathological evidence, so the requirements of the definition would not be fulfilled when only a positive CTC or ctDNA test is presented. However, should liquid biopsies become the gold standard for cancer diagnosis and have proven excellent accuracy, this requirement may no longer be possible to uphold.

## **How to deal with implications for pricing?**

Current pricing assumptions are based on historical experience observed in the context of the historical diagnostic tools. The challenge is to phrase the definition in a way that ensures a similar level even with the advent of a new technology. Explicitly stating the intent of most of today's policies – to cover cancer of specified severity or critical cancer only, is supportive. It is also possible that further developments of the new technologies may come along with measurable thresholds, which could actually help the insurance industry in phrasing severity levels.

Scenarios are also imaginable where the majority of neoplasms are detected in very early – i.e. pre-malignant stages – and can be successfully treated so that eventually the burden of invasive cancers is reduced. This could actually have a positive effect on incidence rates and would improve mortality markedly.

The UK with its traditionally guaranteed premium rates in the protection market clearly faces a different challenge compared to other markets where reviewable premiums are the norm. Considering different scenarios of where the medical progress is heading, one could imagine one with cancer being detected more often or earlier than today. Probably additional or earlier cancers could be of minor severity only, but nevertheless could be valid claims under today's definition. Giving an indication as to the number of cases detected and being labelled "cancer" in the long run is not possible from the medical perspective due to the technological and also biological limitations of the new screening techniques and other unknowns. Thus, the challenge of defining a stable framework for cancer claims is with the insurance industry. In this context it has to be noted that even for new business, definitions cannot flexibly be adjusted to latest medical insights at the insurer level but adjustments are being discussed and agreed upon in a more formal process in the respective ABI committee.

## **Conclusion**

With cancer being the leading cause of claim under Critical Illness insurance, its diagnosis has the strongest impact on the insurers' experience. The new blood tests described here are still in their infancy but have the

potential to overhaul the diagnostic process – with yet unknown consequences for the frequency of cancer detection.

Much depends not only on continued technical progress of the new technology but also on how national health services will promote its use in combination with existing screening programmes and how availability and take up is in the private sector. Even if the diagnostic approach does not undergo dramatic change immediately it is possible that a different level of cancer incidence rates than that we currently observe will emerge in future.

In CI it is important to review disease definitions regularly, adjusting them to the highest standard in terms of being future-proof and following objective, measurable severity criteria. Already more generous ABI+ definitions are widely available in the UK market and this makes appropriate severity criteria important to prevent the cover shifting from substantial support on incidence of a life-threatening disease to a pay-out for incidental findings of an asymptomatic one. Allowing for such a potential shift in pricing could render CI products unaffordable as common minor diseases could be covered that might not have been priced for and where no substantial insurance need exists. Applying in-depth expertise to assess the progress in cancer diagnostics will allow insurers to continue to offer the fullest range of living benefits to those most in need of financial support following a serious illness.

---

<sup>i</sup> Daily Mail Online, <http://www.dailymail.co.uk/health/article-3446428/New-cheap-highly-accurate-saliva-test-tell-home-just-10-minutes-cancer.html>, accessed on 17.03.2016

<sup>ii</sup> Lu, J., Droste, W. “Gen Re’s Dread Disease Survey 2004–2008” in Topics No. 20, [http://media.genre.com/documents/Topics20\\_Lu\\_Droste-en.pdf](http://media.genre.com/documents/Topics20_Lu_Droste-en.pdf)

<sup>iii</sup> Ashworth, T. R (1869). “A case of cancer in which cells similar to those in the tumours were seen in the blood after death...” Australian Medical Journal 14: 146–7.

<sup>iv</sup> Allard, W.J. et al (2004) “Tumor Cells Circulate in the Peripheral Blood of All Major Carcinomas but not in Healthy Subjects or Patients with Nonmalignant Diseases”, American Association for Cancer Research, 2004, Vol.10, 6897–6904.

<sup>v</sup> Ilie M., Hofman, V., Long–Mira, E., Vignaud, J.M., Padovani, B., Mouroux, J., Marquette, C.–H., Hofman, P. (2014) “‘Sentinel’ Circulating Tumor Cells Allow Early Diagnosis of Lung Cancer in Patients with Chronic Obstructive Pulmonary Disease”, PLOS One 2014; Volume 9, Issue 10, e111597.

<sup>vi</sup> Schiffman, J.D., Fisher, P.G., Gibbs, P. (2015) “Early Detection of Cancer: Past, Present, and Future“, 2015 ASCO Educational Book, 57–65.

<sup>vii</sup> Bettegowda et al (2014) “Detection of Circulating Tumour DNA in Early– and Late–Stage Human Malignancies” Sci Transl Med. 2014 February 19; 6(224): 224ra24.

<sup>viii</sup> Chan K.C. A. et al. (2013) “Early Detection of Nasopharyngeal Carcinoma by Plasma Epstein–Barr Virus DNA Analysis in a Surveillance Program”, Cancer 2013;119:1838–42.

<sup>ix</sup> <http://www.grandviewresearch.com/press-release/global-circulating-tumor-cells-market> accessed on 17.03.2016

<sup>x</sup> ABI Statement of Best Practice for Critical Illness Cover, December 2014, [https://www.abi.org.uk/~/\\_media/Files/Documents/Publications/Public/2014/Protection/Statement%20of%20Best%20Practice%20for%20Critical%20Illness%20Cover%20Dec%202014.pdf](https://www.abi.org.uk/~/_media/Files/Documents/Publications/Public/2014/Protection/Statement%20of%20Best%20Practice%20for%20Critical%20Illness%20Cover%20Dec%202014.pdf) accessed on 17.03.2016

<sup>xi</sup> Achieving World–Class Cancer Outcomes – A Strategy for England 2015–2020, p. 5, [http://www.cancerresearchuk.org/sites/default/files/achieving\\_world-class\\_cancer\\_outcomes\\_-\\_a\\_strategy\\_for\\_england\\_2015-2020.pdf](http://www.cancerresearchuk.org/sites/default/files/achieving_world-class_cancer_outcomes_-_a_strategy_for_england_2015-2020.pdf) accessed on 17.03.2106

<sup>xii</sup> Achieving World–Class Cancer Outcomes – A Strategy for England 2015–2020, p. 72, [http://www.cancerresearchuk.org/sites/default/files/achieving\\_world-class\\_cancer\\_outcomes\\_-\\_a\\_strategy\\_for\\_england\\_2015-2020.pdf](http://www.cancerresearchuk.org/sites/default/files/achieving_world-class_cancer_outcomes_-_a_strategy_for_england_2015-2020.pdf) accessed on 17.03.2106



# Institute and Faculty of Actuaries

**DISCLAIMER** The views expressed in this publication are those of invited contributors and not necessarily those of the Institute and Faculty of Actuaries. The Institute and Faculty of Actuaries do not endorse any of the views stated, nor any claims or representations made in this publication and accept no responsibility or liability to any person for loss or damage suffered as a consequence of their placing reliance upon any view, claim or representation made in this publication. The information and expressions of opinion contained in this publication are not intended to be a comprehensive study, nor to provide actuarial advice or advice of any nature and should not be treated as a substitute for specific advice concerning individual situations. On no account may any part of this publication be reproduced without the written permission of the Institute and Faculty of Actuaries.

## **London**

7<sup>th</sup> Floor · Holborn Gate · 326-330 High Holborn · London · WC1V 7PP  
Tel: +44 (0) 20 7632 2100 · Fax: +44 (0) 20 7632 2111

## **Edinburgh**

Maclaurin House · 18 Dublin Street · Edinburgh · EH1 3PP  
Tel: +44 (0) 131 240 1300 · Fax: +44 (0) 131 240 1313

## **Oxford**

1<sup>st</sup> Floor · Park Central · 40/41 Park End Street · Oxford · OX1 1JD  
Tel: +44 (0) 1865 268 200 · Fax: +44 (0) 1865 268 211

## **Hong Kong**

2202 Tower Two · Lippo Centre · 89 Queensway · Hong Kong  
Tel: +11 (0) 852 2147 9418 · Fax: +11 (0) 852 2147 2497

[www.actuaries.org.uk](http://www.actuaries.org.uk)

© 2013 Institute and Faculty of Actuaries