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How does the growing genomic knowledge affect us?

Cancer genomics, liquid biopsies and personalised medicine: The impact on life insurance

Introduction

Since the completion of the full human genome mapping in 2003[1], there has been an exponential growth in interest and awareness of genetic developments within the life insurance industry. In particular, 'cancer genomics' – the study of the totality of DNA sequence and gene expression differences between tumour cells and normal host cells[2] – is flipping our risk philosophy on its head.

By 'looking under the hood' of a tumour, clinicians – and in turn, insurers – are able to gain a greater understanding of what the problem is and why previously normal tissue has become cancerous. Understanding the deepest mechanics of a patient's particular tumour enables bio-scientists to develop the most suitable, personalised treatment. The effect of such targeted therapies can be compared to 'switching the tumour's engine off for good', leading to its ultimate destruction by exposing it to a person's immune system. As a result, patients could survive longer and potentially suffer fewer adverse effects, as contemporaneous evidence supports their use over the age-old chemotherapy regimes.

So how does this growing genomic knowledge affect us? What effect could it have on anti-selection? What underwriting response would be required with a new understanding of genetic abnormalities? Moreover, should our 'think tanks' develop smarter and more suitable products in the cancer space? This article gives an overview of cancer classification, novel tests and targeted drugs that are influencing how cancers are addressed, both by clinicians and by insurers.

Cancer classification

Cancers are conventionally classified using histological tissue type and staged using various staging systems, the most common being the TNM staging system that has been in use since its development in the late 1940s.[3]

However, with the ability to analyse cancers at a genetic level we shift the paradigm in the way we classify cancers. One method is gene expression profiling.

Genomic sequencing is a laboratory method used to determine the entire genetic makeup of a cell type and can be used to detect any changes in the DNA of normal tissue that has triggered the development of a disease such as a tumour.[4]

Gene expression (molecular) profiling is a laboratory method that identifies the genes required to make the proteins that are essential determinants of disease such as tumour behaviour.[5]

[1] National Human Genome Research Institute; The Human Genome Project; retrieved on 22/06/2022
[2] Nature Portfolio; Cancer Genomics; retrieved on 22/06/2022
[3] Brierley J; National Cancer Institute of Canada Committee on Cancer Staging. The evolving TNM cancer staging system: an essential component of cancer care. CMAJ. 2006;174(2):155-156.
[4] National Cancer Institute; NCI Dictionaries, Genomic Sequencing; retrieved on 22/06/2022
[5] National Cancer Institute; NCI Dictionaries, Gene Expression Profile retrieved on 22/06/2022

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Gene expression profiling enables 'precision medicine' to be incorporated into patient care. The ability to test for certain genes means that highly specific drugs can be developed targeting the faulty mechanisms of the tumour. As 'simple' as this may seem, it is more complex as multiple faults are simultaneously present, and the therapeutic action on one targeted pathway often leads to the upregulation of another synergistic pathway. This in part explains the basis of treatment resistance that occurs after an initial period of successful treatment response.

Looking closer at breast cancer, we have always broadly classified these tumours as being ductal or lobular carcinomas with high or low-grade features based on histopathological findings. The use of gene expression profiling has allowed for an improved classification of breast cancers – namely Luminal A, Luminal B, HER2/NEU, or 'triple negative' subtype which represents a lack of these three surface markers.[6] This classification can be used to drive treatment and estimate prognosis more accurately.

'Luminal A' subtype for example is more common in woman older than 50 and with tumours less than 2cm in size, while the 'triple negative' subtype is more prevalent in woman younger than 50 and with tumours between 2-5cm in size.[7] Consequently, there is a relationship between gene expression subtype, treatment given, and overall prognosis.

Tumour-based gene expression profiling panels can be of value in predicting clinical outcomes and guiding treatment.[8] Using specific gene profiles, recurrence scores can be used to identify women with early stage (node-negative, hormone-receptor-positive) breast cancer who could benefit from the addition of chemotherapy to tamoxifen.[9] Similarly, scores can help predict the ten-year risk of distant metastasis in node-negative breast cancer patients, further guiding which patients could benefit from systemic chemotherapy.[10] Such molecular genetic panel tests, whilst still attached to a sizeable price tag, have become the backbone driving 'personalised therapies'.

Liquid biopsies

The idea of diagnosing a cancer at the earliest possible stage seems logical, however it has continued to be a challenge in the clinical arena. How can we design a screening test that can detect all cancers with high sensitivities and specificities, be affordable, accessible, safe, easy to evaluate, and be regularly conducted on individuals throughout their life? Satisfying all these requirements is extremely challenging.

The liquid biopsy assay is one such test and can detect any of the following:

- Cells – both blood cells as well as circulating tumour cells (CTCs)
- Circulating free DNA (cfDNA) – both circulating tumour DNA (ctDNA) and wild type host tissue DNA
- Extracellular vesicles
- Extracellular proteins

The moniker 'biopsy' implies that it should bear comparable results to a solid tissue biopsy if it is to be relied on. Liquid biopsies detect specific mutations in cfDNA and whilst first commercially available in 2000, the actual detection of cfDNA has been possible since 1994. In June 2016, the US Food and Drug Administration (FDA) approved the first liquid biopsy to be used as a cfDNA companion diagnostic test for detecting the Epidermal Growth Factor Receptor (EGFR) gene in DNA derived from plasma or tumour tissue in lung cancer patients.[11] Patients with the EGFR gene are candidates for treatment with novel tyrosine kinase inhibitors that prolong survival. Since then, a number of other companion diagnostic tests have been approved. A comparison between tissue biopsies and liquid biopsies can be seen in Table 1.[12]

[6] Al-Thoubaity FK. Molecular classification of breast cancer: A retrospective cohort study. Ann Med Surg (Lond). 2019; 49:44-48.
[7] Hamdan D, Nguyen TT, Leboeuf C, Meles S, Janin A, Bousquet G. Genomics applied to the treatment of breast cancer. Oncotarget. 2019; 10(46):4786-4801
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[9] Breastcancer.org; Oncotype DX Tests; retrieved on 22/06/2022
[10] Breastcancer.org; MammaPrint Test; retrieved on 22/06/2022
[11] LabCE; The History of Liquid Biopsy Assays; retrieved on 22/06/2022
[12] Chen, M., Zhao, H. Next-generation sequencing in liquid biopsy: cancer screening and early detection. Hum Genomics 13, 34 (2019).

Table 1

Tissue biopsy	Liquid biopsy
• Cannot use prior to tumour formation • Assesses focal site of tumour • Used for initial diagnosis • Guides treatment selection • Guides prognostic evaluation	• Better for heterogeneity • Assesses focal and metastatic tumours • "Real-time" snapshot of clinical picture; can change over time • Used for evaluation of residual disease • Used for determining risk of relapse • Less invasive

The clinical application of liquid biopsies is three-fold. Their current value is in detecting the presence of tumour recurrence; assessing an individual's risk of relapse; and identifying treatment targets (and monitoring effects thereof). Ultimately, it is hoped to use them for early cancer detection.

NGS (next-generation sequencing) – a sequencing technology that offers ultra-high throughput to determine a portion of the nucleotide sequence of an individual's genome, with capability of processing multiple DNA sequences in parallel.[13]

PCR (polymerase chain reaction) – a technique used to 'amplify' small specific segments of DNA.[14]

The detection of ctDNA allows for further NGS or PCR testing to identify various genetic aberrations such as genetic deletions or insertions, translocations, point mutations, gene amplifications and epigenetics.[15] These represent the drivers behind the tumour and their details are beyond the scope of this paper.

One particular liquid biopsy panel test, aimed at detecting the presence of an early-stage tumour before it spreads, has been in the making for over a decade. It assesses 8 different cancers with high accuracy, reportedly detecting early-stage cancers in a median of 70 percent of cases.[16] Whilst a blood test is unlikely to replace current screening methods, its greatest potential could lie in the early detection of pancreatic, ovarian, liver, stomach and oesophageal cancers, all which typically present in an advanced stage.

A large prospective explorative trial conducted in 2020 evaluated the value of using an initial blood test to screen over 10,000 women aged 65 to 75 with no history of cancer. In addition to those found to have cancer through standard-of-care screening, 26 women were diagnosed with cancer that was first detected by the blood test. The researchers reported, "All that we can confidently conclude at present is that a minimally invasive blood test can be safely used to detect several types of cancers in patients not previously known to have cancer".[17]

Another test that identifies cfDNA circulating in the blood and, through next-generation sequencing, is currently undergoing various trials to determine its ability to detect a number of cancers. Preliminary findings have shown a high specificity of over 99% however detection rates for 12 prespecified cancer types across various stages were much lower.[18]

Similarly, a test that detects DNA methylation patterns and designed to identify cancers in asymptomatic individuals, was tested over a decade long study in participants using three-yearly plasma and tissue samples. The test showed a specificity of 96% for 5 different types of cancers. Of significance was the 95% detection rate of asymptomatic participants who were then diagnosed with one of the respective cancers within 4 years of enrolment. Whilst unable to exactly locate the cancer, this test (if validated) could become an initial step in screening, with further diagnostic tests being prompted if required.[18]

Gene therapy

Gene therapy is the treatment or prevention of a disease by correcting the underlying genetic problem.[19] Two dominant gene therapies have recently made headlines. One gene therapy is tisagenlecleucel, a CAR-T therapy that works as a one-time immunocellular therapy and is manufactured individually for each patient. T cells are extracted through a specialised blood filtration process called leukapheresis and then genetically re-engineered

[13] National Cancer Institute; NCI Dictionaries; Next-generation Sequencing; retrieved on 22/06/2022
[14] National Human Genome Research Institute; Fact Sheets about Genomics; retrieved on 22/06/2022
[15] Heidrich, I et al. Liquid Biopsies: Potential and challenges. International Journal of Cancer. 2021; 2021; 148(3): 528-545.
[16] Cohen JD, Li L, Wang Y, Thoburn C, et al. Papadopoulos N. Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science. 2018 Feb 23
[17] Lennon, A. M., et al. Feasibility of blood testing combined with PET-CT to screen for cancer and guide intervention. Science. 2020. 3;369(6499), eabb9601.
[18] Beer, T.M. Novel Blood-Based Early Cancer Detection: Diagnostics in Development. Am J Manag Care. 2020; 26:S292-S299.
[19] National Library of Medicine; MedlinePlus; What is gene therapy?; retrieved on 22/06/2022

and programmed to recognise and destroy cancer cells before being delivered back to the patient, resulting in tumour cell death. This revolutionary treatment received Australian Therapeutic Goods Administration (TGA) approval in 2018 for effectively treating two aggressive blood cancers:

1. Paediatric and young adult patients up to 25 years of age with B-cell precursor acute lymphoblastic leukaemia (ALL) that is otherwise refractory with clinical relapse
2. Adult patients with relapsed or refractory diffuse large B cell lymphoma after two or more lines of systemic therapy

The TGA approval was based on two breakthrough clinical trials where the therapy delivered complete and sustained response rates for patients who otherwise had dismal chance of remission.[20]

Another gene therapy is axicabtagene ciloleucel, used for treating large B-cell or follicular lymphomas that have relapsed or shown poor response after initial treatment with at least two other types of systemic therapies.[21] This therapy also showed staggering survival outcomes including patients who required no further treatment – data suggesting that it is potentially curative.[22]

Conclusion

As the whirlwind of genetic research progresses, it is almost inevitable that cancers will be diagnosed earlier. Consumers will have improved access to commercial tests and there is a danger that health inequalities are exacerbated, both within countries and between rich and poor countries. More favourably though, an overall improvement in cancer outcomes will arise.

Whilst leaders in cancer staging systems, such as the American Joint Committee on Cancer (AJCC) still currently rely on the TNM system, it is likely that molecular genetics will reshuffle the way cancers are classified, potentially even resulting in molecular genetics overlapping across different organ systems.

However, insurers are bound by various legislative and regulatory requirements such as genetic moratoriums and may not be able to utilise the results of predictive panel tests or molecular profiling at underwriting stage. Where allowed, insurers would need to consider the most appropriate way of acquiring this information in order for it to be used within the applicable regulatory framework.

It is likely that fewer cancers will satisfy a 12-month Terminal Illness definition with the movement towards personalised medicine and targeted drug therapies that are demonstrating prolonged survival outcomes. Whilst current cancer definitions within Critical Illness products still generally rely on histological evidence to confirm the diagnosis of a certain cancer, the commercial availability of a liquid biopsy could potentially result in anti-selective behaviour accompanied by an early claim. On the positive side, we could expect to see more favourable outcomes in cancer survivors and a reduction in disability duration. Significantly, there appears to be scope for insurers to use genetic developments to design innovative products that could benefit the customer both pre-policy, intra-policy, and at claim stage.

Author

Monique Esterhuizen
Chief Medical Officer
Tel. +612 9251 6911
monique.esterhuizen@hlra.com.au

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