CANCER GENOMICS

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Annie Joubert explains how DNA technology is changing the face of cancer

Cancer is ultimately a disease of DNA – mutations in your genome influence your risk of being diagnosed with it, and may determine what happens during the course of the disease. The advent of modern DNA technologies, and particularly next-generation sequencing, is rapidly changing the face of diagnostics and treatment.

The possibility of screening for DNA mutations in genes that may increase the risk of cancer, especially breast cancer, is advancing with the production of panel testing kits, some of which can target hundreds of genes. There is no doubt that the development and roll-out of these tests will save lives.

Today the complete genome sequence of a cancer patient, together with the profile of genes being activated and deactivated, can be obtained. This genomic picture can be used to assess a patient's cancer risk and progression, and to design tailor-made treatment strategies.

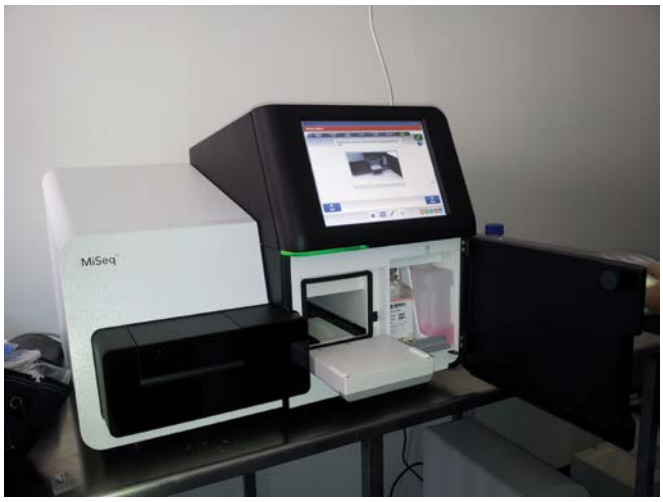
There are two approaches to analysing mutations in DNA: tests that analyse the mutations a person was born with and which assess the risk of being diagnosed with cancer (germline cancer susceptibility analysis), and tests that analyse the mutations in tumours or other sources in cancer patients (somatic mutation analysis). Cancer susceptibility analysis may help to determine whether someone should be examined for cancer more regularly with additional screening tests, whereas somatic mutation tests may help oncologists understand what happened when cancer developed, and guide them in recommending further testing and treatment.

The genome may be studied for mutations using different approaches. Targeted chip-based analyses report the status of mutations only in positions previously known to be important. This includes testing for mutations at genome sites known to increase cancer risk, mutations related to the prediction of cancer outcome or mutations that guide oncologists in designing the best treatment approach.

When evaluating the genome sequence of an individual, next-generation DNA sequencing approaches are used, and novel or previously less-studied mutations may also be detected. These types of approaches include whole genome sequencing (all DNA), whole exome sequencing (sequencing the sections of the genome that make proteins) and targeted sequencing (where genes or other non-protein-producing, but important, parts of the genome are selectively sequenced).

An additional type of analysis includes whole transcriptome sequencing, where messenger RNA molecules (which act from DNA to create a template for the production of a protein molecule) are sequenced and quantified to determine which genes are abnormally active or inactive. Also, duplications of sections in the genome can be analysed in the form of copy number variation, where the duplication of certain genes may lead to cancer.

Breast cancer is one of the most common forms of the disease in women – the lifetime risk of South African women getting breast cancer is one in 27. The role of many mutations in the BRCA1 and BRCA2 genes in breast cancer



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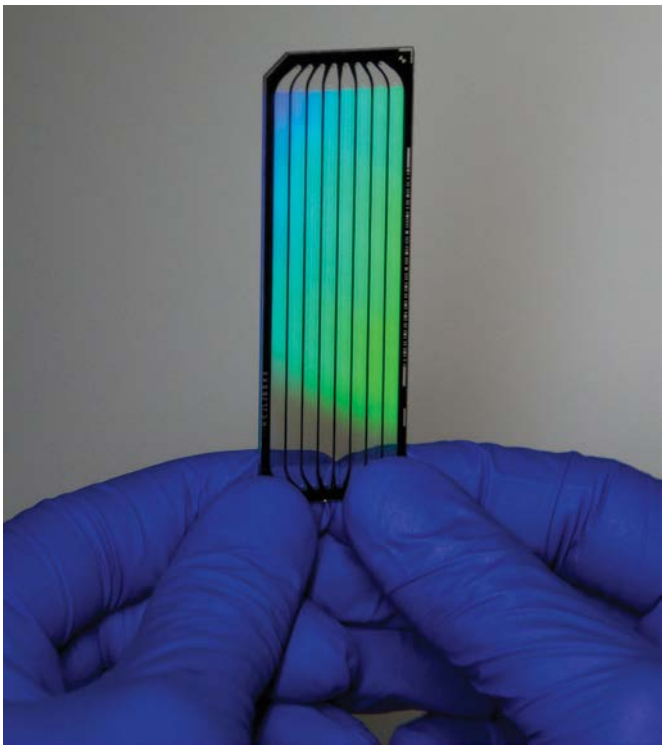
The Illumina MiSeq is one of the most widely used next-generation sequencing platforms. It uses a double-sided, single-lane flow cell and reagent cartridge supplied in kit form.

susceptibility has been well studied. These genes produce proteins involved in processes that repair errors occurring in DNA. If they do not function correctly, these errors may lead to the development of cancer.

Many other genes also play a role in determining the risk of breast cancer, albeit with smaller effects than BRCA genes. About 15 genes that have mutations more often than expected in women who are diagnosed with breast cancer have been identified. However, hundreds of other genes potentially play a role. In some instances, mutations do not act alone but lead to cancer only when they occur in concert with mutations in other genes.

The possibility of screening for DNA mutations in genes that may increase the risk of breast cancer is rapidly advancing as scientific companies are producing cancer panel testing kits, such as the Illumina TruSight cancer panel developed with Cancer UK, which analyses the sequences of 94 important cancer susceptibility-related genes (not only for breast cancer) and monitors for a series of other possible mutations that have been related to an increased risk of cancer. This is one of the smaller testing kits; others target hundreds of genes. There are also kits that may determine the specific mutations that took place in the tumour of cancer patients, as well as those that do not focus on the DNA sequence per se, but assess abnormal protein expression levels. The MammaPrint breast cancer assay analyses the levels of 70 different gene products that are used to help determine whether a patient should proceed with chemotherapy.

For individuals, access to advanced testing is typically through a cancer centre or an oncologist, who will arrange for a pathology company or specialised DNA analysis company to analyse samples, followed by subsequent consultations with an oncologist and a genetic counsellor. While a few years ago only BRCA1 and BRCA2 testing was commonly available, cancer centres – particularly in the USA, Europe and Asia – are now making regular use of large cancer susceptibility and somatic mutation testing panels. International consortia are building huge databases of



Daniel Sone, NCI

A DNA sequencing flow cell.

mutations in cancer patients and correlating the mutations to the choice of successful treatment methods.

As with most cutting-edge technologies, many of the new testing approaches are costly, not yet commonly available, have not yet been approved for clinical use in all countries, are not part of health insurers' benefits and are sometimes available only to patients that are included in large research trials. Still, the rapid development and roll-out of these tests are starting to save lives.

About 5–10% of cancers can be attributed to genetic inheritance. DNA mutations may occur for several other reasons after birth. These mutations may be triggered by risk factors such as tobacco products, alcohol consumption, diet, environmental pollutants, ultraviolet radiation, reproductive and hormonal factors, occupational exposures and infection-attributable cancers.

As Richard Dawkins said, "DNA neither cares nor knows. DNA just is. And we dance to its music." The dance between DNA and genomic research impacts our lives hugely. Advances in genomic research reveal the biology of disease and ultimately contribute to redefining our health management, today and in the future.

Prof. Annie Joubert is head of the Department of Physiology at the University of Pretoria. Her research focus is cancer cellular physiology. She studies cancer drug design and cancer cell signalling to identify targets for therapeutic intervention in the fight against cancer.

This article is an amended version of a news story originally posted on the University of Pretoria's website on 25 April 2020 to celebrate DNA Day, and republished with permission.
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