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The Expert Forum on Cancer Diagnostics brought together international experts from diverse fields to engage in wide ranging discussions and debates with Swiss Re experts on the potential impact novel diagnostic techniques, such as liquid biopsy, may have on the insurance industry’s critical illness book of business. Similar to other new diagnostics introduced into clinical practice, liquid biopsies have the potential to increase cancer incidence rates and affect the number of critical illness or standalone cancer product claims. With cancer diagnosis being a leading cause of claim under critical illness insurance, this could have a substantial impact on the experience of the insurance industries’ critical illness portfolio.

The morning session focused on cancer biomarker technologies, while the afternoon sessions focused on advances in imaging techniques and the regulatory environment for cancer diagnostics.

The take-home message from the morning session was that the use of liquid biopsies for early detection of cancer is still in its infancy and more clinical validation is needed before it can be used in supporting cancer diagnosis and screening. Current applications of liquid biopsy in clinical practice include monitoring of minimal residual disease, disease prognosis, drug response and development of treatment resistance, and the identification of genetic determinants for targeted therapy. For the foreseeable future the standard for diagnosing cancer remains traditional tissue biopsy.

The take-home message from the afternoon session was that imaging technologies play a vital role in locating and staging cancer. This is needed for deciding best treatment options and for monitoring recurrences. The speakers highlighted the fact that imaging techniques play an important role in the early detection for mainly breast and lung cancer. However, even state-of-the-art imaging techniques have limited ability to be used alone for early cancer diagnosis, but when combined with other diagnostic tools, such as liquid biopsy, diagnostic sensitivity and specificity could be greatly increased.

To conclude, new cancer biomarkers and imaging technologies are extremely useful in the treatment, prognosis and surveillance of cancer. However, no tumour marker or imaging technology identified to date is sufficiently sensitive or specific to be used on its own for early detection of cancer. Tissue biopsy remains the standard for diagnosing cancer in the foreseeable future.

Christoph Nabholz
Head Life & Health Research & Development
Swiss Re
Introduction

A broader understanding of less-invasive new methods for detecting cancer is important for Swiss Re’s business. The topic is particularly relevant for critical illness insurance, which offers financial protection against severe illnesses such as cancer, heart attack, and stroke.

In 2012, critical illness insurance represented 13% of Swiss Re’s new business, but this sector is growing rapidly, with an expected share of 23% by 2019. Key risk drivers for our critical illness portfolio include 1) medical developments that identify critical illnesses earlier; 2) operational risks arising from the accuracy and clarity of policy terms and conditions; 3) regulatory risk covering potential changes to legal interpretation of claim definitions; 4) behavioural changes such as changes in lapse rates or in propensity to claim; and finally, 5) risk of mispricing treaties.

In our Life & Health business, we are seeking ways to work with our clients to help close the protection gap and provide more security for individuals and their families. These forum discussions will help us prepare to write the right business at the right margins and allow us to fill an important need for consumers.

Russell Higginbotham
Head of Life & Health Products
Swiss Re
The future of early molecular cancer diagnostics and preventive immunotherapy

**Kenneth Bloom, President, Human Longevity Inc.**

Most cancers result from the acquisition of a variety of different mutations over the course of a lifetime. To predict the course of this complex disease, we must look at the regulation of many different pathways, including the immune system, said Kenneth Bloom.

With regard to cancer screening, most of our current theories assume that early detection will reduce mortality — that is, treating a cancer before it becomes invasive. And while uterine, colorectal, and breast cancers have had significant decreases in mortality over time, it’s unclear whether this is due to improved screening or better therapies. Of note: The incidence of breast cancer rose after the introduction of mammography, but the incidence of metastatic breast cancer is still relatively flat. “The question is: Have we provided a great benefit if the metastatic rate is about the same?” Bloom asked.

As oncologist Bert Vogelstein summarized in The New England Journal of Medicine last year, it take three strikes to form a cancer. The first phase is **breakthrough**: A single cell acquires a driver-gene mutation and begins to divide abnormally. During the second phase, **expansion**, a cell acquires a second driver-gene mutation and becomes a benign tumour. Finally, in the third phase, **invasive**, a cell acquires a third driver-gene mutation in at least one of the key pathways that allows it to invade the surrounding tissue.

![](Mutations_do_not_always_behave_the_same.png)

Mutations do not always behave the same

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<th>Phase</th>
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<th>Cervical Carcinoma</th>
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But as Bloom pointed out, assessing tumour DNA in the blood is not straightforward. Blood taken from a vein directly leaving a tumour looks wildly different than blood taken from a peripheral vein. Tumours shed dying cells into the bloodstream, but do you care about those cells, or cells that are still growing? he asked. And some of the most common cancer-associated mutations, such as TP53, can be present both in benign and invasive lesions. The science underlying two key questions — what are we measuring, and what are we going to do with it — still needs to be explored.

At this time, treating cancer with genetically targeted therapies is only somewhat effective. For example, if we give lung cancer patients with an EGFR mutation a drug targeted against that mutation, they do much better than patients given standard chemotherapy. But in other examples with different mutations and targeted drugs, overall survival is about the same. If you add more targets, you get better responses — but this adds significant toxicities, Bloom said.

Currently, the hot topic in cancer is immunotherapy, which has responses across a wide variety of different cancers and appears to have a broader impact on overall survival. Three drugs approved in the US are showing dramatic effects in some patients, and we have some diagnostic tests that can help determine who may respond. These treatments aim to predict which new cancer-related antigens are being recognised by your immune system and then re-engage that process. To do this, we create libraries from the tumour DNA and RNA sequences, identify the specific mutations, and grow them with the patient’s blood. You can then formulate a personalised vaccine against that individual’s cancer, said Bloom.
Liquid biopsies and the future of cancer detection

Nicola Aceto, Group Leader Department of Biomedicine, Cancer Metastasis, University of Basel

Nicola Aceto began with a brief overview of liquid biopsy — a test that looks for circulating tumour cells (CTC) or pieces of DNA from tumour cells (ctDNA) in the blood. A tube of whole blood contains about 50 billion red cells, 50 million white cells, and between 0 and 100 CTCs. There may only be one ctDNA fragment per 100 to 10000 fragments of normal DNA. But using different technologies, it is now possible to fish out both CTCs as well as ctDNA with great precision, he explained.

Aceto then described a success story using CTCs. Typically, oncologists give women with metastatic breast cancer a first-line therapy, which works for a while until the tumour develops resistance and returns. This happens again with second and third line therapies, which is then followed by several clinical trials, after which the patient dies. “The costs are very high, not just for the patient but for everyone, and the benefits are very low,” Aceto said.

Tumours constantly adapt to therapy, so choosing a treatment based on a tumour biopsy that was taken months or even years beforehand doesn’t work. Aceto and colleagues at Massachusetts General Hospital in Boston realised that CTCs offered an opportunity to overcome this issue. Culturing CTCs is inefficient but feasible, and mice injected with the cells grow tumours that retain the properties of the original tumour. Aceto’s team analysed 1 000 cancer-associated “hot spots” in CTC-derived cell lines from six women with metastatic breast cancer.

In theory, these women would have been treated the same way, but the mutational profile of their CTCs shows that they all had different mutations, Aceto explained. They then tested a panel of FDA-approved drugs that target different pathways and ended up with a defined map of responsiveness to every drug for every CTC-derived cell-line from those patients. “This was essentially the first example of how CTCs can be used in the context of personalised medicine to help oncologists define the best drug for a specific patient,” said Aceto.

Many centers are also using ctDNA as a diagnostic tool. Aceto showed data from 50 patients with metastatic non-small cell lung cancer treated at the Basel University Hospital, all of whom had detectable but extremely variable concentrations of circulating free DNA in their blood. They were able to identify mutations — often more than one — in most patients, including mutations not found in biopsies of the primary tumour. One man with lung cancer initially responded to EGFR-targeted therapy but then relapsed. A second sequencing of his tumour revealed additional mutations. He received immunotherapy, which worked for a while before the tumour returned again. He then was reluctant to provide additional lung biopsies. Yet several months later, they were able to sequence ctDNA in this patient and found a new EGFR mutation, which made him eligible for newer, third-generation EGFR-targeted therapy.

In summary, liquid biopsy is rapidly evolving as an accepted method for cancer diagnosis in patient stratification, said Aceto. Whether CTC and ctDNA can also be used to enable early cancer detection is up for discussion.
We are experiencing a massive change in medicine, driven by recent advances in information technology and genetics, said Vincent Mooser, noting that the cost of sequencing an entire genome has dropped to $1 000. “That this change will lead to an evolution is absolutely clear. Whether it will be a revolution remains to be seen,” he said.

Currently, the main application of these advances is focused on somatic mutations that occur in tumour cells, with liquid biopsy being one application. Liquid biopsies can help us understand on a molecular level why a cancer recurs, and the mechanism that led to resistance to the primary treatment. That knowledge will also help tailor the treatment for the relapse, said Mooser.

Mooser then broadened the discussion to germline genetics — that is, the genes you receive from your mother and father — and how germline mutations also impact cancer in terms of prediction, prevention, and tailored therapy. As an example, he noted the ‘Angelina Jolie’ effect, alluding to the actress’ much-publicised revelation of her inherited BRCA1 mutation. Soon, Mooser predicted, whole genome sequencing will be part of our medical records. Various scientific societies are working on ways to deal with the implications of these genetic findings, which will include cancer-causing mutations like BRCA1. For instance, the American College of Medical Genetics and Genomics has published recommendations for reporting incidental findings from clinical exome and genome sequencing. The paper lists 25 genes that cause familial forms of cancer and offers advice on how to deliver this information to patients.

But it’s fair to say that these familial forms of cancer only account for a fraction of all cancers, Mooser noted. The vast majority of cancers are far more complex, and there is a great deal of information about common genetic variants associated with cancer. However, this information does not appear to improve cancer prediction beyond the known risk factors, at least for prostate cancer, he said.

In anticipation of the coming age of genomic medicine, Mooser instituted a program at the University of Lausanne Biobank to systematically get consent to collect DNA from hospitalised patients. So far, 75% of the 35 000 patients contacted have consented to participate in the study, including more than 5 000 people 80 years of age and older. Nearly all (85%) of all the participants were interested in knowing about any clinically actionable findings in their genomes, according to Mooser.

In conclusion, said Mooser, the power of genomics will come from combining germline genomics and tissue genetics, including information from liquid biopsies. The clear added value of liquid biopsies will be in screening people who are at high risk because of their genetic makeup.
Advanced cancer diagnostics - a global medical perspective

Damian Page, Associate Group International Scientific Director, Roche

Cancer care has entered a new paradigm, Damian Page noted. It has evolved from the “one drug fits all” model of unspecified chemotherapy, which began prior to our understanding of the strong genetic drivers of cancer. But as scientists came to better understand the disease, they were able to discern different patient populations within one type of cancer. “We could then define the molecular change with a biomarker and develop a targeted drug together with a companion diagnostic,” said Page. The drug Herceptin, for HER-2 positive breast cancer, is probably the best example of this first paradigm of personalised medicine. But this is probably not going to be repeated that often, in light of all the complexity that we now see. Now, thanks to advances in genetic sequencing and information technology, it’s possible to have a comprehensive genomic profile for one patient and determine the best therapeutic options for that individual, said Page.

He then explained how Roche is addressing current limitations in cancer diagnostics. These limitations include insufficient tissue from biopsy samples, biomarkers that don’t provide sufficient information to reliably inform treatment decisions, and diagnostics that are not optimally automated or standardised.

In 2015, Roche entered a broad strategic collaboration with a molecular information company that is leading a transformation in cancer care called Foundation Medicine Inc. Their database and analytics interface captures high quality, standardised, automated molecular information from next-generation sequencing. This information improves patient care and outcomes by aiding treatment selection. But it also makes the company’s research and development smarter and more efficient, both by enhancing the molecular understanding of cancer, and by helping to match patients to clinical trials, said Page.

One example is FoundationOne, a clinical decision support tool for tissue-based sequencing. Instead of multiple, single-gene companion diagnostics, it uses a comprehensive panel of more than 300 gene alterations. Likewise, FoundationOneHeme analyses an even larger set of 405 genes known to play a key role in haematological malignancies.

FoundationACT, a liquid biopsy product, interrogates four classes of genomic alterations in 62 cancer-related genes frequently found in ctDNA. Like the other products, it is highly accurate, with 99% sensitivity and 99% specificity.

Going forward, Roche’s plan is to move toward comprehensive diagnostics for cancer immunotherapy as well as making blood-based monitoring a reality and broadly accessible for patients and physicians. “We are very interested in working together with all the stakeholders to reduce out-of-pocket spending,” said Page. Private insurance represents a key opportunity to enable patient access, he added.
Panel discussion on liquid biopsy in clinical practice

Christoph Nabholz, Head Life & Health Research & Development, Swiss Re
Kenneth Bloom, President, Human Longevity Inc.
Walter Weder, Professor, Clinic of Thoracic Surgery, University of Zurich
Robert Rubens, Oncologist, Swiss Re
David Lu, Deputy Regional Chief Medical Officer, Swiss Re
Bill Baker, Senior Product Expert EMEA, Swiss Re

To start the discussion, moderator Christoph Nabholz summarised Swiss Re’s key concern with respect to liquid biopsies. If these tests — which are currently available in clinics — are validated for early cancer diagnosis, this could affect the company’s critical illness insurance performance, as the result could trigger an early payout, he explained.

Kenneth Bloom asserted that while liquid biopsy may impact late stage cancer therapy, its role in diagnosing cancer is far more uncertain. “Getting reproducible results from tissue can be problematic, so when you don’t have a gold standard in tissue, how can you apply it to molecular techniques?” Molecular alterations can occur in benign lesions, and in some cases, more so than in malignant lesions, he added.

Robert Rubens agreed, noting that for critical illness, histological confirmation is a requirement. “By no stretch of the imagination can you say finding a molecule is equal to a histological diagnosis.”

These assessments were reassuring to Bill Baker. “From a critical illness perspective, I think that this isn’t ringing the alarm bells that some people have suggested.” For Swiss Re’s other products, where mortality is the risk, the news sounds good, although the impact of liquid biopsy on survival remains to be seen, he noted.

For critical illness, we’re typically focused on lives in the working age group rather than those at older ages, Baker said. Breast cancer is a big concern, as is prostate cancer, largely because of the suspicion that there’s a lot of undiagnosed prostate cancer. If someone comes up with a good test, there may be an increase in claims, he pointed out.
The UK market requires histological proof which is a stringent diagnostic condition, said Nabholz. But Asia is different, he noted, inviting David Lu to elaborate. There is no standard definition for a cancer diagnosis, and it varies depending on the different products and insurance companies, said Lu.

You should be more concerned about germline mutations, said Bloom. If you have a gene for an inherited cancer, it doesn’t say you’ll get the disease but rather predicts that you are at a higher risk. For example, a BRCA mutation would lead you to do testing other than mammography, such as an MRI. If you screen for prostate cancer with MRI, which is in vogue now, you’ll find lots of cancers in asymptomatic men. One study found a rate of 60%. “If I were paying claims on that, that figure would scare me,” said Bloom. Physicians don’t know what to do with these people because clearly, they don’t need to be treated. “Otherwise, the death rate from prostate cancer would be through the roof,” he said.

Walter Weder noted that even validated screening tools that save lives are not always adopted into clinical practice. For example, in certain high-risk groups, low-dose CT scans improve survival of lung cancer, but none of the European or Asian countries use this test. New gene tests, such as the Roche 62-gene panel, will cost six to eight thousand francs, but only a few patients will benefit from this information. “We’ve heard examples of fantastic treatment response, but with no impact on survival,” Weder said. The entire process, particularly with immunotherapy, is associated with enormous costs. “Until we develop new guidelines, it will be a challenge for the whole community,” he said.

Most of the forum participants believe that liquid biopsies will become a screening test for people with a risk factor for cancer within three to ten years. Also, it was noted that some commercial companies in Asia have started to sell liquid biopsy tests directly to consumers, without any professional medical involvement, confirming the trend.

Bloom expressed concerns about that possibility. “I can see that potentially doing more harm than good,” he said. You might deviate something that otherwise would have been a treatable cancer into an untreatable cancer, he pointed out. It’s possible that it might work, but we just don’t know. Cancer is not simple, he stressed.

Another discussion point focused on non-invasive prenatal testing (NIPT), which analyses fetal DNA circulating in a pregnant woman’s blood to check for a genetic problem in the fetus. What if the results suggest that the fetus is healthy but that the woman may have cancer? There are two published case studies of this happening, and cancers were confirmed after additional testing, said Bloom. But these tests aren’t sensitive enough to be used for screening. You don’t know how many women who come back with a negative screen but actually do have cancer, he pointed out. Statistically, we should have seen considerably more than the number reported. Most pregnant women in the US get NIPT. We can predict how many of them actually have cancer, and it’s significantly higher than the case reports, he said.
Big pharma companion diagnostics and the future of preventive immunotherapy for early stage cancers

Luigi Catanzariti, Former Executive Director & Senior Global Program Director Diagnostics, Novartis

Companion diagnostics, which reveal which patients are likely to benefit from a specific targeted drug, are now an integral part of the strategy for pharmaceutical companies, said Luigi Catanzariti. But this strategy comes with considerable challenges, because the diagnostic development piece and the drug development piece each have their own rules and regulations, he explained.

Despite these challenges, the pharmaceutical industry is quite optimistic about this evolution, particularly in oncology. As an example, Catanzariti showed the treatment responses for non-small-cell lung cancer drugs in phase III trials. The success rate was 31% from targeted drugs, but 62% if the drug choice was guided by a companion diagnostic.

However, the traditional sequential approach to testing fails if you run out of tissue, which is why pharmaceutical companies are now working with technology companies to create multi-test panels. The challenge is developing a standardised, distributable test to submit for FDA approval. While the FDA has released some guidance documents, the standards are not yet completely defined. “Keep in mind that some of these tests rely on a significant amount of software at the back end, which would also have to be approved, as well as approving an integrated system with the chemistry,” noted Catanzariti.

In the United States, you can’t even start certain clinical trials unless your companion diagnostic test is essentially approved — not in the market sense but in terms of its analytical validation, he pointed out. In global clinical trials, key opinion leaders and principal investigators don’t always appreciate that point.

As an example, testing for ALK mutations in lung cancer patients is routine in many regions around the world. In the US, however, the FDA wants to make sure that the efficacy of the drug is not a function of regional local testing variability and therefore selection. In a global trial, the positivity rate for rare indications like ALK will vary enormously depending on whether or not clinical sites do their own testing (pre-selection) prior to sending the samples to the central clinical trial lab. Some places may not do any testing for the clinical trial over low positivity rates that reflect the expected frequency of occurrence. Others will have relatively high positivity rates that can reach up to 50% because of local testing (enrichment) and the consequent dispatch of mostly positive samples to the central clinical trial lab for testing. Does that impact your clinical trial efficacy and possibly bias your clinical trial? Catanzariti asked. These are tricky regulatory questions that need to be addressed.

In the short run, traditional single-gene companion diagnostics will be increasingly integrated with new liquid biopsy sampling technologies, using circulating tumour cells (CTCs) and circulating-tumour DNA (ctDNA). This should move the field toward earlier detection, treatment, and monitoring for drug resistance, likely within two to five years, Catanzariti predicted.

He also anticipates that select next-generation sequencing technologies will meet strict regulatory requirements during that same time frame. The same goes for clinical validation for specific drugs in conjunction with tissue biopsies, CTC, and ctDNA.

Within a decade, he expects that all of these technical developments will converge, and with that, we’ll see the emergence of personalised tumour vaccines based on novel targets. This will allow us to detect and genetically map tumour evolution much earlier, and improve efficacy for companion diagnostic-based drug therapies.
Pierre Hutter began his talk with a quote from Steve Jobs, whose tumour genome was among the first ever to be fully sequenced. In 2007, Jobs said, “I’m either going to be one of the first to be able to outrun a cancer like this, or I’m going to be one of the last to die from it.” At that time, however, our understanding of molecular driver mutations and how they might inform treatment decisions was still in its infancy, said Hutter.

But a few years after the emergence of powerful genome sequencing platforms, the focus shifted to the enormous challenge of analysing and interpreting the massive and complex amount of data generated from these platforms. Addressing that challenge is the goal of Sophia Genetics, which Hutter and colleagues created five years ago. The company is currently working with more than 200 hospitals in 35 countries. By the end of 2016, they will have analysed 80,000 patients, Hutter said.

Sophia Genetics employs data-driven medicine, meaning that all the data the company collects helps to further enrich and fine-tune the artificial intelligence algorithms that are used to analyse the data, Hutter explained. Currently, the largest volume of data comes from inherited cancers. Other domains include cardiology, metabolism, and paediatrics.

Through a secure site, Sophia Genetics receives raw data directly from a hospital’s sequencing machine, which is then analysed and interpreted by their algorithms. Within two hours, the hospital receives a full display of all the identified genetic variants. For example, with BRCA1 and 2, the variants are classified into four major categories, ranging from most likely pathogenic to most likely benign. “By accumulating this enormous amount of data, we can constantly improve the capacity of the artificial intelligence that allows us to better interpret the variance at the end of the exercise,” said Hutter.

The samples are routed to more than 115 distinct pipelines that take into account the sample type (from blood or a tumour, for example) and other metrics, such as the specific technology and instrument used for the genetic analysis. The hospitals receive reports only after the performance reaches at least 99% for both sensitivity and specificity for all the genes included in the panel, Hutter explained.

One of Sophia Genetics’ new technologies, OncoPortal, features information on the treatment and prognosis for different variants of both solid and haematological cancers. The information, which is updated every four weeks, is classified based on disease and drug availability. For example, if you specify a tumour type and variant, you can see several treatment options, which you can click on to reveal more detail.

Currently, the company is analysing data from more than 5,000 patients per month and Hutter expects this number to rise sharply in the near future. A major goal of the company’s goal is to help oncologists in critical decisions. When faced with a new patients, said Hutter, “The main thing they would like to know is ‘Are there other patients who are similar to mine? How were they treated, and how did they respond to the various options?’”
Advancing treatment of cancer through advanced imaging technology

Hans Hofstraat, Head Innovation Research, Philips

At Philips, imaging technologies have a key role across the continuum of oncology care, starting with obtaining a confident diagnosis as early as possible, said Hans Hofstraat. Generally, diagnostic imaging is the first port of call, but you cannot determine whether a lesion is benign or malignant.

Getting the right piece of tissue during the biopsy is essential, and image-guided biopsy can help. So-called precision biopsy is a combination of magnetic resonance imaging (which shows changes in soft tissue) and ultrasound imaging, which can be done in real time, Hofstraat explained.

Imaging is also important for enabling minimally invasive therapy targeted to the precise tumour location, known as informed therapy guidance. This allows for precise placement of brachytherapy (internal radiation therapy using seeds or pellets).

Currently, Philips focuses on screening for early diagnosis and risk assessment for breast cancer (mammography) and lung cancer (computed tomography scans)—the only two imaging technologies that are currently reimbursed for screening.

Bringing screening and early diagnostics to the world of public health requires a great deal of work, Hofstraat noted. “To include liquid biopsy in that tool set, particularly if you want to have it reimbursed, will require an extensive clinical trial,” he said. The findings must prove the added value of the screening procedure and consider the implications throughout the entire health care system, he added.

Developments in imaging procedures, such as digital magnetic resonance imaging, digital positron emission tomography, and spectral computed tomography will lead to faster, more efficient imaging that is less costly per exam. These advances will help create more precise and searchable databases, which are amenable to radiomics, defined as the quantification of tumour phenotypes by applying a large number of image features. “Combined with outcome data, we will be able to do more precise outcome-oriented diagnostic imaging,” said Hofstraat. This is important from a clinical perspective, as the introduction of new technologies is entirely driven by value-based health care, he added.

A program Philips developed called OncoSuite provides minimally invasive, targeted cancer treatment. In liver cancer, for example, a technique called transarterial chemoembolisation can deliver chemotherapy directly to the tumour or block its blood flow, using imaging to guide the procedure. “What we have now is a great opportunity to drive this from localised therapy into giving feedback directly to a surgeon or a radiologist for treatment planning and execution, as well as treatment response,” said Hofstraat.

Combining all this information offers a holistic view on disease progression and provides a dashboard to advise the oncologist on the assessment, execution, and efficacy of therapy. Feeding back the information will, in turn, optimise outcomes in the future. Of course, we need to recognise that every patient is different and has his or her own priorities, wishes, and desires. “We can do a lot of measurements, but in the end, it’s how to use this information in a dialogue with the patient that will help us come to the right decision for a particular individual,” Hofstraat concluded.
Cancer imaging/screening in clinical practice

Thomas Hany, Board certified in radiology and nuclear medicine, Zurich University

Thomas Hany began with an overview of the main imaging tests: x-ray, computed tomography (CT), positron emission tomography (PET), PET/MR, and PET/CT. He then described how these tests may be useful in the top four cancer killers — lung, colon, breast, and prostate cancer.

For lung cancer detection, the accuracy of an X-ray is only 70% to 80%, said Hany. CT scans are far more accurate and can find both the primary tumour and the lymph node metastases. In fact, a study in The New England Journal of Medicine found that screening with low-dose CT scanning can reduce mortality from lung cancer. But it doesn’t make sense to screen everyone, Hany noted. In the US, the Centers for Disease Control and Prevention recommends CT screening only for a select group of patients: those who are older than 55 and have a history of heavy smoking for at least 15 years. In other countries, including Switzerland, there is no lung cancer screening. No one wants to pay for CT, Hany said.

For breast cancer, screening mammography — an X-ray of the breast — is recommended annually for women starting at age 40. This test, which will detect 85% of breast cancers, costs an average of $100. But Hany then referenced a 2016 study in The New England Journal of Medicine, which suggests that mammography has led to an overdiagnosis of breast cancer. Quoting the final sentence of the abstract, he said: “The reduction in breast cancer mortality after the implementation of screening mammography was predominantly the result of improved systemic therapy.” These results call into question the benefits of screening mammography, Hany said.

PET/CT scans are not appropriate for screening tests but rather for staging and risk assessment in people who already have cancer. These tests can also reveal whether a person is responding to chemotherapy. But there is no evidence that using PET/CT can affect overall mortality, Hany noted.

PET/MR combines both technologies so the patient doesn’t need to move from the table between scans. PET scans also use radioactive tracers (most commonly fluorodeoxyglucose or FDG), which can show differences between healthy and diseased tissue. A prostate-specific membrane antigen or PSMA study is a molecular imaging test that is used to see if prostate cancer has spread to the lymph nodes. These approaches may improve cancer staging, but we don’t know if they can improve survival.

Hany then mentioned the earlier discussion of circulating tumour cells (CTC). He cited a 2009 study in the Journal of Clinical Oncology showing that the detection of five or more CTCs during therapeutic monitoring can accurately predict prognosis in metastatic breast cancer. PET/CT may have a role for patients with fewer than five CTCs at midtherapy. “I believe PET/CT will have a minor role, except for therapy response assessment,” said Hany.
Panel discussion on the impact of liquid biopsy to critical illness

John Schoonbee, Global Chief Medical Officer, Swiss Re
David Miles, Consultant Medical Oncologist, Mount Vernon Cancer Centre
Pierre Hutter, Chief Scientific Officer and Co-Founder, Sophia Genetics
Vincent Mooser, Head Lab Department, CHUV, University of Lausanne
Urs Widmer, Life Guide Medical Officer, Swiss Re
Melanie Slack, Head of Life & Health Products Asia, Swiss Re

Clearly, the value of liquid biopsy is in the later stages of cancer to better monitor and treat the disease, said moderator John Schoonbee. “But what we face from a critical illness point of view is not the clinician’s approach but what consumers do,” he pointed out. There are companies that want to make money off these tests, and the “worried well” will buy them.

This brings up two concerns. First, if a test shows that a person has circulating tumour cells, this may drive further testing, which may pick up indolent cancer. The second is that people will say “Pay me, I’ve got cancer. I don’t need any other test” said Schoonbee.

David Miles noted that indolent cancers, which grow slowly and may never cause any problems, are likely to increase as the population ages. This is likely true for prostate cancer, said Vincent Mooser, adding that breast and lung cancers are probably more aggressive.

Screening tests can generate false positives that trigger additional testing, including biopsies, said Schoonbee. If people were fully informed about the risks from these tests, which can generate anxiety with no real benefit, most people would hesitate to have them, said Pierre Hutter.

“What if a person requested a $50 million life cover but had test results showing circulating tumour cells (CTC) or circulating tumour DNA (ctDNA)?” Schoonbee asked. Most people responded that further investigation would be necessary, and some questioned the accuracy of the testing. “Who said it’s a circulating tumour cell, and what is the technology that underpins that statement?” asked Miles.

Perhaps we can learn from earlier biomarkers, such as PSA, Mooser suggested. People predicted that PSA testing would catch prostate cancer very early, allowing us to remove the cancer and be done. Thirty years later, we still don’t know whether it’s good to measure PSA, he said. Liquid biopsies may go the same way, but we need to build the knowledge.

Melanie Slack brought up the issue of moral hazard. “If someone is applying for a $50 million policy, you have to ask yourself, why? What’s the insurable loss, and why do they need that?” We ask about a lot more than the medical situation, she said.

Another question involved a scenario in which a person had a test that showed a set of cancer driver mutations indicating a very high probability of a certain cancer, for which they then received targeted therapy. Would you be much or somewhat more likely to pay them if they submitted a critical illness claim?
Robert Rubens questioned whether any policies be admitted on the basis of treatment decisions. There are always options, and sometimes the best option is no treatment, he said. "If there is a monetary payment in the background, it can have a profound effect on a patient or claimant’s attitude as to whether they would like treatment or not," he added.

Slack concurred, pointing out that the whole point of critical illness is supposed to be that if you have a severe medical event, you are compensated. "The spirit of the contract is helping out in times of medical adversity," she said.

In considering the drivers that could lead people to liquid biopsy testing, Schoonbee asked Mooser about the commercial viability of these tests. "I think we will probably see more and more of them, including direct-to-consumer tests," said Mooser. The worry is that people will think that if a test is negative, they don’t have cancer and if it’s positive, that the cancer can be easily cured, when that's not necessarily true. Slack also wondered whether a negative result would discourage people from buying insurance, which would lead to a high-risk pool among those who were insured.

Most of the panellists agreed that consumer education would be important, but exactly who should provide that education is not clear. Often, it falls upon physicians, said Miles. "A lot of the time, I’m going to say, 'I’ve got absolutely no idea,'" he said.

David Lu mentioned that genetic companies in Asia are very active in selling genetic tests including liquid biopsy directly to consumers (DTC), and there is no regulation on the DTC market. Consumers may not have the knowledge on how to interpret the results. Lu also brought up the possibility of patients delaying insurance purchases until they get a positive result. The bigger issue, Slack said, is that people may be getting something we haven’t asked for, and how do we manage that?

At this point, it looks like this test does not really offer much predictive value over a conventional cancer test, so we won’t accept it or require it before it has been validated, said Urs Widmer. If the results could inform treatment, we could consider financing it to improve mortality. As an option, it could be an opportunity, not only a threat, he said.
Closing remarks and next steps
Melanie Slack, Head of Life & Health Products Asia, Swiss Re

In her summation of the forum, Melanie Slack reiterated Swiss Re’s growth in critical illness policies, particularly in Asia. Cancer-only products, which include cancer relapse, are a new trend, as are products that focus on older lives, she said. People buy these products for mortgage or lifetime cover.

Our risk assumption models therefore must account for a very long time frame — up to 40 years. The landscape is changing with respect to how early we can diagnose cancer, which will impact incidence, said Slack.

Monitoring profitability demands that you pay attention to the risk drivers related to that product. “Are people behaving differently? Have terms and conditions changed?” she asked.

Overall, Slack said she felt reassured from the day’s presentations, which suggest that we’re a long way from using liquid biopsy for early cancer detection. But the reality that companies are financially motivated to market this test to healthy people affirmed that it’s important to pay attention to this topic, she said.

Advances in cancer diagnostic and treatment will likely impact morbidity, mortality, medical insurance, and medical reimbursement, said Slack. “No matter how we spin this topic, it has an impact on at least one aspect of the different types of products we write or the types of protection needs that people have.”