No. 5, 2020

RISK INSIGHTS

Liquid Biopsy and the Early Diagnosis of Cancer

By Dr. John O'Brien, Gen Re, London

Although cancer and cardiovascular disease are the main causes of death worldwide, major advances have been made in the prevention and management of them both. In treating most medical conditions, early diagnosis with appropriate intervention will result in improved outcomes; however, cancer screening programmes have had varying success. Some have resulted in significant improvements in outcomes, whereas others have identified many relatively unimportant cancers and resulted in high costs, unnecessary anxiety and complications from investigation.

Screening Shortcomings

Many screening initiatives remain controversial, partly explained by the fact that not all cancers progress predictably. Many cancers grow slowly, and if they are detected by screening programmes, those cancers will be treated earlier, but this will not affect cancer-associated mortality. Other cancers are extremely aggressive and, by the time they are identified with screening, have already spread. Breast cancer is a good example of how screening has identified many cancers at an earlier stage, but improvements in outcome can largely be ascribed to lead time and length bias for small breast cancers and improvement in treatment for larger breast cancers.[1]

The conventional way of diagnosing cancer is to first identify an abnormality either on clinical examination or imaging modalities. This lump is then investigated invasively with a biopsy or needle aspiration for cytology; the process of investigation is not without risk and discomfort. Existing screening is designed to identify specific cancers with the result that comprehensive screening involves participation in several different programmes (e.g. breast, colon and cervical cancer). Even participation in all the screening programmes will not guarantee identification of less common cancers, particularly those that are difficult to identify early without sophisticated imaging, such as pancreatic cancer. The five cancers with existing screening programmes in the U.S. represent less than 50% of the cancers in those aged 50-79 years.

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About This Newsletter

Risk Insights is a technical publication produced by Gen Re for life and health insurance executives worldwide. Articles focus on actuarial, underwriting, claims, medical and risk management issues. Products receiving emphasis include life, health, disability income, long term care and critical illness insurance.

The promise of new blood tests in cancer screening

It would therefore be ideal if there could be a simple blood test that would detect cancer early, particularly the aggressive cancers. Very few cancers have biomarkers such as the PSA (prostate specific antigen) in prostate cancer. Aggressive cancers tend to spread and disseminate early as cancer cells enter the circulation and are transported to distant sites. The early diagnosis of cancer has been focussing in recent years on liquid biopsies – blood tests that detect circulating cancer cells, circulating cell-free DNA and RNA and exosomes. Isolating and identifying these cells is challenging but can be done using specialised techniques that rely on the different characteristics of cancer cells.

Cancer cells can also release DNA and other cellular components called microsomes into the circulation. Circulating cell-free DNA (cfDNA) was first identified in 1948. The development of technology to rapidly identify and analyse DNA led to interest in detecting circulating cancer DNA for early detection of cancers. Cancer cells develop because of genetic mutations. Identifying circulating tumour DNA (ctDNA) relies on identifying these genetic mutations. Limitations to this technique include the wide variation in the amount of circulating DNA that is of cancer origin. It can vary from 1% to over 80%, and cfDNA is cleared from the circulation with a half-life of an hour or less.[2] Another major limitation is that previously identified mutations may only occur in a small percentage of the cancers associated with those mutations and many are specific for a cancer type.

For circulating tumour DNA to be useful, there must be concordance with samples from the primary tumour. Concerns about this were raised in a study where identical samples from 40 subjects with prostate cancer were sent to two different commercial laboratories.

Congruence between the two laboratories was found to be poor.[3] This may be partially explained by the study design, which entered subjects with low prostate specific antigen so that the cfDNA levels may have been below the level of detection. Other studies have shown higher concordance rates.

For a liquid biopsy system to be effective for cancer screening, it must have high specificity and sensitivity. A study of the CancerSEEK blood test, for example, coupled analysis for ctDNA with protein biomarkers. The researchers included mutated sequences in 16 genes with eight known biomarkers. This test was designed to identify eight common cancers and was trialed in 1000 patients with cancer and in 800 healthy controls. The test detected between 33% and 98% of cancer cases, the highest positive being ovarian cancer and the lowest breast cancer. Importantly, there were only seven false positive results.[4] An earlier article in *Risk Insights* describes how liquid biopsy techniques are evolving fast, pointing to what will be possible in the future.[5]

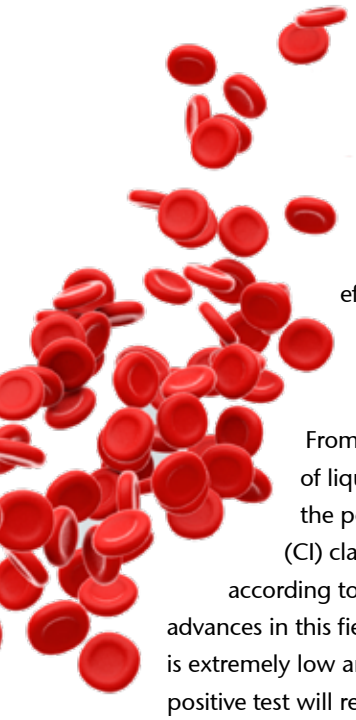
The limitations of liquid biopsies

To fully screen for all mutations remains complex, costly and time-consuming. Many cancers have more than one genetic mutation contributing to the cancer bulk. While this has implications for cancer screening, it also has relevance for treatment: A treatment may be effective against one of the mutations, but meanwhile the other mutations are allowed to multiply, resulting in further progression.

Researchers have tried various approaches, none of which attempt to identify thousands of mutations of DNA indicative of specific cancer. One example is identifying the size of the DNA fragment that is likely to represent tumour DNA.[6]

Another is the recognition that methylation (or the addition of a methyl group) to certain areas of DNA is a characteristic of many cancers. Finding methylated DNA in specific regions can identify cancerous DNA and assist with identifying its cell of origin. A recent study involving 6689 participants (2482 cancer and 4207 non-cancer), and targeting methylation regions, had an excellent specificity of 99.3% with only a 0.7% false positive rate. Detection increased with increasing cancer stages and was also affected by cancer types. Sensitivity for stage 1 was 39% and was 93% in stage 4.[7]

The major limitation of liquid biopsy has been in its inability to identify cases early, and clearly for a screening test to be useful, early detection is important. Until now these tests have been unable detect small tumours because they are less likely than older, larger tumours to release cancer DNA into the circulation. However, a recent study from China has demonstrated the fact that liquid biopsy can detect cancer years before the clinical diagnosis. Plasma samples from 605 asymptomatic subjects, 191 of which were subsequently diagnosed with cancer were analysed for ctDNA. Cancers diagnosed were stomach, oesophageal, colorectal, lung and liver cancer. Cancer was detected in 88% with a specificity of 96% in samples taken up to 4 years earlier.[8] An earlier article in *Risk Insights* also discussed the impact of such developments on insurance – how this diagnostic shift will lead to higher incidence rates as more people are diagnosed earlier and more often, and how therapeutic gains will also play a role as medical interventions become more effective.[9]



The impact of liquid biopsies on insurance

From an insurance perspective, the prospect of liquid biopsies has raised concern about the possibility of triggering a Critical Illness (CI) claim that would not be admitted according to conventional policy criteria. The advances in this field indicate that the false positive rate is extremely low and clinical practice dictates that a positive test will result in a tumour search to confirm the presence and extent of a cancer. It is very unlikely that these investigations will result in claims that would not otherwise have been paid. Indeed, the intention is for early detection to improve outcomes, which may well have a positive effect on Life claims and even for CI claims, which are tiered, as the cancer would be diagnosed at earlier stage. Gen Re has previously addressed the concept that advances in medical science could mean adjusting CI benefit triggers in order to maintain the same level of "criticality".[10] While it may be naive to believe that a single blood test will accurately identify all early cancers, it is certainly plausible that as techniques improve and costs come down, the liquid biopsy will be introduced as part of cancer screening in the not too distant future.

About the Author

Dr. John O'Brien *is the Chief Medical Officer (CMO) for Gen Re Life/Health Research and Development, based in the UK. Before joining Gen Re as CMO, he worked as consultant for Gen Re in Cape Town while running a pulmonology practice and clinical trial centre. Dr. O'Brien is a past president of the South African Thoracic Society and served on the editorial committees for the South African Thoracic Society guidelines for asthma and COPD. He has been a clinical investigator in more than 70 clinical trials in asthma and COPD.*

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