How cancer genomics is transforming diagnosis and treatment

Genome sequencing is providing physicians with more data about the causes of cancer and changing the way some forms of the disease are treated.

By Bianca Nogrady

When cancer was first described by the ancient Greek physician Hippocrates, he identified just two forms: the non-ulcer-forming carcinos and the ulcer-forming carcinoma. In the late nineteenth century, physicians found, with the help of the microscope, that cancer had multiple cellular forms.

Now, technology is once again transforming our understanding of cancer's origins and complexity. Instead of broad categorizations based on the location of tumours, genome sequencing is providing detailed characterizations of the combination of genetic mutations that trigger or aid cancer development in an individual.

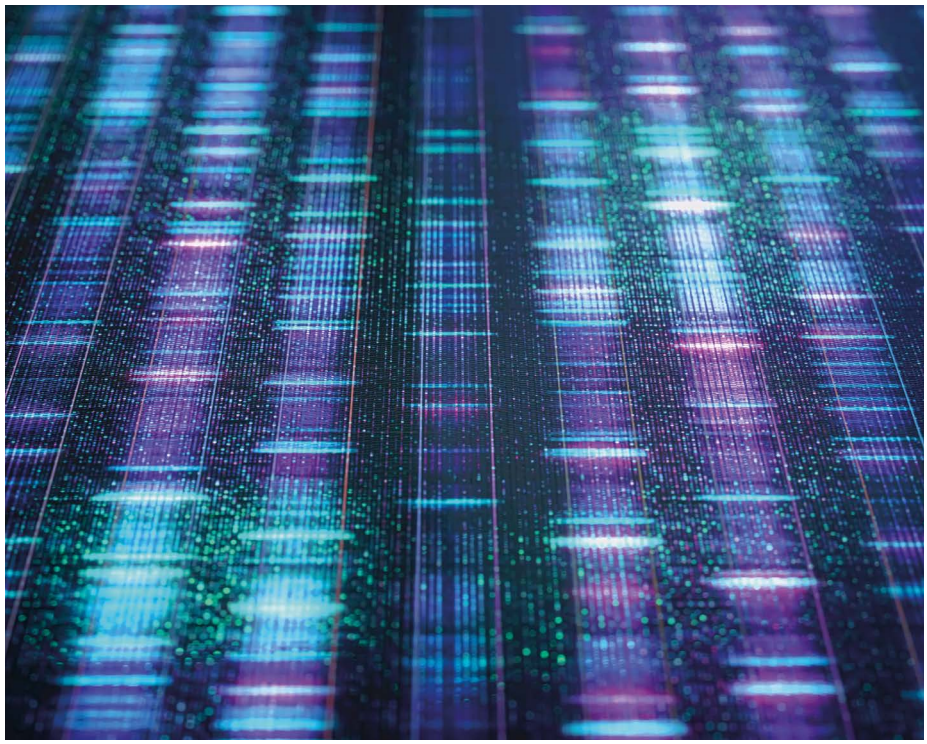
"What you now see is that every cancer is a rare cancer," says Emile Voest, an oncologist and medical director of the Netherlands Cancer Institute in Amsterdam. Ten years ago, he says, lung cancer was classified as either small cell or non-small cell. It's now described by the presence or absence of nearly 30 genetic mutations.

As well as advancing physicians' understanding of what causes each person's cancer, genomics is providing insights into how an individual's cancer might progress, and its likely response to treatment.

For some, this information will save their lives — knowledge of the genetic drivers of cancer is already changing how some people's cancer is treated. For others, it currently only adds new data, not years to their lives or new treatment options. But each cancer-causing or cancer-influencing genetic mutation that is discovered is a potential target for drug development, including for cancers for which there are currently few treatment choices.

Genetic cancer culprits

"We've known for decades that genes and genetic alterations are the foundation to cancer," says Kenna Shaw, executive director of the Khalifa Institute for Personalized Cancer Therapy at the University of Texas MD Anderson Cancer Center in Houston.



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DNA sequencing allows oncologists to characterize tumours on the basis of genetic mutations.

Some of these genetic alterations interrupt the normal functioning of tumour-suppressor genes, which regulate cell growth and death, and are usually protective against cancer. Mutations in the tumour-suppressor genes *BRCA1* and *BRCA2*, for example, have been linked to a much higher risk of breast, ovarian and prostate cancer.

Mutations that impair the function of genes that underpin a cell's ability to repair damaged DNA have also been implicated in cancer, as have mutations that generate oncogenes: genes that can actively transform a healthy cell into a cancer cell. For example, *HER2*-positive breast cancers involve a mutated *HER2* oncogene, which produces a protein that increases the growth of cancer cells. Sometimes, as in the case of *BRCA1* and *BRCA2*, these mutations are inherited. But most are not.

Identifying cancer-causing mutations can be essential to diagnosis, particularly when it comes to haematological cancers, says Piers Blombery, a haematologist at the Peter MacCallum Cancer Centre in Melbourne, Australia. Diagnosis of these 'liquid' tumours is usually informed, and sometimes explicitly decided, by genetic abnormalities. For example, chronic myeloid leukaemia (CML) is diagnosed by the presence of a mutated gene called *BCR-ABL*, which is created by the transfer of genetic material from one chromosome to another. Most people with CML also have an unusually short chromosome called the Philadelphia chromosome, the presence of which is also key to diagnosis.

Genetic mutations do not have such a central role in all cancer diagnoses, but even if they don't, their presence or absence might

change how each person's cancer is described. "We're realizing the relative unsophistication of calling something diffuse large B-cell lymphoma, which doesn't capture the full biological heterogeneity of that condition," Blombery says. A 2018 study found four distinct genetic subtypes of diffuse large B-cell lymphoma, each of which differed in clinical presentation, progression and, most importantly, response to treatment[1].

Categorizations based on the location of the cancer and the type of cell involved are still essential. "But it's getting from these broad-basket diagnoses into the subcategories of these diagnoses, which can only really be defined genetically, that is really finessing our treatment within those categories," Blombery says.

Treating the mutation

One of the biggest impacts that cancer genomics is having is on treatment choices. "Having the right diagnosis is the most potent determinant of getting the right treatment," Blombery says. One early treatment targeted at people with cancer who carried a particular mutation was trastuzumab, which was approved for the treatment of *HER2*-positive breast cancer in 1998. It was followed in 2001 by imatinib for forms of leukaemia with the Philadelphia chromosome mutation. And gefitinib, which targets the epidermal growth factor receptor in some lung cancers, was approved in 2003.

Some genetic mutations can significantly alter the choice of treatment, even if those treatments do not directly target the mutation. For example, in chronic lymphocytic leukaemia, the presence of a mutation in the *TP53* gene means that the cancer probably won't respond to chemoimmunotherapy. If physicians know that a person has that mutation, they might instead opt for a stem-cell transplant. And in colorectal cancers, mutations in the *KRAS* gene mean that patients will not respond to drugs such as cetuximab or panitumumab. Certain mutations can also signal that a cancer is more likely to become resistant to a treatment. In acute myeloid leukaemia, for example, some people carry mutations that make their cancer more likely to become resistant to a class of drug called isocitrate dehydrogenase (IDH) inhibitors.

The possibility of treating cancer on the basis of an individual tumour's genetic profile has led to a surge in cancer-genome profiling of patients. At the Netherlands Cancer Institute, every person with metastatic cancer has their cancer genome sequenced. Its database now contains genomic-sequencing information from around 5,000 people. The institute has focused on people with metastatic cancer because it would be too costly to sequence everyone, and many people with primary cancer can be cured with existing treatments. The idea, says Voest, is to give the people at the highest risk of dying from cancer access to a wider pool of potential treatments, whether these are the standard of care for a particular cancer, an off-label treatment or even an experimental agent.

In 2016, the institute launched the Drug Rediscovery Protocol, in which people who have so far not responded to standard treatment, but who have DNA anomalies that suggest they might respond to therapies not approved for their particular cancer, are treated with those drugs in an experimental setting. The approach is showing clinical benefit in around one-third of people[2].

Shaw says that she takes a more focused approach by sequencing people with cancer only when a known actionable molecular target exists for that cancer type, or when patients have run out of treatment options. She estimates that there are only about 130–140 "therapeutically actionable" genes for solid tumours, and even fewer for liquid tumours.

But Voest says that whole-genome sequencing of people with metastatic disease isn't just about finding mutations that are currently treatable, but also about targets and treatments yet to be discovered. Identifying people's mutations in advance means that, when researchers do discover a treatment option for a particular mutation, "we can identify patients that we can help". And even when sequencing reveals only bad news for a person, the knowledge of their likely prognosis can be useful. "Sometimes it's very important to be able to tell a patient that, unfortunately, with this particular molecular lesion, you've only got 3–6 months to live, and no chemotherapy will work," Blombery says.

Future targets

The Cancer Genome Atlas programme, set up by the US National Cancer Institute (NCI), has sequenced more than 20,000 primary cancer samples of 33 cancer types. This is just one of a suite of NCI initiatives to collect and analyse cancer-genomic data, and support the translation of those data into new treatments.

The NCI also supports the Cancer Target Discovery and Development Network — a group of 12 cancer research teams and centres across the United States, including the Dana-Farber Cancer Institute in Boston, Massachusetts and Johns Hopkins University in Baltimore, Maryland. "It's kind of a bridge programme between all the data generated through these large-scale genomic initiatives," says Subhashini Jagu, scientific programme manager for the network, which is based at the NCI's Office of Cancer Genomics. "All that raw data generated through high-throughput screening will be deposited to the data portal," where researchers can access it, she adds.

To help scientists make sense of the troves of data, the centres are also developing and sharing computational and analytical tools. "The goal is to integrate systems biology with the cancer biology," Jagu says, so researchers can, for example, stratify patients according to their responses to a particular therapy, or find specific genes in the data sets. "This is the best time to work in the field," Jagu says.

However, genomics isn't the only answer to the cancer challenge, Voest warns. "It's a starting point," he says. He notes that newer technologies, such as RNA sequencing, gene-expression profiling and proteomics, are also bringing in a wealth of information to help characterize and treat cancer. "We need to integrate all types and all levels of information."

At the same time, some treatment options, such as checkpoint inhibitors and immunotherapy, are leapfrogging cancer genomics altogether. These therapeutic approaches target the tumour's ability to suppress the cellular immune response that might otherwise identify and destroy it. Checkpoint inhibitors do not target a particular mutation and they are not affected by cancer mutations. However, there is emerging evidence that checkpoint-inhibitor treatments for diseases such as lung cancer might work better when patients have a greater quantity of mutations[3].

Despite the wealth of data being accumulated about cancer genomics, the actual benefits are still murky. For people with a cancer mutation that can be targeted by an available therapy, there is no question that cancer-genome sequencing leads to better outcomes and survival. But Voest acknowledges that if overall cancer-survival data are taken as the endpoint, the benefits might not yet be as clear. The number of known cancer-causing mutations still far outweighs the number of treatments targeting those mutations. "You need to look at the impact that it has on those very small subgroups," he says. "Then I would consider that the impact of genomics is really big."

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1. Schmitz, R. *et al. N. Engl. J. Med.* **378**, 1396–1407 (2018).
2. van der Velden, D. L. *et al. Nature* **574**, 127–131 (2019).
3. Berland, L. *et al. J. Thorac. Dis.* **11**, S71–S80 (2019).