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Cancer Diagnostics 2.0 – What Does It Mean for Insurers?

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The general media has drawn a lot of attention to promising medical research in the field of cancer diagnostics. Headlines proclaiming the availability of new "simple blood tests" to diagnose tumors have appeared on a regular basis.[1] Gen Re has conducted its own research within the medical community to investigate the—at times—rather simplified information played out in the media. The ultimate goal has been to gauge what these emerging techniques imply for insurance, especially Critical Illness (CI) products where protection against the risk of cancer plays an important part.

A rush of companies are offering new blood-based cancer tests—unsurprising as the global market for CTC testing alone is estimated to be worth $2.28 billion by 2020.

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 circulating tumor cells (CTCs), circulating tumor DNA (ctDNA) or microRNA/exosomes in the blood. Another method that has received attention is refined imaging technologies, such as MRI scans, allowing differentiation of normal and cancerous cells.

This article will not only describe the medical background and implications of new technologies—focusing on solid cancer detection—but also take a look at the broader picture of what CI insurance is all about, and what needs to be taken into account for continuously offering a successful protection for major diseases.

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 tumor 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 tumor size, lymph node involvement and existence of metastasis. Could this be overhauled with the advent of biomarkers offering a different type of information on cancerous cells?

In any cancer diagnostic tool, it is essential that the assays identify all existing cancers (sensitivity) and do not show positive results in healthy cancer-free patients (specificity). Poor sensitivity makes any assay inapplicable for diagnosis, whereas poor specificity may lead to overdiagnosis and potentially overtreatment in otherwise healthy patients.

NEW CANCER DIAGNOSTICS

It is important to be clear that none of the new tests have 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 are offering new blood-based cancer tests—unsurprising as the global market for CTC testing alone is estimated to be worth $2.28 billion by 2020.[2] 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. The other detection techniques are even less advanced.

In sum, 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 tumor size appears to exist, the influential factors for the outcome of any such test are not yet fully understood.

CIRCULATING TUMOR CELLS

Circulating tumor cells (CTCs) in the peripheral blood were first described in the 19th century.[3] More recently, methods have been developed for detection, isolation and characterizing CTCs in multiple different cancers arising in solid organs. The stage at which a tumor may shed tumor cells in the bloodstream is not fully understood by medical scientists and is assumed to vary by tumor type, size and/or aggressiveness.

With "CELLSEARCH," so far one technology has been approved by the U.S. Food and Drug Administration (FDA) for evaluating CTCs in order to assess patient prognosis or predict progression-free and overall survival.

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 sensitivity and specificity, CTCs are rarely found in healthy people or in people with non-malignant tumors.[4]

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 vascularization of the tumor, sites of metastasis or aggressiveness of the tumor—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 only two available 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 percent of these COPD patients.[5]

CIRCULATING TUMOR DNA

Circulating tumor (or cell-free) DNA (ctDNA) originates from tumor cells and can be found in the blood of a cancer patient. Testing for ctDNA provides opportunities for minimally invasive cancer diagnosis, prognosis and tumor monitoring. In the context of cancer, testing for ctDNA involves finding known mutations identical to those in common tumors. 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 tumor 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.[6] It is also a more sensitive marker since it is present in over 80 percent 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 tumors that are already large enough to be diagnosed easily using current techniques, again aiming at improved outcomes in these patients.

Revisiting sensitivity and specificity, a study of patients with various cancer types found ctDNA in more than 75 percent 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 percent of primary brain, renal, prostate or thyroid cancers.[7]

Trials of ctDNA are underway to predict hepatocellular cancer in hepatitis B virus carriers and to detect nasopharyngeal cancer in Epstein-Barr virus carriers.[8] 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.

MICRORNA AND EXOSOMES

In the recent past, both microRNA and exosomes have emerged as a promising field of research in cancer diagnosis, prognosis and therapeutics. Exosomes, which are small vesicles involved in the process of breaking down metabolic waste, act as shuttles for bioactive molecules, such as microRNA, between cells. Research suggests that tumor cells release excessive amounts of exosomes, potentially influencing tumor growth or building of metastases. There is evidence that exosomes play critical roles in almost all aspects of cancer, such as transformation of normal cells into cancer cells, tumor growth or tumor metastasis, thus having some potential as diagnostic biomarker.[9] The majority of circulating microRNA is concentrated in the exosomes. Also, the circulating microRNA itself could be a promising non-invasive biomarker. Studies in both areas, however, suggest that the exact mechanisms and complex roles of exosomes and microRNA in cancer development need to be explored further "for the proper use of … biomarkers in evidence-based medicine."[10] Given the early stage of research in the context of exosomes and microRNA, there is as of yet no information on their accuracy.

REFINED IMAGING TECHNOLOGY

Imaging technology can detect tumors, but for distinction between benign growth and cancerous tissue, a biopsy is typically required. A recent study suggests that fine-tuned MRI scanning could one day make at least some biopsies unnecessary.

Researchers show that imaging can detect sugars attached to a particular protein, allowing for normal and cancerous cells to be differentiated. The technology is at a very early stage and has so far only been tested with lab-grown cancer cells and mice.

To show if the technique has any value in human cancer diagnosis requires "much more testing."[11,12]

CHALLENGES AND OPPORTUNITIES FOR THE INSURANCE INDUSTRY

Current terms and conditions of CI policies covering cancer typically require the finding of malignant cells characterized by uncontrolled growth and spread, confirmed through histopathological evidence. The medical experts are in agreement 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.

While these new technologies develop, it makes good sense to revisit the language in CI benefit triggers and consider a future 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?

Certainly, cancer definitions in the insurance context require uncontrolled growth, invasion of tissue and histopathological evidence, so the requirements of the definition would not be fulfilled in the circumstances described above. 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.

On the other hand, further developments may come along with measurable thresholds, which could actually help the insurance industry in phrasing severity levels, according to the intent of

most of today's policies—to cover cancer of specified severity or critical cancer only. 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.

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 take high hurdles in terms of evidence-based accuracy, cost-effectiveness and treatability of additionally detected cancers, which experts expect to take quite some time based on the need for large scale population studies.

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 and could thus 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 payout of the sum insured under their Critical Illness policy.

The AJCC staging of cancer has taken "circulating cells" into account for breast cancer staging. An additional category has been created, supplementing the current distinction between metastases present (M1) or not present (M0) by "M0(i)," which is defined by the presence of circulating tumor cells. While there has been no change to the overall group staging applied, it is not certain this will remain unaltered in the future. Application of higher group stages, based on additional information gained through the blood tests, could thus have an immediate impact on tiered products where the benefit amount is directly linked to the stage at diagnosis.

CONCLUSION

Cancer is the leading cause of claim under Critical Illness (CI) insurance, which means its diagnosis has the strongest impact on the insurers' experience. The new 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 the continued technical progress of the new technology, but also on national health systems using it in combination with existing screening. Even if the diagnostic approach does not undergo dramatic change immediately it is possible that a very different level of cancer incidence rates than that we currently observe will emerge in the 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. The latter in particular prevents the cover shifting from substantial support after survival of a life-threatening disease to a payout for incidental findings of an asymptomatic one. A shift like this could render CI products unaffordable as common minor diseases are being covered where no substantial insurance need meets significant benefit pay-outs.

Pricing should allow for the level of uncertainty being outlined here, be it by offering cover on a reviewable basis only or by including additional margins commensurate with the associated risk. Applying 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. ■

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ENDNOTES

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